Protocol Number:	SGN35-015
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Protocol Title:	A phase 2 open-label study of brentuximab vedotin in front-line therapy of Hodgkin lymphoma (HL) and CD30-expressing peripheral T-cell lymphoma (PTCL) in older patients or patients with significant comorbidities ineligible for standard chemotherapy
Brief Title:	A study of brentuximab vedotin with Hodgkin lymphoma (HL) and CD30-expressing peripheral T-cell lymphoma (PTCL)
Investigational Drug:	Brentuximab vedotin
Indication:	Hodgkin lymphoma and CD30-expressing peripheral T-cell lymphoma
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Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
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SAE Email or Fax:	See email or fax number specified on the SAE report form.

PROTOCOL SYNOPSIS

Protocol Number SGN35-015 **Version** Amendment 13; 05-May-2020 **Phase** 2	**Product Name** Brentuximab vedotin **Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A phase 2 open-label study of brentuximab vedotin in front-line therapy of Hodgkin lymphoma (HL) and CD30-expressing peripheral T-cell lymphoma (PTCL) in older patients or patients with significant comorbidities ineligible for standard chemotherapy.

Study Objectives

Objectives are applicable to all parts of the study unless otherwise specified.

Primary

To assess the objective response rates (ORR) of single-agent brentuximab vedotin and brentuximab vedotin in combination with other agents as frontline therapy in patients age ≥60 years and in patient's ineligible for conventional combination chemotherapy due to comorbidities.

Secondary

- To evaluate safety and tolerability of single-agent brentuximab vedotin and the safety of brentuximab vedotin when given in combination with other agents
- To assess duration of response
- To assess complete remission (CR) rate
- To assess progression-free survival (PFS)
- To assess resolution of B symptoms
- To assess pharmacokinetics and immunogenicity of brentuximab vedotin (all parts) and nivolumab (Part D only)
- To assess overall survival (OS) (Parts E and F only)

Additional

- To assess event-free survival (EFS)
- To assess OS (Parts A, B, C, and D)
- To assess biomarkers in serum and tumor biopsies
- To assess the relationship between pharmacokinetics and disease response
- To assess immunomodulatory effects of the combination of brentuximab vedotin and nivolumab in peripheral blood (Part D only)
- To assess indeterminate response (IR) rate and subsequent response (Part D only)

Study Population

To be eligible, patients in Parts A, B, C, D, and E must have classical HL, excluding nodular lymphocyte-predominant HL; patients in Part F must have CD30-expressing PTCL. Patients are to be treatment-naive.
In Parts A, B, C, and D, patients must be ≥60 years of age, and ineligible for or have declined initial conventional combination chemotherapy.
In Parts E and F, patients must be ≥18 years of age and considered unsuitable or unfit for conventional combination chemotherapy, due to the presence of comorbidity-related factors, as documented by either a) a

Cumulative Illness Rating Scale (CIRS) score ≥10 (according to the criteria specified by Salvi and colleagues (Salvi 2008) excluding current active lymphoma) or b) requiring assistance with or dependence on others for any Instrumental Activities of Daily Living (IADL).
Patients must have disease that is fluorodeoxyglucose (FDG)-positron emission tomography (PET)-avid and bidimensionally measurable (≥1.5 cm in the longest axis); an Eastern Cooperative Oncology Group (ECOG) performance status ≤3 (≤2 Part D only); and adequate organ function. In Part C patients are to have an estimated creatinine clearance ≥40 mL/min, in Part D patients are to have an estimated creatinine clearance ≥30 mL/min, and in Parts E and F, patients are to have an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m². Patients are not eligible for enrollment if they have baseline peripheral neuropathy Grade ≥2 or the demyelinating form of Charcot-Marie-Tooth syndrome. Patients are also excluded if they have a history of progressive multifocal leukoencephalopathy (PML), kidney disease requiring ongoing dialysis, or any active Grade 3 or higher viral, bacterial, or fungal infection within 2 weeks prior to the first dose of brentuximab vedotin. Patients requiring concurrent use of other investigational agents are not eligible and patients may not receive chemotherapy, radiotherapy (RT), biologics, or immunotherapy that is not completed 4 weeks prior to study entry (not applicable to retreatment patients on Part D).

Number of Planned Patients

Up to 30 evaluable patients will be enrolled in Part A of the study (single-agent brentuximab vedotin), approximately 20 evaluable patients will be enrolled in Part B of the study (brentuximab vedotin+dacarbazine), and while initially approximately 30 patients were to be enrolled in Part C (brentuximab vedotin+bendamustine), enrollment into Part C of the study ceased as of 7 Oct 2015. Approximately 20 evaluable patients will be enrolled in Part D of the study (brentuximab vedotin+nivolumab), and approximately 50 evaluable patients each will be enrolled in Parts E and F of the study (single-agent brentuximab vedotin).

Study Design

This is a phase 2 open-label study designed to evaluate the efficacy and tolerability of brentuximab vedotin as monotherapy and in combination with other agents as frontline therapy in patients who are ineligible for or have declined initial conventional combination chemotherapy. There are 6 parts of the study.

- In Part A, treatment with brentuximab vedotin 1.8 mg/kg will be given on Day 1 of each 21-day cycle. Patients achieving stable disease (SD) or better will receive up to 16 cycles of single-agent treatment with brentuximab vedotin.
- In Part B, treatment with brentuximab vedotin 1.8 mg/kg in combination with dacarbazine 375 mg/m^2 will be given on Day 1 of Cycles 1 through 12, followed by single-agent brentuximab vedotin 1.8 mg/kg on Day 1 of Cycles 13 through 16 or more.
- In Part C, treatment with bendamustine 70 mg/m^2 will be given in combination with brentuximab vedotin 1.8 mg/kg on Day 1 and then as a single agent on Day 2 of each cycle for up to 6 cycles, followed by single-agent brentuximab vedotin 1.8 mg/kg on Day 1 of the remaining cycles for up to 16 cycles.
- In Part D, treatment with brentuximab vedotin 1.8 mg/kg and nivolumab 3 mg/kg will be given on Day 1 for up to 16 total cycles.
- In Parts E and F, treatment with brentuximab vedotin 1.8 mg/kg will be given on Day 1 of each 21-day cycle. Patients achieving a CR, partial remission (PR), or SD will receive up to 16 cycles of single-agent treatment with brentuximab vedotin.

After discussion with the medical monitor, any patient on Parts A, B, or C who complete 16 cycles of treatment and experience clinical benefit per the investigator will be eligible to receive continued brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure. For Part D, patients who experience clinical benefit per the investigator will be eligible after discussion with the medical monitor to receive continued treatment with the combination of brentuximab vedotin and nivolumab, single-agent brentuximab vedotin treatment (if nivolumab discontinued for toxicity), or single-agent nivolumab (if brentuximab vedotin discontinued for toxicity) until disease progression, unacceptable toxicity, or study closure. Patients with a response of IR will continue on treatment until demonstration of progressive disease (PD) via radiographic imaging or biopsy. Retreatment with brentuximab vedotin plus nivolumab is permitted with medical monitor approval, for patients who achieve a CR or PR on study and then discontinue treatment. Patients eligible for

retreatment must meet all inclusion and exclusion criteria and experience disease progression after discontinuing treatment with brentuximab vedotin and nivolumab. The retreatment dose levels will be determined by the medical monitor and the site investigator for each patient with consideration of prior study treatment dose levels and dose modification criteria if the patient experienced prior treatment-related toxicities.

Study Treatment in Each 21-day Cycle	Part A	Part B	Part C	Part D	Part E	Part F
Brentuximab vedotin 1.8 mg/kg IV on Day 1	X[a]	X[a]	X	X	X	X
Dacarbazine 375 mg/m^2 IV on Day 1[b]		X				
Bendamustine 70 mg/m^2 on Day 1[b] and Day 2[c]			X			
Nivolumab 3 mg/kg on Day 1[d]				X		

a Patients enrolling on study with estimated creatinine clearance <30 mL/min will receive 1.2 mg/kg brentuximab vedotin every 3 weeks either as a single agent in Part A or in combination with a reduced dose of dacarbazine (262 mg/m2; ~30% reduced) in Part B.

b Administered within approximately 1 hour of completing treatment with brentuximab vedotin administered via IV on Day 1 of each 21-day cycle.

c Bendamustine is administered as a single agent on Day 2 of each 21-day cycle.

d Administered at least 30 minutes after completing treatment with brentuximab vedotin.

Test Product, Dose, and Mode of Administration

Part A: Brentuximab vedotin, 1.8 mg/kg, will be administered via intravenous (IV) infusion every 3 weeks.

Part B: Combination treatment with brentuximab vedotin, 1.8 mg/kg IV, and dacarbazine, 375 mg/m^2 IV, every 3 weeks.

Part C: Combination treatment with brentuximab vedotin, 1.8 mg/kg IV on Day 1, and bendamustine, 70 mg/m^2 IV on Days 1 and 2, every 3 weeks.

Part D: Combination treatment with brentuximab vedotin, 1.8 mg/kg IV, and nivolumab, 3 mg/kg IV, every 3 weeks.

Part E: Brentuximab vedotin, 1.8 mg/kg IV, every 3 weeks.

Part F: Brentuximab vedotin, 1.8 mg/kg IV, every 3 weeks.

Patients enrolling on study with estimated creatinine clearance <30 mL/min will receive 1.2 mg/kg brentuximab vedotin every 3 weeks either as a single agent in Part A or in combination with a reduced dose of dacarbazine (262 mg/m^2; ~30% reduced) in Part B.

Duration of Treatment

Patients who achieve at least SD will be eligible to receive single-agent brentuximab vedotin treatment (Parts A, E, and F) for up to 16 cycles, brentuximab vedotin and dacarbazine administered in combination for up to 12 cycles (Part B), brentuximab vedotin and bendamustine administered in combination for up to 6 cycles (Part C), or brentuximab vedotin and nivolumab administered in combination for up to 16 cycles (Part D). For Parts A, B, and C, patients who complete 16 cycles of treatment and experience clinical benefit per the investigator will be eligible to receive continued single-agent brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure. For Part D, patients who experience clinical benefit per the investigator will be eligible to receive continued treatment with the combination of brentuximab vedotin and nivolumab, single-agent brentuximab vedotin treatment (if nivolumab discontinued for toxicity), or single-agent nivolumab (if brentuximab vedotin discontinued for toxicity) until disease progression, unacceptable toxicity, or study closure. Patients with a response of IR will continue on treatment until demonstration of PD via radiographic imaging or biopsy.

Efficacy Assessments

Parts A, B, C, and D

For Parts A, B, and C, disease response and progression will be assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). For Part D of the study, disease response will be assessed using the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Lugano criteria) (Cheson 2014) and Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016). PD also includes clinical disease progression per investigator.

Imaging with computed tomography (CT) will be performed at baseline, at Cycles 2, 4, 8, 12, and at end of treatment (EOT) approximately 1 month after discontinuation of study treatment. For Parts A, B, and C, imaging with PET will be performed at baseline, at Cycles 2 and 8, and at EOT. For Part D, PET scans will be performed at baseline, at Cycles 4, 8, and 12, and at EOT. Once a patient achieves a PET CR, PET scan will no longer be required. Clinical lymphoma assessments will be performed predose in every treatment cycle.

In patients eligible for continued treatment with brentuximab vedotin (and/or nivolumab for Part D only) beyond 16 cycles, CT (and PET for Part D only) will be performed at Cycle 16. Then for Cycles 17 and beyond, CT will be performed per institutional standard of care, or at least every 6 cycles, and PET scans will be performed per institutional standard of care.

For Parts A, B, and C, visual interpretation will be used for evaluation of interim PET scan results with response scored with reference to sites of presumed lymphomatous involvement using the 5-Point Scale per the Deauville Criteria (Barrington 2010; Meignan 2009).

For patients on Part D with a response determination of IR, radiographic assessment (CT/PET) of disease must be performed 12 weeks following IR or earlier if clinically indicated. If a patient has a second determination of IR, then subsequent repeat imaging must be performed between 4 and 8 weeks. Follow-up radiographic assessment for patients with IR is not required, if a follow-up biopsy has been performed that confirms response.

After completion of therapy, disease status will be assessed by CT imaging per institutional standard of care or intervals of at least every 6 months for the first 2 years, an annual assessment for the third year, then per institutional standard of care until progression.

Parts E and F

Disease response will be assessed using modified Lugano criteria; the assessment will be per blinded independent central review.

Imaging with CT and PET will be performed at baseline, at Cycles 2, 6, 11, and at EOT approximately 1 month after discontinuation of study treatment. Clinical lymphoma assessments will be performed predose in every treatment cycle. Once a patient achieves a PET CR, PET scans will no longer be required. Patients discontinuing study treatment without progression will be followed until progression or initiation of further anti-cancer therapy. Follow-up CT scans will be performed every 4 months for 2 years and then per institutional standard of care, and follow-up PET scans will be performed per institutional standard of care.

Pharmacokinetic/Pharmacodynamic/Immunogenicity Assessments

For Parts A, B, C, E, and F, serum concentrations of brentuximab vedotin antibody-drug conjugate (ADC) and plasma concentrations of monomethyl auristatin E (MMAE) will be measured. Samples will be retained for measurement of total antibody, if needed. Antitherapeutic antibodies (ATA) to brentuximab vedotin will also be measured. Pharmacodynamic assessments include but are not limited to the measurement of soluble CD30. For Part D, serum concentrations of brentuximab vedotin ADC and nivolumab, and plasma concentrations of MMAE will also be measured at selected time points. ATA against brentuximab vedotin, ATA against nivolumab, and immunomodulatory effects of treatment will also be assessed in Part D.

Safety Assessments

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

A Safety Monitoring Committee (SMC) monitored patient safety in Part C of the trial. The SMC reviewed safety data after the first 5 patients in Part C completed 1 cycle of brentuximab vedotin and bendamustine and again after the first 5 patients completed 2 cycles of treatment with brentuximab vedotin and bendamustine. It was noted in the second safety call that 4 of 7 patients in Part C had experienced serious adverse events (SAEs). The starting dose of bendamustine was then reduced from 90 mg/m^2 to 70 mg/m^2 (Amendment 6). Additional key safety observations were reported at a subsequent SMC meeting; 12 of 20 patients enrolled on Part C had experienced SAEs and 2 of those patients died within the 30-day safety reporting period. Although no safety signal was identified, and neither of the deaths were considered related to study treatment, the sponsor has suspended enrollment of patients into Part C and has discontinued bendamustine treatment for all patients currently enrolled in Part C as of 7-Oct-2015 (the date of the Dear Investigator Letter). Single-agent brentuximab vedotin may be continued for patients who tolerate the therapy and have demonstrated clinical benefit.

Safety review of patients treated with the combination of brentuximab vedotin and nivolumab was conducted by the study SMC after the first 5 patients in Part D completed treatment through Cycle 3 Day 1, and will continue throughout the study as needed.

Statistical Methods

Summaries of patient disposition, demographics, disease characteristics, safety, disease response, and exposure to study drug will be provided. All analyses of safety and efficacy endpoints will be descriptive in each study part. In addition, the pharmacokinetic parameters of brentuximab vedotin and MMAE, as well as nivolumab (Part D only), will be estimated and summarized with descriptive statistics. No formal statistical hypotheses have been formulated for primary efficacy, secondary or additional endpoints in any study part. However, the secondary and additional endpoints will be analyzed and provided as supporting evidence for the overall clinical benefit of brentuximab vedotin.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

5HT3	serotonin receptor
A+ABVD	brentuximab vedotin combined with ABVD
A+AVD	brentuximab vedotin combined with AVD
A+CHP	brentuximab vedotin combined with CHP
ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine
ACE-27	Adult Comorbidity Evaluation-27
ADC	antibody-drug conjugate
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
AUC	area under the concentration-time curve
auto-HSCT	autologous hematopoietic stem cell transplantation
AVD	doxorubicin, vinblastine, and dacarbazine
β-hCG	beta human chorionic gonadotropin
BACOPP	BEACOPP with etoposide omitted and anthracycline dose increased
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BICR	blinded independent central review
BMI	body mass index
BPH	benign prostate hypertrophy
C_{eoi}	concentration at the end of infusion
C_{max}	maximum concentration
C_{trough}	trough concentration
CBC	complete blood count
CCI	Charlson Comorbidity Index
CFR	Code of Federal Regulations
ChlVPP	chlorambucil, vinblastine, procarbazine, and prednisone
ChlVPP/ABV	ChlVPP plus doxorubicin, bleomycin, and vincristine
CHOEP	cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHP	cyclophosphamide, doxorubicin, and prednisone
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CIRS-G	Cumulative Illness Rating Scale-Geriatric
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
CR	complete remission

CRF	case report form
CT	computed tomography
DILI	drug-induced liver injury
DLCO	diffusing capacity of the lung for carbon monoxide
DSM	Diagnostic and Statistical Manual of Mental Disorders
DVT	deep venous thrombosis
EBV	Epstein-Barr Virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
FDG	fluorodeoxyglucose
G-CSF	granulocyte-colony stimulating factor
GERD	gastroesophageal reflux disease
GHSG	German Hodgkin Study Group
GI	gastrointestinal
HL	Hodgkin lymphoma
HRS	Hodgkin Reed-Sternberg
HSR	hypersensitivity reaction
IADL	instrumental activity of daily living
IEC	Independent Ethics Committee
IND	Investigational New Drug
IR	indeterminate response
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
Lugano criteria	Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
MMAE	monomethyl auristatin E
MMSE	Mini Mental Sate Examination
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer

NSAID	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAD	peripheral arteries disease
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1, PD-L2	ligands to PD-1
PET	positron emission tomography
PK	pharmacokinetic
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRN	pro re nata (as needed)
PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma–not otherwise specified
PVAG	prednisone, vinblastine, doxorubicin, and gemcitabine
RECIL	Response Evaluation Criteria in Lymphoma
RNA	ribonucleic acid
RT	radiotherapy
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
sCD30	soluble CD30
Scr	serum creatinine
SD	stable disease
SMC	Safety Monitoring Committee
SPD	sum of the products of the largest diameter
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TIA	transient ischemic attack
T_{max}	time at which the C_{max} occurs
TSH	thyroid-stimulating hormone
TURP	transurethral resection of the prostate
ULN	upper limit of normal
USAN	United States adopted name
UTI	urinary tract infection
WBC	white blood cell
WHO	World Health Organization

1 INTRODUCTION

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30; 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell. Other nonclinical studies suggest additional contributory mechanisms of action, including antibody-dependent cellular phagocytosis; bystander effects on nearby cells in the tumor microenvironment due to released MMAE; and immunogenic cell death due to endoplasmic reticulum stress which drives exposure of immune activating molecules that can promote a T-cell response (Cao 2016; Gardai 2015; Kim 2015; Li 2014; Muller 2014; Oflazoglu 2007).

Frontline treatment options are needed for patients who cannot tolerate multi-agent chemotherapy regimens. This study will provide data regarding the safety and efficacy of brentuximab vedotin used as a single agent in the frontline treatment of patients with newly diagnosed classical Hodgkin lymphoma (HL; i.e., excluding nodular lymphocyte predominant HL) or CD30-expressing peripheral T-cell lymphoma (PTCL) who cannot tolerate or have declined multi-agent chemotherapy. In addition, the efficacy and tolerability of brentuximab vedotin combined with dacarbazine, bendamustine, or nivolumab will be evaluated in the frontline treatment of classical HL.

1.1 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. The characteristic surface antigen expressed on HRS cells is CD30. It is estimated that 8110 patients will be diagnosed with HL in the US in 2019 and 1000 patients will die of the disease (Siegel 2019).

For most patients, treatment of HL has improved over the past 30 years with combination chemotherapy regimens. The current anthracycline-containing regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), given with or without consolidative radiotherapy (RT), has proved superior to alkylator-based regimens and results in long-term cure rates on the order of 70% and higher. However, unlike the majority of younger patients with HL who have impressive cure rates with standard frontline therapy, patients 60 and over and patients with significant comorbidities experience more severe toxicity and higher rates of relapse with this combination regimen.

1.1.1 Hodgkin Lymphoma in Patients Aged 60 Years and Above

Of newly diagnosed HL patients, population-based studies estimate that up to 20% are age 60 years and above (Stark 2002). Older patients (≥60 years of age) with HL have disproportionately inferior outcomes as compared to younger patients with HL (Klimm 2007). Studies cite 5-year event-free survival (EFS) and freedom from treatment failure rates of 30% to 45% in older patients, as compared to rates of 75% to 80% expected in younger patients (Evens 2008; Proctor 2009).

The disease differs in histopathologic presentation, more frequently exhibiting an aggressive mixed-cellularity subtype and Epstein-Barr Virus (EBV) positivity. Clinically, older HL patients are more likely to present with B symptoms, poorer performance status, elevated sedimentation rate, and advanced-stage disease, with a lower incidence of bulky disease. In addition to differences in biology and disease-related features, poorer overall outcomes in older patients with HL can also be attributed to treatment-related factors which compromise cure rates.

There is a paucity of data concerning outcomes of older patients treated for early stage HL, likely due to the preponderance of this patient population presenting with advanced stage disease. In 1w review of 67 early stage older HL patients treated with RT alone, 82% achieved a complete remission (CR) but 43% went on to relapse, and 11 of the 67 patients developed secondary malignancies (Landgren 2006).

The majority of older patients with HL present with advanced stage disease, for which systemic combination chemotherapy is typically administered. Several studies have been conducted to examine a variety of chemotherapy regimens in this population. In a recent retrospective review of outcomes in older patients with HL, the most common treatment given was ABVD-based therapy (Evens 2012). While the CR rate was reasonable at 73%, the 5-year overall survival (OS) rate for older patients with advanced HL was 46%. In the recently reported ECHELON-1 study that compared ABVD to brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine (A+AVD) for the frontline treatment of patients with advanced classical HL, the brentuximab vedotin + cyclophosphamide, doxorubicin, and prednisone (A+CHP) arm showed a significant improvement in modified progression-free survival (PFS) (HR=0.77 [0.603, 0.982], p-value=0.035). The A+AVD regimen was associated with more myelotoxicity and neurotoxicity, which was managed with growth factor support and dose modifications, than ABVD, but less pulmonary toxicity (Connors 2018).

Other regimens such as escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) have been utilized for younger fit patients in some regions including Germany. Variants including standard BEACOPP and BACOPP (with etoposide omitted and anthracycline dose increased) have been studied in older HL patients and have shown to be too toxic to be recommended in this setting (Ballova 2005; Halbsguth 2010).

Several studies have evaluated the role of anthracycline-based regimens in older patients with HL. In a study comparing chlorambucil, vinblastine, procarbazine, and prednisone (ChlVPP) with the hybrid ChlVPP/ABV (ChlVPP plus doxorubicin, bleomycin, and vincristine), a subset of 56 patients age ≥60 treated with ChlVPP had a poorer outcome than those treated with ChlVPP/ABV in terms of 5-year OS (30% versus 67%; p=0.0086) and EFS (24% versus 52%; p=0.011) (Weekes 2002). A recent small Scandinavian study evaluated the CHOP-21 regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) ± RT in a 29 patient cohort of older patients with early and advanced stage HL, revealing a 3-year OS and PFS of 79% and 76%, respectively (Kolstad 2007). Other recent non-bleomycin containing strategies have included prednisone, vinblastine, doxorubicin, and gemcitabine (PVAG), with published OS and PFS rates of 66% and 58% when studied in early unfavorable and advanced stage HL patients between 60–75 years of age (Boll 2011). The need to reduce drug intensity of PVAG remained a challenge, with relative dose intensity of ≥80% delivered in only 45 of the 57 evaluable patients mainly due to frequent omissions of whole cycles of therapy. Additionally, although there is little information regarding frontline treatment with bendamustine in HL, results from a phase 2 study in the relapsed or refractory setting demonstrated that patients treated with bendamustine had an objective response rate (ORR) of 53% (CR, 33%; partial response [PR], 19%) (Moskowitz 2013a). Thus far, no agreed upon standard treatment approach exists for patients age ≥60 with HL.

Furthermore, higher rates of treatment-related toxicities have also been reported in older patients with HL. In a comprehensive retrospective analysis of older patients with HL by the German Hodgkin Study Group (GHSG), severe toxicities (World Health Organization [WHO] Grade 4) occurred more often in patients age 60 and older (42% versus 27%; P<0.001) including infectious complications and fatal acute treatment-related events (Engert 2005). Similarly, in a retrospective multicenter analysis of 95 HL patients age ≥60 in the Chicago area who most commonly received ABVD for frontline therapy, the incidence of bleomycin-associated pulmonary toxicity was 32%, with an associated mortality rate of 25% in those affected (Evens 2012).

Older patients with HL remains a population of unmet need with underrepresentation of patients aged ≥60 in HL clinical trials and inferior outcomes as compared to younger patients.

1.1.2 Hodgkin Lymphoma in Patients with Significant Comorbidities

The presence of significant comorbidities has a major effect on the treatments received, treatment toxicity, dose intensity, and prognosis in the HL population, even though the impact of comorbidities has not been studied as extensively as the impact of age.

Significant comorbidities have been reported to be present in 13% of patients with newly diagnosed HL aged less than 60 years and 56% of patients aged at least 60 (van Spronsen 1999). A review of 45,777 patients with HL in the US National Cancer Database found that a Charlson Comorbidity Index (CCI) score ≥1 resulted in a significantly lower OS, independently of age, disease stage, or use of RT (Parikh 2015). A review of

20,600 early-stage HL patients in the US National Cancer Database found that the presence of at least 1 CCI comorbidity was significantly associated with treatment choice (chemotherapy alone versus combined modality therapy; odds ratio 0.75 [95% confidence interval {CI}: 0.67, 0.85], p<0.001) (Olszewski 2015); lymphoma-specific survival was significantly lower in patients with morbidities (HR 3.05 [95% CI 2.14, 4.35], p<0.001 for CCI ≥2). Retrospective reviews of the effect of age above or below 60 years in patients with relapsed or refractory HL or non-Hodgkin lymphomas (NHL) found CCI to be significantly and independently associated with treatment toxicity, treatment-related mortality, PFS, and OS, while age was not (Martinez 2017) (Wildes 2008). The effect of comorbidities, measured using the Cumulative Illness Rating Scale-Geriatric (CIRS-G), on prognosis has also been confirmed within the population of older patients (>60 years) with frontline HL (Evens 2012). In the prospective Study of Hodgkin in the Elderly/Lymphoma Database (SHIELD) program, no CR were observed in patients determined to be "frail" according to a modified Adult Comorbidity Evaluation-27 (ACE-27) scale, and comorbidity score was significantly associated with CR rate and OS (Proctor 2012). National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recognize that individualized treatment may be necessary for patients with comorbidities. There is a need to develop treatments that can be used safely and efficaciously in patients with HL who have significant comorbidities, irrespective of age.

1.2 CD30-Expressing Peripheral T-Cell Lymphoma

T-cell lymphomas are a subset of aggressive NHL that comprise approximately 10% to 15% of all newly diagnosed cases of NHL in the US. According to the 2008 WHO Classification schema, there are 18 subtypes of mature T- and natural killer (NK)-cell neoplasms (Swerdlow 2008). Various subtypes of T- and NK-cell lymphomas are known to express the cell surface marker CD30; most notably, systemic anaplastic large cell lymphoma (sALCL), in which CD30 expression is a hallmark of the diagnosis (Savage 2008). The median age of patients with the most common PTCL subtypes is approximately 60 years, with anaplastic lymphoma kinase (ALK)-positive PTCL being the exception, having a median age of 34 years (Armitage 2015; Vose 2008).

CD30-expressing PTCL, including ALK-positive and ALK-negative sALCL, peripheral T-cell lymphoma–not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and others, are aggressive lymphoid neoplasms that often present with advanced stage, symptomatic disease. These difficult-to-treat lymphomas are often grouped together for enrollment in clinical trials based on their universally dismal outcomes. Five-year OS in the over 1,300-patient International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study was poor and ranged from 12% to 49% depending on histologic subtype (Vose 2008). Five-year failure-free survival, defined as time from initial diagnosis to progression, relapse after response, or death resulting from any cause, ranged from 6% to 36%. Other studies have reported CR rates to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy between 40% and 50% (Mercadal 2008; Simon 2010).

Although no randomized studies have been conducted to establish the use of CHOP in patients with CD30-expressing PTCL, it is the most commonly used regimen in the frontline treatment of these patients. The International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study results indicate that over 85% of patients were treated with an anthracycline-based multi-agent chemotherapy regimen (Vose 2008). In published studies that have compared new treatment approaches to an established standard of care, CHOP administered every 3 weeks (CHOP-21) has been used as the control arm (Simon 2010). A post-hoc analysis of pooled data from PTCL patients treated on multiple phase 2 and 3 studies suggested that the addition of etoposide to CHOP (CHOEP) resulted in improved 3-year EFS (time to standard PFS or unplanned therapy) but only in patients ≤60 years old with a normal lactate dehydrogenase (LDH) (Schmitz 2010). CHOEP proved too toxic for patients older than 60 (Lunning 2013; Schmitz 2010). In the recently reported ECHELON-2 study that compared CHOP to brentuximab vedotin + CHP for the frontline treatment of CD30-expressing PTCL, the brentuximab vedotin + CHP arm showed a significant improvement in both PFS (hazard ratio 0.71 [95% CI: 0.54, 0.93], p=0.0110) and OS (hazard ratio 0.66 [95% CI: 0.46, 0.95], p=0.0244). The safety profile of both treatment arms was comparable (Horwitz 2018).

Even so, in NCCN guidelines, participation in clinical trials is still the suggested frontline treatment for patients with PTCL, other than sALCL and ALK-positive subtypes, for which multi-agent chemotherapy with or without RT is recommended. The presence of comorbidities can lead to the inability to administer multi-agent chemotherapy, higher rates of toxicity, and consequent decreases in dose intensity. In a recent retrospective study of patients >60 years of age newly diagnosed with PTCL between 2008-2014, a multivariate analysis demonstrated that a CCI ≥2 and high International Prognostic Index score (3-5) were independent risk factors for worse OS and PFS (Zhao 2016). Similarly, multivariate analysis of registry data from Sweden shows that a CCI ≥2 is independently associated with worse OS and PFS outcomes (Ellin 2018).

Frontline treatment regimens for patients with PTCL ineligible for combination chemotherapy due to comorbidities have not been defined, necessitating the evaluation of alternative strategies.

1.3 Experience With Brentuximab Vedotin

A phase 2 pivotal trial of single-agent brentuximab vedotin (1.8 mg/kg, every 3 weeks) evaluated 102 patients whose HL had relapsed or was refractory to multiple-agent, high-dose chemotherapy and autologous stem cell transplant. A 75% ORR and a 34% CR rate were observed and common adverse events (AEs) were primarily mild to moderate in severity and generally constitutional in nature with the exception of peripheral sensory neuropathy (Younes 2012).

The safety and efficacy of brentuximab vedotin has been evaluated in more than 2,700 patients in company-sponsored clinical trials, and approved by multiple regulatory agencies.

FDA indications:

- Classical HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.
- Systemic ALCL after failure of at least 1 prior multi-agent chemotherapy regimen.
- Classical HL at high risk of relapse or progression as post auto-HSCT consolidation.
- Previously untreated Stage III or IV classical HL, in combination with doxorubicin, vinblastine, and dacarbazine.
- Previously untreated sALCL or other CD30-expressing PTCLs, including angioimmunoblastic T-cell lymphoma and PTCL-NOS, in combination with cyclophosphamide, doxorubicin, and prednisone.
- Primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received prior systemic therapy.

EMA indications:

- Previously untreated CD30+ Stage IV HL in combination with doxorubicin, vinblastine and dacarbazine (AVD)
- Treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT)
- Treatment of adult patients with relapsed or refractory CD30+ HL:
  1. Following ASCT, or
  2. Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option
- Treatment of adult patients with relapsed or refractory sALCL
- Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy

The pivotal clinical trials leading to these approvals included a phase 2 study of brentuximab vedotin monotherapy in relapsed or refractory HL after autologous stem cell transplant (SG035-0003), a phase 2 study of brentuximab vedotin monotherapy in relapsed or refractory sALCL (SG035-0004), a phase 3 study of brentuximab vedotin plus best supportive care versus placebo plus best supportive care in the treatment of patients at high risk of residual HL following autologous stem cell transplant (SGN35-005), a phase 3 study of A+AVD versus ABVD as frontline therapy for newly diagnosed Stage III or IV classical HL patients (C25003), a phase 3 study of A+CHP versus CHOP as frontline therapy for newly diagnosed CD30-expressing PTCL (SGN35-014), and a phase 3 study of brentuximab vedotin versus methotrexate or bexarotene in CD30-expressing cutaneous T-cell lymphoma (C25001).

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

1.4 Experience With Brentuximab Vedotin Combined With Dacarbazine

The combination chemotherapy regimen ABVD (doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2) is a standard regimen for the frontline treatment of HL. Because of the efficacy observed with single-agent brentuximab vedotin in patients with relapsed or refractory HL, a phase 1 study was conducted in 51 patients with newly diagnosed HL to evaluate the safety of brentuximab vedotin combined with this standard regimen (A+ABVD) or with a modified standard that omitted bleomycin (A+AVD). In this study, it was found that concomitant administration of brentuximab vedotin with bleomycin was contraindicated due to an unacceptable rate of pulmonary toxicity; however, brentuximab vedotin 1.2 mg/kg combined with AVD administered every 2 weeks was generally well tolerated by patients and resulted in a CR rate of 96% at the end of frontline therapy (Younes 2013).

Brentuximab vedotin was also tested preclinically in combination with chemotherapy. In the L450cy HL tumor model, administration of brentuximab vedotin plus ABVD in tumor-bearing mice demonstrated a marked increase in antitumor activity as compared to the mice treated with brentuximab vedotin or ABVD alone, suggesting a potential synergistic effect. When individual components of ABVD were tested with brentuximab vedotin in the tumor model, brentuximab vedotin plus dacarbazine (A+D) was observed to have similarly robust combined durable activity as compared to A+ABVD (McEarchern 2010).

1.5 Experience With Brentuximab Vedotin Combined with Bendamustine

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring, approved in the US for chronic lymphocytic leukemia (CLL) and NHL; bendamustine is administered as an intravenous (IV) infusion on Days 1 and 2 for up to six 28-day cycles in CLL and for up to eight 21-day cycles in NHL. Though the exact mechanisms of action of bendamustine are unknown, mechlorethamine derivatives form electrophilic alkyl groups, which then form covalent bonds with electron-rich nucleophilic moieties and result in interstrand DNA crosslinks that lead to cell death via several pathways.

The combination chemotherapy regimen brentuximab vedotin and bendamustine is currently being studied in a phase 1/2 trial of patients with relapsed or refractory HL (SGN35-016). Preliminary results showed that after a median of 2 cycles of combination treatment, the ORR was 92% (12/13 patients) and the CR rate was 77% (10/13 patients); 12 of 13 patients with a response assessment at the time of interim analysis remained on treatment and all 13 patients remained free of progressive disease (PD) (LaCasce 2014). Additionally, the combination of brentuximab vedotin and bendamustine did not appear to interfere with stem cell collection for autologous transplant. AEs seen in ≥20% of patients included nausea, rash, fever, fatigue, vomiting, chills, diarrhea, shortness of breath, and lymphopenia. Infusion-related reactions (IRRs) and hypersensitivity reactions (HSR) were noted; 6 patients had treatment-related and serious events and 3 patients discontinued treatment due to IRRs. IRRs were considered related to brentuximab vedotin and bendamustine; most occurred at the Cycle 2 infusion. Symptoms included rash, hives, pruritus, shortness of breath, wheezing, throat tightness, fever, chills, and hypotension. The study protocol was amended to require

premedication with corticosteroids and antihistamines; premedication has reduced the severity of IRRs and HSRs. Based on this information, it is recommended that patients in this study be premedicated with corticosteroids and antihistamines (see Section 5.4.4).

Further study of the combination of brentuximab vedotin and bendamustine on the current study (Part C of Study SGN35-015) showed additional safety observations as detailed in Section 3.1.

1.6 Experience With Brentuximab Vedotin Combined with Nivolumab

Nivolumab is a fully-human monoclonal antibody (IgG4) that targets programmed cell death protein-1 (PD-1). In vitro, nivolumab binds to PD-1 with high affinity (EC_{50} 0.39–2.62 nM), and inhibits the binding of PD-1 to its ligands, PD-L1 and PD-L2 (IC_{50} ±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 enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction, augmentation of IFN-γ secretion from cytomegalovirus (CMV)-specific memory T-cells in a dose-dependent manner in a CMV re-stimulation assay, and enhancement of the antitumor immune response and tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) using a murine analog of nivolumab (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 22% (5/23). The responses obtained have been durable with the median PFS not yet reached after a median 101 weeks of follow-up. No significant difference in the ORR in the subset of 18 patients who had previously failed brentuximab vedotin was observed (Ansell 2015).

A combination therapy regimen of brentuximab vedotin and nivolumab is currently being studied (SGN35-025) at Seattle Genetics, Inc. The phase 1/2, open-label, multicenter study is designed to evaluate the safety and antitumor activity of brentuximab vedotin treatment combined with nivolumab in patients with relapsed or refractory HL after 1 prior treatment. Patients are being treated for up to four 3-week cycles with the first dose of brentuximab vedotin 1.8 mg/kg being given on Cycle 1 Day 1 and the first dose of nivolumab 3 mg/kg on Cycle 1 Day 8. For Cycle 2 and all subsequent cycles, brentuximab vedotin 1.8 mg/kg followed by nivolumab 3 mg/kg is being given on Day 1. As of 27 May 2016, 17 patients have started treatment and were evaluated for safety on Protocol SGN35-025. Preliminary results have demonstrated no dose-limiting toxicities (6 patients in dose-limiting toxicity evaluation period of study [Part 1]) and no Grade 4 or 5 AEs have occurred. One patient has experienced a treatment-related serious adverse event (SAE) of dehydration, hypercalcemia and acute kidney injury after the first dose of brentuximab vedotin. Due to an increased incidence of IRRs at Cycle 2 Day 1 during the administration of the first study drug brentuximab vedotin (5 of 11 patients [45%], with Grade 1 [2 patients], Grade 2 [2 patients], and Grade 3 [1 patient] severity), mandatory premedication was instituted with hydrocortisone 100 mg (or other steroid equivalent) and antihistamines prior to start of

Cycle 2 infusion and subsequent cycles. Symptoms experienced by patients included rash, pruritus, nausea, vomiting, diarrhea, dyspnea, and chest, and throat tightness. Enrollment in the second part of this study is ongoing.

In an ongoing cooperative group trial, brentuximab vedotin and nivolumab are administered sequentially on Day 1 of each 3-week cycle using premedication with H_1- and H_2-antagonists alone. Ten patients with relapsed/refractory HL have received this treatment regimen thus far on the study, and of those patients, only 1 experienced a Grade 1/2 IRR. The patient was able to receive subsequent therapy with additional premedication (Diefenbach 2016). Due to the lower incidence of IRRs observed in this cooperative group trial, Part D of the current study will mirror the same-day dosing regimen and premedications (see Sections 5.2.2, 5.5.3, and 5.5.4).

1.7 Rationale for the Current Study

The prognosis of patients with HL and CD30-expressing PTCL has improved over the years, mainly due to advances in intensified chemotherapy and combined modality regimens. However, these improvements have not been reflected in patients with significant comorbidities or older patients (for the latter perhaps attributable to the frequency of comorbidities) (Martinez 2017). In these patients, chemotherapy-related toxicities, including treatment-related mortality, are believed to be more common than previously recognized. Anthracycline-based regimens pose problems for those with cardiovascular comorbidities, and other chemotherapy-related toxicities such as bleomycin-related pulmonary toxicity are often considered prohibitive. The risk associated with the administration of dose-intensive combination chemotherapy regimens is exacerbated by concomitant cardiac, renal, or other organ dysfunctions. Intensive regimens are typically not well tolerated by these patients, while less intensive regimens are not effective; thus, experts agree that challenges remain in establishing recommendations for standard treatment of less robust patients.

Similar to HL, there is no standard treatment regimen for older patients with PTCL, and comorbidities, such as depressed cardiac or renal function, limit the ability to use combination chemotherapy in many less robust patients. For CD30-expressing PTCL, single-agent brentuximab vedotin is an active and well-tolerated treatment for patients with relapsed and refractory disease (Horwitz 2014) and the ECHELON-2 study showed that the addition of brentuximab vedotin to combination chemotherapy in the frontline treatment improves both PFS and OS (Horwitz 2018).

There is a high unmet need in patients aged >60 years and in patients with significant comorbidities with HL and CD30-expressing PTCL for novel therapeutic approaches that are well-tolerated and active; brentuximab vedotin has the potential to fill this role. This phase 2 study will evaluate the efficacy, safety, and tolerability of brentuximab vedotin as frontline monotherapy for HL and CD30-expressing PTCL in older patients and patients with significant comorbidities. The efficacy, safety, and tolerability of combination treatment with brentuximab vedotin and dacarbazine, bendamustine, or nivolumab will also be evaluated.

Monotherapy with brentuximab vedotin

The ADC brentuximab vedotin has an acceptable toxicity profile in clinical studies, with robust activity demonstrated as a single agent in HL patients refractory to several lines of chemotherapy. The aim of this study is to discover a tolerable regimen with long-term clinical benefit for patients with HL and CD30-expressing PTCL ineligible for multi-agent chemotherapy.

Combination with dacarbazine

Dacarbazine has proven to be a critical component of the ABVD regimen and has not been reported to have prohibitive toxicities, unlike bleomycin and doxorubicin. In the GHSG HD13 trial, a significant loss of efficacy was observed when dacarbazine was omitted from the combination (Borchmann 2010). Therefore, it is reasonable to evaluate the combination of brentuximab vedotin with dacarbazine, a highly active alkylator component from the ABVD regimen.

Combination with bendamustine

Also of note, current studies suggest that single-agent bendamustine produces CR rates as high as 38% in relapsed and refractory HL (Anastasia 2014; Moskowitz 2009; Moskowitz 2013b). As both brentuximab vedotin and bendamustine have demonstrated efficacy in lymphoma and act via independent mechanisms, it is rational to expect the combination is likely to be effective as treatment in frontline therapy of HL. The combination of brentuximab vedotin and bendamustine has demonstrated an ORR of 92% (CR rate 77%) in an ongoing study of patients with relapsed or refractory HL (SGN35-016) (LaCasce 2014).

Combination with nivolumab

Furthermore, recent results with the PD-1 blocking agent nivolumab have demonstrated efficacy for relapsed or refractory HL of the CD28 family of T-cell co-stimulatory receptors (Chen 2013b; 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 evidence that HRS cell-mediated PD-1 signaling to 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 staining, is present in more than 80% of HL cases, with similar rates of expression in all HL pathological subtypes (Chen 2013a). Several mechanisms contribute to upregulated expression of PD-L1 and PD-L2 in HRS cells, including amplification of chromosome 9p24.1, which contains the genes PD-L1, PD-L2, and JAK2, and results in a direct increase in their copy number. The increase in JAK2 copy number also indirectly contributes to PD-ligand overexpression through STAT1 mediated transcriptional upregulation of the PD-L1 and PD-L2 genes (Green 2010). Furthermore, EBV

infection of malignant HRS cells, which is found in up to 40% of HL cases, contributes to overexpression of PD-L1 through direct and indirect effects of the EBV latent membrane protein 1 on PD-L1 promoter and enhancer elements (Green 2012). These data provide a firm basis for the use of a PD-1 blocking agent to activate an antitumor immune response against HRS cells. Furthermore, recent evidence indicates that auristatin-based ADCs like brentuximab vedotin may also initiate an antitumor immune response through the induction of stress on the endoplasmic reticulum of HRS cells and enhancement of antigen presentation (Muller 2014), providing a strong scientific rationale for combining brentuximab vedotin with an immune stimulatory agent like nivolumab. Together with clinical data demonstrating that brentuximab vedotin and nivolumab both have high single-agent response rates in patients with heavily pretreated relapsed or refractory HL, it is hypothesized that the combination therapy will be more effective than administration of either agent alone, particularly in the frontline setting. Moreover, both agents are well tolerated, have few overlapping toxicities, and can be infused in the outpatient setting, making this a potentially attractive treatment option for older and medically fragile patients. This study will evaluate the safety and antitumor activity of combination therapy with brentuximab vedotin and nivolumab in a population of previously untreated older patients with HL.

2 OBJECTIVES

All objectives and endpoints are applicable to all parts of the study unless otherwise specified.

2.1 Primary Objective

- To assess the ORR of single-agent brentuximab vedotin and brentuximab vedotin in combination with other agents as frontline therapy in patients age ≥60 years and in patients ineligible for conventional combination chemotherapy due to comorbidities

2.2 Secondary Objectives

- To evaluate safety and tolerability of single-agent brentuximab vedotin and the safety of brentuximab vedotin when given in combination with other agents
- To assess duration of response
- To assess CR rate
- To assess PFS
- To assess resolution of B symptoms
- To assess pharmacokinetics (PK) and immunogenicity of brentuximab vedotin (all parts) and nivolumab (Part D only)
- To assess OS (Parts E and F only)

2.3 Additional Objectives

- To assess EFS
- To assess OS (Parts A, B, C, and D)
- To assess biomarkers in serum and tumor biopsies

- To assess the relationship between PK and disease response
- To assess immunomodulatory effects of the combination of brentuximab vedotin and nivolumab in peripheral blood (Part D only)
- To assess indeterminate response (IR) rate and subsequent response (Part D only)

2.4 Endpoints

2.4.1 Primary Endpoint

- ORR according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007) (Parts A, B, and C)
- ORR according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Lugano criteria) and the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016; Cheson 2014) (Part D)
- ORR according to modified Lugano criteria. The assessment will be per blinded independent central review (BICR) (Parts E and F)

2.4.2 Secondary Endpoints

- Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities
- CR rate, disease control rate, duration of ORR, duration of CR, and PFS
- ORR according to Lugano criteria per BICR (Parts E and F)
- B symptom resolution rate
- Estimates of selected PK parameters
- Incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin (all parts) and nivolumab (Part D only)
- OS (Parts E and F only)

2.4.3 Additional Endpoints

- ORR according to the Response Evaluation Criteria in Lymphoma (RECIL) (Younes 2017) (Appendix J), per BICR (Parts E and F)
- EFS
- OS (Parts A, B, C, and D)
- Co-expression of CD30 and PD-L1/PD-L2 by HRS cells; accompanying T-cell, macrophage, and myeloid cell populations in diagnostic tumor specimens; and correlation with response rates (Part D only)
- Immune status changes, including immunophenotyping of blood immune cells, in response to treatment (Part D only)
- IR rate and subsequent response of CR, PR, or PD (Part D only)

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

Part A of this phase 2 open-label study is designed to evaluate the efficacy and tolerability of brentuximab vedotin as frontline monotherapy in adults age 60 and above with HL. Brentuximab vedotin, 1.8 mg/kg, will be administered IV every 3 weeks. Patients enrolling on study with estimated creatinine clearance <30 mL/min will receive 1.2 mg/kg brentuximab vedotin. Patients achieving a CR, PR, or stable disease (SD) will be allowed to continue on treatment for up to 16 cycles. After discussion with the medical monitor, patients who experience clinical benefit per the investigator will be eligible to receive continued brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure.

Part B of the study is designed to evaluate the efficacy and tolerability of brentuximab vedotin in combination with dacarbazine as frontline therapy in adults age 60 and above with HL. Treatment with brentuximab vedotin 1.8 mg/kg in combination with dacarbazine 375 mg/m^2 will be given on Day 1 of Cycles 1 through 12, followed by single-agent brentuximab vedotin 1.8 mg/kg on Day 1 of Cycles 13 through 16. Patients enrolling on study with estimated creatinine clearance <30 mL/min will receive 1.2 mg/kg brentuximab vedotin in combination with a reduced dose of dacarbazine (262 mg/m^2; ~30% reduced) every 3 weeks. Patients who have unacceptable toxicity to dacarbazine prior to completion of 12 cycles may continue to receive brentuximab vedotin as a single agent on Day 1 of each cycle for a total of 16 cycles or more of treatment. After discussion with the medical monitor, patients who complete 16 cycles of treatment and experience clinical benefit per the investigator will be eligible to receive continued single-agent brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure.

Part C of this study is designed to evaluate the efficacy and tolerability of brentuximab vedotin in combination with bendamustine as frontline therapy in adults age 60 and above with HL. Treatment with bendamustine 70 mg/m^2 will be given in combination with brentuximab vedotin 1.8 mg/kg on Day 1 and then as a single agent on Day 2 of each cycle for up to 6 cycles, followed by single-agent brentuximab vedotin 1.8 mg/kg on Day 1 of the remaining cycles for up to 16 cycles. Patients who have unacceptable toxicity to bendamustine, including developing estimated creatinine clearance <40 mL/min, prior to completion of up to 6 cycles may continue to receive brentuximab vedotin as a single agent on Day 1 of each cycle for a total of 16 cycles or more of treatment. After discussion with the medical monitor, patients who complete 16 cycles of treatment and experience clinical benefit per the investigator will be eligible to receive continued single-agent brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure.

In Parts A, B, and C, disease response and progression will be assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). PD also includes clinical disease progression per investigator.

Part D of the study is designed to evaluate the tolerability and efficacy of brentuximab vedotin in combination with nivolumab as frontline therapy in adults age 60 and above with HL. Treatment with brentuximab vedotin 1.8 mg/kg in combination with nivolumab 3 mg/kg will be given on Day 1 of each 3-week cycle. Brentuximab vedotin will be administered at least 30 minutes prior to nivolumab. Patients with PD or patients with unacceptable toxicity at any time will not continue on treatment. Patients with a response of IR will continue on treatment until demonstration of PD via radiographic imaging or biopsy. If patients have unacceptable toxicity that is attributable to only 1 agent, as determined by the investigator, they will be eligible to continue on treatment with the tolerated drug as a single agent. Patients may be treated for up to 16 cycles. Additional cycles may be allowed following approval from the sponsor medical monitor. Disease response will be assessed using the Lugano criteria (Cheson 2014) and LYRIC (Cheson 2016). PD also includes clinical disease progression per investigator.

Parts E and F of the study are designed to evaluate the safety, efficacy, and tolerability of brentuximab vedotin as frontline monotherapy in patients with classical HL or CD30-expressing PTCL, respectively, who are unsuitable or unfit for combination chemotherapy. Unsuitability or unfitness for conventional combination chemotherapy will be justified by the presence of comorbidity-related factors, as documented by either a) a Cumulative Illness Rating Scale (CIRS) score ≥10 (according to the criteria specified by Salvi and colleagues (Salvi 2008) excluding current active lymphoma) or b) requiring assistance with or dependence on others for any instrumental Activities of Daily Living (IADL). Brentuximab vedotin, 1.8 mg/kg, will be administered IV every 3 weeks. Patients achieving a CR, PR, or SD will be allowed to continue on treatment for up to 16 cycles. Disease response will be assessed according to modified Lugano criteria, according to the original Lugano criteria, and according to RECIL. The assessment will be per BICR.

Computed tomography (CT) and positron emission tomography (PET) scans are required for all patients at baseline. Radiographic imaging for response assessment will be performed as follows:

- Parts A, B, and C: Restage assessments with CT will be performed at Cycles 2, 4, 8, 12, and at End of Treatment (EOT). Imaging with PET will be performed at Cycles 2, 8, and at EOT. CT will be performed at Cycle 16 for patients eligible for continued brentuximab treatment beyond 16 cycles. Response assessments performed after 16 cycles of treatment will include CT scans per institutional standard of care or at least every 6 cycles and PET scans per institutional standard of care.
- Part D: Restage assessments will be performed with CT at Cycle 2 and with CT and PET at Cycles 4, 8, 12, and EOT. CT and PET are required at Cycle 16 for patients eligible for continued treatment with brentuximab vedotin and/or nivolumab beyond 16 cycles. For patients with a response determination of IR, radiographic assessment (CT/PET) of disease must be performed 12 weeks following IR or earlier if clinically indicated. If a patient has a second determination of IR, then subsequent repeat imaging must be performed between 4 and 8 weeks. Follow-up radiographic

assessment for patients with IR is not required if a follow-up biopsy has been performed that confirms response.

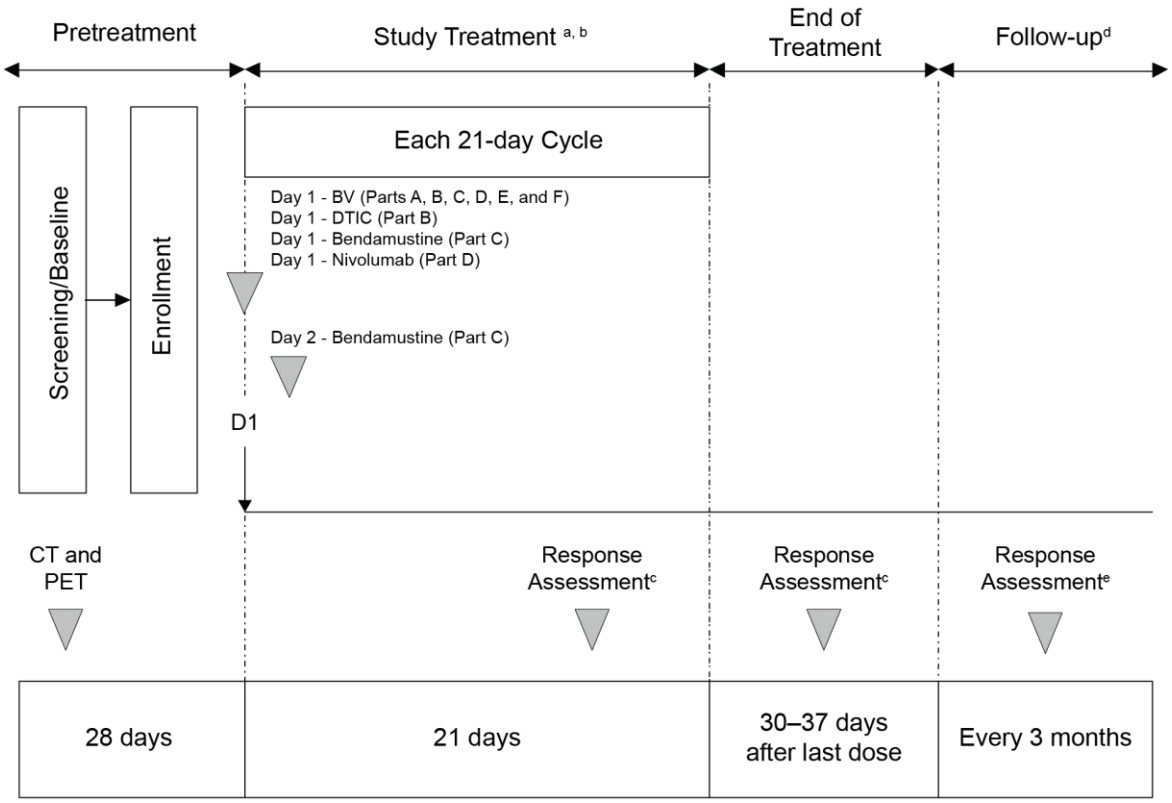
- Parts E and F: Restage assessments with CT and PET will be performed at Cycles 2, 6, 11, and at EOT approximately 1 month after discontinuation of study treatment. Following the EOT visit, patients discontinuing study treatment without progression will be followed until progression or initiation of further anti-cancer therapy. Follow-up CT scans will be performed every 4 months for 2 years and then per institutional standard of care, and follow-up PET scans will be performed per institutional standard of care.

CT/PET of diagnostic quality may be utilized for CT and PET scanning. Once a patient achieves a PET CR, PET scans are no longer required. PET scans performed as part of institutional standard of care may be collected at any time during the study, as available.

Patients who receive any amount of brentuximab vedotin will be followed for survival every 3 months (Parts A to D) or 4 months (Parts E and F) until withdrawal of consent, death, or study closure, whichever comes first. Patients who have not progressed will have response assessments until disease progression (see Section 6.8). Initiation of alternative treatment for lymphoma will also be collected.

A study schema is provided below in Figure 1.

Figure 1: Study design



a Parts A, B, C, and D: brentuximab vedotin administered IV on Day 1 of each treatment cycle for up to 16 cycles or more.
Part B only: dacarbazine administered IV on Day 1 of each treatment cycle for up to 12 cycles.
Part C only: bendamustine administered IV on Days 1 and 2 of each treatment cycle for up to 6 cycles.
Part D only: nivolumab administered IV on Day 1 of each treatment cycle for up to 16 cycles or more.
Parts E and F: brentuximab vedotin administered IV on Day 1 of each treatment cycle for up to 16 cycles.

b Brentuximab vedotin monotherapy dosing in Part A may be interrupted or may be followed after completion of treatment, by consolidative radiotherapy (RT); in Part B, combination treatment with brentuximab vedotin and dacarbazine may be followed by consolidative RT after concluding dacarbazine treatment; single-agent brentuximab vedotin may be resumed after RT; in Part C, combination treatment with brentuximab vedotin and bendamustine may be followed by consolidative radiotherapy (RT) no less than 3 weeks after treatment and only after concluding bendamustine treatment; single-agent brentuximab vedotin may be resumed no less than 2 weeks after RT; in Part D, brentuximab vedotin plus nivolumab dosing may be interrupted or may be followed after completion of treatment, by consolidative radiotherapy (RT) (see Section 5.6.2 for timing); in Parts E and F, brentuximab vedotin monotherapy dosing may be followed after completion of treatment, by consolidative radiotherapy (RT), no sooner than 2 weeks after treatment.

c Response assessment performed between Days 15–21 at Cycles 2, 4, 8, 12, and at EOT. For Parts A, B, and C, CT and PET at Cycles 2, 8, and at EOT; CT only at Cycles 4 and 12; CT at Cycle 16 only for patients eligible for continued treatment beyond 16 cycles. For Part D only, CT at Cycle 2; CT and PET at Cycles 4, 8, 12, and EOT; and CT and PET at Cycle 16 for patients eligible for continued treatment with brentuximab vedotin and/or nivolumab beyond 16 cycles. For Parts E and F, CT and PET at Cycles 2, 6, 11, and at EOT. For patients with a response determination of IR, radiographic assessment (CT/PET) of disease must be performed 12 weeks following IR or earlier if clinically indicated. If a patient has a second determination of IR, then subsequent repeat imaging must be performed between 4 and 8 weeks. Follow-up radiographic assessment for patients with IR is not required if a follow-up biopsy has been performed that confirms response. For Parts A, B, C, and D only, response assessments performed after 16 cycles of treatment will include CT per institutional standard of care or at least every 6 cycles and PET scans per institutional standard of care. Once a patient achieves a CR, PET scans are no longer required. PET scans performed as part of institutional standard of care may be collected at any time during the study, as available.

d All patients who receive at least one dose of brentuximab vedotin will be followed for survival every 3 months until withdrawal of consent, death, or study closure.

e For Parts A, B, C, and D, patients who have not progressed will have restage assessments per institutional standard of care or at least approximately every 6 months following the most recent prior radiographic response evaluation for the first 2 years, an annual assessment for the third year, then per institutional standard of care until progression. For Parts E and F, disease status will be assessed by CT imaging every 4 months for 2 years and then per institutional standard of care. Lymphoma assessments performed at least approximately every 6 months.

3.2 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) consisting of the medical monitor, drug safety and risk management representative(s), participating investigators, and study-specific steering committee members will be responsible for monitoring patient safety of Parts C and D of the trial. The roles and responsibilities of the SMC will be detailed in a separate charter.

3.2.1 Part C

The initial starting dose of bendamustine was 90 mg/m^2. In order to provide a safety assessment of acute toxicities of the combination regimen of brentuximab vedotin with bendamustine at the 90 mg/m^2 dose, including an assessment of IRRs that were previously seen with this combination treatment during Cycle 2 on Study SGN35-016, the SMC reviewed safety data after the first 5 patients in Part C completed 1 cycle of brentuximab vedotin and bendamustine, and again after the first 5 patients completed 2 cycles of treatment with brentuximab vedotin and bendamustine.

It was noted in the second safety call that 4 out of 7 patients in Part C had experienced SAE. Two patients were hospitalized for Grade 3 asthenia, 1 patient was hospitalized for febrile neutropenia, and 1 patient was hospitalized for a delayed HSR. The SAEs occurred between Cycles 2 and 4. Subsequent to the second safety call, the protocol was amended (Amendment 6) to reduce the starting dose of bendamustine to 70 mg/m^2 in order to improve the safety and tolerability of this combination regimen.

Additional key safety observations were reported at a subsequent SMC meeting; 12 of the 20 patients enrolled on Part C had experienced SAEs and 2 of those patients died within the 30-day safety observation period. Additionally, although the study was not designed to compare treatment arms, a higher incidence of specific treatment-emergent AEs (diarrhea, asthenia/fatigue, hypokalemia, dehydration, weight decrease, hypotension, neutropenia, candidiasis, and pneumonia) and an overall higher incidence of treatment-emergent AEs $\geq$ Grade 3 were observed in Part C compared with Parts A and B. Although no specific safety signal was identified, and neither of the deaths were considered related to study treatment, the sponsor's interpretation of the safety data is that the combination of brentuximab vedotin (at 1.8 mg/kg) and bendamustine at the dose levels evaluated (70 and 90 mg/m^2) does not represent a low toxicity regimen for this patient population, which is generally considered ineligible for conventional combination chemotherapy. Therefore, as of 7-Oct-2015 (the date of the Dear Investigator Letter), the sponsor has suspended enrollment of patients into Part C and discontinued bendamustine treatment for all patients enrolled in Part C. Single-agent brentuximab vedotin may be continued for patients who tolerate the therapy and have demonstrated clinical benefit.

3.2.2 Part D

Safety review of patients treated with the combination of brentuximab vedotin and nivolumab will be conducted by the study SMC after the first 5 patients complete treatment through Cycle 3 Day 1, and throughout the study as needed.

3.3 Retreatment (Part D Only)

Retreatment with brentuximab vedotin plus nivolumab is permitted, with medical monitor approval, for patients who achieve a CR or PR on study and experience disease progression ≥6 months after discontinuing study treatment. To be eligible for retreatment, patients must meet all inclusion and exclusion criteria specified in Sections 4.1 and 4.2. The retreatment regimen will be brentuximab vedotin 1.8 mg/kg in combination with nivolumab 3 mg/kg on Day 1 of each 3-week cycle, unless otherwise specified by the medical monitor or the site investigator. Patients who previously required a brentuximab vedotin dose reduction due to AEs will start brentuximab vedotin at a dose of 1.2 mg/kg and will not escalate to 1.8 mg/kg. Retreatment can continue for an unlimited number of cycles.

3.4 End of Study

The study will be closed 2 years after the last patient receives their last dose or when the last patient completes the last visit, last contact, discontinues from the study, or when no patients remain in follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.3.2).

3.5 Discussion and Rationale for Study Design

Part A of this study is designed as an open-label phase 2 study that evaluates the efficacy and tolerability of brentuximab vedotin as monotherapy in adults age 60 and above with previously untreated HL. As a way to further evaluate efficacy and tolerability of novel regimens for older patients and provide additional treatment options, Part B of the study is designed to evaluate brentuximab vedotin in combination with dacarbazine, Part C of the study is designed to evaluate brentuximab vedotin in combination with bendamustine, and Part D of the study is designed to evaluate brentuximab vedotin in combination with nivolumab as frontline therapy in these patients. The endpoints of this study are appropriate for evaluating efficacy and safety in this population. The frequency of blood draws for evaluation of PK and ATA is appropriate based on prior experience with brentuximab vedotin.

Rationale for Eligibility Criteria in Parts E and F

Parts E and F of the study are designed to evaluate brentuximab vedotin as monotherapy in previously untreated patients with HL or CD30-expressing PTCL, respectively, who are considered unsuitable or unfit for multiagent chemotherapy treatment of curative intent due to coexisting medical conditions. Selection of patients will be based on the following comorbidity-related criteria:

a. CIRS score ≥10 (according to the criteria specified by Salvi and colleagues (Salvi 2008) and excluding current active lymphoma) (see Appendix G), or
b. requiring assistance with or dependence on others for any IADLs (Appendix H).

While there is not a standard definition for such patients within the classical HL and PTCL populations, the proposed criteria are based upon the recent approval of venetoclax

(VENCLEXTA®) in combination with obinutuzumab as a frontline regimen for CLL, available data in the literature on comorbidities in patients with classical HL and PTCL (Evens 2018), and communication with key opinion leaders.

Cumulative Illness Rating Scale

Originally developed in 1968, CIRS is a widely used tool to quickly but comprehensively assess physical impairment (Linn 1968). The proposed CIRS criteria, developed by Salvi et al., incorporates conditions typically seen in the elderly and comprehensively evaluates 14 organ systems, rating each from 0 to 4 based on increasing severity/impairment and yielding a score for each organ system and a cumulative score (Salvi 2008). A greater CIRS score indicates poorer health status and is widely utilized in trials as an assessment of comorbidities (Extermann 2000), and as a measure of the burden of acute and chronic illness in adults as measured by mortality over a 24-month period (Mistry 2004). In CLL, a cumulative CIRS ≥6 in combination with creatine clearance is used to determine fitness for aggressive treatment as part of a "Go-go," "Slow-go," or "No-go" algorithm. CLL14, the phase 3 trial that led to the approval of venetoclax in frontline CLL in May 2019, used the CIRS score both in the inclusion and exclusion criteria to identify patients with coexisting medical conditions and determine fitness to receive treatment (VENCLEXTA package insert, July 2019).

CIRS Scoring and IADL in Classical Hodgkin Lymphoma

In a recent study by Evens et al., a combination regimen of brentuximab vedotin + AVD was evaluated in 48 older patients (age ≥60 years) with untreated classical HL (Evens 2018). The median CIRS-G score (based on the CIRS by Salvi et al., and with the same scoring criteria) at baseline was 7 (range 1 to 20) with 25/48 (52%) patients having at least 1 Grade 3 or 4 deficit. Fifteen (31%) patients had a CIRS-G score ≥10. Patients with CIRS-G score ≥10 only tolerated a median of 5 cycles (range 1 to 12) while patients with CIRS-G <10 received a median of 12 cycles (range 6 tp 12) with 68% receiving all 12 intended cycles. The most common reason for early discontinuation from the study was toxicity or AE (35%), which was more commonly seen in patients with CIRS-G scores ≥10. It has been suggested that the primary reason for the poorer outcomes observed in patients with CIRS-G ≥ 0 was the presence of significant co-morbidities preventing the patients from tolerating the full regimen (personal communication by investigator). Patients with CIRS-G scores of ≥10 (N=14) had a 2-year PFS rate of 45% (95% CI: 15, 71) vs. 100% (95% CI: 100, 100) in patients with CIRS-G scores <10 (N=30). In addition, patients with loss of an IADL at baseline (N=6) had 2-year PFS rates of 25% (95% CI: 1, 65) vs. 94% (95% CI: 79, 99) in patients without loss of an IADL at baseline (N=36) (Evens 2018). Lastly, in patients with a CIRS-G score ≥10, 5/15 (33%) had loss of IADLs and of patients with loss of IADLs at baseline, 4/6 (67%) had a CIRS-G score ≥10.

3.5.1 Method of Assigning Patients to Treatment Groups

Part A is a single-arm evaluation of 1.8 mg/kg brentuximab vedotin administered as a single IV infusion on Day 1 of each 3-week treatment cycle, Part B is a single-arm evaluation of combination treatment with 1.8 mg/kg brentuximab vedotin and 375 mg/m^2 dacarbazine, Part C is a single-arm evaluation of combination treatment with 1.8 mg/kg brentuximab vedotin on Day 1 and 70 mg/m^2 bendamustine on Days 1 and 2, Part D is a single-arm evaluation of combination treatment with 1.8 mg/kg brentuximab vedotin and 3 mg/kg nivolumab given on Day 1 of each cycle, and Parts E and F are each a single-arm evaluation of 1.8 mg/kg brentuximab vedotin administered as a single IV infusion on Day 1 of each 3-week treatment cycle. Enrollment in Part A will halt once Part B is open for enrollment at a site or a total of 30 patients have been enrolled in Part A. Enrollment in Part B will halt once approximately 20 patients have been enrolled and Part C is open for enrollment at a site. Enrollment on Part C was suspended as of 7-Oct-2015 based on SMC recommendation and sponsor decision. Approximately 50 evaluable patients each will be enrolled in Parts E and F. In Part F, there will be an enrollment cap of 50% on patients with sALCL (approximately 25 patients).

Patients enrolling on study with estimated creatinine clearance <30 mL/min will receive 1.2 mg/kg brentuximab vedotin either as a single agent in Part A or in combination with a reduced dose of dacarbazine (262 mg/m^2; ~30% reduced) in Part B.

3.5.2 Rationale for Selection of Doses

In a phase 1 dose-escalation study of brentuximab vedotin (SG035-0001), the maximum-tolerated dose was defined as 1.8 mg/kg IV administered every 3 weeks. This dose and schedule was further evaluated in 2 pivotal phase 2 studies (SG035-0003 and SG035-0004) in patients with CD30-expressing hematologic malignancies. Based on historic brentuximab vedotin PK data from patients with HL and patients with anaplastic large cell lymphoma, including a limited number of older patients, age is not a significant covariate for drug exposure. Thus, a dose adjustment specifically for age based on PK is not warranted.

The dose of dacarbazine to be administered in combination with brentuximab vedotin in Part B is the standard dose level (375 mg/m^2) that is combined with other therapeutic agents for frontline treatment of HL. The standard dosing frequency of dacarbazine is on Days 1 and 15 of a 28-day cycle, but dacarbazine administration for this study will be on Day 1 of each 21-day cycle to align with approved brentuximab vedotin dosing. In a phase 1 study of brentuximab vedotin + ABVD or + AVD, the maximum-tolerated dose of brentuximab vedotin when combined with these chemotherapeutic agents was not exceeded at 1.2 mg/kg every 2 weeks (the maximum planned dose). The maximum planned dose of 1.2 mg/kg brentuximab vedotin was chosen because this dose administered every 2 weeks was expected to achieve the same exposure (area under the curve [AUC]) as the approved single-agent dose of 1.8 mg/kg every 3 weeks (Younes 2013). Brentuximab vedotin exposures were similar to that obtained with the approved monotherapy regimen when administered in combination with AVD every 2 weeks.

The starting dose of bendamustine that was initially administered in combination with brentuximab vedotin in Part C was 90 mg/m^2. Although bendamustine is approved for clinical use at a starting dose of 100 mg/m^2 for CLL and 120 mg/m^2 for NHL, a lower starting dose of bendamustine was used because of the overlapping toxicities of the 2 agents, in particular myelosuppression. Additionally, interim results from the SGN35-016 study supported the administration of a lower dose of bendamustine combined with 1.8 mg/kg brentuximab vedotin. The 90 mg/m^2 dose is within the effective range of bendamustine; however, preliminary safety results observed in Study SGN35-016 suggested that IRRs may occur more frequently and at a higher severity with this combination (LaCasce 2014). Thus, the safety of the combination at this dose level was to be assessed in 5 patients who completed Cycle 1 and again once 5 patients completed Cycle 2 (see Section 3.1). Lower dose levels of bendamustine (70 and 50 mg/m^2) were to be recommended in the case of unacceptable toxicity at the higher dose. Subsequent to Amendment 6, the starting dose of bendamustine has been lowered to 70 mg/m^2 (see Section 5.4.5). As of 7-Oct-2015, the sponsor suspended enrollment of patients into Part C and discontinued bendamustine treatment for all patients enrolled in Part C based on SMC recommendation. Single-agent brentuximab vedotin may be continued for patients who tolerate the therapy and have demonstrated clinical benefit (Section 3.1).

The dose of 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 every 2- and 3-week dosing, suggesting that dosing nivolumab at 3 mg/kg every 3 weeks is appropriate in the current study. Dosing of 3 mg/kg nivolumab in combination with 1.8 mg/kg brentuximab vedotin on Day 1 every 3 weeks has also been evaluated in 10 patients with relapsed/refractory HL in an ongoing cooperative group trial. Patients on that study are premedicated with H_1- and H_2-antagonists. Only 1 patient experienced a Grade 1/2 IRR thus far and the patient was able to receive subsequent therapy with additional premedication (Diefenbach 2016). Due to the low incidence of IRRs observed in this cooperative group trial, Part D of the current study will mirror the same-day dosing regimen and premedications (see Sections 5.2.2, 5.5.3, and 5.5.4). There is no recommended maximum number of cycles for brentuximab vedotin monotherapy treatment of HL in the relapsed setting (after failure of autologous stem cell transplant or after failure of at least 2 prior multi-agent chemotherapy regimens) nor a recommended maximum number of cycles for nivolumab treatment in any of the approved

indications; therefore, this study will evaluate 16 cycles or more of treatment combined with brentuximab vedotin (refer to the package inserts for nivolumab and brentuximab vedotin).

Renal excretion is a minor route of free MMAE elimination in patients, with the major route via feces. The potential impact of renal impairment on the PK of brentuximab vedotin and free MMAE was evaluated in a special populations study (SGN35-008B, data on file). No meaningful change in brentuximab vedotin PK was observed. An apparent increase in MMAE exposure was observed only in the patients with severe renal impairment (estimated creatinine clearance <30 mL/min, n=2). In an effort to mitigate risk due to increased MMAE exposure, dosing will be reduced to 1.2 mg/kg brentuximab vedotin for patients enrolling on Parts A and B of the study with estimated creatinine clearance <30 mL/min. Renal excretion is a significant route of dacarbazine elimination; therefore, a dose reduction of ~30% is recommended for patients with estimated creatinine clearance <30 mL/min for patients enrolled in Part B. Although no formal studies evaluating the impact of renal impairment on the PK of bendamustine have been conducted, bendamustine is not recommended for use in patients with creatinine clearance <40 mL/min, according to prescribing information. Patients in Part C will be excluded from the study if they present with estimated creatinine clearance <40 mL/min. Patients in Part D will be excluded from the study if they present with estimated creatinine clearance <30 mL/min. Patients enrolling on Parts E and F will be excluded from the study if they present with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m².

3.5.3 Blinding

This is an open-label study. No blinding will be performed.

4 STUDY POPULATION

To be eligible for this study, patients must meet all criteria outlined below in Sections 4.1 and 4.2. Eligibility criteria are applicable to all parts of the study unless otherwise specified.

To be eligible for retreatment as described in Section 3.3, patients must meet all inclusion and exclusion criteria outlined in Section 4.1 and Section 4.2.

4.1 Inclusion Criteria

1. Treatment-naive patients with histopathological diagnosis of classical HL, which excludes nodular lymphocyte-predominant HL, (Parts A, B, C, D, and E), or treatment-naive patients with CD30-expressing (≥1%) PTCL (Part F) by local testing. See PTCL histologic subtypes in Appendix L. Patients eligible for retreatment on Part D must have had prior treatment on this study with the combination of brentuximab vedotin plus nivolumab.

2. In Parts A to D: Age ≥60 years; in Parts E and F: age ≥18 years

3. In Parts A to D: Patients must be ineligible for or have declined initial conventional combination chemotherapy for HL (e.g., A+AVD, ABVD, BEACOPP), after being informed of the potential benefits and risks of available treatment options

   In Parts E and F: Patients must be unsuitable or unfit for initial conventional combination chemotherapy for HL (Part E) or CD30-expressing PTCL (e.g., A+CHP, CHOP, CHOEP; Part F) due to the presence of comorbidity-related factors, as documented by:

   a. a CIRS score ≥10 (according to the criteria specified by Salvi and colleagues (Salvi 2008) and excluding current active lymphoma) (see Appendix G), OR
   b. requiring assistance with or dependence on others for any iIADLs (Appendix H).

4. Patients must have fluorodeoxyglucose (FDG)-PET-avid and bidimensional measurable disease of at least 1.5 cm in longest axis as documented by radiographic technique (spiral CT preferred).

5. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤3 (Parts A, B, C, E, and F) or ≤2 (Part D).

6. The following baseline laboratory data:

   a. absolute neutrophil count ≥1000/μL.
   b. platelet count ≥50,000/μL (no platelet transfusions for prior 14 days for Part D only).
   c. serum bilirubin ≤2X upper limit of normal (ULN) (Parts A, B, E, and F) or ≤1.5X ULN (per bendamustine and nivolumab prescribing information) (Parts C or D); or ≤3X ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma (all parts).
   d. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3X ULN or ≤5X ULN for patients with documented hepatic involvement with lymphoma;

patients enrolled in Parts C or D must have ALT and AST ≤2.5X ULN (per bendamustine prescribing information for Part C).

e. hemoglobin ≥8.5 g/dL (no red blood cell transfusions for prior 7 days) (Part D only).
f. As determined by Cockroft-Gault formula, estimated creatinine clearance ≥40 mL/min (Part C only, per bendamustine prescribing information) or ≥30 mL/min (Part D only).
g. As determined by the Modification of Diet in Renal Disease (MDRD) study equation, eGFR ≥30 mL/min/1.73m^2 (Parts E and F only). The eGFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL:
   - eGFR (mL/min/1.73 m^2)=175 x (Scr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)
   - If Scr is reported in µmol/L, the value should be converted to mg/dL using the conversion factor 0.011312 µmol/L to mg/dL.

7. Patients 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. Patients with false positive results and documented verification that the patient is not pregnant are eligible for participation. Patients of non-childbearing potential are those who are postmenopausal >1 year or who have had a bilateral oophorectomy or hysterectomy.

8. If sexually active in a way that could result in pregnancy, patients of childbearing potential and patients who can father children and have partners of childbearing potential must agree to use 2 effective contraception methods (Appendix E) during the study and for 6 months following the last dose of study drug (or 8 months following last dose of nivolumab in Part D).

9. The patient or the patient's legally acceptable representative must provide written informed consent.

10. Diffusing capacity of the lungs for carbon monoxide (DLCO) over 50% (adjusted for hemoglobin) (Part D only).

4.2 Exclusion Criteria

1. Baseline peripheral neuropathy Grade ≥2 (per NCI CTCAE, Version 4.03) or patients with the demyelinating form of Charcot-Marie-Tooth syndrome

2. History of progressive multifocal leukoencephalopathy (PML)

3. Any active Grade 3 or higher (per the NCI CTCAE, Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of brentuximab vedotin. Routine antimicrobial prophylaxis is permitted.

4. Chemotherapy, RT, biologics, and/or other treatment with immunotherapy that is not completed 4 weeks prior to first dose of study drug

5. Concurrent use of other investigational agents
6. Known hypersensitivity to any excipient contained in the drug formulation of brentuximab vedotin (all parts), dacarbazine (Part B only), bendamustine (Part C only) (e.g., mannitol), or nivolumab (Part D only).
7. Kidney disease requiring ongoing dialysis

The following exclusion criteria are applicable to Part D only:

8. Received any prior immune-oncology therapy (e.g., therapies targeting the PD-1, CTLA4, or CD137 pathways) (not applicable to retreatment patients on Part D).
9. 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.
10. Prior allogeneic stem cell transplant.
11. History of another primary invasive malignancy that has not been in remission for at least 1 year.
12. Documented history of a cerebral vascular event (stroke or transient ischemic attack [TIA]), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III–IV (Appendix D) within 6 months prior to the first dose of study drug(s).
13. Active interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
14. Known history of pancreatitis.

The following exclusion criteria are applicable to Parts D, E, and F only:

15. Known cerebral/meningeal disease related to the underlying malignancy.
16. Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 1 week 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.
17. Known to be positive for hepatitis B by surface antigen expression. Known to be positive for hepatitis C infection (positive by polymerase chain reaction [PCR]). Patients who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.

18. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

19. Active hepatitis C infection (positive by serology and confirmed by PCR or on antiviral therapy for hepatitis C within the last 6 months).

20. 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.

The following exclusion criteria are applicable to Parts E and F only:

21. History of another malignancy within 1 year before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year OS ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.

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). The investigators will make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. If a patient withdraws from study treatment, every attempt should be made to follow the patient until death or administrative study closure. Final treatment assessments will be performed before any other therapeutic intervention, if possible. Additionally, any planned alternative treatments should be documented on the patient's medical records and CRF.

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

All patients who receive at least 1 dose of study drug will be followed until withdrawal of consent, death, or study closure, whichever comes first (see Section 6.8).

4.3.2 Patient Withdrawal From Study

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

- Patient withdrawal of consent
- Retreatment (Part D only)
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

All patients enrolled on study will receive brentuximab vedotin, the investigational agent 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.

Patients enrolled in Part B of the study will receive combination treatment with brentuximab vedotin and dacarbazine, a commercially-available chemotherapeutic agent. Patients enrolled in Part C of the study will receive combination treatment with brentuximab vedotin and bendamustine, a commercially-available chemotherapeutic agent. Patients enrolled in Part D of the study will receive combination treatment with brentuximab vedotin and nivolumab, a commercially-available monoclonal antibody.

5.2 Investigational Study Drug

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

5.2.1 Description

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

5.2.2 Dose and Administration

In all parts of the study, brentuximab vedotin will be administered on Day 1 of each 3-week cycle by IV infusion given over approximately 30 minutes. In the absence of IRRs, 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. For Parts B and C, brentuximab vedotin should be administered approximately 30 to 60 minutes prior to the start of the infusion of

dacarbazine or bendamustine, as applicable. For Part D, brentuximab vedotin should be administered approximately 30 minutes prior to the start of the infusion of nivolumab.

Dosing is based on patient weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. An exception to weight-based dosing is made for patients weighing >100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

5.2.3 Required Premedication and Postmedication

In Parts A, B, E, and F, routine premedication should not be administered for the prevention of IRRs prior to the first dose of brentuximab vedotin. However, premedications may be administered prior to the first dose of brentuximab vedotin in Parts A, B, E, and F if required per institutional standard. Patients who experience a Grade 1 or Grade 2 IRR may receive subsequent brentuximab vedotin infusions with premedication as described in Section 5.7.1. In Part C, patients are to receive premedication as noted in Section 5.4.4. In Part D, patients are to receive premedication as noted in Section 5.5.4.

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

5.2.4 Dose Modifications

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

The start of the next cycle may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle. Delays of greater than 3 weeks are prohibited without approval from the sponsor.

In addition, doses reduced for treatment-related toxicity should not be re-escalated without discussion with the sponsor.

For patients receiving 1.2 mg/kg brentuximab vedotin due to renal impairment, those patients who tolerate multiple doses may be administered 1.8 mg/kg brentuximab vedotin following discussion with the sponsor and provision of documentation demonstrating sufficient renal function for this dose. Dose reductions below 1.2 mg/kg are not allowed, and toxicities should be managed with dose delays.

Table 1: Recommended dose modifications for brentuximab vedotin-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	Withhold until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at 1.2 mg/kg[e]	Discontinue treatment
Non-hematologic (except peripheral neuropathy)[f]	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[a].	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, d, e].
Hematologic[c]	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[b]. Growth factor support (G-CSF or granulocyte-macrophage colony-stimulating factor [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[e].	

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

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

c Support with blood product transfusions allowed per institutional standard of care.

d Treatment should be discontinued for patients who experience Grade 4 IRRs.

e Dose reductions below 1.2 mg/kg are not allowed, and toxicities should be managed with dose delays.

f For Parts A, B, and C, dose reductions to 1.2 mg/kg should be considered for patients receiving 1.8 mg/kg dosing who then develop renal impairment with estimated creatinine clearance consistently below 30 mL/min. For Part D, patients who develop renal impairment with estimated creatinine clearance below 30 mL/min should discontinue treatment. For Parts E and F, patients who develop renal impairment with eGFR below 30 mL/min/1.73m² should discontinue treatment.

5.2.5 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 immediately. If not used immediately, reconstituted vials and solutions must be stored no longer than 24 hours from vial reconstitution. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use. Reconstituted vials and solutions must not be shaken.

Drug accountability instructions are provided in the Pharmacy Manual.

5.2.6 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.

5.2.7 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, US Pharmacopeia. The vial should be gently swirled until the contents are completely dissolved. The vial must not be shaken. The reconstituted drug product should be inspected visually for any particulate matter and discoloration.

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

Detailed drug preparation instructions are provided in the Pharmacy Instructions.

5.3 Dacarbazine

Refer to the dacarbazine package insert for detailed information on the description, preparation, administration, and storage of dacarbazine.

5.3.1 Description

Dacarbazine is an anticancer agent that is colorless to an ivory colored solid. It is light sensitive, and each vial contains 200 mg of dacarbazine (the active ingredient), anhydrous citric acid, and mannitol. See the package insert for further information.

5.3.2 Method of Procurement

Dacarbazine is commercially available and approved by the US FDA and other regulatory agencies for use in treating patients with multiple types of cancer. Dacarbazine will be supplied by the study site and billed to patients and/or their third-party payer (insurance, a healthcare provider, or applicable government program).

5.3.3 Dose and Administration

In Part B only, dacarbazine should be administered following completion of brentuximab vedotin on Day 1 of each 21-day cycle, and patients may receive up to 12 doses of dacarbazine while on study. The dose of dacarbazine is 375 mg/m^2 administered by IV infusion according to the package insert or institutional standard of care. It is recommended that the dacarbazine infusion begin within approximately 60 to 90 minutes after the end of the brentuximab vedotin infusion.

Refer to the dacarbazine prescribing information for details on other recommended dose adjustments.

5.3.4 Required Premedication and Postmedication

Antiemetics, such as serotonin receptor ($5HT_3$) antagonists, should be considered for the prevention of nausea and vomiting within approximately 30 to 60 minutes prior to initiating the dacarbazine infusion. Additional premedications for the prevention of nausea and vomiting, including steroids, may be given prior to the dacarbazine infusion in accordance with institutional standard of care or as clinically indicated.

5.3.5 Dose Modifications

Patients enrolling on study with estimated creatinine clearance <30 mL/min will receive 1.2 mg/kg brentuximab vedotin in combination with a reduced dose of dacarbazine (262 mg/m^2; ~30% reduced). Dose modifications of dacarbazine are allowed per institutional standard of care or per the package insert (e.g., For Grade 3 non-hematologic toxicity or for Grade 4 hematologic toxicity, combination treatment may be withheld until toxicity resolves to ≤ Grade 2 or baseline). If unacceptable toxicity to dacarbazine develops, dacarbazine must be permanently discontinued and brentuximab vedotin monotherapy may continue. If unacceptable toxicity to brentuximab vedotin develops, study treatment with single-agent dacarbazine may be continued after discussion with the medical monitor.

5.3.6 Storage and Handling

Refer to the dacarbazine package insert for dacarbazine storage and handling instructions.

5.3.7 Packaging and Labeling

Refer to the dacarbazine package insert for dacarbazine packaging and labeling information.

5.3.8 Preparation

Dacarbazine should be prepared according to the package insert or according to institutional standards.

5.4 Bendamustine (Not Applicable as of 07-Oct-2015)

Refer to the bendamustine package insert for detailed information on the description, preparation, administration, and storage of bendamustine.

5.4.1 Description

Bendamustine is an anticancer agent containing no antimicrobial preservative and is a clear, colorless to yellow solution. Each vial contains either 25 or 100 mg of a lyophilized powder formulation of bendamustine HCl, or 45 or 180 mg of a liquid formulation of bendamustine HCl. See the package insert for further information.

5.4.2 Method of Procurement

Bendamustine is commercially available and approved by the US FDA and other regulatory agencies for use in treating patients with CLL and indolent B-cell NHL Bendamustine will be supplied by the Canadian study site(s) from their usual suppliers.

5.4.3 Dose and Administration

In Part C only, bendamustine will be administered following completion of brentuximab vedotin on Day 1 of each 21-day cycle and again as a single agent on Day 2, approximately 24 hours after Day 1 study drug dose in the absence of IRRs or HSRs. The bendamustine infusion will begin within approximately 30 to 60 minutes after the end of the brentuximab vedotin infusion on Day 1 only.

Patients may receive up to 6 cycles of bendamustine while on study. The dose of bendamustine is 70 mg/m^2 (with possible reduction to 50 mg/m^2) administered by IV infusion given over approximately 60 minutes.

Refer to the bendamustine prescribing information for details on other recommended dose adjustments.

5.4.4 Required Premedication and Postmedication

Common toxicities with bendamustine include myelosuppression (lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia, including Grade 3 and higher events) and nausea, fatigue, vomiting, diarrhea, fever, constipation, anorexia, cough, headache, decreased weight, shortness of breath, rash, and stomatitis. These events should be managed according to institutional standards or accepted guidelines (Smith 2006). Prior to treatment with bendamustine, prophylactic premedication for prevention of IRRs is to be administered. After completion of up to 6 cycles of combination treatment with brentuximab vedotin and bendamustine, prophylactic premedications may be discontinued during single-agent treatment with brentuximab vedotin for subsequent cycles.

Methylprednisolone 100 mg IV or equivalent (e.g., dexamethasone 20 mg IV) and diphenhydramine 25–50 mg IV or equivalent should be given approximately 30 to 60 minutes prior to brentuximab vedotin on Day 1 of each 21-day cycle and 30 to 60 minutes prior to bendamustine on Day 2. Additional premedication may be administered prior to bendamustine on Day 1 at the discretion of the investigator. Acetaminophen may also be given at the discretion of the investigator. Ondansetron, or other premedications for the prevention of nausea and vomiting, is recommended prior to the bendamustine infusion in accordance with institutional standard of care or as clinically indicated. Patients may receive myeloid growth factors such as granulocyte-colony stimulating factor (G-CSF) at the discretion of the investigator or per institutional standards. Dose modifications of required pre- and post-medication are allowed at the discretion of the investigator and only after discussion with the medical monitor.

5.4.5 Dose Modifications

Dose modifications of bendamustine are allowed per institutional standard of care or per the package insert (e.g., treatment with bendamustine may be delayed for Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity). Dose reductions to 50 mg/m^2 are allowed; dose reductions <50 mg/m^2 are not allowed without prior discussion with the medical monitor. If unacceptable toxicity to bendamustine develops, including

developing an estimated creatinine clearance <40 mL/min, bendamustine must be permanently discontinued and brentuximab vedotin monotherapy may continue. If unacceptable toxicity to brentuximab vedotin develops, study treatment with single-agent bendamustine may be continued after discussion with the medical monitor.

5.4.6 Storage and Handling

Refer to the bendamustine package insert for bendamustine storage and handling instructions.

5.4.7 Packaging and Labeling

Refer to the bendamustine package insert for bendamustine packaging and labeling information.

5.4.8 Preparation

Bendamustine should be prepared according to the package insert or according to institutional standards.

5.5 Nivolumab

5.5.1 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.

5.5.2 Method of Procurement

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

5.5.3 Dose and Administration

Nivolumab will be administered on Day 1 of each 21-day cycle. Patients will receive nivolumab at a dose of 3 mg/kg as a 60-minute infusion (per the nivolumab prescribing information). Nivolumab should be administered at least 30 minutes after completing brentuximab vedotin infusion. 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 μm to 1.2 μm). 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, then per institutional standards. 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.

5.5.4 Required Premedication and Postmedication

Prior to combination treatment on Day 1 of each 21-day cycle, prophylactic premedication for prevention of IRRs is to be administered. Antihistamines, including both H_1-receptor antagonists (e.g., diphenhydramine 25–50 mg IV or equivalent) and H_2-receptor antagonists (e.g., ranitidine or cimetidine) should be given approximately 30 to 60 minutes prior to infusion of brentuximab vedotin. If an increase of IRRs is observed, the SMC may recommend additional premedication, including but not limited to hydrocortisone 100 mg IV or equivalent. At the discretion of the investigator, further premedications for symptom management (e.g., acetaminophen, and/or ondansetron) may also be given.

If a patient does not experience an IRR with combination treatment during Cycles 1 through 4, prophylactic premedication may be reduced or stopped at the discretion of the investigator for Cycles 5 and beyond. If treatment with nivolumab or brentuximab vedotin is discontinued, premedication may be reduced or stopped at the discretion of the investigator during single-agent treatment for subsequent cycles.

5.5.5 Dose Modifications

Dose modifications of nivolumab, including escalations or reductions, are not allowed. Patients who discontinue brentuximab vedotin due to an AE may continue treatment with nivolumab monotherapy. 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. See Section 7.7.1.1 for determining causality.

5.5.5.1 Dose Delays

Dose delays of both brentuximab vedotin and nivolumab resulting in interruption of all therapy for >6 weeks require that a patient discontinue from study treatment, with the exception of patients who are receiving protocol-specified consolidative RT (Section 5.6.2) or other exceptions noted in Section 5.5.5.2. Patients who experience a dose delay of either brentuximab or nivolumab >6 weeks must stop treatment with that component of the combination therapy.

Dose delays for nivolumab-related liver function test (LFT) abnormalities are described in Section 5.5.5.3. Otherwise, nivolumab administration should be delayed for the following:

- Any ≥ Grade 2 non-skin, nivolumab-related AEs with the exception of Grade 2 nivolumab-related fatigue or laboratory abnormalities (excluding LFT abnormalities detailed separately)
- Any Grade 3 skin, nivolumab-related AE
- Any Grade 3 nivolumab-related laboratory abnormalities (excluding LFT abnormalities detailed separately) 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. If the dose delay is ≤6 weeks, 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

5.5.5.2 Dose Discontinuation

Dose discontinuations for LFT abnormalities are described in Section 5.5.5.3. 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 (excluding LFT abnormalities detailed separately), nivolumab-related uveitis, pneumonitis, bronchospasm, HSRs, infusion reactions, and endocrinopathies:
  - Grade 3 nivolumab-related uveitis, myocarditis, pneumonitis, bronchospasm, HSRs, 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 requires discontinuation; other Grade 3 nivolumab-related laboratory abnormalities (excluding LFT abnormalities detailed separately), do not require treatment discontinuation

- Any Grade 4 nivolumab-related AE or laboratory abnormality (excluding LFT abnormalities detailed separately), except for the following:
  - 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 unless approved by the medical monitor, 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 3 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.

5.5.5.3 Dose Modifications for Liver Function Test Abnormalities

Doses of nivolumab should be delayed in case of AST/ALT >3 and ≤5 times the ULN or total bilirubin >1.5 and ≤3 times the ULN. Nivolumab may be resumed if the value improves to Grade 0 or 1.

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

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

5.5.6 Storage and Handling

Refer to the nivolumab Pharmacy Binder for nivolumab storage and handling instructions.

5.5.7 Packaging and Labeling

Refer to the investigational product label for information regarding packaging and labeling.

5.5.8 Preparation

Nivolumab should be prepared according to the package insert or according to institutional standards.

5.6 Concomitant Therapy

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

Patients enrolled in Part B of the study should receive premedication as described in Section 5.3.4. Patients enrolled in Part C of the study should receive premedication as described in Section 5.4.4. For Part D of the study, patients may only receive premedication as described in Section 5.5.4.

5.6.1 Required Concomitant Therapy

It is recommended that all patients be up-to-date on vaccinations prior to study entry. Additional vaccination(s) during each cycle of study treatment may be discussed by the medical monitor.

5.6.2 Allowed Concomitant Therapy

For patients enrolled in Parts A, B, E, or F, routine premedication for infusion reactions should not be administered prior to the first dose of brentuximab vedotin. However, patients who experience a Grade 1 or Grade 2 IRR may receive subsequent treatment with premedication as described in Section 5.2.3. Patients enrolled in Part B of the study should receive premedication as described in Section 5.3.4. Patients enrolled in Part C of the study

should receive premedication as described in Section 5.4.4. Patients enrolled in Part D of the study should receive premedication as described in Section 5.5.4.

The use of platelet and/or red blood cell transfusions when applicable is allowed. The use of colony stimulating factors for the treatment or prophylaxis of neutropenia per institutional practice is permitted during therapy. Prednisone (or equivalent) ≤20 mg/day may be used for non-lymphomatous purposes; higher doses of steroids are allowed if indicated for antiemetic purposes or prevention of infusion reactions in Parts B, C, or D of the study.

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

At the investigator's discretion, brentuximab vedotin monotherapy dosing in Part A may be interrupted or may be followed after completion of treatment, by consolidative RT. RT may be given no sooner than 2 weeks after receiving brentuximab vedotin. If dosing is paused for RT, then RT should not be administered starting prior to the Cycle 8 response assessment, and brentuximab vedotin may be resumed no sooner than 2 weeks after RT is completed. RT-related dosing interruptions longer than 10 weeks must be approved by the sponsor.

In Part B, combination treatment with brentuximab vedotin and dacarbazine may be followed by consolidative RT no sooner than 2 weeks after treatment and only after concluding dacarbazine treatment; single-agent brentuximab vedotin may be resumed no sooner than 2 weeks after RT.

In Part C, combination treatment with brentuximab vedotin and bendamustine may be followed by consolidative RT no less than 3 weeks after treatment and only after concluding bendamustine treatment; single-agent brentuximab vedotin may be resumed no less than 2 weeks after RT.

In Part D, brentuximab vedotin plus nivolumab dosing may be interrupted or may be followed after completion of treatment, by consolidative RT. RT may be given no sooner than 2 weeks after receiving treatment and should not be administered prior to the Cycle 8 response assessment. The combination of brentuximab vedotin plus nivolumab may be resumed no sooner than 2 weeks after RT is completed. RT-related dosing interruptions longer than 10 weeks must be approved by the sponsor medical monitor.

Also, in Part D, inhaled or topical steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease. In addition, a steroid pulse is allowed prior to initiation of therapy for management of B symptoms, prophylaxis (e.g., contrast dye allergy), or for treatment of non-autoimmune conditions (e.g., delayed-type HSR caused by contact allergen) at the discretion of the investigator; the recommended dose is 40 mg of methylprednisolone or equivalent daily, and must be completed 1 week prior to initiation of study treatment.

In Parts E and F, brentuximab vedotin monotherapy may be followed after completion of treatment, by consolidative RT, no sooner than 2 weeks after treatment.

5.6.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications (excluding steroids as described in Section 5.6.2), or systemic anti-neoplastic therapy during the study (with the exception of dacarbazine for patients enrolled on Part B, bendamustine for patients enrolled on Part C, and nivolumab for patients enrolled on Part D).

In Part D, complementary medications (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are allowed if they are used as supportive care. Any live/attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella) are not allowed during treatment and until 100 days post last dose.

5.7 Management of Adverse Reactions

5.7.1 Management of Infusion Reactions

IRRs may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRRs.

Patients who have experienced a Grade 1 or Grade 2 IRR to brentuximab vedotin should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30–60 minutes prior to each infusion or according to institutional standards. Patients who experience a Grade 3 IRR to brentuximab vedotin may potentially receive additional treatment with brentuximab vedotin at the discretion of the investigator after discussion with the sponsor. Treatment with brentuximab vedotin should be discontinued for patients who experience Grade 4 IRRs.

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

With the combination of bendamustine and brentuximab vedotin, IRRs and delayed-type HSRs have been observed (LaCasce 2014). To reduce the risk of infusion reactions with bendamustine, all patients will be premedicated as described in Section 5.4.4. Infusion reactions related to bendamustine should be managed according to the package insert and institutional standard of care.

With the combination of nivolumab and brentuximab vedotin (Part D), required premedication is described in Section 5.5.4. 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). Other premedication may be given based on SMC recommendation (e.g., corticosteroids).

If anaphylaxis occurs, brentuximab vedotin administration (and dacarbazine or bendamustine or nivolumab, if applicable) should be immediately and permanently discontinued.

5.7.2 Management of Suspected PML

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

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

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

If PML is confirmed, permanently discontinue treatment with brentuximab vedotin (and dacarbazine, bendamustine, or nivolumab, if applicable).

5.7.3 Management of Overdose

Weight-based dosing for brentuximab vedotin is based on patient actual body weight (see Section 5.2.2), with the exception of patients weighing greater than 100 kg; doses will be based on 100 kg for these individuals. **The maximum dose calculated per cycle in this study is 180 mg for patients receiving the 1.8 mg/kg dose level, and 120 mg for patients receiving 1.2 mg/kg dose level.**

In the event of an overdose of brentuximab vedotin ≥10%, study personnel should:

- Care for and medically stabilize the patient until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of brentuximab vedotin.
- Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of brentuximab vedotin administered, patient weight) and AEs, if any.

For the management of overdoses of dacarbazine, bendamustine, or nivolumab, refer to the prescribing information of each drug.

5.8 Treatment Compliance

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

6 STUDY ACTIVITIES

6.1 Schedule of Events

AE and concomitant medications will be collected from Day 1 (predose) through the safety reporting period (see Section 7.7.1.3). 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. A schedule of events for Parts A, B, and C is provided in Appendix A, a schedule of events for Part D is provided in Appendix B, and a schedule of events for Parts E and F is provided in Appendix C. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7. Activities are applicable to all parts of the study unless otherwise specified.

6.2 Screening Visit (Days –28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria (see Sections 4.1 and 4.2)
- Medical history
- Parts E and F: evaluate CIRS score and IADL score
- CT of chest, abdomen, and pelvis (and neck, if clinically indicated) (within prior 45 days) (see Section 7.2)
- PET (within prior 45 days) (Note: a combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning) (see Section 7.2)
- Archived or fresh tumor specimen collection for biomarker analysis, including CD30 by a central laboratory (see Section 7.6)
- Review pathology report to confirm histopathological diagnosis of HL or PTCL
- Electrocardiogram (ECG)
- Ejection fraction via echocardiogram or multigated acquisition (MUGA) scan (within 12 months prior to treatment initiation for Parts A, B, C, and D only, and within 28 days for Parts E and F)
- Part D only
  - Pulmonary function test (see Section 7.1)
- Parts D, E, and F only:
  - Serology for hepatitis B
  - Hepatitis C serology with reflex to hepatitis C virus ribonucleic acid (RNA) by PCR (see Section 7.7.2)
- Part F only: Bone marrow biopsy (if bone marrow biopsy was previously performed as part of initial diagnostic workup for PTCL and results are available, it is not required to be repeated during screening).

6.2.1 Baseline Visit (Days –7 to Day 1)

- Height (see Section 7.7.3) and weight
- ECOG performance status, Karnofsky score in Parts A to D (Appendix F)
- Physical examination (see Section 7.7.3)
- Serum chemistry panel (see Section 7.7.2)
  - Including LDH, phosphorus, and uric acid
  - Including lipase (Parts C and D only)
  - Including amylase (Part D only)
  - Including thyroid-stimulating hormone (TSH), free T3, and free T4 (Part D only)
- Complete blood count (CBC) with differential (see Section 7.7.2)
- Estimated creatinine clearance (eGFR for Parts E and F)
- Erythrocyte sedimentation rate
- B symptom assessment
- Measurement of oxygen saturation by pulse oximetry (Part D only)
- In Parts A to D: Geriatric assessment (see Section 7.1)
- In Parts E and F: serum or urine β-hCG pregnancy test for patients of childbearing potential

6.3 Treatment Period (Day 1 to Day 21)

6.3.1 Each 21-Day Cycle (Day 1 ±2 days)

- Predose (All results, including lab results, should be captured and reviewed prior to dosing)
  - Weight (Cycle 2 and all subsequent cycles)
  - ECOG performance status
  - Physical examination (Cycle 2 and all subsequent cycles)
  - Serum chemistry panel
    - Including LDH, phosphorus, and uric acid
    - Including lipase (Parts C and D only)
    - Including amylase (Part D only)
    - Including TSH, free T3, and free T4 (every other cycle beginning in Cycle 2; Part D only)
  - CBC with differential
  - Estimated creatinine clearance (Parts C and D; eGFR for Parts E and F)
  - B symptom assessment
  - Brentuximab vedotin (Parts A, B, C, and D only) and nivolumab (Part D only) PK and pharmacodynamic samples (Only Cycles 1, 2, 4, and every 4 cycles thereafter; see Sections 7.4 and 7.5)

- Brentuximab vedotin (Parts E and F only) PK and samples (Cycles 1, 2, and 3 only)
- Brentuximab vedotin (all parts) and nivolumab (Part D only) immunogenicity (ATA) (Only Cycles 1, 2, 4, and every 4 cycles thereafter; see Section 7.4 for collection time points)
- Blood samples for biomarker assessments (Only Cycles 1, 2, and 3; Part D only) (see Section 7.5)

- Study drug administration
  - Brentuximab vedotin administration
  - Dacarbazine administration (Part B only; Cycles 1 to 12)
  - Bendamustine administration (Part C only; Cycles 1 to 6) (not applicable as of 7-Oct-2015)
  - Nivolumab administration (Part D only)

- Postdose
  - Brentuximab vedotin (Parts A, B, C, and D only) and nivolumab (Part D only) PK samples (Only Cycles 1, 2, 4, and every 4 cycles thereafter; see Section 7.4)
  - Brentuximab vedotin (Parts E and F only), PK and samples (Cycles 1, 2, and 3 only)

6.3.2 Cycles 1 to 6 (Day 2 [+1 day]): Part C Only (Not Applicable as of 7-Oct-2015)

In the absence of IRRs or HSRs, patients in Part C only will receive bendamustine approximately 24 hours after the Day 1 study drug dose for up to 6 cycles.

6.3.3 Cycle 1 (Day 8 [±1 day]): Part D Only

- Physical examination (see Section 7.7.3)
- Serum chemistry panel (see Section 7.7.2)
  - Including LDH, phosphorus, and uric acid
  - Including amylase and lipase
- CBC with differential (see Section 7.7.2)
- Measurement of oxygen saturation by pulse oximetry
- Brentuximab vedotin and nivolumab PK samples (see Section 7.4)
- Blood samples for biomarker assessments (see Section 7.5)

6.3.4 Cycle 1 (Day 15 [±1 day]): Part D Only

- Physical examination (see Section 7.7.3)
- Serum chemistry panel (see Section 7.7.2)
  - Including LDH, phosphorus, and uric acid
  - Including amylase and lipase
- CBC with differential (see Section 7.7.2)
- Measurement of oxygen saturation by pulse oximetry
- Brentuximab vedotin and nivolumab PK samples (see Section 7.4)
- Blood samples for biomarker assessments (see Section 7.5)

6.3.5 Cycle 1 (Days 1, 2, 3, 8, and 15): Parts A, B, and C Only

- Brentuximab vedotin PK samples (see Section 7.4)

6.3.6 Cycle 2 (Day 8 [+1 day]): Part D Only

- Blood samples for biomarker assessments (see Section 7.5)

6.3.7 Cycles 2, 4, 8, 12, and 16 (Days 15 to 21 [+2 days]): Parts A, B, C, and D only

Response assessments will be completed prior to dosing for the subsequent treatment cycle.

- CT: CT of chest, abdomen, and pelvis (and neck, if clinically indicated) (see Section 7.2.1 for Parts A, B, and C, and Section 7.2.2 for Part D). CT is required at Cycle 16 only for patients eligible for continued treatment with brentuximab vedotin (and/or nivolumab for Part D only) beyond 16 cycles.
- PET: For Parts A, B, and C, PET scans at Cycles 2 and 8; for Part D, PET scans at Cycles 4, 8, and 12. (Note: a combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning). Also, for Part D, PET is required at Cycle 16 only for patients eligible for continued treatment with brentuximab vedotin and/or nivolumab beyond 16 cycles. For all parts, once a PET CR is achieved, PET scans are no longer required. PET scans performed as part of institutional standard of care may be collected at any time during the study, as available.
- Radiographic imaging for IR response: For patients on Part D with a response determination of IR, radiographic assessment (CT/PET) of disease must be performed 12 weeks following IR or earlier if clinically indicated. If a patient has a second determination of IR, then subsequent repeat imaging must be performed between 4 and 8 weeks. Follow-up radiographic assessment for patients with IR is not required if a follow-up biopsy has been performed that confirms response.

6.3.8 Cycles 2, 6, and 11 (Days 15 to 21 [+2 days]): Parts E and F Only

- CT: CT of chest, abdomen, and pelvis (and neck, if clinically indicated) (see Section 7.2.3).

- PET: (Note: a combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning). Once a CR is achieved, PET scans are no longer required.
- Any imaging performed as part of institutional standard of care at any time during the study should be collected.

6.4 Cycles 17 and Beyond (Days 15 to 21 [+2 days]): Parts A, B, C, and D Only

Response assessments will be completed prior to dosing for the subsequent treatment cycle.

- CT of chest, abdomen, and pelvis (and neck, if clinically indicated) (see Section 7.2) per institutional standard of care or at least every 6 cycles after Cycle 16.
- PET scans performed per institutional standard of care. Once a CR is achieved, PET scans are no longer required.

6.5 At Time of Progression or Relapse (All Parts), or If Residual Disease at Cycle 8 or Suspected Tumor Flare/Pseudoprogression (Part D Only)

- Biopsy (see Section 7.6); optional at progression of disease for all parts of the study, or for Part D, optional if evidence of residual disease is suspected at Cycle 8 to distinguish active HL from inflammatory infiltrate or if tumor flare or pseudoprogression is suspected to determine if there is viable tumor in new or enlarging lesions (Note: It is strongly recommended to confirm that radiological evidence of progression is correlated with active HL; when possible, excisional biopsies should be performed).

6.6 End of Treatment Visit (30 to 37 Days After Last Dose of Study Drug)

If EOT evaluations are completed before 30 days after the last component of study treatment (brentuximab vedotin, dacarbazine, bendamustine, or nivolumab), the patient will be contacted by phone 30 to 37 days following the last component of study treatment to assess for AEs.

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

- ECOG performance status
- Physical examination (see Section 7.7.3)
- Parts E and F: evaluate CIRS score and IADL score
- In Parts E and F: serum or urine β-hCG pregnancy test for patients of childbearing potential
- B symptom assessment
- Serum chemistry panel (see Section 7.7.2)
    - Including LDH, phosphorus, and uric acid
    - Including amylase and lipase (Part D only)
    - Including TSH, free T3, and free T4 (Part D only)
- CBC with differential (see Section 7.7.2)

- Brentuximab vedotin (Parts A, B, C, and D only) and nivolumab (Part D only) PK and pharmacodynamic samples (see Sections 7.4 and 7.5)
- Brentuximab vedotin (all parts) and nivolumab (Part D only) immunogenicity (ATA) (see Section 7.4)
- Blood samples for biomarker assessments (Part D only) (see Section 7.5)
- CT of chest, abdomen, and pelvis (and neck, if clinically indicated). CT not needed if done in prior 6 weeks.
- PET (Note: a combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as CT is of diagnostic quality). PET not needed if done in prior 6 weeks. Once a CR is achieved, PET scans are not required.

6.7 Safety Visit (100 days [+2 weeks] After Last Dose of Nivolumab): Part D Only

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

- ECOG performance status
- Physical examination, including assessment for potential immune-mediated AEs (see Section 7.7.3)
- Serum chemistry panel (see Section 7.7.2)
  - Including LDH, phosphorus, and uric acid
  - Including amylase and lipase
  - Including TSH, free T3, and free T4
- CBC with differential (see Section 7.7.2)
- Nivolumab immunogenicity (ATA) (see Section 7.4)
- Blood samples for biomarker assessments (Part D only) (see Section 7.5)

6.8 Follow-up

After the EOT visit and 30-day safety period (or 100-day safety period relative to nivolumab dosing on Part D), all patients who receive at least 1 dose of brentuximab vedotin will be followed until withdrawal of consent, death, or the study closure. Information regarding survival, disease status, and additional or alternative therapies used for treatment of their lymphoma will be collected.

Prior to Progression

For Parts A, B, C, and D, patients who have not progressed at EOT will be followed for survival status at 3-month intervals (±2 weeks) which may be conducted with a clinic visit or a telephone call. Disease status will be assessed by CT imaging per institutional standard of care or at least approximately every 6 months following the most recent prior radiographic response evaluation for the first 2 years, an annual assessment for the third year, then per institutional standard of care until progression.

For Parts E and F, patients discontinuing study treatment without progression will be followed until progression or initiation of further anti-cancer therapy. Follow-up CT scans will be performed every 4 months for 2 years and then per institutional standard of care, and follow-up PET scans will be performed per institutional standard of care. Lymphoma assessments are to be performed at least approximately every 6 months during follow-up.

Upon progression, data regarding any subsequent anti-cancer therapies administered will be summarized and reported.

After Progression

Survival status follow-up will be conducted for patients who have progressed or started further anti-cancer treatment at 3-month intervals (±2 weeks) in Parts A to D and at 4-month intervals (±2 weeks) in Parts E and F. Survival follow-up contact may be conducted with a clinic visit or a telephone call.

6.9 End of Study/End of Follow-Up

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

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

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

Review of a pathology report from local laboratory will be used to confirm histopathological diagnosis of HL when determining eligibility for this study. For PTCL, tissue from the diagnostic biopsy must confirm CD30 expression by visual assessment using immunohistochemistry. Assessment of CD30 expression to determine eligibility for patients with PTCL will be performed by the institutional lab (using the anti-CD30 BerH2 antibody) with a requirement that CD30 expression be detected in ≥1% of neoplastic cells.

Diagnostic tumor tissue will be sent to a central repository designated by the sponsor and will subsequently be sent to a central laboratory for a retrospective analysis of disease-related biomarkers, including CD30. If archived tissue is not available or of insufficient quantity for central analysis, fresh tissue should be collected.

Performance status will be assessed by the ECOG Performance Status scale and the Karnofsky score in Parts A to D (Appendix F).

In Parts A to D, before initiation of protocol therapy, a baseline geriatric assessment will be performed using components from a tool developed and evaluated by Hurria et al. (Hurria 2011). Assessment variables may include but not be limited to aspects of function, comorbidity, cognition, psychological state, social activity/support, and nutritional status.

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.

For Part D only, pulmonary function tests evaluating spirometry, such as DLCO (hemoglobin adjusted), diffusing capacity of the lungs volume adjusted, diffusing capacity of the lungs volume and hemoglobin adjusted, total lung capacity, forced vital capacity, and forced expiratory volume in 1 second, are required for all patients at screening. DLCO over 50% (adjusted for hemoglobin) must be confirmed by a pulmonary function test of lung diffusion capacity prior to study enrollment.

For Parts E and F, the reason(s) for patients being unsuitable or unfit to receive multi-agent chemotherapy determined at screening (the presence of comorbidity-related factors, as documented by a CIRS score ≥10 [Appendix G] (according to the criteria specified by Salvi and colleagues (Salvi 2008) and excluding current active lymphoma) or requiring assistance with or dependence on others for any IADLs [Appendix H]) will documented on the CRF.

7.2 Response Assessments

7.2.1 Parts A, B, and C

For Parts A, B, and C of the study, treatment response will be assessed by spiral CT scan of the chest, abdomen, and pelvis (and neck, if clinically indicated) and PET scans performed at protocol-specified time points (see Section 6 and Appendix A), and whenever disease progression is suspected. A combined CT/PET of diagnostic quality may be obtained to satisfy the requirements for CT and PET scanning. With either CT/PET or diagnostic CT, it is preferred that both oral and IV contrast are used, except when contraindicated or not feasible.

The determination of antitumor efficacy will be based on objective response assessments made according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007) and treatment decisions by the Investigator will be based on these assessments. Clinical response of PD, SD, PR, or CR will be determined at each assessment. Progressive disease also includes clinical disease progression per investigator. Selection of up to 6 of the largest dominant nodes or nodal masses to follow for response assessment must be PET FDG-avid at baseline. Investigator evaluation of baseline radiographic assessment will enable study enrollment per Inclusion Criterion 4. In addition, per the Revised Response Criteria for Malignant Lymphoma, these nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved. The nodes or masses should have bidimensional measurements of at least 1.5 cm in the longest axis.

In addition, visual interpretation will be used for exploratory evaluation of interim PET scans with response scored with reference to sites of presumed lymphomatous involvement using the 5-Point Scale per the Deauville Criteria in Appendix I (Barrington 2010; Meignan 2009). For interim PET scans performed while patients are receiving study therapy, scores of 1, 2, and 3 with uptake in sites abnormal on the staging scan equal or less than liver uptake will be regarded as “negative” while scores of 4 and 5 with uptake greater than liver will be regarded as positive. PET scans performed at the EOT and beyond will be evaluated per the Revised Response Criteria for Malignant Lymphoma (Cheson 2007; Juweid 2007). PET scans performed per institutional standard of care may be collected at any time during the study, as available, for this exploratory evaluation.

Once a CR is documented, no further PET scans are required during the study. After the patient is withdrawn from study drug for any reason, an additional response assessment will be performed at the EOT visit if an assessment has not been performed within the prior 6 weeks. Patients with SD or better may continue on study drug for up to 16 cycles or more. After discussion with the medical monitor, patients who complete 16 cycles of treatment and experience clinical benefit per the investigator will be eligible to continue receiving additional brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure.

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.

7.2.2 Part D

For Part D of the study, the determination of antitumor activity will be based on response assessments made according to the Lugano criteria (Cheson 2014) and according to LYRIC (Cheson 2016) (Appendix J). Treatment decisions by the investigator will be based on these assessments. Staging will be performed by PET/CT of diagnostic quality at protocol-specified time points (see Section 6 and Appendix B), with disease involvement determined by focal FDG uptake in nodal and extranodal (including spleen, liver, bone marrow, and thyroid) sites that is consistent with lymphoma, according to the pattern of uptake and/or CT characteristics. Up to 6 of the largest nodes, nodal masses, or other involved lesions that are measurable in 2 diameters should be identified as target lesions at baseline; 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 (Days 15–21), 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 pseudoprogression is suspected. If tumor flare or pseudoprogression is **not** suspected, PD includes radiological evidence of progression per Lugano criteria. If clinical progression is determined by the investigator, radiographic staging should also be performed to determine response assessment per Lugano criteria. The PET scan metabolic uptake will be graded using the Deauville 5 point scale (Appendix I) (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 pseudoprogression is suspected by the Investigator during treatment with the combination of brentuximab vedotin and nivolumab, during single-agent nivolumab therapy (if brentuximab vedotin discontinued), or during single-agent brentuximab vedotin therapy within 12 weeks of discontinuing nivolumab, then a clinical response of IR will be determined until subsequent mandatory evaluation of radiographic imaging or biopsy confirms or refutes PD. IR is defined below. See Appendix J for further details and criteria for follow-up of a response of IR.

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 1 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 [Appendix I]) of 1 or more lesion(s) without a concomitant increase in lesion size or number.

Repeat imaging 12 weeks (or earlier if clinically indicated) after a response of IR is determined by the Investigator is mandatory and PD must be confirmed or refuted based LYRIC follow-up criteria for IR (Cheson 2016). If a patient has a second determination of IR, then subsequent repeat imaging must be performed between 4 and 8 weeks. Follow-up radiographic assessment for patients with IR is not required if a follow-up biopsy has been performed that confirms 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.

7.2.3 Parts E and F

Treatment response will be assessed by spiral CT scan of the chest, abdomen, and pelvis (and neck, if clinically indicated) and PET scans performed at protocol-specified time points (see Section 6 and Appendix C), and whenever disease progression is suspected. A combined CT/PET of diagnostic quality may be obtained to satisfy the requirements for CT and PET scanning. With either CT/PET or diagnostic CT, it is preferred that both oral and IV contrast are used, except when contraindicated or not feasible. If a patient has an allergy to the IV CT contrast agent, magnetic resonance imaging (MRI) with and without gadolinium contrast is to be used; if, in addition, the patient cannot tolerate gadolinium, CT without IV contrast should be used. Oral contrast should be used whenever possible, even if IV contrast is contraindicated. After the patient has discontinued from study drug for any reason, an additional response assessment will be performed at the EOT visit if an assessment has not been performed within the prior 6 weeks. Patients with SD or better may continue on study drug for up to 16 cycles. Clinical data will be submitted. If clinical progression is determined by the investigator, radiographic imaging should also be performed to determine response. If new lesions are suspected based on the CT/PET assessment, a conformational biopsy may be considered.

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

7.2.3.1 Modified Lugano Criteria

Although, treatment decisions and response assessment by the Investigator will be based on local disease assessments according to Lugano criteria (Section 7.2.3.2), the primary determination of antitumor efficacy will be ORR according to modified Lugano criteria: the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014) modified to take into account CT response in the event of a PET PR (Appendix M). Disease response of PD, SD, PR, CR, or not evaluable (NE) will be determined at each assessment by BICR. Selection of up to 6 of the largest dominant nodes or other tumor lesions to follow for response assessment must be PET FDG-avid at baseline. Investigator evaluation of baseline radiographic assessment will enable study enrollment per Inclusion Criterion 4. In addition, per Lugano criteria, these nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved. The nodes or masses should have bidimensional measurements with at least 1.5 cm in the longest axis. For PET scans, Deauville scores of 1, 2, and 3 will be regarded as "negative" while scores of 4 and 5 with uptake greater than background liver uptake will be regarded as positive.

As detailed in the Independent Review Charter, the integrated response at each disease assessment will be determined on the basis of PET and CT responses according to modified Lugano criteria, as summarized in Appendix M.

For time points where both PET and CT disease assessments are available, the response assessment will in general default to the PET assessment; however, when a PR is determined by PET but the CT response in neither CR nor PR, the integrated response will be SD. Once a CR has been determined by PET assessment, the integrated response will continue to be CR until PD is detected by PET or CT, even if there are no further PET assessments. When the CT response is PD and PET was not evaluated the integrated response will be PD.

7.2.3.2 Lugano Criteria

Both the Investigator and the BICR will assess response according to the unmodified Lugano criteria (Cheson 2014). Assessment of response will be undertaken in the same manner as for modified Lugano criteria (Section 7.2.3.1), with the exception that if the PET response is PR the integrated response will be PR, irrespective of CT response (Table 2).

Table 2 Integrated PET and CT response according to Lugano criteria

PET Response	CT Response		Integrated Response
CR	Any		CR
PR	Any		PR
SD	Any		SD
PD	Any		PD
Not done or Not evaluable	Prior PET response [a]	CT Response	
	CR	Non-PD	CR [b]
	non-CR	Non-PD	NE
	Any	PD	PD
No FDG-avid disease at baseline [c]	No disease present (NE)		NE
	PD		PD

NE=not evaluable

a "Prior PET response" refers to the latest prior PET assessment that was evaluable. PET responses may be carried forward over multiple CT assessments.

b A CR according to PET will be carried forward irrespective of CT response, until CT shows PD or is assessed as NE.

c Per protocol all patients must have FDG-avid disease at baseline.

7.2.3.3 International Working Group Consensus Response Evaluation Criteria in Lymphoma

ORR according to RECIL per BICR assessment will be evaluated as an additional efficacy endpoint. See Appendix K for details concerning RECIL assessment.

7.3 Lymphoma Assessments

Lymphoma assessments are to be performed at the time points outlined in Section 6.8, Appendix A, Appendix B, and Appendix C. Every effort must be made to perform lymphoma assessments according to the schedule of events to prevent the introduction of bias based on treatment delays.

An adequate focused lymphoma assessment consists of:

- Patient medical history, including a thorough review of:
  - The patient's current signs and symptoms, including B symptoms.
  - Concomitant medications.
- Physical examination, including evaluation of skin, head, eyes, ears, nose, and throat, lymph nodes, heart, lungs, abdomen, back, extremities, and neurology.

7.4 Pharmacokinetic and Pharmacodynamic Assessments

For Parts A, B, and C, serum concentrations of brentuximab vedotin ADC and plasma concentrations of MMAE will be measured at selected time points in Cycle 1 and at predose and end of infusion in subsequent cycles (see Table 3). ATA to brentuximab vedotin will also be measured predose on Cycles 1, 2, 4, every 4 cycles thereafter, and EOT. Samples will be retained for measurement of total antibody, if needed.

For Part D, serum concentrations of brentuximab vedotin ADC and nivolumab, and plasma concentrations of MMAE will be measured at selected time points (see Table 4). ATA against brentuximab vedotin and ATA against nivolumab will also be assessed.

For Parts E and F, serum concentrations of brentuximab vedotin ADC and plasma concentrations of MMAE will be measured at predose and end of infusion in Cycles 1, 2, and 3 only. ATA to brentuximab vedotin will also be measured predose on Cycles 1, 2, 4, every 4 cycles thereafter, and EOT. Samples will be retained for measurement of total antibody, if needed.

PK parameters to be estimated include the AUC, maximum concentration for MMAE (C_{max}) and the time C_{max} occurred (T_{max}), concentration at the end of infusion (C_{eoi}) for brentuximab vedotin ADC (all parts) and nivolumab (Part D only), and trough concentration (C_{trough}). PK, demographic, and clinical laboratory data may be incorporated into the brentuximab vedotin population PK model for further model refinement and parameter estimation. The incidence of ATA to brentuximab vedotin (all parts) and nivolumab (Part D only) will also be assessed.

For Parts A, B, C, E, and F, blood samples will be collected (predose at each cycle) for measurement of pharmacodynamic biomarkers, such as soluble CD30 (sCD30), cytokines, chemokines, or other disease-related biomarkers and brentuximab vedotin-related species.

Table 3 presents the PK, pharmacodynamic, and immunogenicity sample collection time points for Parts A, B, and C. Table 4 presents the PK and immunogenicity sample collection time points for Part D; see Section 7.5 for pharmacodynamics in Part D. Table 5 presents the PK, pharmacodynamic, and immunogenicity sample collection time points for Parts E and F. All sampling times are relative to the start of brentuximab vedotin infusion, except for the end of infusion concentrations, which are relative to the end of brentuximab vedotin infusion. Refer to the Research Specimen Manual for information on collection, processing, storage, and shipment of samples.

Table 3: Pharmacokinetic, pharmacodynamic, and immunogenicity sampling time points (Parts A, B, and C)

Cycle	Study Day	Time	Window	Relative Time[a]	PK	Biomarkers[c]	ATA[b]
1	Day 1	Predose	Within 24 hours prior to start of infusion	Start of infusion	X	X	X
		End of infusion	Within 15 min post end of infusion	End of infusion	X		
	Day 2	24 hours	±4 hours	Start of infusion	X		
	Day 3	48 hours	±4 hours	Start of infusion	X		
	Day 8	168 hours	±24 hours	Start of infusion	X		
	Day 15	336 hours	±24 hours	Start of infusion	X		
2 and subsequent cycles	Day 1	Predose	Within 8 hours	Start of infusion	X	X	X
		End of infusion	Within 15 min post end of infusion	End of infusion	X		
EOT					X	X	X

a The relative time is related to the administration of brentuximab vedotin.

b Samples for immunogenicity will be collected predose on Cycles 1, 2, 4, every 4 cycles thereafter, and EOT.

c Biomarkers include, but are not limited to, pharmacodynamics biomarkers such as sCD30, cytokines, chemokines, or other disease-related biomarkers and brentuximab vedotin-related species.

Table 4: Pharmacokinetic and immunogenicity sampling time points (Part D only)

Cycle	Study Day	Time	Window	Relative Time[a]	Brentuximab Vedotin PK	Nivolumab PK	Brentuximab Vedotin + nivolumab ATA
Baseline							
1	Day 1	Pre-dose	Within 24 hours prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X
		End of infusion	Within 15 min post end of brentuximab vedotin infusion	End of brentuximab vedotin infusion	X		
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion		X	
	Day 8	168 hours post-dose	±24 hours	Start of brentuximab vedotin infusion	X	X	
	Day 15	336 hours post-dose	±24 hours	Start of brentuximab vedotin infusion	X	X	
2 and 4, and every 4 cycles thereafter	Day 1	Pre-dose	Within 24 hours prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X
		End of infusion	Within 15 min post end of brentuximab vedotin infusion	End of brentuximab vedotin infusion	X		
		End of infusion	Within 15 min post end of nivolumab infusion	End of nivolumab infusion		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 The relative times are related to the administration of brentuximab vedotin or nivolumab as specified.

Table 5: Pharmacokinetic and immunogenicity sampling time points (Parts E and F)

Cycle	Study Day	Time	Window	Relative Time[a]	PK	ATA
1	Day 1	Predose	Within 24 hours prior to infusion	Start of infusion	X	X
		End of infusion	Within 15 min post end of infusion	End of infusion	X	
2	Day 1	Predose	Within 8 hours	Start of infusion	X	X
		End of infusion	Within 15 min post end of infusion	End of infusion	X	
3	Day 1	Predose	Within 8 hours	Start of infusion	X	
		End of infusion	Within 15 min post end of infusion	End of infusion	X	
4 then every 4 cycles	Day 1	Predose	Within 8 hours	Start of infusion		X
EOT						X

a The relative time is related to the administration of brentuximab vedotin.

7.5 Biomarker Studies: Part D Only

Blood and tumor samples will be collected for measurement of other potential pharmacodynamic and patient stratification biomarkers.

For peripheral blood sampling time points for biomarker analyses for Part D, see Table 6. 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
- Serum and/or plasma sCD30, CD153 (sCD153), and inflammatory cytokines/chemokines including, but not limited to, IFN-γ, IL-6, IL-18, CXCL11 (I-TAC), CXCL9, CXCL10, MIP1 β, and TNF-α
- Peripheral blood T-cell receptor (TCR) repertoire and T-cell responses from peripheral blood mononuclear cells (PBMCs) to assess the impact of brentuximab vedotin alone and in combination with nivolumab on immune status
- RNA expression profiling

Table 6: Peripheral blood sampling time points for biomarker analyses (Part D only)

Cycle	Study Day	Time	Window	Relative Time	Flow Cytometry	Plasma and Serum Cytokines	Serum Bio-markers	RNA	PBMC	TCR
1	Day 1	Pre-dose	Within 24 hours prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 8	168 hours post-dose	±24 hours	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 15	336 hours post-dose	±24 hours	Start of brentuximab vedotin infusion	X	X	X	X	X	X
2	Day 1	Pre-dose	Within 24 hours prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X	X	X	X	X	X
	Day 8	168 hours post-dose	±24 hours	Start of brentuximab infusion	X	X	X			
3	Day 1	Pre-dose	Within 24 hours prior to start of brentuximab vedotin infusion	Start of brentuximab vedotin infusion	X					
EOT	30+7 days post last dose of study drug(s)				X	X	X	X	X	X
Safety Follow-up	100 days post last dose of nivolumab				X	X	X	X	X	X

Baseline biomarker levels will be assessed by a central laboratory using tissue blocks or unstained slides obtained at screening to evaluate potential sensitivity or resistance to brentuximab vedotin and/or nivolumab (e.g., CD30 expression, PD-L1/L2 amplification and expression). For biomarker analyses on optional tumor biopsies obtained after disease progression or on residual disease at Cycle 8 (see Sections 6.5 and 7.6), 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 mechanisms.

Assessments may include, but are not limited to the following:

- 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 immunohistochemistry, 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 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 of other immune checkpoint molecules if an assay becomes available
  - EBV infection status, if not previously known

7.6 Other Study Assessments

For Parts A, B, C, E, and F, at the time of study entry, tissue blocks (preferred) or unstained slides (if tumor block is unavailable) are required. If archived tissue is not available or of insufficient quantity for central analysis, fresh tissue should be collected. Prior to initiation of new therapy, additional tissue blocks or unstained slides are required at the time of progression or relapse unless re-biopsy would result in unacceptable risk in the setting of potential marginal benefit (Parts A, B, and C only). Exploratory assessments are planned for disease-related biomarkers.

For Part D, tissue blocks (preferred) or unstained slides (if tumor block is unavailable) are to be collected at screening. 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 block with the highest tumor content is preferred. 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. If tissue is unavailable, then discuss with sponsor medical monitor.

Also for Part D, efforts should be made to take an additional biopsy in patients who demonstrate disease progression on study, residual disease at Cycle 8 (biopsy should be taken prior to RT if patient is going to have RT administered on study), or if tumor flare or pseudoprogression is suspected unless re-biopsy would result in unacceptable risk in the setting of potential marginal benefit.

For patients who provide additional consent on any part of the study, 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 ADCs, the biology of ADC sensitivity and resistance mechanisms, and to identify predictive pharmacodynamic biomarkers of ADCs. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and applicable regulatory obligations have been met.

For Parts E and F, if the etiology of new lesions on CT/PET is uncertain, biopsy or interval scanning should be considered.

7.7 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AE including SAE, recording of concomitant medication and measurements of protocol-specified physical examination findings and laboratory tests. For Part D only, pulse oximetry tests (O_2 saturation) will also be performed.

Safety will be monitored for patients in Parts C and D by an SMC as described in Section 3.2.

7.7.1 Adverse Events

7.7.1.1 Definitions

Adverse Event

According to the International Council for Harmonisation E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational patient 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 AEs 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.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and postdose) through the end of the safety reporting period (see Section 7.7.1.3). 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 SAE 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 malignancy 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. Potential DILI also is considered a medically significant event (see Section 7.7.1.2 for the definition of potential DILI.)

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 SAEs).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to brentuximab vedotin, dacarbazine, bendamustine, or 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

For Part D, the Investigator's Brochures for brentuximab vedotin and nivolumab individually describe AEs commonly observed with either agent (i.e., neutropenia or peripheral neuropathy with brentuximab vedotin; and immune-mediated AEs with nivolumab), as well as less common serious findings. The respective Investigator's Brochures should be referenced when attributing causality.

7.7.1.2 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.

For Parts A, B, C, E, and F, important exceptions are adverse reactions associated with the infusion of study drug. For IRRs, do not use the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or HSR.' Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

For Part D, adverse reactions associated with the infusion of study drug must be recorded as both the NCI CTCAE term for IRR (i.e., cytokine release syndrome, acute infusion reaction, or allergic or HSR) and as each sign or symptom that occurs within a given infusion-related event. Level of severity for both the overall IRR term and the individual signs and symptoms should also be recorded.

Recording Serious Adverse Events

For SAEs, record the primary event on both the CRF and an SAE form; events occurring secondary to the primary event should be described on the SAE form in the narrative description of the case.

The following should be considered when recording SAEs:

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

Progression of the Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported AEs or SAEs.

Pregnancy

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 study drug, including brentuximab vedotin, dacarbazine, or bendamustine (or 8 months after the last dose of nivolumab), whichever is later, including any pregnancies that occur in a male patient's partner if the estimated date of conception is after the male patient's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. On the AE and Pre-Existing Conditions CRF, record all pregnancies that occur from time of informed consent to within 30 days of last study drug dose for Parts A, B, C, E, F or for Part D, from the time of informed consent until 6 months after the last dose of brentuximab vedotin or 8 months after the last dose of nivolumab, whichever is later, (i.e., based on the estimated date of conception) including any pregnancies that occur in the partner of a male study patient. 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 7.7.1.1) should be reported as SAEs.

As part of the study, all pregnancies will be monitored for the full duration and all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Potential Drug-Induced Liver Injury

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law (Reuben 2004). Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential hepatotoxicity in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 x ULN

AND

2. Total bilirubin >2 x ULN, without initial findings of cholestasis (i.e., elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as a suspected unexpected serious adverse reaction (SUSAR) associated with the use of the drug and reported promptly to the Sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3 x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug.

7.7.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit, or 30 days after the last study treatment (brentuximab vedotin [all parts], dacarbazine [Part B], or bendamustine [Part C]), or 100 days after the last nivolumab dose (Part D), whichever is later. However, all study protocol-related AEs are to be collected from the time of informed consent. All SAEs that occur after the safety reporting period and are considered related to any component of study treatment 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, the patient dies or withdraws consent, or study closure. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.7.1.4 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 (see email address or fax number included on the SAE report form) within 24 hours.

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

7.7.1.5 Sponsor Safety Reporting Requirements in the US

According to the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA final guidance Safety Reporting Requirements for INDs and Bioavailability/Bioequivalence Studies (December 2012), endpoints that assess disease-related mortality or major morbidity as well other SAEs that are not study endpoints, but are known consequences of the underlying disease or condition that are anticipated to occur in the study population should not be reported to the FDA as individual IND safety reports.

For Parts A, B, C, and D of this study, the SAEs that do not require individual IND safety reports are disease progression. For Parts E and F, disease progression is not reported as an AE and will be monitored as an efficacy endpoint. Therefore, disease progression will not be reported as an individual IND safety report to the FDA. Other SAEs that are anticipated to occur in the study population including Parts A, B, C, D, E, and F will be submitted to the FDA as individual IND safety reports per the IND safety reporting final rule.

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

7.7.2 Clinical Laboratory Tests

The following laboratory assessments will be performed by local laboratories at scheduled time points (see Appendix A, Appendix B, and Appendix C) 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, potassium, sodium, total bilirubin, and glucose.
  - LDH, phosphorus, and uric acid will also be obtained as part of the chemistry panel. Lipase will be obtained for patients in Parts C and D only. For Part D only, amylase will be obtained as well as TSH, free T3, and free T4.
- The CBC with differential is to include the following tests: white blood cell (WBC) count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count, platelet count, and hemoglobin/hematocrit.
- Erythrocyte sedimentation rate (at baseline only).
- Hepatitis B and C serologies; if hepatitis C serology is positive, hepatitis C virus RNA test by PCR is required to confirm (Parts D, E, and F only).

- For Parts E and F only, the eGFR should be calculated using the MDRD equation as applicable, with Scr reported in mg/dL:
  - eGFR (mL/min/1.73 m^2)=175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
  - If Scr is reported in µmol/L, the value should be converted to mg/dL using the conversion factor 0.011312 µmol/L to mg/dL.

7.7.3 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Height is to be measured; measurements obtained within the prior 12 months may be utilized. Vital signs should also be recorded at each physical examination (Part D only).

7.8 Appropriateness of Measurements

The Revised Response Criteria for Malignant Lymphoma (Cheson 2007) and the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014) will be employed to evaluate tumor lesion size in the determination of response rate in this study. Tumor imaging at the specified intervals is consistent with general oncological practice and appropriately balances measurement of tumor control with the expense and patient inconvenience associated with CT and PET scanning.

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. AEs and, when applicable, clinical laboratory data will be graded using NCI CTCAE Version 4.03.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to brentuximab vedotin (all parts) and nivolumab (Part D only). PK assessments for drug activity and biomarker assessments are also common in clinical studies.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

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

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's Brochure/package insert
- Recording and reporting AE and SAE
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval process
- Informed consent process
- Good Clinical Practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Patient coding and randomization (if applicable)
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

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

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for electronic CRF 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 electronic CRF.

8.3 Access to Source Data

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

8.4 Accuracy and Reliability of Data

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

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

8.5 Quality Assurance Procedures

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

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained. Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system.

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

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

8.6.2 Investigator Record Retention

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

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size

Parts A, B, C and D of this study will evaluate whether the ORR (CR + PR) for single-agent brentuximab vedotin or brentuximab vedotin in combination with dacarbazine, bendamustine, or nivolumab is >25% using a single-arm study design. The objective of Parts A to D is to be able to detect an ORR of at least 25%, which is considered to show minimal clinical benefit given that the patient population may not have other options for initial conventional chemotherapy.

For Parts A, B, and C of the study, disease response and progression will be assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). For Part D of the study, disease response will be assessed using the Lugano criteria (Cheson 2014) and LYRIC (Cheson 2016). For Parts A, B, C, and D, PD also includes clinical disease progression per investigator. For Parts E and F of the study, disease response will be assessed using the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014). For Parts E and F, the assessment will be per BICR.

With 30 patients for Part A and an overall significance level of 0.1, observing 13 or more objective responses (43% ORR [lower limit of exact 90% CI: 27.87%]) would allow us to reject the null hypothesis and claim that the true ORR is >25%. Similarly, with a sample size of 20 patients for Part B and an overall significance level of 0.1, observing 9 or more objective responses (45% ORR [lower limit of exact 90% CI: 25.87%]) would allow us to reject the null hypothesis and claim that the true ORR is >25%. For Part C, approximately 30 patients will be enrolled, with at least 20 patients treated using the lower starting dose of bendamustine (70 mg/m^2) combined with 1.8 mg/kg brentuximab vedotin. Using this sample size of 20 patients included in the analysis for Part C and an overall significance level of 0.1, observing 9 or more objective responses (45% ORR [lower limit of exact 90% CI: 25.87%]) in this group would allow us to reject the null hypothesis and claim that the true ORR is >25%. An analysis will also be performed for all 30 patients in Part C. With the assumption of a true ORR of 75%, Parts A, B, and C of the study will have over 90% power (nQuery). For Part D, with a sample size of 20 patients and an overall significance level of 0.1, observing 9 or more objective responses (45% ORR [lower limit of exact 90% CI: 25.87%]) would allow us to reject the null hypothesis and claim that the true ORR is >25%.

Part E (the classical HL cohort) is designed to estimate the ORR at a reasonable level of precision. Approximately 50 patients will be enrolled to ensure adequate data for safety and efficacy evaluation. If 35 responses are observed, the estimated ORR and the associated 2-sided 95% CI using the Clopper-Pearson method is 70% (95% CI: 55.4%, 82.1%) (Clopper 1934).

Part F (the PTCL cohort) is designed to estimate the ORR at a reasonable level of precision. Approximately 50 patients will be enrolled to ensure adequate data for safety and efficacy evaluation. Enrollment of patients with sALCL will be capped at 50% of the total enrollment in Part F (approximately 25 patients out of 50). If 25 responses are observed, the estimated

ORR and the associated 2-sided 95% CI using the Clopper-Pearson method is 50% (95% CI: 35.5%, 64.4%) (Clopper 1934).

9.2 Study Endpoint Definitions

9.2.1 Objective Response Rate

The ORR is defined as the proportion of patients with CR or PR, according to the disease assessment criteria specified in Section 2.4 for each study part. For Parts E and F, the assessment will be per BICR.

9.2.2 Complete Remission Rate

The CR rate is defined as the proportion of patients with CR, according to the disease assessment criteria specified in Section 2.4 for each study part. For Parts E and F, the assessment will be per BICR.

9.2.3 Disease Control Rate

Disease control rate is defined as the proportion of patients with CR, PR, or SD, according to the disease assessment criteria specified in Section 2.4 for each study part. For Parts E and F, the assessment will be per BICR.

9.2.4 Duration of Response

Duration of response is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression or to death due to any cause, whichever comes first. Duration of response data will be censored on the day following the date of the last disease assessment documenting absence of PD for patients who do not have tumor progression and are still on study at the time of an analysis, are given antitumor treatment (including stem cell transplant) other than the study treatment, or are removed from study prior to documentation of tumor progression. Duration of response will only be calculated for the subgroup of patients achieving a CR or PR. Responses will be assessed according to the disease assessment criteria specified in Section 2.4 for each study part. For Parts E and F, the assessment will be per BICR.

9.2.5 Duration of Complete Remission

Duration of CR is defined as the time from start of the first documentation of CR to the first documentation of tumor progression or to death due to any cause, whichever comes first. Duration of CR data will be censored on the day following the date of the last disease assessment documenting absence of PD for patients who do not have tumor progression and are still on study at the time of an analysis, are given antitumor treatment (including stem cell transplant) other than the study treatment, or are removed from study prior to documentation of tumor progression. Responses will be assessed according to the disease assessment criteria specified in Section 2.4 for each study part. For Parts E and F, the assessment will be per BICR.

9.2.6 Progression-Free Survival

PFS is defined as the time from start of study treatment to first documentation of tumor progression or to death due to any cause, whichever comes first. PFS data will be censored on the day following the date of the last disease assessment documenting absence of PD for patients who do not have tumor progression and are still on study at the time of an analysis, are given antitumor treatment (including stem cell transplant) other than the study treatment, or are removed from study prior to documentation of tumor progression. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at 1 day.

Responses will be assessed according to the disease assessment criteria specified in Section 2.4 for each study part. For Parts E and F, the assessment will be per BICR.

9.2.7 Indeterminate Response Rate

The IR rate is defined as the proportion of patients with IR according to LYRIC (Cheson 2016).

9.2.8 B Symptom Resolution Rate

B symptom resolution rate is defined as the proportion of patients with lymphoma-related B symptoms at baseline who achieve resolution of all B symptoms at any time during the treatment period.

9.2.9 Incidence of ATA

The ATA incidence rate is defined as the proportion of patients who develop ATA to brentuximab vedotin (or nivolumab for Part D) at any time during the study.

9.2.10 Event-free Survival

EFS is defined as the time from start of study treatment to any treatment failure including disease progression, or discontinuation of treatment for any reason (e.g., disease progression, toxicity, patient preference, initiation of new treatment excluding consolidative RT in the absence of progression, but including stem cell transplant without documented progression or death). EFS will be censored on the last follow-up date if none of the above events occur during the study.

Responses will be assessed according to the disease assessment criteria specified in Section 2.4 for each study part. For Parts E and F, the assessment will be per BICR.

9.2.11 Overall Survival

OS is defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond the day of first dose will have their survival time censored at 1 day.

9.3 Statistical and Analytical Plans

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

9.3.1 General Considerations

This is a phase 2, open-label study where for each part, the primary endpoints will be summarized descriptively. The secondary and additional endpoints will be analyzed and provided as supporting evidence for the overall clinical benefit of brentuximab vedotin (and nivolumab for Part D).

For each part, descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be used to describe continuous variables. Frequencies and percentages will be used to describe categorical variables. Summaries will be displayed separately for single-agent brentuximab vedotin and combination treatment.

9.3.1.1 Randomization and Blinding

Not applicable.

9.3.1.2 Adjustments for Covariates

Covariates such as risk factors will be considered for adjustment in the association analyses.

9.3.1.3 Handling of Dropouts and Missing Data

With the exception of time-related endpoints, no imputation will be conducted for missing data unless otherwise specified in the SAP.

For time-related endpoints (e.g., duration of response, PFS, and OS, etc), patients who have no specified event will be censored at the time of the last valid assessment of the endpoint(s).

Patients whose disease response cannot be assessed will be counted as non-responders.

9.3.1.4 Multicenter Studies

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

9.3.1.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned. For retreatment patients, the first treatment experience will be used in all analyses. Subsequent treatment experiences will be summarized separately.

9.3.1.6 Data Transformations and Derivations

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

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

9.3.1.7 Analysis Sets

Full Analysis Set

The full analysis set includes all patients who receive any amount of brentuximab vedotin. The full analysis set will be used for efficacy analyses and all safety analyses.

Efficacy Evaluable Analysis Set

The efficacy evaluable analysis set includes all treated patients with the histology of classical HL (Parts A, B, C, D, and E) and CD30-expressing PTCL (Part F), who had both a baseline and at least 1 post-baseline disease assessment or who had documented progression of disease any time after receiving any amount of brentuximab vedotin.

Per-protocol Analysis Set

The per-protocol analysis set includes all patients who receive any amount of brentuximab vedotin and who had both a baseline and at least 1 post-baseline disease assessment and no major protocol deviations that could potentially affect tumor response.

The per-protocol analysis set will be used for secondary analyses of all efficacy endpoints.

9.3.1.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be carried out for selected endpoints. The subgroups that may be examined include but are not limited to the following:

- Patients who were ineligible/unsuitable/unfit for versus patients who had declined initial conventional chemotherapy for HL
- Sex (Male, Female)
- Baseline ECOG performance status
- International Prognostic score at initial disease diagnosis
- Disease staging at initial diagnosis

Additional details and other subgroups will be specified in the SAP.

9.3.1.9 Timing of Analyses

The trial is not designed to allow for early stopping for futility or favorable efficacy results (see Section 9.3.10 for details) and there is no plan to stop the study for treatment effect.

The primary analysis for Parts A, B, C, and D will occur when the last patient in each part completes Cycle 8 restage. The primary analysis for Parts E and F will be conducted when all treated patients have been followed for at least 6 months, discontinued from study, or had 30 days safety follow-up after PD, whichever comes first.

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.

9.3.2 Patient Disposition

An accounting of study patients by disposition will be tabulated. The number of patients enrolled, receiving brentuximab vedotin or brentuximab vedotin in combination with dacarbazine, bendamustine, or nivolumab, and completing the study will be summarized. Patients who discontinue study treatment and patients who withdraw from the study will be summarized by reason for discontinuation or withdrawal and listed.

9.3.3 Patient Characteristics

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

9.3.4 Treatment Compliance

The dose (mg/kg) administered at each cycle will be assessed and compliance will be summarized. Details will be provided in the SAP.

9.3.5 Efficacy Analyses

All efficacy analyses for Parts A to D will be presented using the efficacy evaluable analysis set and the full analysis set will be used to present efficacy analyses for Parts E and F. Efficacy analyses for all parts may be presented using the per protocol analysis set, as applicable. Analyses may also be performed using the subgroups listed in Section 9.3.1.8.

9.3.5.1 Primary Efficacy Analyses

The ORR and its 2-sided 95% exact CI will be calculated using the Clopper-Pearson method (Clopper 1934).

For all parts, primary efficacy endpoints will be summarized descriptively and no formal statistical hypothesis testing will be performed.

This endpoint may also be tabulated by covariates such as sex, age, race, categorized weight, categorized tumor size at baseline, and ECOG performance status, etc. The maximum percent reduction in the SPD of the nodes or nodal masses being followed for response assessment will be graphically displayed.

9.3.5.2 Secondary Efficacy Analyses

The CR rate will be derived and its two-sided 95% exact CI will be calculated using the Clopper-Pearson method (Clopper 1934). Duration of response, duration of CR, and PFS will be estimated using Kaplan-Meier survival methodology and Kaplan-Meier survival plots will be provided. The median duration of response, duration of CR, and PFS and their two-sided 95% CI by Brookmeyer and Crowley (Brookmeyer 1982) will be calculated. These endpoints may also be summarized by covariates such as sex, age, race, categorized weight, categorized tumor size at baseline, prior treatment, and ECOG performance status, etc.

9.3.5.3 Additional Efficacy Analyses

EFS and OS will be estimated using Kaplan-Meier survival methodology and Kaplan-Meier survival plots will be provided. The median EFS and OS and their two-sided 95% CI by Brookmeyer and Crowley (Brookmeyer 1982) will be calculated. Analyses for other efficacy endpoints and other additional/exploratory analyses will be specified in the SAP.

9.3.5.4 Subsequent Therapies

The data for subsequent therapies will be summarized and listed.

9.3.6 Pharmacokinetic and Pharmacodynamic Analyses

Brentuximab vedotin ADC and MMAE concentrations and nivolumab concentrations will be listed at each PK sampling time point. All concentrations below the limit of quantification or missing data will be labeled as such in the listings.

Brentuximab vedotin ADC AUC after the first dose, and C_{eoi} and C_{trough} for all cycles will be summarized (per collection schedule; Section 7.4).

Brentuximab vedotin MMAE AUC, C_{max}, T_{max} after the first dose, and C_{trough} for all cycles will be summarized.

The incidence of ATA to brentuximab vedotin and nivolumab will be assessed. Pharmacodynamic biomarkers data (such as sCD30) will be reported descriptively.

Correlative analysis may be conducted to explore the relationships between PK and immunogenicity and any of the measured pharmacodynamic biomarkers.

9.3.7 Biomarker Analyses

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

9.3.8 Health Outcomes Analyses

Not applicable.

9.3.9 Safety Analyses

9.3.9.1 Extent of Exposure

Duration of treatment, number of cycles, total dose and dose intensity will be summarized and listed by cycle. Dose modifications will also be summarized and listed. Details will be provided in the SAP.

9.3.9.2 Adverse Events

AEs will be defined as treatment-emergent if they are newly occurring or worsen following treatment with brentuximab vedotin or any component of combination therapy. The incidence of all AEs, treatment-emergent AEs, and treatment-related AEs will be tabulated by treatment group. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by treatment group, MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 patient, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner.

9.3.9.3 Deaths and Serious Adverse Events

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

9.3.9.4 Clinical Laboratory Results

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by scheduled visit. Patients with laboratory values outside of the normal reference range at any post-baseline assessment will be listed. Shifts from baseline laboratory values will be tabulated as appropriate.

Laboratory results will also be graded per NCI CTCAE Version 4.03. Patient incidence of laboratory values will be summarized by lab test and by maximum grade. Shifts from baseline laboratory values in both lab abnormality and NCI CTCAE grade will be tabulated as appropriate.

9.3.9.5 Other Safety Analyses

ECOG status will be summarized for each visit. Shifts from baseline to the best and worst post-baseline score will be tabulated.

All other assessments that are not described here will be summarized in the SAP.

9.3.10 Interim Analyses

An SMC will be responsible for monitoring patient safety in Parts C and D of the study (see Section 3.2).

This study is not designed to allow for early stopping for futility or favorable efficacy results. A formal interim efficacy or futility analysis is not considered meaningful or practical for this study. An ongoing real-time review of SAEs will be conducted by the Seattle Genetics Drug Safety Department.

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. Interim analyses may also be presented in manuscript form.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 [R2]; FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil, 2015), and all applicable regulatory requirements.

10.1 Informed Consent

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

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

10.2 Ethical Review

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

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

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required

- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

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

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

10.3 Regulatory Considerations

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

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

10.3.1 Investigator Information

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

10.3.2 Protocol Amendments and Study Termination

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

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

10.4 Study Documentation, Privacy and Records Retention

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

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

Records containing patient medical information must be handled in accordance with the requirements of the Health Information Portability and Accountability Act (HIPAA) Privacy Rule and consistent with the terms of the patient authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, 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: STUDY SCHEDULE (PARTS A, B, AND C)

Study Procedures		Screening/ Baseline		Enrollment	Study Cycle/Day					End of Treatment[h]	Follow-up[j]
					Cycle 1 ONLY	Each 21-Day Cycle	Cycles 1 to 6 (Part C only)	Cycles 2, 4, 8, 12, and 16	Cycles 17 and Beyond		
		Day –28 to Day 1	Day –7 to Day 1		Days 1, 2, 3, 8, and 15	Day 1 (±2 days)	Day 2 (+1 day)	Days 15–21 (+2 days)[o]	Days 15–21 (+2 days)	30–37 days after last dose	Every 3 mos (±2 weeks)
Baseline Assessments	Informed consent	X									
	Inclusion[a]/exclusion criteria	X									
	Medical history	X									
	Tumor specimen collection[b]	X									
Screening and Safety Assessments	Electrocardiogram (ECG)	X									
	Echocardiogram or MUGA scan[c]	X									
	Height[c]		X								
	Weight		X			X[s,t]					
	ECOG		X			X[s]				X	
	Karnofsky score		X								
	Physical exam		X			X[s,t]				X	
	Serum chemistry panel[m]		X			X[s]				X	
	CBC with differential		X			X[s]				X	
	Estimated creatinine clearance[d]		X			X[q,s]					
	Erythrocyte sedimentation rate		X								
	Geriatric assessment[e]		X								
	Adverse events	Study protocol-related			Collect from Day 1 (predose) to EOT or 30 days after last study treatment, whichever is longer						
	Concomitant medications										
Treatment	Brentuximab vedotin					X					
	Dacarbazine					X[p] (Part B only)					
	Bendamustine (not applicable as of 07–Oct–2015)					X[r] (Part C only)	X[r]				
PK/PD	Pharmacokinetic samples[f]				X	X				X	
	Pharmacodynamic samples[f]					X				X	
	Immunogenicity (ATA)[f]					X				X	
Other	Tumor biopsy[b]				If applicable, to be done at time of relapse						
Response Assessments	CT scan	X[n]						X[k]	X[l]	X[i]	X
	PET scan[g]	X[n]						X	X[l]	X[i]	
	B symptom assessment		X			X[s]				X	
	Survival and disease status										X

a For inclusion criterion No.1, review pathology report to confirm histopathological diagnosis of classical HL; assessment may occur any time prior to study entry.
b See Section 7.6.
c Within prior 12 months prior to treatment initiation.
d As determined by Cockroft-Gault formula.
e See Section 7.1.
f See Section 7.4, Table 3 for applicable cycle of collection, sampling windows, and relative times of sampling.
g Required at Cycles 2 and 8. PET scans performed as part of institutional standard of care may be collected at any time during the study, as available.
h If EOT performed prior to 30 days post last dose, a follow-up phone call must be made on or within 7 days after Day 30.
i Response assessments at EOT not needed if done in the prior 6 weeks.
j See Section 6.8.
k CT scan at Cycle 16 only for patients continuing treatment beyond 16 cycles if not completed within last 6 weeks.
l CT performed per institutional standard of care or at least approximately every 6 months after Cycle 16 while on treatment. PET scans performed per institutional standard of care. Once a CR is achieved, PET scans are no longer required (see Section 6.4).
m Including LDH, phosphorus, and uric acid; lipase for Part C only.
n Within prior 45 days.
o Response assessments will be completed prior to dosing for the subsequent treatment cycle.
p Part B only, for Cycles 1 to 12.
q Part C only, on Day 1 for up to 6 cycles.
r Not applicable as of 07–Oct–2015 - Part C only, on Days 1 and 2 (+1 day in the absence of IRRs or HSRs) for up to 6 cycles.
s Predose.
t Cycle 2 and all subsequent cycles.

APPENDIX B: STUDY SCHEDULE (PART D)

Study Procedures		Screening/ Baseline		Enrollment	Study Cycle/Day					EOT[r]	Safety Visit	Follow-up[u]
		Day –28 to Day 1	Day –7 to Day 1		Each 21-Day Cycle Day 1 (±2 days)	Cycle 1 ONLY Days 8 and 15 (±1 day)	Cycles 2, 4, 8, 12, and 16 Day 15 to 21 (+2 days)[p]	Cycles 17 and Beyond Day 15 to 21 (+2 days)	At Time of Progression, if Residual Disease At Cycle 8, or Suspected Tumor Flare/ Pseudoprogression	30 to 37 days after last dose	100 days (+2 weeks) after last dose of nivolumab	Every 3 mos (±2 weeks)
Baseline Assessments	Informed consent	X										
	Inclusion[a]/exclusion criteria	X										
	Medical history	X										
	Tumor specimen collection or biopsy[b]	X										
Screening and Safety Assessments	Electrocardiogram (ECG)	X										
	Echocardiogram or MUGA scan[c]	X										
	Serology for hepatitis B	X										
	Serology for hepatitis C[d]	X										
	Pulmonary function test[e]	X										
	Oxygen saturation by pulse oximetry		X			X						
	Height[c]		X									
	Weight		X		X[m, n]							
	ECOG		X		X[m]					X	X	
	Karnofsky score		X									
	Physical exam		X		X[m, n]	X				X	X[t]	
	Serum chemistry panel[f]		X		X[m]	X				X	X	
	CBC with differential		X		X[m]	X				X	X	
	Estimated creatinine clearance[g]		X		X[m]							
	Erythrocyte sedimentation rate		X									
	Geriatric assessment[e]		X									
	Adverse events	Study protocol-related			Collect from Day 1 (predose) to 100 days after last dose of nivolumab or 30–37 days after last dose of brentuximab vedotin, whichever is later							
	Concomitant medications											
Treatment	Brentuximab vedotin				X							
	Nivolumab				X							
PK/PD	Pharmacokinetic samples[h]				See Table 4 in Section 7.4							
	Immunogenicity (ATA)[h]											
	Biomarker samples[i]				See Table 6 in Section 7.5							
Other	Tumor biopsy								X[q]			
Response Assessments	CT scan[j]	X[l]					X	X		X[s]		X
	PET scan[k]	X[l]					X	X		X[s]		
	B symptom assessment		X		X[m]					X		
	Survival and disease status											X

a For inclusion criterion No.1, review pathology report to confirm histopathological diagnosis of classical HL; assessment may occur any time prior to study entry.
b See Section 7.6.
c Within prior 12 months prior to treatment initiation.
d See Section 7.7.2.
e See Section 7.1.
f Including LDH, phosphorus, uric acid, lipase, amylase, as well as TSH, free T3, and free T4.
g As determined by Cockroft-Gault formula.
h See Section 7.4.
i See Section 7.5.
j CT scan at Cycle 16 only for patients continuing treatment beyond 16 cycles. CT at EOT not needed if completed within last 6 weeks. After EOT, performed per institutional standard of care or at least approximately every 6 months for the first 2 years, an annual assessment for the third year, then per institutional standard of care until progression. See Section 6.3.7 for radiographic imaging for patients with IR.
k Required at Cycles 4, 8, and 12. PET scan at Cycle 16 only for patients continuing treatment beyond 16 cycles. Performed per institutional standard of care after Cycle 16. PET at EOT not needed if completed within last 6 weeks. PET scans performed as part of institutional standard of care may be collected at any time during the study, as available. Once a CR is achieved, PET scans are not required. See Section 6.3.7 for radiographic imaging for patients with IR.
l Within prior 45 days.
m Predose.
n Cycle 2 and all subsequent cycles.
o Cycle 1 Day 8 only.
p See Sections 6.3.7 and 7.2; response assessments will be completed prior to dosing for the subsequent treatment cycle.
q Optional at progression of disease, if evidence of residual disease is suspected to distinguish active HL from inflammatory infiltrate, or if tumor flare or pseudoprogression is suspected to determine if there is viable tumor in new or enlarging lesions (Note: It is strongly recommended to confirm that radiological evidence of progression is correlated with active HL; when possible, excisional biopsies should be performed).
r If EOT performed prior to 30 days post last dose, a follow-up phone call must be made on or within 7 days after Day 30.
s Response assessments at EOT not needed if done in the prior 6 weeks.
t Including assessment for potential immune-mediated AEs.
u See Section 6.8.

APPENDIX C: STUDY SCHEDULE (PARTS E AND F)

Study Procedures		Screening/ Baseline		Enrollment	Study Cycle/Day		End of Treatment[h]	Follow-up[j]
					Each 21-Day Cycle	Cycles 2, 6, and 11		
		Day –28 to Day 1	Day –7 to Day 1		Day 1 (±2 days)	Days 15–21 (+2 days)[o]	30–37 days after last dose	Every 4 mos (±2 weeks)
Baseline Assessments	Informed consent	X						
	Inclusion[a]/exclusion criteria	X						
	Medical history	X						
	Tumor specimen collection[b]	X						
Screening and Safety Assessments	Electrocardiogram (ECG)	X						
	Echocardiogram or MUGA scan, within 28 days of treatment initiation	X						
	Serology for hepatitis B	X						
	Serology for hepatitis C[c]	X						
	CIRS score and IADL score	X					X	
	Height[d]		X					
	Weight		X		X[p]			
	ECOG performance status		X		X[p]		X	
	Serum or urine β-hCG pregnancy test for patients of childbearing potential		X				X	
	Physical exam		X		X[p]		X	
	Serum chemistry panel[m]		X		X[p]		X	
	CBC with differential		X		X[p]		X	
	eGFR[e]		X		X			
	Erythrocyte sedimentation rate		X					
	Adverse events	Study protocol-related			Collect from Day 1 (predose) to EOT or 30 days after last study treatment, whichever is longer			
	Concomitant medications							
Treatment	Brentuximab vedotin				X			
PK/PD	Pharmacokinetic samples[f]	See Table 5 in Section 7.4			See Table 5 in Section 7.4			
	Immunogenicity (ATA)[f]							
Response Assessments	CT scan & PET scan[g,l]	X[n]				X	X[i]	X[k]
	B symptom assessment		X		X[p]		X	
	Survival and disease status							X
	Bone marrow biopsy (Part F Only)	X[r]				X[q]	X[q]	X[q]

a For inclusion criterion No.1, review pathology report to confirm histopathological diagnosis of classical HL or CD30-expressing PTCL; assessment may occur any time prior to study entry.

b See Section 7.6.

c See Section 7.7.2.

d Within prior 12 months.

e As determined by the MDRD study equation.

f See Section 7.4, Table 5 for applicable cycle of collection, sampling windows, and relative times of sampling.

g Treatment response will be assessed by spiral CT scan of the chest, abdomen, and pelvis (and neck, if clinically indicated) and PET scans performed at the specified time points and whenever disease progression is suspected. A combined CT/PET of diagnostic quality may be used for CT and PET scanning. Both oral and IV contrast should be used with CT/PET and diagnostic CT, except when contraindicated or not feasible. In case of allergy to the CT contrast agent, MRI with and without gadolinium contrast is to be used; if, in addition, the patient cannot tolerate gadolinium, CT without contrast should be used. Imaging performed as part of institutional standard of care at any time during the study should be collected.

h If EOT is performed prior to 30 days post last dose, a follow-up phone call must be made on or within 7 days after Day 30.

i Response assessments at EOT not needed if done in the prior 6 weeks.

j See Section 6.8.

k Follow-up CT scans will be performed every 4 months for 2 years and then per institutional standard of care, and PET scans will be performed per institutional standard of care.

l Once a PET CR is achieved, PET scans are no longer required (see Section 6.3.8).

m Including LDH, phosphorus, and uric acid.

n Within prior 45 days.

o Response assessments will be completed prior to dosing for the subsequent treatment cycle.

p Predose.

q Only needs to be done to confirm a CR by imaging in patients with PTCL who had a positive baseline bone marrow.

r If bone marrow biopsy was previously performed as part of initial diagnostic workup for PTCL and results are available, it is not required to be repeated during screening.

APPENDIX D: 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 E: GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the patient's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 6 months after the final dose of study drug or 8 months following last dose of nivolumab in Part D; see Section 4.1).

Acceptable Methods for Highly Effective Birth Control (preventing conception)

Patients who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods:

- Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method/s (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

Acceptable Methods for Preventing Secondary Exposure to Seminal Fluid

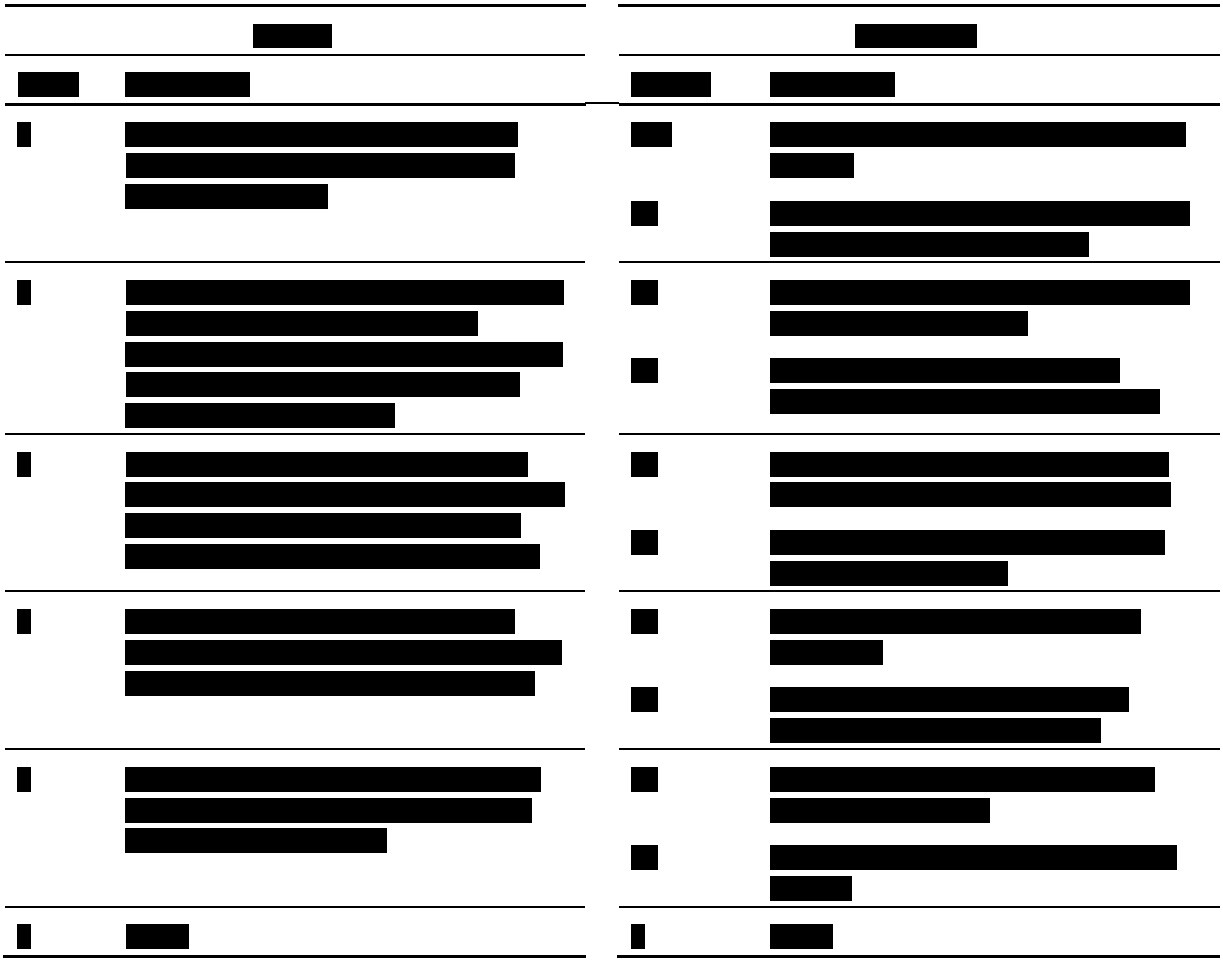
Patients born male and who are sexually active with a pregnant or breastfeeding person, must use the contraceptives in Option 1 or 2:

- Option 1: Male condom (with or without spermicide) and cervical cap
- Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable Methods of Contraception

- Periodic abstinence
- No method
- Withdrawal
- Rhythm
- Spermicide only
- Progestin-only pills
- Concomitant use of female and male condoms

APPENDIX F: PERFORMANCE STATUS SCALES



APPENDIX G: THE CUMULATIVE ILLNESS RATING SCALE

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APPENDIX H: THE LAWTON INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE

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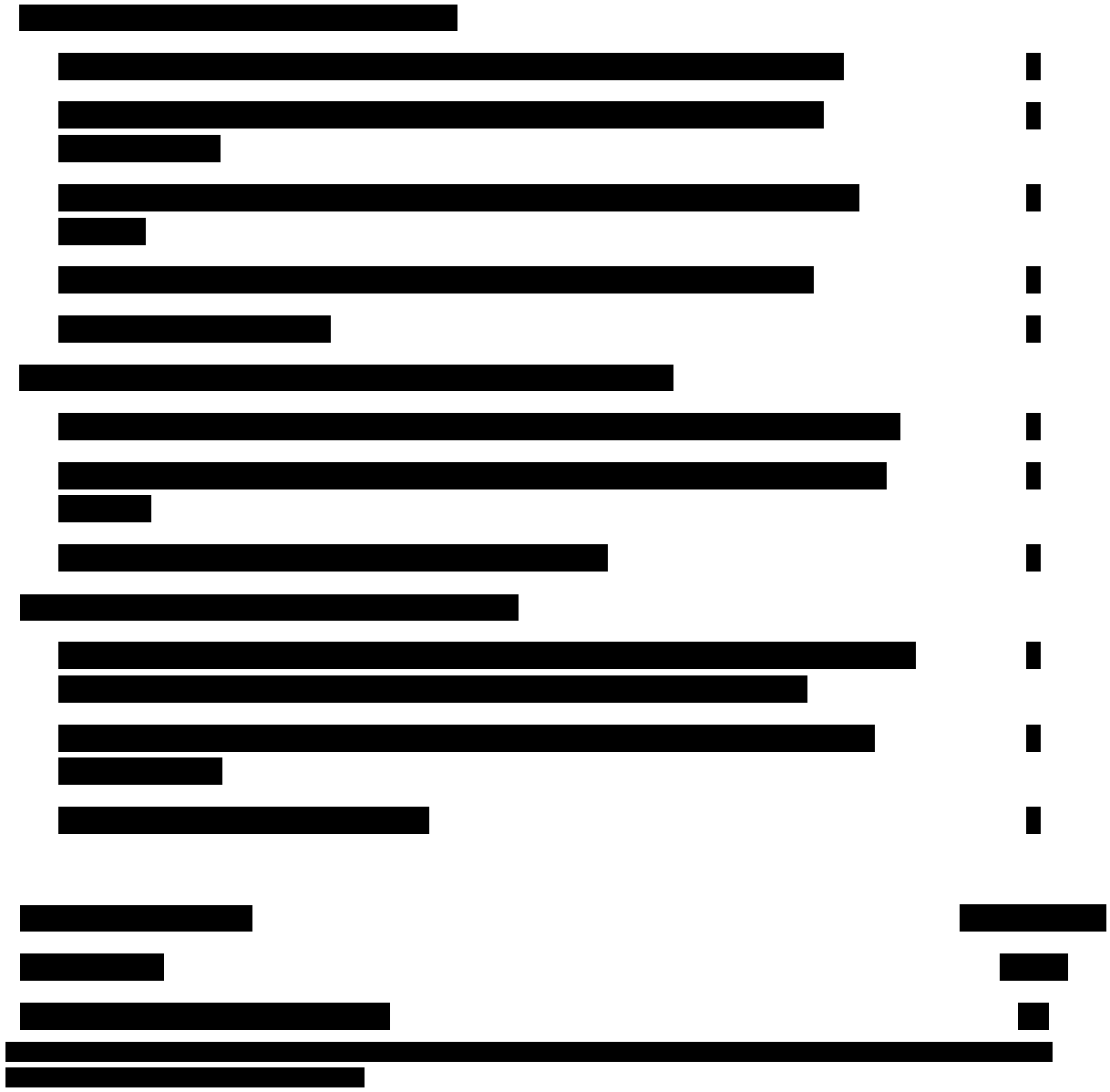


APPENDIX I: THE 5-POINT VISUAL ASSESSMENT SCALE (DEAUVILLE CRITERIA)

Negative

1. No uptake
2. Uptake ≤ mediastinal blood pool
3. Uptake > mediastinal blood pool but ≤ liver

Positive

1. Uptake > liver
2. Marked uptake > liver with multiple sites or development, or new uptake consistent with PD

From the First International Workshop on Interim-PET Scan in Lymphoma (Barrington 2010; Meignan 2009)

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

If tumor flare or pseudo-progression is suspected, then a clinical response of IR should be reported based on LYRIC (Cheson 2016).

Definition of Indeterminate Response

- **IR1:** An increase in overall tumor burden (as assessed by 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 structure, may not be considered as clinical deterioration in this context.

- **IR2:** Appearance of new lesions, or growth of 1 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 FDG uptake (using the 5-Point Scale per the Deauville Criteria [Appendix I]) of 1 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 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 1 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 IR1 or IR2 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).

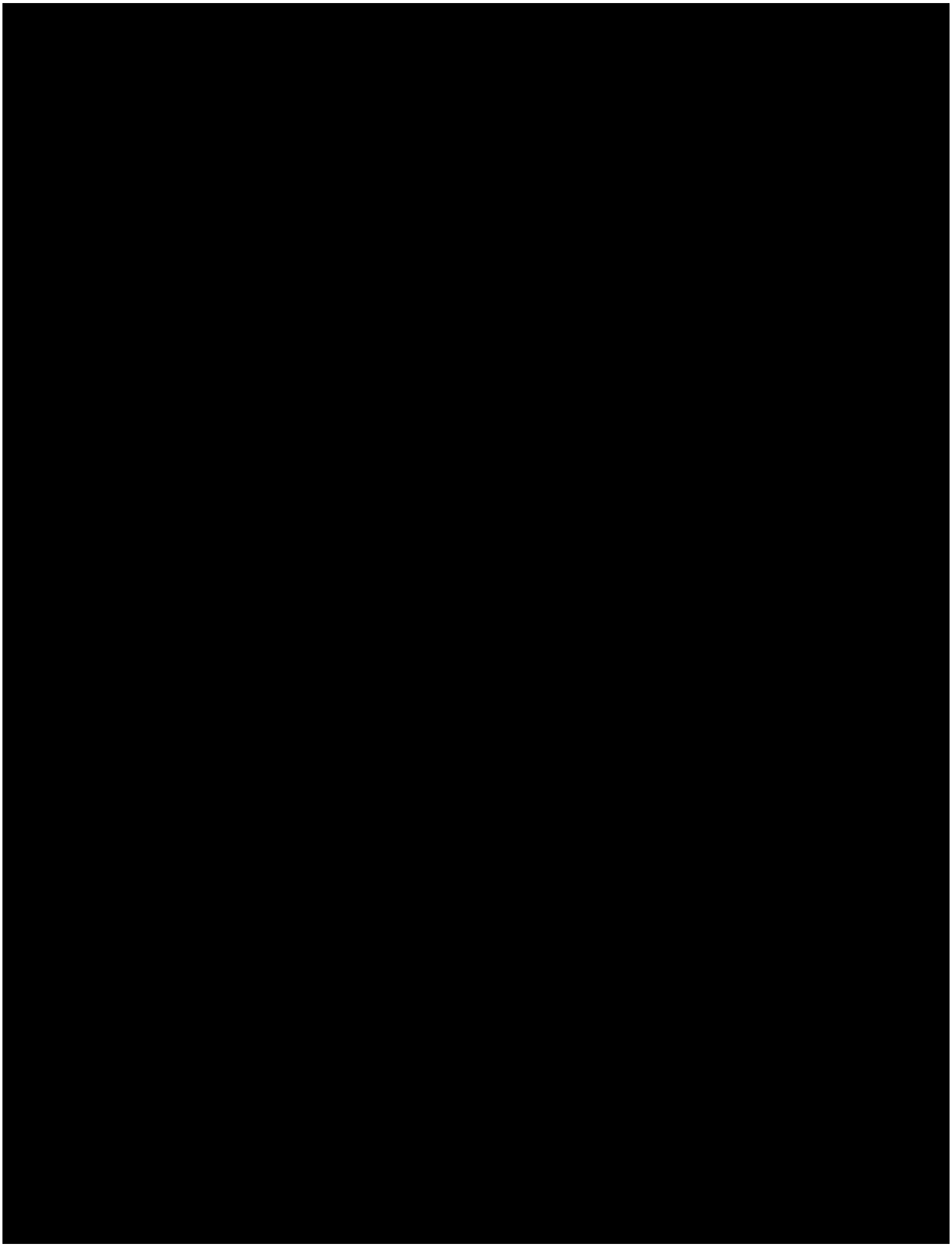
Follow-Up of Indeterminate Response

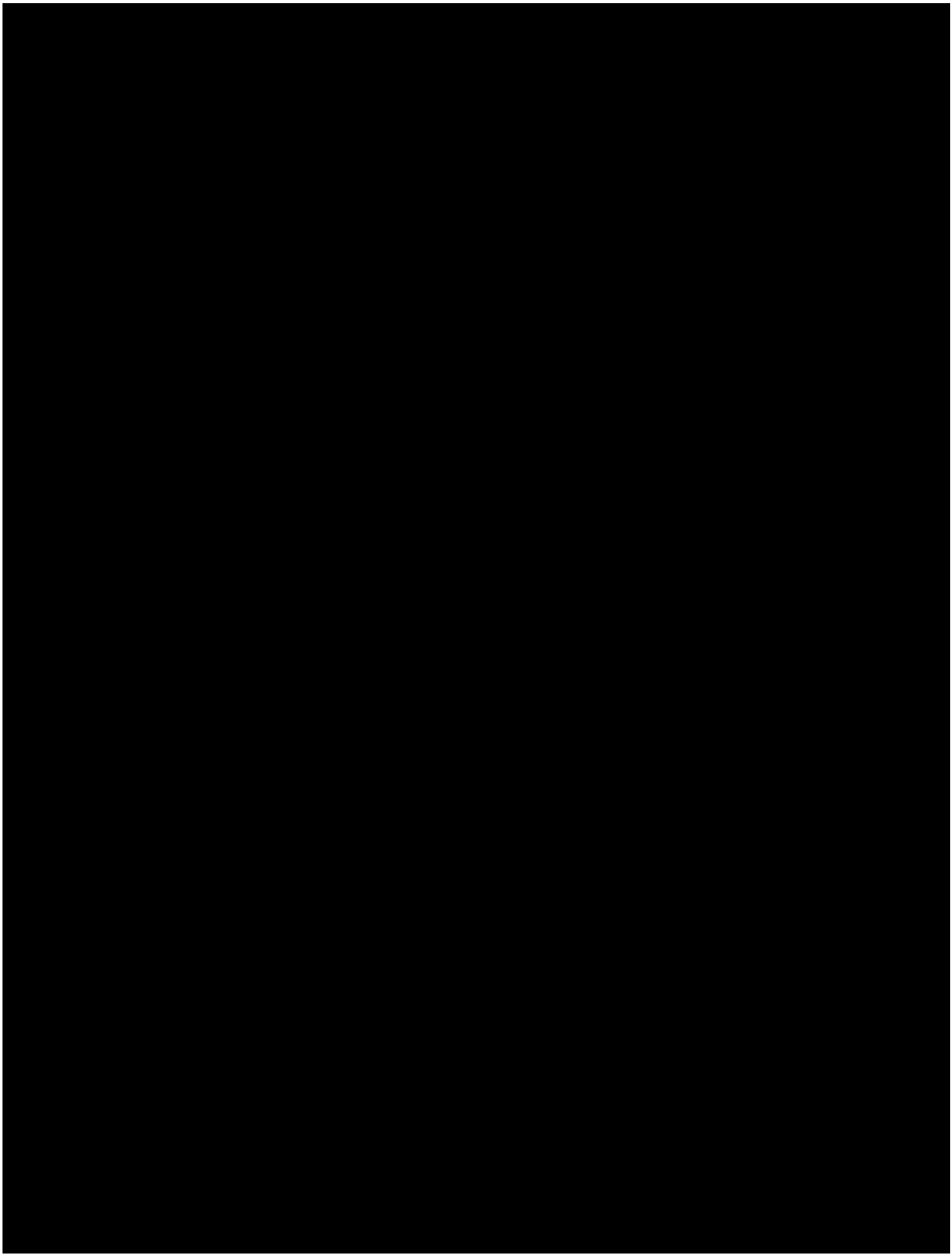
At 12 weeks (or earlier if clinically indicated) after a response of IR is determined by the Investigator, repeat imaging is mandatory and PD must be confirmed or refuted based LYRIC follow-up criteria for IR. PD should be reported if the SPD of the target lesion has increased further, with the considerations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

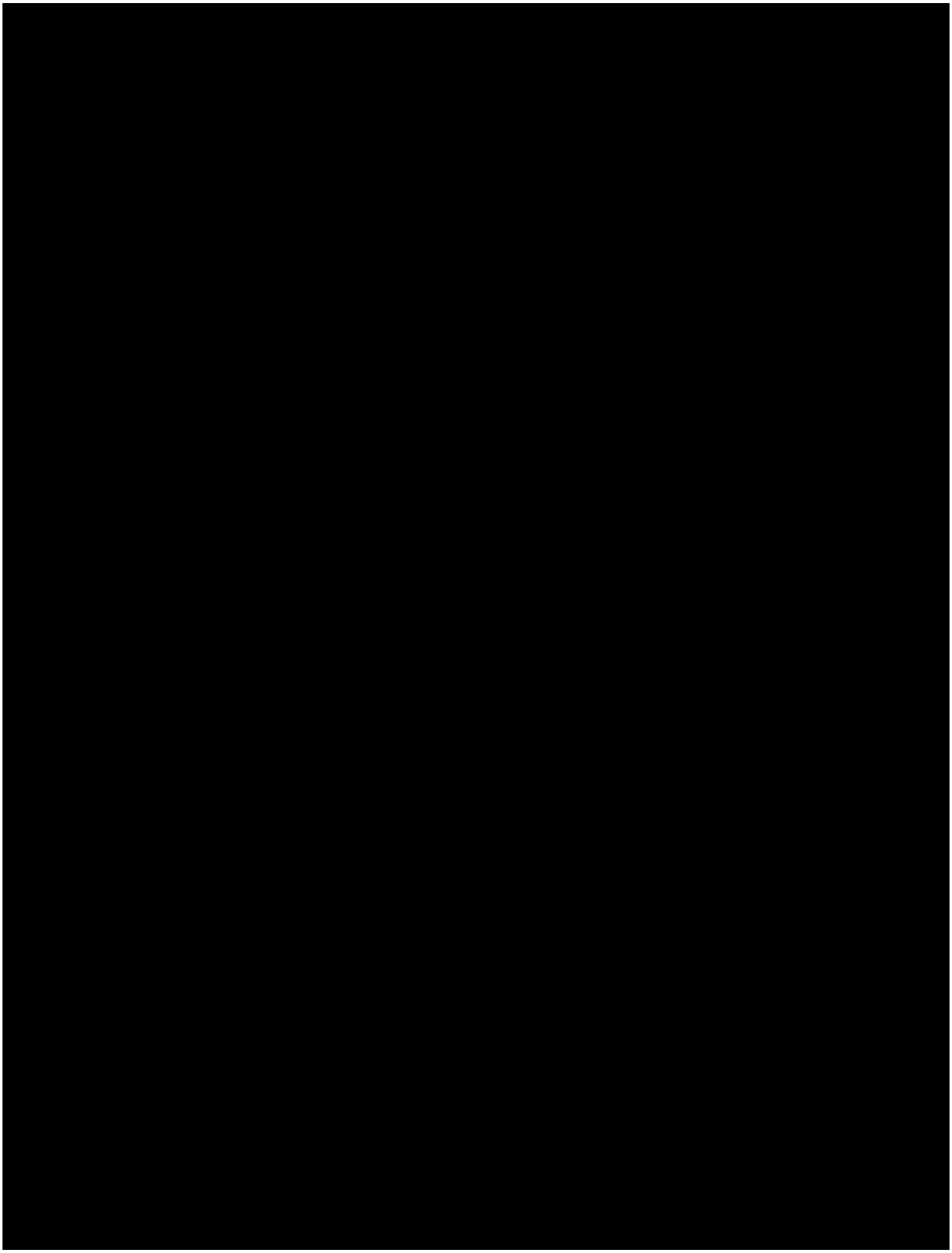
- In the case of IR1, the comparison should be between the first IR1 and the current SPD, with an increase of >10% constituting PD. In addition, there should be an increase of >5 mm (in either dimension) of at least 1 lesion for lesions <2 cm, and 10 mm for lesions >2 cm, to be consistent with the Lugano classification (Cheson 2014). 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 >5mm in either dimension of at least 1 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.

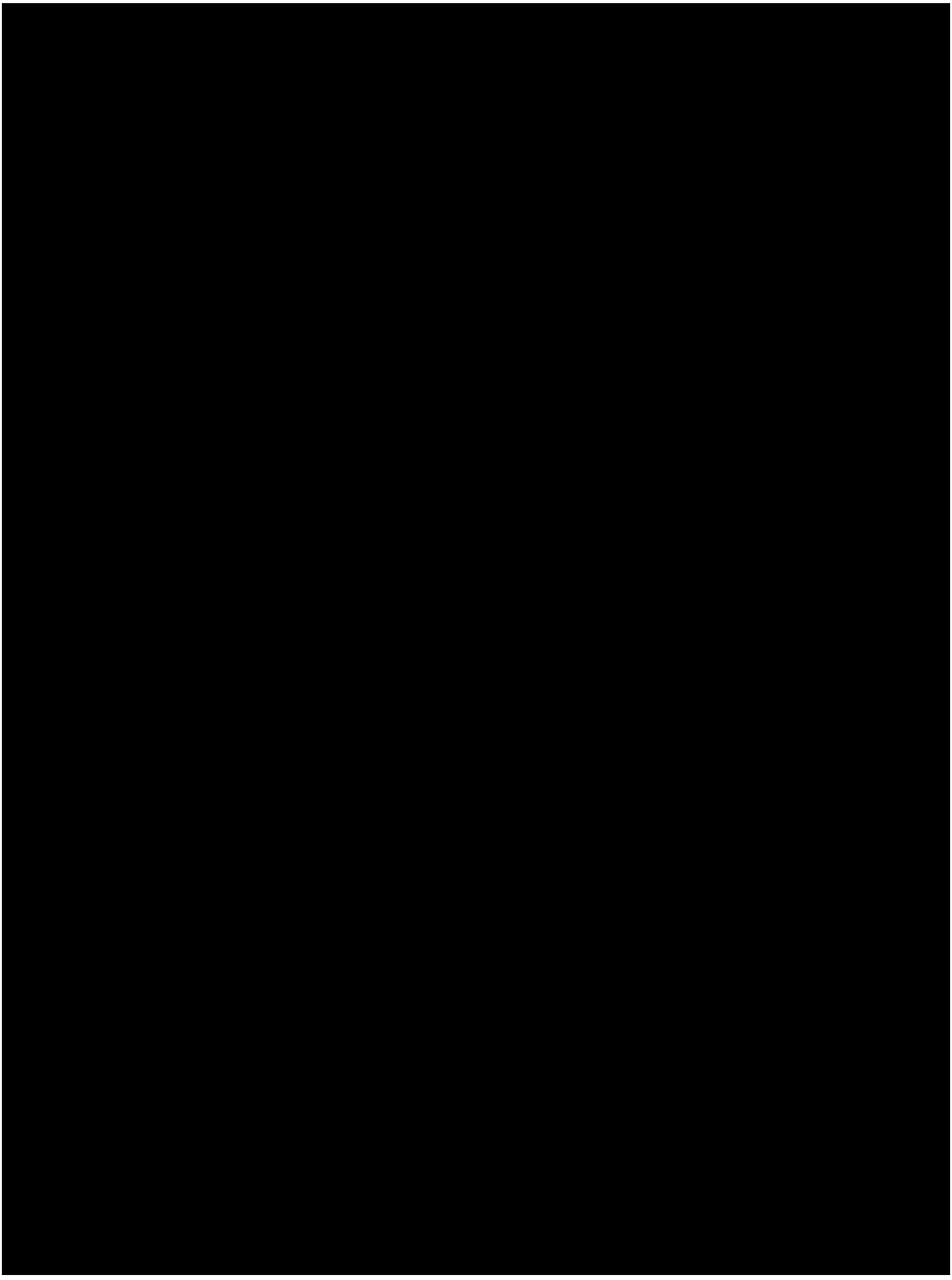
APPENDIX K: RESPONSE EVALUATION CRITERIA IN LYMPHOMA

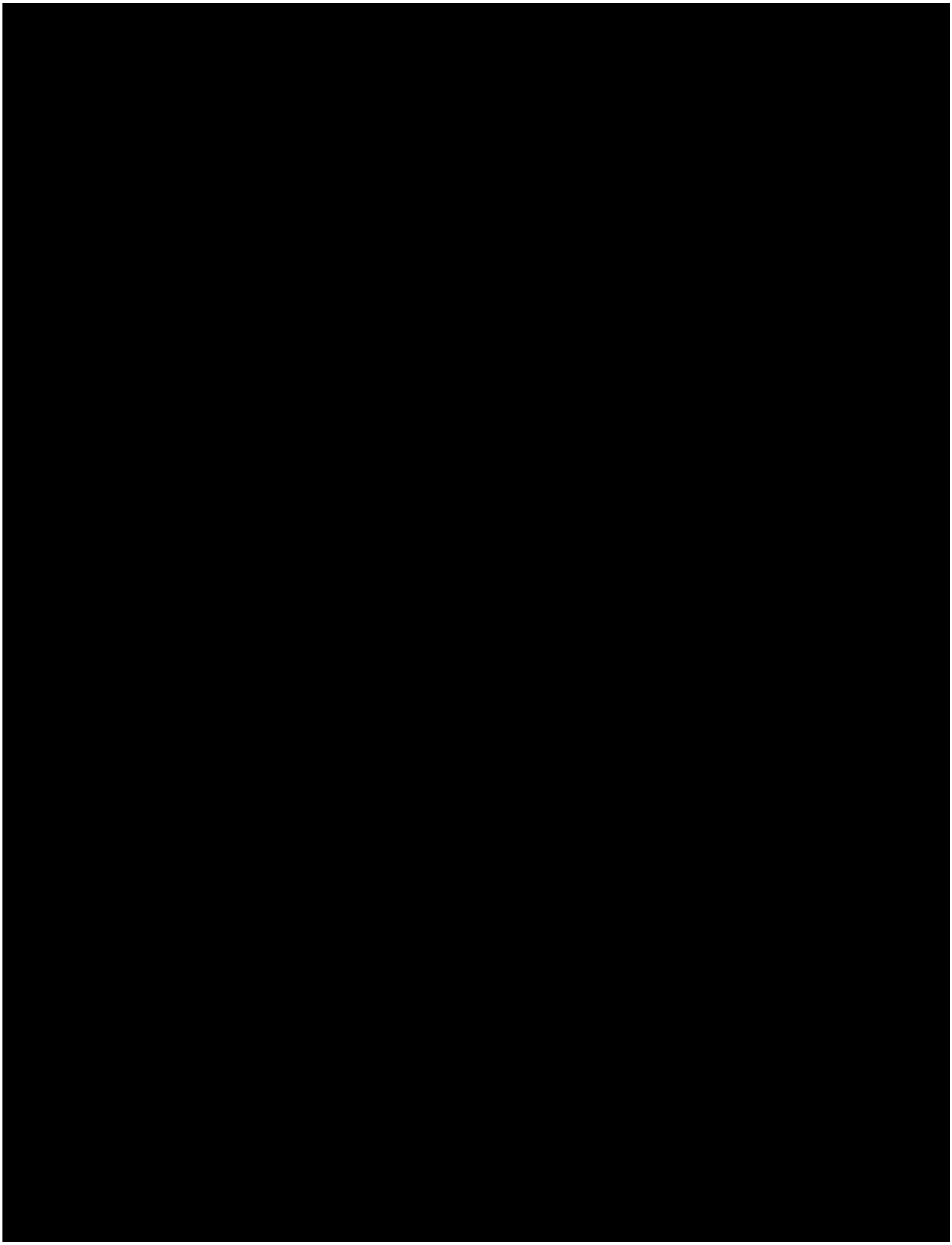
(See next page)

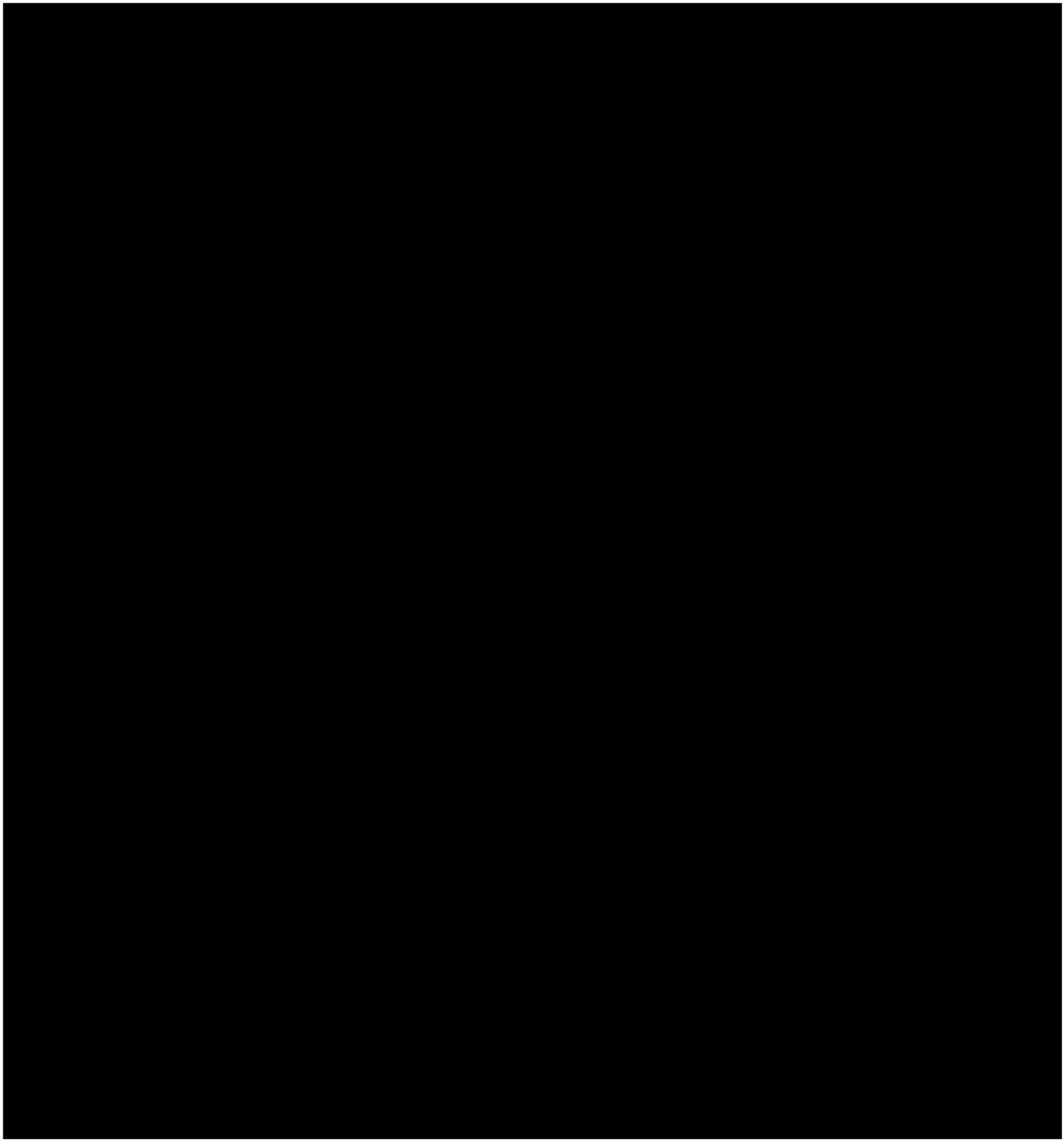












APPENDIX L: HISTOLOGIC SUBTYPES OF PTCL

Patients with any of these histologic subtypes of PTCL from the WHO 2016 classification of lymphomas (Swerdlow 2016) may be eligible for Part F of the 35-15 study:

- Peripheral T-cell lymphoma (PTCL), not otherwise specified
- Anaplastic large-cell lymphoma (ALCL), ALK+
- Anaplastic large-cell lymphoma (ALCL), ALK2
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the GI tract
- Hepatosplenic T-cell lymphoma
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal PTCL with TFH phenotype
- Breast implant–associated anaplastic large-cell lymphoma

In addition, cases of T cell leukemias with measurable disease may be eligible on a case by case basis. Contact the medical monitor for review of these cases.

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90.

APPENDIX M: INTEGRATED PET AND CT RESPONSE ACCORDING TO MODIFIED LUGANO CRITERIA PER BICR

PET Response	CT Response		Integrated Response
CR	Any		CR
PR	CR, PR		PR
	Non-CR, Non-PR		SD
SD	Any		SD
PD	Any		PD
Not done or Not evaluable	Prior PET response[a] CR non-CR Any	CT Response Non-PD Non-PD PD	 CR[b] NE PD
No FDG-avid disease at baseline [c]	No disease present (NE) PD		NE PD

NE=not evaluable.

a "Prior PET response" refers to the latest prior PET assessment that was evaluable. PET responses may be carried forward over multiple CT assessments.

b A CR according to PET will be carried forward irrespective of CT response, until CT shows PD or is assessed as NE.

c Per protocol all patients must have FDG-avid disease at baseline.

APPENDIX N: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "A phase 2 open-label study of brentuximab vedotin in front-line therapy of Hodgkin lymphoma (HL) and CD30-expressing peripheral T-cell lymphoma (PTCL) in older patients or patients with significant comorbidities ineligible for standard chemotherapy".

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 O: DOCUMENT HISTORY

Version	Date
Original	07-May-2012
Amendment 1	19-Nov-2012
Amendment 2	08-May-2013
Amendment 3	12-Nov-2013
Amendment 4	21-Aug-2014
Amendment 5	18-Jan-2015
Amendment 6	22-Apr-2015
Amendment 7	30-Jul-2015
Amendment 8	30-Oct-2015
Amendment 9	31-Oct-2016
Amendment 10	07-Sep-2018
Amendment 11	11-Apr-2019
Amendment 12	06-Nov-2019
Amendment 13	05-May-2020

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Section 1.4	Added a statement to note a segment of the patient population with concomitant organ dysfunction including renal impairment.	Provide background for allowing patients with renal impairment to enter the study at a reduced dose of 1.2 mg/kg brentuximab vedotin.
Sections 3.1, 3.2.1, and Synopsis	Added dose of 1.2 mg/kg for patients enrolling on study with estimated creatinine clearance <30 mL/min.	Specify dose for patients enrolling with estimated creatinine clearance <30 mL/min.
Section 3.1, Figure 1, Section 6.4, Synopsis	Added restage computed tomography (CT) scan at Cycle 16 only for patients eligible for continued treatment beyond 16 cycles.	Specify timing of restage assessments for patients continuing on treatment beyond 16 cycles.
Section 3.1, Figure 1, Section 6.5, Synopsis	Added CT and positron emission tomography (PET) scanning frequency for patients continuing beyond 16 cycles.	Specify timing of restage assessments for patients continuing on treatment beyond 16 cycles.
Section 3.1, Figure 1, Section 6.4, Section 7.2	PET scans performed as part of institutional standard of care may be collected at any time during the study, as available.	Clarify collection of PET scans performed per institutional standard of care.
Section 3.2.2	Added MMAE PK and safety information from the SGN35-008B (special populations) study and designation of a 1.2 mg/kg dose for patients with estimated creatinine clearance <30 mL/min.	Provide rationale for selection of 1.2 mg/kg dose for patients with estimated creatinine clearance <30 mL/min.
Section 4.1	Removed inclusion criterion No.6e: ~~Estimated creatinine clearance >50 mL/min (as determined by the Cockroft-Gault formula)~~	Allow enrollment of patients with estimated creatinine clearance <50 mL/min.
Section 4.1, Synopsis	Added exclusion criterion No.7: Kidney disease requiring ongoing dialysis.	Patients will not be excluded due to renal impairment, with the exception of patients who require ongoing dialysis.
Section 4.2, Synopsis	Exclusion criterion No.1 was clarified as follows: Symptomatic neurologic disease compromising instrumental activities of daily living (IADLs) or requiring medications (e.g., ≥ Grade 2 neuropathy [per the National Cancer Institute Common Terminology Criteria for Adverse Events, NCI CTCAE], Version 4.03), with the exception of patients with mild cognitive impairment who are still able to perform age-appropriate IADLs, even if on medication.	Clarification
Section 5.2.6, Table 1	Added dose modification guidance for patients dosed at 1.2 mg/kg due to renal impairment.	To detail conditions for dose increase to 1.8 mg/kg and to prohibit dose reductions below 1.2 mg/kg.
Section 5.2.6, Table 1	Added recommendation to consider dose modification for patients receiving 1.8 mg/kg who then develop renal impairment with	To allow dose reduction to 1.2 mg/kg prior to Grade 4 toxicity.

Section(s)	Change	Rationale
	estimated creatinine clearance consistently below 30 mL/min.	
Section 5.2.9	Removed specification of infusion bag types with no-known incompatibilities with brentuximab vedotin.	This information is provided in the Pharmacy Manual.
Section 6.3.1	Added reference to Section 7.4 for ATA collection time points.	Clarification
Section 7.1, Section 7.5	Added fresh tissue collection.	Allow the collection of a fresh tissue sample for central analysis if archived tissue is unavailable or of insufficient quantity for central analysis.
Section 7.2	Added the following: With either CT/PET or diagnostic CT, it is preferred that both oral and intravenous contrast are used, except when contraindicated or not feasible.	Clarification
Section 7.4, Table 2	Updated ATA collection frequency as follows: Antitherapeutic antibodies (ATA) to brentuximab vedotin will also be measured predose on Cycles 1, 2, 4, ~~8, 12, 16~~, every 4 cycles thereafter, and EOT.	Add ATA sampling for patients that may continue on study beyond 16 cycles.
Section 7.6.2	Corrected the components of the hematology panel to be assessed as follows: The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), ~~bands, blasts,~~ red blood cell count, platelet count, and hemoglobin/hematocrit.	Measurement of bands and blasts as part of the hematology panel does not pertain to HL patients.
Appendix A	Updated study schedule to include changes in CT and PET scanning frequency. Added study activities for those patients continuing on study beyond Cycle 16.	Reflect changes in study schedule incorporated in Amendment 1

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Synopsis and Section 9.1	Added 10 patients to the number of planned patients for a total of 30 evaluable patients to be enrolled on this study.	To further characterize the safety and efficacy of brentuximab vedotin in this patient population.
Synopsis and Section 7.2	Added clinical disease progression per investigator to the definition of progressive disease.	To specify that disease progression may be documented by either radiographic (Cheson 2007) or clinical evaluation.
Sections 6.2, 6.3, and Appendix A	Expanded the window for the baseline CT and PET scans.	To provide operational flexibility for sites to perform/collect CT and PET scans.
Sections 6.2.1, 6.3.1, 6.7, 7.6.2, and Appendix A	Specified for clarity that the lactate dehydrogenase (LDH), phosphorus, and uric acid tests are to be included in the serum chemistry panel.	Clarification
Sections 6.4, 6.5, and Appendix A	Added 2 additional days to the window for restage assessments and that restage assessments are to be completed prior to dosing for the subsequent treatment cycle.	Since each 21-day cycle has a 2-day window for dosing, adding 2 days to the window for restage assessments allows patients to be assessed in the appropriate time period.
Section 7.6.1.2	Added reporting period for pregnancies occurring in a patient on study or the partner of a male patient on study.	To ensure that all pregnancies occurring within 6 months of the last dose of study drug are reported.
Section 9.3.1.2	Clarified that adjustments for covariates will be considered in the association analyses.	Clarification
Section 9.3.1.3	Revised definition of patients who will be counted as non-responders.	Since the definition of progressive disease now includes clinical disease progression per investigator, only patients whose disease response cannot be assessed will be counted as non-responders instead of patients who do not have post-baseline response assessments.
Section 9.3.1.7	Redefined the per-protocol analysis set	To ensure that the per-protocol analysis set is defined as a subset of the efficacy-evaluable analysis set since the per-protocol analysis set will be used for efficacy analyses.
Section 9.3.1.9	Changed ‘final’ analysis to ‘primary’ analysis occurring when the last patient completes Cycle 8 restage.	Correction
Throughout document	Minor administrative changes	For clarity and consistency

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Sections 1, 2.1, 2.3, 2.4, 3.1, 3.2, 3.2.1, 3.2.2, 5.1, 5.2.2, 5.2.2, 6.3.1, 7.6.1.1, 9.1, 9.3.1, 9.3.1.9, 9.3.2, 9.3.8.2, Figure 1, Synopsis, and Appendix A	Added Part B to enroll and treat with combination treatment of brentuximab vedotin and dacarbazine in approximately 20 efficacy-evaluable patients.	To describe a new study cohort.
Sections 1.4, 1.5, and 3.2	Added the background and rationale for evaluating brentuximab vedotin in combination with dacarbazine for the frontline treatment of HL patients aged 60 and above.	To provide data from prior studies showing that preclinical and clinical studies have demonstrated efficacy of the combination of brentuximab and dacarbazine with a manageable safety profile.
Section 3.2.1	Specified that enrollment in Part A will halt once Part B is open for enrollment at a site or a total of 30 patients have been enrolled in Part A	To clarify method of assigning patients to treatment groups based on addition of Part B.
Sections 3.1, 3.2.1, 3.2.2, and 0, and Synopsis	Added that renal excretion is a significant route of dacarbazine elimination; therefore, a dacarbazine dose reduction of ~30% is recommended for patients with estimated creatinine clearance <30 mL/min. Added other dose modifications for dacarbazine, including discontinuation of treatment.	To increase patient safety for those enrolling with estimated creatinine clearance <30 mL/min and to allow other dose modifications of dacarbazine per institutional standard of care or per the package insert.
Section 4.1 and Synopsis	Made the following change to inclusion criteria: 3. Patients must be ineligible for or have declined initial conventional <u>combination</u> chemotherapy for Hodgkin lymphoma (e.g., ABVD, BEACOPP) after being informed of the potential benefits and risks of available treatment options.	To clarify that conventional chemotherapy in the inclusion criteria means conventional combination therapy since the chemotherapeutic agent dacarbazine was added to study treatment for Part B.
Section 4.2 and Synopsis	Made the following change to exclusion criteria: 6. Known hypersensitivity to any excipient contained in the drug formulation of brentuximab vedotin <u>(Parts A and B) or dacarbazine (e.g., mannitol) (Part B only).</u>	To exclude patients from Part B if they have a known hypersensitivity to any component of the dacarbazine formulation, specifically mannitol, which is common for sensitivities.
Section 5.2.5	Added that dacarbazine dosing (if applicable) should be held if PML is suspected and permanently discontinued if PML is confirmed.	For safety of patients in whom PML may be suspected or confirmed.

Section(s)	Change	Rationale
Sections 5.3, 5.3.1, 5.3.2, 5.3.3, 5.3.4, 5.3.5, 5.3.5, 5.3.6, 5.3.7, and 5.3.8	Added dacarbazine description, method of procurement, dose and administration details, required premedication and postmedication, management of infusion reactions, dose modifications, storage and handling, packaging and labeling, and preparation information,	To provide instructions and details for additional study treatment, dacarbazine.
Section 5.3.2	Added the drug procurement method for dacarbazine.	To specify that sites will procure the commercially-available dacarbazine.
Sections 5.3.4, 5.4, 5.5.2, and 5.5.3	Specified that for Part B patients, antiemetics or other premedications should be considered for the prevention of nausea and vomiting prior to initiating the dacarbazine infusion.	To allow investigators to provide patients with appropriate premedications to minimize patient discomfort following treatment with dacarbazine.
Section 5.5.2	Added that routine vaccine prophylaxis is permitted.	To allow patients to receive routine vaccines (e.g., flu vaccine).
Section 5.5.2 and Figure 1	Specified that for Part B patients, combination treatment with brentuximab vedotin and dacarbazine may be followed by consolidative RT and that single-agent brentuximab vedotin may be resumed 2 weeks after RT.	To allow consolidated RT as part of the frontline combination regimen.
Section 5.5.3	Clarified that prohibited systemic anti-neoplastic therapy does not include dacarbazine for patients enrolled on Part B of the study.	Clarification
Section 9.2.8	Added that ATA incidence rate is relevant to patients who develop ATA to brentuximab vedotin.	Clarification needed due to addition of combination treatment.
Section 9.3.1.7	Revised analysis sets to include patients who receive any amount of brentuximab vedotin.	Clarification needed due to addition of combination treatment.
Throughout protocol	Specified Part B where applicable.	To account for new cohort
Throughout protocol	Administrative changes and corrections.	To improve clarity and achieve consistency.

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Sections 1, 2.1, 2.3, 2.4, 3.1, 3.2, 3.2.1, 3.2.2, 5.1, 5.2.2, 6.3.1, 7.6.1.1, 9.1, 9.3.1, 9.3.1.9, 9.3.2, 9.3.8.2, Figure 1, Synopsis, and Appendix A	Added Part C to enroll and treat with combination treatment of brentuximab vedotin and bendamustine in approximately 20 efficacy-evaluable patients.	To describe a new study cohort.
Sections 1.4, 1.5, and 3.2	Added the background and rationale for evaluating brentuximab vedotin in combination with bendamustine for the frontline treatment of HL patients aged 60 and above.	To provide data from prior studies showing that preclinical and clinical studies have demonstrated efficacy of the combination of brentuximab and bendamustine with a manageable safety profile.
Section 3.1	A new paragraph has been added to describe how a Safety Monitoring Committee (SMC) will be responsible for monitoring patient safety in Part C of the study.	To provide details regarding how safety will be monitored for patients in Part C.
Section 3.2.1	Specified that only one part of the study may be open at a time and certain parts will take priority for enrollment.	To clarify method of assigning patients to treatment groups based on addition of Part C.
Sections 3.1, 3.2.1, 3.2.2, and 5.4.5, and Synopsis	Added dose modifications for bendamustine, including discontinuation of treatment.	To allow other dose modifications of bendamustine per institutional standard of care or per the package insert.
Section 4.1	Made the following changes to inclusion criterion No.6: c. serum bilirubin ≤2X upper limit of normal (ULN) or ≤3X ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma; <u>patients enrolled in Part C must have serum bilirubin ≤1.5X ULN (per bendamustine prescribing information)</u> d. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3X ULN or ≤5X ULN for patients with documented hepatic involvement with lymphoma; <u>patients enrolled in Part C must have ALT or AST ≤2.5X ULN (per bendamustine prescribing information)</u> e. <u>creatinine clearance ≥40 mL/min (Part C only, per bendamustine prescribing information)</u>	To clarify that baseline laboratory data in the inclusion criteria is different for Part C, based on prescribing information for bendamustine.
Section 4.2 and Synopsis	Made the following change to exclusion criteria: 6. Known hypersensitivity to any excipient contained in the drug formulation	To exclude patients from Part C if they have a known hypersensitivity to any component of the bendamustine formulation, including mannitol.

Section(s)	Change	Rationale
	of brentuximab vedotin, dacarbazine (Part B only), or bendamustine (Part C only) (e.g., mannitol).	
Section 5.6	Moved the information regarding the management of adverse events (specifically infusion reactions and PML) to a new section. Added that bendamustine dosing (if applicable) should be held if PML is suspected and permanently discontinued if PML is confirmed. Added information regarding infusion reactions related to bendamustine.	For safety of patients in whom PML may be suspected or confirmed and who may experience infusion reactions with bendamustine.
Sections 5.3, 5.3.1, 5.3.2, 5.3.3, 5.3.4, 5.3.5, 5.3.6, 5.3.7, and 5.3.8	Added bendamustine description, method of procurement, dose and administration details, required premedication and postmedication, management of infusion reactions, dose modifications, storage and handling, packaging and labeling, and preparation information,	To provide instructions and details for additional study treatment, bendamustine.
Section 5.3.2	Added the drug procurement method for bendamustine.	To specify how sites will procure the commercially-available bendamustine.
Sections 5.3.4, 5.4, 5.5.2, and 5.5.3	Specified that for Part C patients, premedications should be considered for the prevention of nausea and vomiting, infusion reactions, and myeloid growth colony-stimulating factor prior to initiating the bendamustine infusion.	To allow investigators to provide patients with appropriate premedications to minimize patient discomfort following treatment with bendamustine.
Section 5.5.2 and Figure 1	Specified that for Part C patients, combination treatment with brentuximab vedotin and bendamustine may be followed by consolidative RT and that single-agent brentuximab vedotin may be resumed 2 weeks after RT.	To allow consolidated RT as part of the frontline combination regimen.
Section 9.3.9	Information has been added regarding interim analysis and the SMC.	To specify that an SMC will be responsible for monitoring patient safety in Part C of the study.
Section 5.5.3	Clarified that prohibited systemic anti-neoplastic therapy does not include bendamustine for patients enrolled on Part C of the study.	Clarification
Throughout protocol	Specified Part C where applicable.	To account for new cohort
Throughout protocol	Administrative changes and corrections.	To improve clarity and achieve consistency.

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Section 4.1	Changed inclusion criterion.6d for Part C to require that patients have both ALT and AST ≤2.5X ULN to enroll.	Correction.
Section 5.4.1	Changed description and vial sizes of bendamustine.	Updated to align with new liquid formulation and vial sizes released by the manufacturer in November 2014.
Section 5.4.2	Deleted that for US sites, bendamustine will be provided by the sponsor.	To provide flexibility for procurement of bendamustine for Part C of the study; allowing either the sponsor or sites to purchase drug if needed.
Section 5.5.3	Added that bendamustine is not a prohibited anti-neoplastic therapy for patients in Part C.	Correction.
Synopsis and Section 7.4	Changed “blood” concentrations to “serum or plasma” concentrations of brentuximab vedotin ADC and MMAE.	Correction.

Summary of Changes in Amendment 6

Section(s)	Change	Rationale
Synopsis, Sections 3, 5.4.3, and 5.4.5	Lowered the starting dose of bendamustine in Part C from 90 mg/m^2 to 70 mg/m^2	Additional safety precaution
Cover page	Changed the medical monitor for the study	Administrative change
Cover page, Sections 7.6.1.2 and 7.6.1.4	Indicated SAE forms can be emailed to the sponsor	Administrative change

Summary of Changes in Amendment 7

Section(s)	Change	Rationale
Synopsis and Section 9.1	Increased the number of patients treated with the combination of brentuximab vedotin and bendamustine in Part C of the study to 30 evaluable patients.	To ensure collection of sufficient safety and efficacy data on approximately 20 patients treated with brentuximab vedotin and the reduced dose of bendamustine at 70 mg/m^2.
Section 6.3.1and Appendix A	Specified which study procedures must be performed prior to dosing and after dosing.	Clarification
Sections 9.1and 9.3.1.5	Corrected methods in which statistical parameters will be presented.	Correction
Section 9.3.1.7	Added that patients included in the efficacy evaluable analysis set are ones with the histology of classical HL.	Clarification
Appendix A	Added to the Study Schedule table that PD assessments are to be done at EOT.	Correction to align with Section 6.7.

Summary of Changes in Amendment 8

Section(s)	Change	Rationale
Synopsis, Sections 1.6, 3.1, 3.3, 3.4.2, 5.4, 6.3.1, and 6.3.2	Added that enrollment on Part C (combination treatment of brentuximab vedotin and bendamustine) has been suspended, treatment with bendamustine has been stopped, and single-agent brentuximab vedotin may be continued for patients who tolerate the therapy and have demonstrated clinical benefit.	Based on SMC recommendation and sponsor decision, combination was not deemed to be a low toxicity alternative to conventional chemotherapy for HL in this fragile patient population.

Summary of Changes in Amendment 9

Section(s)	Change	Rationale
Sections 1, 2.2, 2.3, 2.4, 3.1, 3.4.1, 4, 5.1, 5.2.2, 5.2.3, 5.6.3, 5.7.2, 6.1, 7.8, 9.1, 9.3.1, 9.3.1.9, 9.3.2, Figure 1, Synopsis, and Appendix B	Added Part D to enroll and treat with combination treatment of brentuximab vedotin and nivolumab in approximately 20 efficacy-evaluable patients.	To describe a new study cohort.
Sections 1.6 and 1.8	Added the background and rationale for evaluating brentuximab vedotin in combination with nivolumab for the frontline treatment of HL patients aged 60 and above.	To provide data from prior studies showing that preclinical and clinical studies have demonstrated efficacy of the combination of brentuximab and nivolumab with a manageable safety profile.
Sections 2.3, 2.4.3, 3.1, 6.3.7, 6.5, 7.2.2, 7.6, and 0	For Part D of the study, disease response will be assessed using the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014) and Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016).	To provide consistent criteria for determination of response and to align response evaluation with the most recently available published standards for evaluating response in Hodgkin lymphoma.
Sections 3.2.2, 5.5.4, 5.5.5, 7.7, and 9.3.10	Added descriptions of how a Safety Monitoring Committee (SMC) will be responsible for monitoring patient safety in Part D of the study.	To provide a description of how safety will be monitored for patients in Part D.
Sections 3.3, 4, 4.1, 4.3.2, and 9.3.1.5	Added retreatment option for patients on Part D who progress after discontinuing treatment.	To provide the retreatment option for patients who achieve a CR or PR on Part D, but later progress.
Section 3.4.2	Added rationale for selection of doses for Part D.	To describe approved dose levels of nivolumab and results from prior studies showing efficacy at the 3 mg/kg dose level.
Section 4.1	Made the following changes to the inclusion criterion No.5: An Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤3 <u>(Parts A, B, and C) or ≤2 (Part D).</u>	To clarify that patients in Part D must have at least an ECOG Performance Status of 2 to be eligible.
Section 4.1	Made the following changes to the inclusion criteria No.6: b. platelet count ≥50,000/μL <u>(no platelet transfusions for prior 14 days for Part D only)</u> c. serum bilirubin ≤2X upper limit of normal (ULN) <u>(Parts A and B) or ≤1.5X ULN (per bendamustine and nivolumab prescribing information) (Parts C or D);</u> or ≤3X ULN for patients with Gilbert's disease or	To clarify that baseline laboratory data in the inclusion criteria is different for Part D, based on prescribing information for nivolumab for some parameters or for further safety precautions.

Section(s)	Change	Rationale
	documented hepatic involvement with lymphoma (all parts); ~~patients enrolled in Parts C or D must have serum bilirubin ≤1.5X ULN (per bendamustine and nivolumab prescribing information)~~ d. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3X ULN or ≤5X ULN for patients with documented hepatic involvement with lymphoma; patients enrolled in Parts C or D must have ALT and AST ≤2.5X ULN (per bendamustine prescribing information for Part C) e. hemoglobin ≥8.5 g/dL (no red blood cell transfusions for prior 7 days) (Part D only) f. creatinine clearance ≥40 mL/min (Part C only, per bendamustine prescribing information) or ≥30 mL/min (Part D only).	
Section 4.1	Made the following changes to the inclusion criteria No.8: Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last dose of study drug (or 8 months following last dose of nivolumab in Part D; 2 effective contraceptive methods required for Part D).	The half-life of nivolumab is longer than the half-life of brentuximab vedotin, so male patients who have partners of childbearing potential must use contraception for at least 8 months following the last dose of nivolumab (if later than the 6 months following the last dose of brentuximab vedotin). Two contraceptive methods required for additional safety precaution.
Section 4.1	Added inclusion criterion No.10 for Part D: Diffusing capacity of the lungs for carbon monoxide (DLCO) over 60% (adjusted for hemoglobin) (Part D only).	To ensure patients enrolled on Part D have DLCO over 60%.
Section 4.2	Made the following change to exclusion criterion No.6: Known hypersensitivity to any excipient contained in the drug formulation of brentuximab vedotin (all parts), dacarbazine (Part B only), bendamustine (Part C only) (e.g., mannitol), or nivolumab (Part D only).	To exclude patients from Part D if they have a known hypersensitivity to any component of the nivolumab formulation.
Section 4.2	The following exclusion criteria have been added and are applicable to Part D only: 8. History of another primary invasive malignancy that has not been in remission for at least 1 year. 9. Known cerebral/meningeal disease related to the underlying malignancy. 10. Received any prior immune-oncology therapy (e.g., therapies targeting the PD-1, CTLA4, or CD137 pathways). 11. Systemic treatment with either corticosteroids (>10 mg daily prednisone	To provide additional parameters for the patients who are eligible to enroll on Part D of the study.

Section(s)	Change	Rationale
	equivalent) or other immunosuppressive medications within 1 week 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. 12. Positive for hepatitis B by surface antigen expression, or any other positive test for hepatitis B virus indicating acute or chronic infection. 13. 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). 14. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). 15. 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 B) within 6 months prior to the first dose of study drug(s). 16. 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. 17. Active interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. 18. Known history of pancreatitis. 19. Prior allogeneic stem cell transplant 20. 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.	
Sections 5.2.3, 5.5.4, 5.6, 5.6.2, and 5.7.1	Added required premedications for brentuximab vedotin plus nivolumab combination.	To provide prophylactic premedications for potential infusion-related reactions with the combination of brentuximab vedotin and nivolumab. To allow investigators to provide patients with appropriate premedications to minimize patient discomfort following treatment with brentuximab vedotin or nivolumab.

Section(s)	Change	Rationale
Sections 5.2.3, 5.2.4, 5.5.5, 5.5.5.1, 5.5.5.2, and 5.5.5.3	Added dose modifications for brentuximab vedotin plus nivolumab combination, including discontinuation of treatment.	To allow other dose modifications of the combination of brentuximab vedotin and nivolumab.
Sections 5.5, 5.5.1, 5.5.2, 5.5.3, 5.5.4, 5.5.5, 5.5.6, 5.5.7, and 5.5.8	Added nivolumab description, method of procurement, dose and administration details, required pre- and post-medication, dose modifications, storage and handling, packaging and labeling, and preparation information.	To provide instructions and details for additional study treatment, nivolumab.
Section 5.6.2	Specified that for Part D patients, combination treatment with brentuximab vedotin and nivolumab may be followed by consolidative RT and that the combination of brentuximab vedotin and nivolumab may be resumed 2 weeks after RT.	To allow consolidated RT as part of the frontline combination regimen in Part D.
Sections 6.2, 6.2.1, 6.3.1, 6.3.3, 6.3.4, 6.3.5, 6.3.6, 6.3.7, 6.5, 6.6, 6.7, 6.8, 7.7.2, and 7.7.3	Added study activities for Part D.	To support additional eligibility criteria and provide detailed activities required for study conduct of Part D of the study.
Section 6.7	Added an additional safety visit at 100 days (+2 weeks) after the last dose of nivolumab	Because of the longer half-life of nivolumab (~27 days), additional safety data should be collected.
Section 7.1	Added that for Part D only, pulmonary functions tests are to be performed and patients must have DLCO over 60% at screening.	To ensure spirometry is evaluated for each patient and that patients enrolled on Part D have DLCO over 60%.
Section 7.2	Added that nodes or masses should have bidimensional measurements of at least 1.5 cm in the longest axis.	Clarification.
Sections 7.2 and 7.6	Added that patients on Part D who experience PD should consider optional biopsy.	Because pseudoprogression and delayed responses have been experienced by patients treated with immunotherapeutic agents. To ensure that patients who are determined to have disease progression do indeed have disease progression and to perform additional assessments on tumors after disease progression.
Sections 7.4, 9.2.9, 9.3.5.4 and Table 3	Added PK and ATA sampling time points and parameters to be measured for Part D.	To specify when sampling should occur and what parameters are to be measured for Part D.
Sections 7.5 and 9.3.7	Added biomarker studies for Part D.	To specify when sampling should occur for biomarker analyses and what biomarkers are to be measured for Part D.
Section 7.6	Added details for tissue and unstained slides required at screening.	To ensure that patients either have tissue block or unstained slides

Section(s)	Change	Rationale
		available for pathology and baseline biomarker assessment.
Section 7.7	Added safety assessment of pulse oximetry test for Part D.	To evaluate O_2 saturation at selected time points.
Sections 7, 7.7.1.1, 7.7.1.2, and 7.7.1.3	Edited safety definitions and reporting periods for Part D.	To update safety definitions to align with the safety reporting for the combination of brentuximab vedotin and nivolumab.
Appendix A	Changed footnote l to read as follows: CT performed per institutional standard of care or at least approximately every 6 months after Cycle 16 while on treatment. PET scans performed per institutional standard of care. Once a CR is achieved, PET scans are no longer required (see Section 6.5).	Correction.
Throughout protocol	Specified Part D where applicable.	To account for new cohort.
Throughout protocol	Administrative changes and corrections.	To improve clarity and achieve consistency.

Summary of Changes in Amendment 10

Section(s)	Change	Rationale
Cover page	Changed the medical monitor for the study	Administrative change
Sections 4.1 and 7.1	Changed inclusion criteria to a DLCO over 50%	Inclusion criteria broadened
Appendix B	Remove footnote ‘n’ from Nivolumab treatment on Day 1 in the table. Remove ‘Note: thyroid hormones not assessed on Days 8 and 15 of Cycle 1’ from footnote ‘f’.	Corrections to align with Section 6.3.1

Summary of Changes in Amendment 11

Section(s)	Change	Rationale
Cover page and Synopsis, 1, 1.3, 1.4, 1.8, 3.1, 3.4, 4, 4.1, 7.1, and Appendix C	Changed the protocol title and indication to include CD30-expressing PTCL.	Label expansion.
Cover page	Changed the medical monitor for the study.	Administrative change.
Synopsis, Figure 1, Sections 3.1, 3.4, 4.1, and Appendix C	Added Parts E and F to enroll and treat with single-agent treatment of brentuximab vedotin in approximately 30 efficacy-evaluable patients each with classical HL (Part E) or CD30-expressing PTCL (Part F) who are ineligible for combination chemotherapy. For Parts E and F, the assessment will be per BICR.	To describe new study cohorts.
Synopsis, Figure 1, Sections 3.1, 6.3.8, and Appendix C	For Parts E and F, added restage CT and PET scans at baseline, at Cycles 2, 6, 11, and at end of treatment (EOT) approximately 1 month after completion of therapy.	Specify timing of restage assessments for patients in Parts E and F.
Synopsis, Sections 3.1 and 6.8	For Parts E and F, added follow-up CT response assessments every 4 months for 2 years and then per institutional standards.	Specify timing of response assessments for patients in Parts E and F.
Section 1.3	Added the background and rationale for evaluating brentuximab vedotin for the frontline treatment of CD30-expressing PTCL patients 60 years of age and above.	To provide data from prior studies demonstrating efficacy of the treatment of brentuximab vedotin in relapsed or refractory B- and T-cell lymphomas to support an indication of CD30-expressing PTCL in patients with a manageable safety profile.
Section 1.4	Added recent approval language for new indications.	To update experience with brentuximab vedotin.
Section 1.8	Added rationale for the population of patients with classical HL and CD30-expressing PTCL who are 75 years of age and above and those 60 years of age and above who are not candidates for combination chemotherapy and have a depressed ejection fraction or moderately severe renal dysfunction.	To provide rationale for an unmet need in this population.
Synopsis, Sections 2.2, 2.3, 2.4.2, and 2.4.3	Added secondary objective of OS for Parts E and F. Clarified that the additional objective of OS is only for Parts A, B, C, and D.	To characterize the safety and efficacy of brentuximab vedotin in the patient population of Parts E and F.
Synopsis, Sections 2.4.1, 3.1, 9.1, 9.2.1, 9.2.2, 9.2.3, 9.2.4, 9.2.5, 9.2.6, and 9.2.10	For Part D of the study, disease response will be assessed using the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014) and LYRIC (Cheson 2016).	To provide consistent criteria for determination of response.

Section(s)	Change	Rationale
Synopsis, Sections 2.4.1, 3.1, 9.1, 9.2.1, 9.2.2, 9.2.3, 9.2.4, 9.2.5, 9.2.6, and 9.2.10	For Parts E and F of the study, disease response will be assessed using the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014) and the assessment will be per BICR.	To provide consistent criteria for determination of response.
Section 4.1	Made the following changes to the inclusion criterion No.5: An Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤3 (Parts A, B, C, E, and F) or ≤2 (Part D).	To clarify that patients in Parts E and F must have an ECOG Performance Status of at least 3 to be eligible.
Sections 4.1 and 7.7.2	Made the following addition to inclusion criterion No. 6 footnote g (eGFR) and Clinical Laboratory Tests, as applicable: As determined by the Modification of Diet in Renal Disease (MDRD) study equation, an eGFR ≥30 mL/min/1.73m^2 and <50 mL/min/1.73m^2 (Parts E and F only). The eGFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL: • eGFR (mL/min/1.73 m^2)=175 x (Scr)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American) • If Scr is reported in µmol/L, the value should be converted to mg/dL using the conversion factor 0.011312 µmol/L to mg/dL.	To document a change in the calculation method of creatinine clearance with the Cockroft-Gault formula to eGFR with the MDRD study equation, and to update inclusion criteria based on eGFR.
Section 4.1	The following inclusion criteria are applicable to Parts E and F only (meets at least one of the following to define ineligible for combination therapy): 11. Age ≥75 years. 12. Age ≥60 years and a. a confirmed ejection fraction <45% or b. an estimated eGFR ≥30 mL/min/1.73m^2 and <50 mL/min/1.73m^2, as determined by the MDRD study equation as applicable (see Section 7.7.2).	To provide additional parameters for the patients who are eligible to enroll on Parts E and F of the study (i.e., to define the population of ineligible for combination therapy).
Section 4.2	Updated or reorganized Exclusion Criteria Nos. 8-20. Added new No. 21 for Parts E and F only: History of another malignancy within 1 year before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer,	To account for new cohorts.

Section(s)	Change	Rationale
	ductal carcinoma in situ, or Stage I uterine cancer.	
Section 7.7.1.2	The following language replaced the current language: Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported AEs or SAEs.	FDA feedback that terms directly related to the underlying disease progression should be excluded from relevant safety analyses.
Sections 9.1 and 9.3.5.1	Added language to distinguish between the primary efficacy hypothesis for Parts A, B, C, D, and E versus Part F, including the following addition: Part F of this study will evaluate whether ORR for single-agent brentuximab vedotin is >20% using a single-arm study design. The hypothesis to be tested is H0: ORR ≤0.20 versus H1: ORR >0.20.	To define the primary efficacy hypothesis in determination of sample size for each part of the study.
Sections 9.3.1 and 9.3.5.1	For Parts A, B, C, and D, no formal statistical hypothesis for primary efficacy endpoints will be performed. For Parts E and F, formal statistical inference will be conducted and include CIs and P values.	To update the formal statistical hypotheses to be performed for previous and new cohorts.
Section 9.3.1.7	Added CD30-expressing PTCL to the efficacy evaluable analysis set and updated language to clarify all parts related to classical HL.	To account for new cohorts.
Section 9.3.1.9	The primary analysis for Parts E and F will be conducted when all treated patients have been followed for at least 6 months, discontinued from study, or had 30 days safety follow-up after PD, whichever comes first.	To provide timing of analyses for new cohorts.
Section 9.3.5.4	Added new section to describe the data for subsequent therapies.	Clarification.
Throughout protocol	Specified Parts E and F where applicable.	To account for new cohorts.
Throughout protocol	Minor administrative changes and corrections.	To improve clarity and achieve consistency.

Summary of Changes in Amendment 12

Section(s)	Change	Rationale
Synopsis, Sections 2.1, 3.1, 3.4, 4.1, 6.2, 6.6, 7.1, Appendix C, Appendix F, and Appendix G	Specified criteria for patients in Parts E and F to be considered unsuitable or unfit for combination chemotherapy in terms of comorbidity scores (Cumulative Illness Rating Scale [CIRS] and Instrumental Activities of Daily Living [IADL]).	In order to clearly define in which circumstances patients are considered ineligible for combination chemotherapy.
Synopsis, Sections 2.1, 3.1, 3.4, and 4.1	Changed the eligibility criteria for Parts E and F from patients aged ≥60 years to patients aged ≥18 years.	Given that ineligibility for combined chemotherapy in Parts E and F is now defined in terms of comorbidity (CIRS and IADL scores) there is no need to limit the population to older patients, as all age groups can potentially have significant comorbidities.
Synopsis, Sections 3.1 and 4.1	Indicated that patients cannot be eligible for Parts E and F if they declined combination chemotherapy, as opposed to being unsuitable or unfit for chemotherapy.	Comorbidity now defines unsuitable or unfit.
Synopsis, Sections 3.1, 3.4, 3.5.2, and 4.1	For Parts E and F, removed the eligibility criteria requiring that patients have at least 1 of the following: impaired cardiac function defined as a confirmed ejection fraction <45% or moderate renal insufficiency defined as an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m^2 and <50 mL/min/1.73m^2.	The comorbidity-related factors determining ineligibility for combination chemotherapy are now CIRS and IADL.
Synopsis, Sections 3.5.1 and 9.1	The number of patients to be enrolled in Parts E and F was changed from 30 to 50 in each part.	Sample size was increased to accommodate changes in statistical hypotheses.
Synopsis, Sections 3.1 and 6.8	Specified that patients will be followed post-treatment until progression or initiation of further anti-cancer treatment, rather than just until progression.	On-study disease assessments are not applicable once further anti-cancer treatment is initiated.
Synopsis	Rearranged “Efficacy Assessments” section.	To increase clarity regarding disease assessments in each study part.
Synopsis, Sections 9.3.1 and 9.3.5.1	Removed specification that formal statistical hypothesis testing and statistical inference will be performed for the primary endpoint in Parts E and F.	Formal statistical hypothesis testing will not be performed, given that each study part is single-armed.
Section 1	Added text regarding additional contributory mechanisms of action for brentuximab vedotin.	Update to standard description of mechanism of action.
Sections 1.1 and 1.2	Modified, rearranged, and added new text giving background on HL and PTCL.	To take into account the fact that the study population will no longer all be aged >60 years, and to add elements concerning the effect of comorbidities on treatment choice and outcome.
Section 1.7	Updated Study Rationale.	To take into account the changes to eligibility criteria in Parts E and F.

Section(s)	Change	Rationale
Section 2.4	For Parts E and F: changed primary endpoint to ORR per modified Lugano criteria, added a secondary endpoint for ORR per unmodified Lugano criteria, and added an additional endpoint for ORR per Response Evaluation Criteria in Lymphoma (RECIL).	Regulatory feedback indicated that Lugano criteria should be modified in the trial context.
Section 3.1	Specified that EOT is approximately 1 month after discontinuation of study treatment, rather than after completion	Clarification to specify that EOT visit does also occur in patients who do not complete treatment.
Sections 3.1, 6.8, and Appendix C	Changed follow-up after progression or further anti-cancer treatment from 3 months to 4 months in Parts E and F.	To harmonize with the 4-month follow-up before progression.
Section 3.3	Specified that for retreatment in Part D, patients must experience disease progression ≥6 months after last study treatment, and specified the brentuximab vedotin and nivolumab doses to use in retreatment.	For greater clarity on conditions for retreatment.
Section 3.4	Added rationale for use of CIRS and IADL scales in determination of ineligibility for combination chemotherapy.	To establish that these scales correctly identify patients with too high a burden of comorbidities for conventional treatment.
Sections 3.5.1 and 9.1	Specified an enrollment cap of 50% on patients with systemic anaplastic large cell lymphoma (sALCL) in Part F.	In order to ensure that all types of PTCL are adequately represented in the Part F cohort.
Section 4.1	Revised the inclusion criteria concerning patients of childbearing potential and use of contraception.	To take into account that potentially fertile patients <60 years of age will now be enrolled.
Section 4.1	Revised the inclusion criteria for informed consent.	Update to Seattle Genetics standard language.
Section 4.2	Revised the exclusion criteria for hepatitis B.	Update to Seattle Genetics standard language.
Section 5.5.5.2	Added Grade 3 myocarditis as a reason for permanent discontinuation of nivolumab.	Update to nivolumab prescribing information.
Section 5.5.5.3	Revised dose modification criteria for nivolumab in the event of liver function test abnormalities.	Update to nivolumab prescribing information.
Section 5.5.5	Removed specification that SMC could decide that patients receive nivolumab 1 mg/kg.	Update to nivolumab prescribing information.
Section 5.5.7	Revised packaging and labeling information for nivolumab.	Update to nivolumab prescribing information.
Section 5.6.3	Added complementary medications and live/attenuated vaccines to list of prohibited concomitant medications for nivolumab.	Update to nivolumab prescribing information.
Section 5.7.3	Added section on management of overdose.	Update to conform to the Seattle Genetics standard language.

Section(s)	Change	Rationale
Section 6.2 and Appendix C	Specified that ejection fraction needs to be evaluated with 28 days of treatment initiation for Parts E and F.	To have an accurate cardiac baseline in patients with significant comorbidities.
Sections 6.2.1, 7.1, and Appendix C	Removed assessment of Karnofsky performance status from Parts E and F.	Simplification of assessments, as all sites now use ECOG performance status.
Sections 6.2.1, 7.1, and Appendix C	Geriatric assessment removed from Parts E and F	No longer applicable as population is no longer restricted to patients aged >60 years
Sections 6.2.1, 6.6, 7.1, and Appendix C	Added serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy tests for patients of childbearing potential.	To take into account that potentially fertile patients <60 years of age will now be enrolled.
Section 7.2.3 and Appendix C	In Parts E and F, added the use of magnetic resonance imaging (MRI) with and without gadolinium contrast for patients with allergy to CT contrast agents, and use of CT without contract for patients with allergy to both.	To take into account the evaluation of patients with allergies to contrast agents.
Section 7.2.3 and Table 2	Added text and tables to specify how PET and CT response assessments are integrated for modified Lugano criteria and unmodified Lugano criteria.	For clarity.
Section 7.4	Separated the specification of pharmacokinetic, pharmacodynamic, and immunogenicity sampling time points for Parts A to C and Parts E and F into separate tables.	For clarity.
Section 7.6	Added specification that, after completion of the study, biological samples will not be destroyed until applicable regulatory obligations have been met.	Update to conform to the Seattle Genetics standard language.
Sections 7.7.1.1 and 7.7.1.2	Added section and text on drug-induced liver damage.	Update to conform to the Seattle Genetics standard language and regulatory guidance.
Section 8.3	Specified that all source data and study records must also be available for inspection by Institutional Review Board (IRB)/Independent Ethics Committee (IEC).	Update to conform to the Seattle Genetics standard language.
Section 8.5	Changed the name for the group responsible for audits to Research and Development Quality group.	Update to Seattle Genetics organization structure.
Section 9.1	Revised the statistical assumptions for the sample size calculation in Parts E and F, and revised the sample size calculation.	In light of available information, higher assumed true objective response rates (ORRs) for study treatment were justified.
Section 9.3.1.5	Simplified text concerning multiple comparisons.	Clarification.
Section 9.3.5	Specified that the full analysis set will be used to present efficacy analyses for Parts E and F.	Alignment with regulatory guidance.

Section(s)	Change	Rationale
Throughout protocol	In descriptions of the study population, removed specifications such as "aged ≥60 years".	To account for the inclusion of patients aged <60 years in Parts E and F.
Throughout protocol	Minor administrative changes, corrections, clarifications, and rearrangements of text.	To improve clarity and achieve consistency.

Summary of Changes in Amendment 13

Section(s)	Change	Rationale
Title Page	Addition of NCT Number and EudraCT Number	Updated to meet EU Regulatory requirements
Section 1.3	Addition of EMA indications for brentuximab vedotin	Updated to add EMA indications
Section 3.4	Definition of End of Study added	Updated to meet EU Regulatory requirements
Synopsis, Section 4.2	Exclusion Criteria #1 ~~Symptomatic neurologic disease compromising IADLs or requiring medications (e.g., ≥ Grade 2 neuropathy [per the National Cancer Institute Common Terminology Criteria for Adverse Events, NCI CTCAE], Version 4.03), with the exception of patients with mild cognitive impairment who are still able to perform age-appropriate IADLs, even if on medication.~~ Baseline peripheral neuropathy Grade ≥2 (per NCI CTCAE, Version 4.03) or patients with the demyelinating form of Charcot-Marie-Tooth syndrome	Clarification and removal of redundant criteria
Section 4.1	Inclusion Criteria #1Treatment-naive patients with histopathological diagnosis of classical HL, which excludes nodular lymphocyte-predominant HL, (Parts A, B, C, D, and E), or treatment-naive patients with CD30-expressing (≥1%) PTCL (Part F) by local testing. See PTCL histologic subtypes in Appendix L. Patients eligible for retreatment on Part D must have had prior treatment on this study with the combination of brentuximab vedotin plus nivolumab.	Clarification
Section 4.2, Appendix E	Additional information on acceptable contraception methods	Update to meet EU Regulatory requirements. Guidance to investigators that encompasses US and EU contraception requirements.
Section 6.9	Modified section header 6.9 End of Study/End of Follow-Up	Modified section header to distinguish it from Section 3.4 (End of Study)
Section 10	Text added: This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 [R2]; FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil, 2015), and all applicable regulatory requirements.	Updated to meet EU Regulatory requirements
Appendix C	Addition of days for eGFR testing per Sections 6.2.1 and 6.3.1.	Correction
Appendix L	Subtypes of PTCL	Clarification
Appendix M	Table 'Integrated PET and CT responses according to modified Lugano criteria per BICR' moved to Appendix M.	Clarification
Throughout protocol	Minor administrative changes, corrections, clarifications, and rearrangements of text.	To improve clarity and achieve consistency.