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Investigational Product:	Brentuximab vedotin
Brief Title:	Clinical Trial of Brentuximab Vedotin in Classical Hodgkin Lymphoma
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PROTOCOL SYNOPSIS

Protocol Number SGN35-027 **Version** Amendment 7 **Phase** 2	**Product Name** Brentuximab vedotin **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

Multiple Part Clinical Trial of Brentuximab Vedotin in Classical Hodgkin Lymphoma Subjects

Study Objectives – Part A

Primary

- To assess the treatment-emergent febrile neutropenia (FN) rate in subjects with previously untreated, advanced stage, classical Hodgkin lymphoma (cHL) treated with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) and granulocyte colony stimulating factor (G-CSF) primary prophylaxis (G-PP)

Secondary

- To assess the incidence and severity of adverse events of clinical interest (AECI)
- To assess dose intensity, dose reductions, and dose delays related to any component of A+AVD
- To assess primary refractory disease rates
- To assess subsequent anticancer therapy utilization
- To assess end of treatment (EOT) complete response (CR) rates
- To assess physician-reported progression-free survival (PFS) rate at 2 years

Study Objectives – Parts B and C

Primary

- To assess the CR rate at EOT with brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD) in subjects with previously untreated cHL.

Secondary

- To assess the safety and tolerability of AN+AD
- To assess the overall response rate (ORR)
- To assess the duration of response (DOR)
- To assess the duration of complete response (DOCR)
- To assess event-free survival (EFS)
- To assess PFS
- To assess overall survival (OS)

Study Population

Key eligibility criteria include treatment-naïve subjects (aged ≥12 years in the US and aged ≥18 years outside the US) with classical Hodgkin lymphoma (cHL). Part A will enroll subjects with Ann Arbor Stage III or IV cHL. Part B will enroll subjects with Ann Arbor Stage I or II cHL with bulky mediastinal disease (defined as a single node or nodal mass with a diameter ≥10 cm on computed tomography [CT] imaging) or Stage III or IV cHL. Part C will enroll subjects with Ann Arbor Stage I or II cHL without bulky disease. Subjects must have bidimensional measurable disease, as documented by positron emission tomography (PET)/CT or CT imaging, and qualifying baseline laboratory data. Subjects are excluded if they have nodular lymphocyte predominant

HL. Subjects with active cerebral/meningeal disease related to the underlying malignancy, including signs or symptoms of progressive multifocal leukoencephalopathy (PML) or history of PML, are also excluded.

Number of Planned Subjects

Approximately 240 subjects will be enrolled in this study: approximately 40 in Part A, approximately 50 in Part B, and approximately 150 in Part C.

Study Design

This is an open-label, multiple part, multicenter, phase 2 clinical trial. Part A will assess the incidence of febrile neutropenia, efficacy, and dose intensity in subjects receiving G-PP during treatment with A+AVD. Subjects will be treated using institutional standard of care practices for the majority of treatment decisions. A+AVD will be administered as described below on days 1 and 15 of a 28-day cycle, with the addition of G-PP 24–36 hours postdose. Part B will evaluate the efficacy and tolerability of AN+AD in subjects with Stage I or II cHL with bulky mediastinal disease or Stage III or IV cHL. Part C will evaluate the efficacy and tolerability of AN+AD in subjects with Stage I or II cHL without bulky mediastinal disease. AN+AD will be administered as described below. Subjects will receive up to 6 cycles of treatment in Parts A and B. Subjects in Part C will receive 4 cycles of treatment. For Part C, one interim analysis will be performed after approximately 50 subjects have completed response assessment at EOT.

Safety will be monitored by collecting and evaluating information regarding adverse events (AEs) and laboratory test results. The Safety Monitoring Committee consisting of the study medical monitor, drug safety representative, study site investigators, and study biostatistician will evaluate the safety of AN+AD over the course of the study. Disease assessments will be conducted at Cycle 2 (Parts B and C only) and at EOT. Follow up assessments for Part A will occur per institutional standard of care and must include an EOT PET scan. For Parts B and C, disease assessments will be performed during follow-up every 3 months after the EOT visit for the first year, then every 6 months for 2 additional years. Subjects will then continue in follow-up for 2 additional years (5 years total), with physical exams required every 6 months and disease assessments required every 12 months. PET will continue after EOT if CT scan is positive, following the same schedule as CT scans. An additional safety visit will be required for Part B and C subjects 100 days after the last dose of nivolumab or 30 days after the last dose of brentuximab vedotin (concurrent with EOT), whichever is later. **As of Amendment 6, Parts A and B were completed.**

Treatment Product, Dose, and Mode of Administration – Part A

A+AVD treatment consists of brentuximab vedotin 1.2 mg/kg (A) plus doxorubicin 25 mg/m^2 (+A), vinblastine 6 mg/m^2 (V) and dacarbazine 375 mg/m^2 (D). A+AVD will be administered by intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle as follows:

A: Brentuximab vedotin will be administered at 1.2 mg/kg

+A: Doxorubicin will be administered at 25 mg/m^2

V: Vinblastine will be administered at 6 mg/m^2

D: Dacarbazine will be administered at 375 mg/m^2

Brentuximab vedotin will be administered at 1.2 mg/kg IV over approximately 30 minutes.

G-PP will be administered following all doses of A+AVD, beginning with Cycle 1 and continuing throughout all treatment cycles. G-PP will be administered as follows:

- Pegfilgrastim: 6 mg subcutaneous (SC) 24 to 36 hours after A+AVD per dose
- Filgrastim: 5 mcg/kg (300 to 480 mcg, rounded to the nearest vial) SC daily, beginning 24 to 36 hours after A+AVD per dose, for a minimum of 5 days. Additional doses beyond 5 days are at the discretion of the investigator.

Treatment Product, Dose, and Mode of Administration – Parts B and C

AN+AD consists of brentuximab vedotin 1.2 mg/kg (A), nivolumab 240 mg (N), doxorubicin 25 mg/m^2 (A), and dacarbazine 375 mg/m^2 (D). All study drugs will each be administered separately by IV infusions on Days 1 and 15 of each 28-day cycle for up to 6 cycles in Part B and for 4 cycles in Part C.

The study drugs for AN+AD must be administered in the following order: doxorubicin and dacarbazine, followed by brentuximab vedotin, followed by nivolumab. Nivolumab will be administered at least 30 minutes after the end of the brentuximab vedotin infusion.

Duration of Treatment

Subjects will receive up to 6 cycles (approximately 6 months) of treatment with either A+AVD and G-PP (Part A) or AN+AD (Part B); subjects in Part C will receive 4 cycles (approximately 4 months) of treatment with AN+AD.

Efficacy Assessments

For Part A, disease response and progression will be assessed by investigators using the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014). CT scans of chest, neck, abdomen, and pelvis will be conducted at baseline and at EOT. PET scans will be conducted at baseline and EOT.

For Parts B and C, CT scans of the chest, neck, abdomen, and pelvis will be conducted at Baseline, Cycle 2, and EOT. During follow-up, CT scans will be required every 3 months after EOT for a year, followed by every 6 months for 2 years. The final 2 years of follow up will require CT scans once every 12 months. To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline. In Parts B and C, PET scans will be conducted at Baseline, Cycle 2, and EOT. PET will only continue after EOT if CT is positive, following the same schedule as the CT scans.

Disease response and progression will be assessed by investigators using the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2016).

Safety Assessments

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

Statistical Methods

Safety and efficacy endpoints will be summarized with descriptive statistics. For Part A, the rate of FN and its 95% confidence interval (CI) will be presented. For Parts B and C, the CR rate at EOT and its 95% CI will be presented.

Descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages for categorical variables. Time to event endpoints will be analyzed using Kaplan-Meier methodology.

Unless otherwise specified, exact CIs will be presented, calculated at 2-sided 95% level.

The sample size for each part was chosen to provide adequate precision for estimation of the primary endpoint. For Part A, if 4 of 40 subjects have FN, the FN rate and associated 95% exact CI would be 10% (95% CI: 2.8%, 23.7%). For Part B, if 45 of 50 subjects have a CR at EOT, the CR rate at EOT and associated 95% exact CI would be 90% (95% CI: 78.2%, 96.7%). For Part C, if 142 of 150 subjects have a CR at EOT, the CR rate at EOT and associated 95% exact CI would be 95% (95% CI: 89.8%, 97.7%).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
AE	adverse event
AECI	adverse event of clinical interest
ALT	alanine aminotransferase
AN+AD	brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
A+AVD	brentuximab vedotin, doxorubicin, vinblastine, dacarbazine
AVD	doxorubicin, vinblastine, dacarbazine
β-hCG	beta human chorionic gonadotropin
BNP	B-type natriuretic peptide
BV	brentuximab vedotin
CBC	complete blood count
cHL	classical Hodgkin lymphoma
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CYP	cytochrome P450
CZ	Czechia
DILI	drug-induced liver injury
DOCR	duration of complete response
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FEV1	forced expiratory volume in 1 second
FFPE	formalin fixed paraffin-embedded
FFS	failure-free survival
FN	febrile neutropenia
G-CSF	granulocyte colony stimulating factor
G-PP	G-CSF primary prophylaxis

GFR	glomerular filtration rate
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HRS	Hodgkin Reed-Sternberg
HuMAb	humanized monoclonal antibody
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN-γ	interferon gamma
IMAE	Immune-mediated adverse event
IND	investigational new drug
I-O	immuno-oncology
IR	indeterminate response
IRB	institutional review board
IV	intravenous
JCV	John Cunningham virus
LDH	lactate dehydrogenase
LFT	liver function test
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MDRD	Modification of Diet in Renal Disease [study]
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
mPFS	modified progression-free survival
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PET	positron emission tomography
PmD	progressive metabolic disease
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PPS	per-protocol analysis set
PR	partial response
q2wk	every 2 weeks
SAE	serious adverse event
SAP	statistical analysis plan

SC	subcutaneous
Scr	serum creatinine
SD	standard deviation
SD	stable disease
SMC	safety monitoring committee
SPD	sum of the product of the largest diameters
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USP	United States Pharmacopeia

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. Targeted delivery of MMAE to CD30-expressing tumor cells is the primary mechanism of action of brentuximab vedotin. 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.

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

This is an open-label, multiple part, multicenter, phase 2 clinical trial. Part A is designed to evaluate the impact of granulocyte colony stimulating factor (G-CSF) primary prophylaxis (G-PP) administration in the frontline treatment of advanced classical Hodgkin lymphoma subjects (cHL) treated with brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD). Brentuximab vedotin is approved for treatment of previously untreated Stage III or IV cHL subjects in combination with chemotherapy. Subjects will be treated with up to 6 cycles of A+AVD. All subjects will receive G-PP support beginning with Cycle 1, and for every subsequent dose throughout all administered treatment cycles. The components of A+AVD will be administered as described in Section 5.

Part B is designed to evaluate the combination of brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD) as frontline treatment in subjects with advanced cHL (Stage I/II with bulky mediastinal disease [defined as a single node or nodal mass with a diameter ≥10 cm on computed tomography (CT) imaging], or Stage III or IV). Part C is designed to evaluate AN+AD as frontline treatment in subjects with early stage cHL (Stage I/II without bulky mediastinal disease). Subjects will be treated with 6 cycles of A+AVD in Part A, up to 6 cycles of AN+AD in Part B, and 4 cycles of AN+AD in Part C.

The components of AN+AD will be administered as described in Section 5. For both Part B and Part C, after approximately 10 subjects have completed Cycle 2, the Safety Monitoring Committee (SMC) will assess the safety of AN+AD. Safety will be assessed separately for Part B and Part C. An additional SMC meeting will occur after approximately 50 subjects in Part C have completed their end of treatment (EOT) assessment.

For summaries of clinical and non-clinical data, please refer to the brentuximab vedotin Investigator's Brochure, and prescribing information for all other agents.

1.1 Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a neoplasm of lymphoid tissue, 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. In 2018, approximately 8500 new cases of HL were estimated to be diagnosed in the US (Siegel 2018). Approximately 40% of subjects will be diagnosed with advanced HL, defined here as Ann Arbor Stage III or IV disease (Shenoy 2011; Noone 2017). Advanced HL is characterized by supra- and sub-diaphragmatic or more widespread disease. It is associated with diminished survival; the 5 year failure-free survival (FFS) rate for subjects with Stage III/IV HL is 67%, in contrast with an 82% 5 year FFS rate for subjects with Stage I/II HL (Gordon 2013).

The presence of bulky mediastinal disease on chest x-ray has historically been considered a poor prognostic factor in early stage HL (Mauch 1978). Bulky mediastinal disease is often defined by the maximal transverse diameter of the largest lymph node mass ≥ 10 cm, or more than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT, retaining the criteria previously measured with chest x-ray (Cheson 2014). Kumar et al demonstrated that subjects without bulky mediastinal disease showed improved 4-year relapse-free survival on multidimensional CT imaging (using a novel definition of ≥7 cm) vs subjects with bulky disease (94% vs 81%, respectively). This retrospective analysis reviewed 185 subjects with early stage HL treated with chemotherapy alone vs combined modality therapy (Kumar 2016).

1.2 Clinical Experience with Brentuximab Vedotin and A+AVD

Brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine received approval in patients with previously untreated, advanced cHL in the US (Stage III and IV) and Europe (Stage IV) based on the ECHELON-1 trial, an open-label, international, multicenter, randomized Phase 3 clinical trial in subjects with previously untreated Stage III or IV cHL. Subjects were assigned to receive up to six 28-day cycles of treatment with either doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or A+AVD. The primary endpoint of the trial was modified progression-free survival (mPFS), defined as the time to progression, death, or noncomplete response and use of subsequent anticancer therapy, as adjudicated by an independent review committee.

ECHELON-1 demonstrated that treatment with A+AVD, in comparison with standard treatment with ABVD, resulted in a statistically significant improvement in mPFS (Connors 2018). The 2 year mPFS rate in the A+AVD group was 82.1% (95% confidence interval (CI): 78.8, 85.0) vs 77.2% (95% CI: 73.7, 80.4) for the ABVD group; the hazard ratio for progression, death, or modified progression was 0.77 (95% CI: 0.60, 0.98). Additionally, treatment with A+AVD resulted in lower incidence of pulmonary toxicity (1% vs 3% treated with ABVD). However, the incidence of neutropenia, including ≥ Grade 3 neutropenia and febrile neutropenia (FN), and rates of ≥ Grade 3 infections, were higher in the A+AVD treatment group than in the ABVD treatment group. The prevalence of neutropenia and FN was mitigated in a sub-set of subjects who received G-PP (29% vs 70% without G-PP, and 11% vs 21% without G-PP, respectively) (Straus 2018a). This resulted in the independent data monitoring committee's recommendation of primary prophylaxis with G-CSF and the recommendation for the use of G-PP beginning in Cycle 1 in the product labeling. Peripheral neuropathy (PN) was reported for 67% of subjects treated with A+AVD and 43% of subjects treated with ABVD. Grade 3 neuropathy was reported for 10% of A+AVD-treated subjects and 2% of ABVD-treated subjects.

Recent data from Abramson et al of 34 subjects with previously untreated Stage I/II cHL with non-bulky mediastinal disease showed a 100% complete response (CR) rate at EOT with brentuximab vedotin, doxorubicin, and dacarbazine. Additionally, the study reported progression-free survival (PFS) and overall survival (OS) rates of 100% at the time of last follow up (median duration 15 months). These data suggest that vinblastine may not be required for efficacy (Abramson 2018). Furthermore, toxicity was notable for a low incidence of peripheral neuropathy (56%, consisting of Grade 1 or 2 only). Eight of 34 subjects (24%) had neutropenia, but only 2 subjects (6%) had Grade 3 neutropenia; there were no cases of Grade 4 neutropenia or febrile neutropenia. No subject received growth factor support.

1.3 Clinical Experience with Nivolumab

The combination of brentuximab vedotin and nivolumab appears to be active and well tolerated in cHL. In one trial in 62 subjects in the first salvage setting, the combination produced a 61% CR rate (Herrera 2018) and subjects were able to undergo subsequent stem cell transplant. Adverse events (AEs) were mostly Grades 1 and 2. Infusion-related reactions occurred in 44% of subjects overall; however, <10% of subjects required treatment with systemic corticosteroids. In another trial of 19 subjects with relapsed/refractory cHL who had received a median of 3 prior therapies, the combination produced a 50% CR rate (Diefenbach 2017). The regimen was also considered to be well tolerated in this setting, although 2 subjects experienced pneumonitis (1 Grade 3 event that was considered to be a dose-limiting toxicity and 1 Grade 5 event in an elderly subject). Grade 3 AEs were rash, pruritus, and neutropenia, and occurred in 1 subject each. In another trial in 11 previously untreated subjects with cHL over 60 years-old and ineligible for or declining conventional combination chemotherapy, the combination of brentuximab vedotin and nivolumab

produced a 55% CR rate (Friedberg 2018). No new safety signals were identified and the combination was considered to be well tolerated.

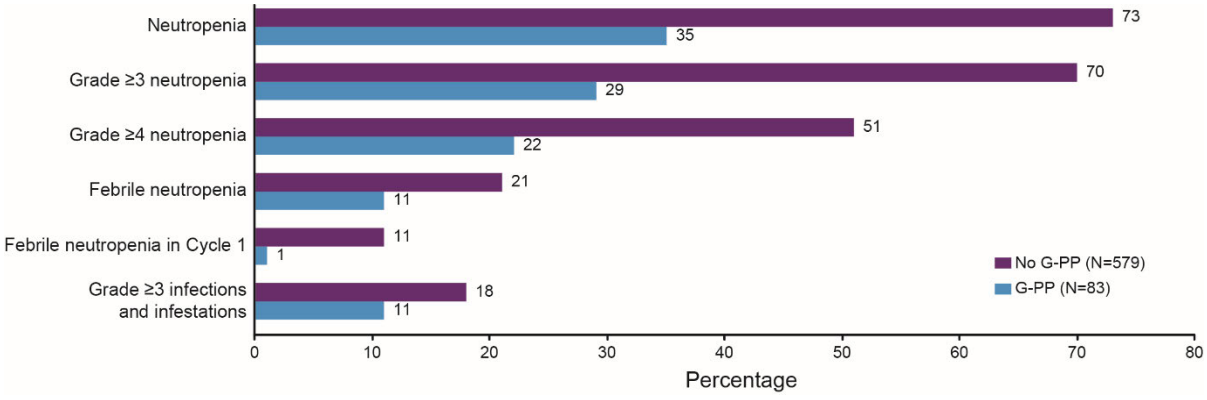
The combination of nivolumab has also been shown to be well tolerated when combined with doxorubicin, vinblastine, and dacarbazine (N+AVD). Ramchandren and colleagues observed a 67% CR rate with the multi-agent combination in 51 subjects with newly-diagnosed advanced stage cHL (Ramchandren 2019). Neutropenia was reported for 55% of subjects and treatment-related febrile neutropenia was reported for 10% of subjects.

1.4 Study Rationale

1.4.1 Part A

Based on the results of the ECHELON-1 clinical trial, the FDA has approved the use of brentuximab vedotin in combination with chemotherapy in previously untreated subjects with Stage III/IV HL, and recommended the use of G-PP beginning in Cycle 1. In the sub-set of subjects who received G-PP in ECHELON-1, there were lower rates of Grade 3 or higher neutropenia (29% vs 70% without G-PP) and FN (11% vs 21% without G-PP) (Straus 2018a). The highest incidence of FN occurred in the ECHELON-1 study during Cycle 1 (Connors 2018). When G-PP was administered during Cycle 1 to a sub-set of subjects, the rate of Cycle 1 FN decreased from 11% to 1% (Figure 1), (Straus 2018a). In addition, these subjects experienced fewer infections and Grade 3 or higher AEs (Straus 2018a). Furthermore, subjects who received G-PP in ECHELON-1 had an improved efficacy as demonstrated by 84.6% mPFS at 2 years vs 81.7% without G-PP (Straus 2018a). The 2-year mPFS for subjects treated with ABVD in ECHELON-1 was 77.2%. Support with G-PP resulted in fewer dose delays during A+AVD treatment (35% vs 49% without G-PP), dose reductions (20% vs 26% without G-PP), and hospitalizations (29% vs 38% without G-PP).

Figure 1: Incidence of febrile neutropenia with G-PP administration in Cycle 1



Part A will further assess the impact of G-PP administration during A+AVD treatment on the incidence of FN, efficacy, and dose intensity, and may provide additional information on the dosing of G-CSF in subjects receiving A+AVD.

1.4.2 Parts B and C

The combination of brentuximab vedotin and nivolumab as well as each agent combined separately with doxorubicin, vinblastine, and dacarbazine have been shown to be active and well tolerated in the treatment of cHL.

Part B will evaluate the combination of AN+AD in advanced stage HL. Yasenchak et al examined the combination of brentuximab and nivolumab as frontline treatment for subjects ≥60 years with advanced stage HL who were ineligible for or declined conventional chemotherapy. Preliminary results showed an overall response rate (ORR) of 100%, a CR rate of 72%, and a partial response (PR) rate of 28% (Yasenchak 2019). The regimen was well tolerated; the most common treatment-related AEs of any grade were fatigue (48%), peripheral sensory neuropathy (38%), diarrhea, infusion-related reactions, and pyrexia (24% each). Three subjects had immune-related AEs with a maximum severity of Grade 3.

Part C will evaluate the combination of AN+AD in early stage HL. Preliminary results from Abramson et al regarding the combination of brentuximab vedotin, doxorubicin, and dacarbazine for frontline treatment in early stage HL showed high interim and EOT CR rates of 94% and 100%, respectively, suggesting that vinblastine may not be required for efficacy and may contribute to toxicity in the frontline setting (Abramson 2018). The most common treatment-related AEs of any grade included nausea (79%), peripheral sensory neuropathy (56%), fatigue (50%), constipation (38%) and alopecia (35%). Grade 3 or higher AEs were limited to nausea (3%), neutropenia (6%), and vomiting (3%).

It is therefore reasonable to expect that the replacement of vinblastine with nivolumab, in combination with doxorubicin, brentuximab vedotin, and dacarbazine will result in high response rates and be well tolerated, with potentially less toxicity than vinblastine-containing regimens (A+AVD, N+AVD, ABVD).

Subjects in Part B will be treated with up to 6 cycles of brentuximab, nivolumab, doxorubicin, and dacarbazine (AN+AD), while subjects in Part C will be treated with 4 cycles of AN+AD. The components of AN+AD will be administered as described in Section 5. After approximately 10 subjects have completed Cycle 2, the SMC will assess the safety of AN+AD. Safety will be assessed separately for Part B and Part C. An additional SMC meeting will occur after approximately 50 subjects in Part C have completed their EOT assessment. For Part C, one interim analysis will be performed after approximately 50 subjects have completed response assessment at EOT.

1.4.3 Risk:Benefit

Historical standard of care treatment options for patients with advanced HL have been associated with poor survival (Gordon 2013). In the ECHELON-1 trial, an open-label, international, multicenter, randomized Phase 3 clinical trial in subjects with previously untreated Stage III or IV cHL, the complementary mechanisms of action of brentuximab vedotin with A+AVD, enhanced antitumor activity with significant improvement in mPFS (see Section 1.2).

The combination of brentuximab vedotin and nivolumab was active and well tolerated in cHL with improved CR rate of 61% in relapsed or refractory cHL (Herrera 2018). The combination of N+AVD as found to have a 67% CR rate in subjects with newly diagnosed advanced stage cHL (Ramchandren 2019; Section 1.3). In another trial of 11 previously untreated subjects with cHL over 60 years-old and ineligible for or declining conventional combination chemotherapy, the combination of brentuximab vedotin and nivolumab produced a 55% CR rate (Friedberg 2018). Section 1.4.2 provides additional information on the better outcome of this combination therapy. Given the demonstrated activity of brentuximab vedotin as well as nivolumab as treatment of cHL, the evaluation of this regimen is anticipated to provide benefit to these patients with acceptable known toxicity. The toxicity profile of the combination in cHL is expected to be consistent with that of previous studies. Neutropenia and associated complications, including febrile neutropenia and infections, infusion related reactions, and peripheral neuropathy were considered the most clinically important AEs for the combination regimen. Investigators may decide to discontinue study treatment at any time for any of the reasons listed in Section 4.3.1.

The same rationale regarding the use of brentuximab vedotin and nivolumab applies when considered as treatment of early stage cHL. Current accepted therapies for early stage cHL include chemotherapy regimens, radiation, and combined modality therapy of chemotherapy and radiation. These regimens are associated with high cure rates of 85-90% (Meyer 2012) but are also associated with high rates of serious morbidity and mortality in long-term survivors, particularly second primary malignancies and cardiovascular disease (Straus 2018b).

Recent data in 34 subjects with previously untreated Stage I/II cHL with non-bulky disease, treatment with brentuximab vedotin, doxorubicin, and dacarbazine showed CR, PFS and OS rates of 100% at EOT (Abramson 2018). The promising responses observed with the combination of brentuximab vedotin and nivolumab as treatment of advanced cHL as well as the evidence of activity in earlier stage disease provide a compelling rationale to evaluate the combination of brentuximab vedotin and nivolumab.

2 OBJECTIVES

This study will evaluate the efficacy and safety of A+AVD in advanced cHL subjects treated with G-PP in Part A, and the treatment of cHL with AN+AD in Parts B and C. Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

Table 1: Objectives and corresponding endpoints

Primary Objectives	Corresponding Primary Endpoints
• Part A: To assess the treatment-emergent febrile neutropenia rate in subjects with previously untreated, advanced stage, cHL treated with A+AVD and G-CSF primary prophylaxis (G-PP)	• Part A: The febrile neutropenia rate in subjects treated with A+AVD and G-PP
• Parts B and C: To assess the complete response (CR) rate at EOT with AN+AD in subjects with previously untreated cHL	• CR rate at EOT
Secondary Objectives	**Corresponding Secondary Endpoints**
Part A: • To assess the incidence and severity of adverse events of clinical interest	Part A: • The rates and severity of each AECI
• To assess dose intensity, dose reductions, and dose delays related to any component of A+AVD	• Mean dose intensity; the rates of dose reduction and dose delays related to any component of A+AVD
• To assess primary refractory disease rates	• The primary refractory disease rate
• To assess subsequent anticancer therapy utilization	• The rates of each subsequent anticancer therapy taken by subjects
• To assess end of treatment (EOT) complete response rate	• The complete response rate at EOT
• To assess physician-reported progression-free survival rate at 2 years	• Physician-reported PFS
Parts B and C: • To assess the safety and tolerability of AN+AD	Parts B and C: • Incidence, severity, seriousness, and relatedness of AEs; incidence and severity of lab abnormalities
• To assess the overall response rate (ORR)	• Estimate the ORR
• To assess the duration of response (DOR)	• DOR
• To assess the duration of complete response (DOCR)	• DOCR
• To assess the event-free survival (EFS)	• EFS
• To assess the progression-free survival (PFS)	• PFS
• To assess the overall survival (OS)	• OS

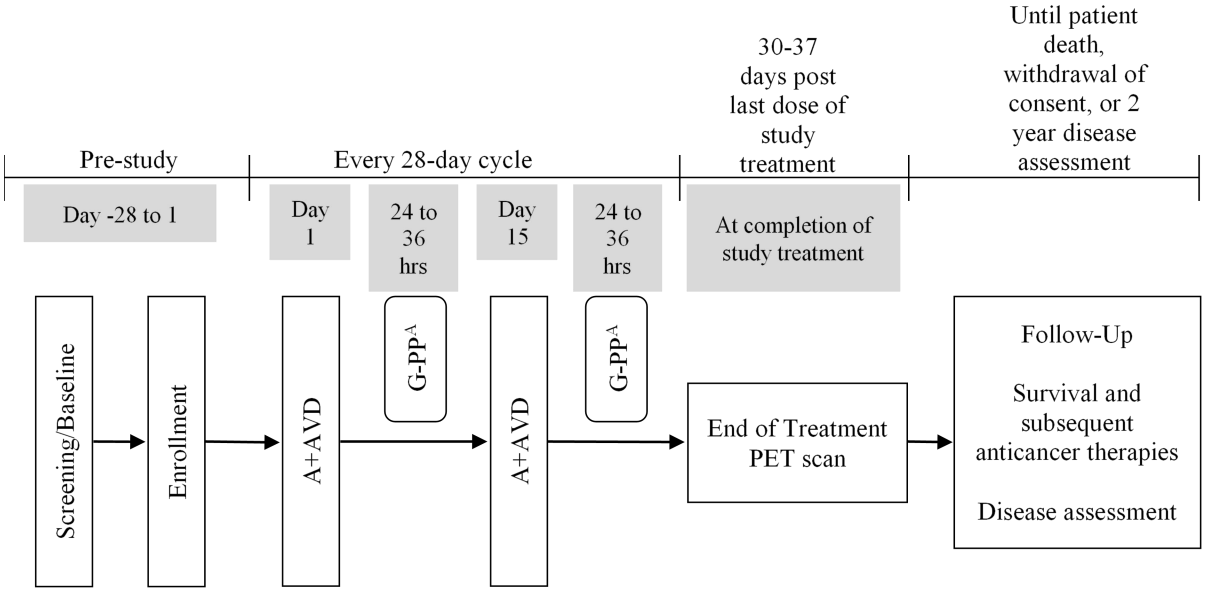
3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is an open-label, multiple part, multicenter, phase 2 clinical trial. Part A is designed to evaluate the rate of FN for treatment-naïve subjects with advanced classical HL (cHL) who have been treated with A+AVD and G-PP. In Part A, subjects will receive 6 cycles of A+AVD as described in Sections 5.2.2 and 5.3.3. Parts B and C are designed to evaluate the CR rate in subjects treated with AN+AD. Up to approximately 240 subjects will be treated in this clinical trial.

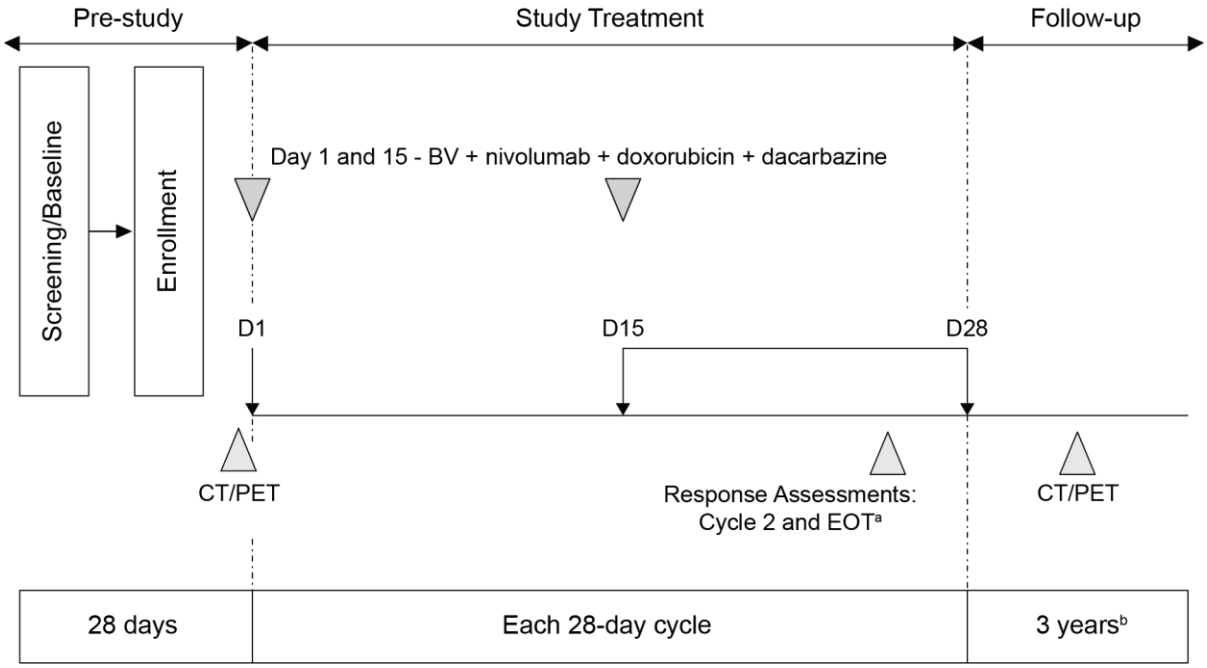
A study schema for Part A is provided in Figure 2 and for Parts B and C in Figure 3. See Appendix A for the schedule of events for Part A; Appendix B provides the schedule of events for Parts B and C. **As of Amendment 6, Parts A and B were completed.**

Figure 2: Study design – Part A



A. Note: G-PP should be started 24 to 36 hours from A+AVD and follow instructions in Section 5.4.3

Figure 3: Study design – Parts B and C



a Response assessments will include PET and diagnostic-quality CT scan on Day 25-28 of Cycle 2, and at EOT.
b Follow-up period for Parts B and C includes 2 additional years (5 years total).

3.1.1 End of Study

The study will be closed approximately 5 years after the last subject receives the last dose, or when no subjects remain in follow-up, whichever occurs first (Section 6.6). In addition, the Sponsor may terminate the study at any time (see Section 10.3.2).

3.1.2 Safety Monitoring Committee

For Parts B and C, the SMC will monitor the safety of AN+AD throughout the study. The SMC is composed of the study medical monitor, study biostatistician, drug safety representative, and study site investigators.

The SMC will meet to evaluate safety after approximately 10 subjects have completed Cycle 2. An additional SMC meeting will be held after approximately 50 subjects in Part C have completed their EOT assessment. The committee will also monitor the safety of participants through regular and/or ad hoc meetings that include review of AEs and lab abnormalities.

Further details are provided in the SMC charter.

3.2 Discussion and Rationale for Study Design

3.2.1 Part A

The use of G-PP was not mandated in the ECHELON-1 clinical trial. However, the use of G-PP is recommended per approved product labeling. Thus, an open-label trial design with

consistent use of G-PP will allow for additional clinical assessment of the safety and efficacy of A+AVD when used with G-PP as described in the approved product labeling. Further, Part A will include subjects with inclusion and exclusion criteria that are somewhat broader than the original ECHELON-1 clinical trial, allowing for assessment of a more representative subject population. Additional analyses may compare the results with those observed in the ECHELON-1 trial.

3.2.2 Parts B and C

The combination of brentuximab vedotin and nivolumab has shown promising preliminary antitumor activity and is well tolerated as discussed in Section 1.3 (Diefenbach 2017; Herrera 2018; Hong 2018). Thus, evaluation of the safety and efficacy of AN+AD combination is warranted.

The endpoints of the study are appropriate for evaluating the efficacy and safety of the combination of AN+AD. The primary efficacy endpoint of this study, CR rate at EOT, is a direct measure of antitumor activity. To further assess the efficacy in this study, ORR, duration of response (DOR), duration of complete response (DOCR), event-free survival (EFS), PFS, and OS will be evaluated as secondary endpoints.

3.2.3 Method of Assigning Subjects to Treatment Groups

Upon approval of subject registration, eligible subjects with advanced cHL will be assigned to Part A or Part B based on subject and investigator preference. Subjects with Stage I or II cHL with bulky mediastinal disease will be assigned to Part B. Subjects with Stage I or II cHL without bulky disease will be assigned to Part C. **As of Amendment 6, Parts A and B were completed.**

3.2.4 Rationale for Selection of Doses

3.2.4.1 Part A

The recommended dose for brentuximab vedotin in combination with chemotherapy for treatment-naïve subjects with Stage III or IV cHL is 1.2 mg/kg intravenous (IV) every 2 weeks (q2wk) for a maximum of 6 cycles (12 doses).

Treatment with 1.2 mg/kg brentuximab vedotin in combination with doxorubicin at 25 mg/m^2, vinblastine at 6 mg/m^2, and dacarbazine at 375 mg/m^2 was studied in the ECHELON-1 trial. This dosing regimen has been established as effective and safe for treatment of subjects with Stage III or IV HL. As the additional analyses in this study depend in part on data from ECHELON-1 subjects, this dosing regimen will be used in this clinical trial.

3.2.4.2 Parts B and C

All subjects will be treated with brentuximab vedotin 1.2 mg/kg, nivolumab 240 mg, doxorubicin 25 mg/m^2, and dacarbazine 375 mg/m^2. Each study drug will be administered

separately by IV infusion on Days 1 and 15 of each 28-day cycle. Subjects in Part B will receive up to 6 cycles of treatment. Subjects in Part C will receive 4 cycles of treatment.

The recommended dose for brentuximab vedotin in combination with chemotherapy for previously untreated Stage III or IV cHL is 1.2 mg/kg up to a maximum of 120 mg based on 100 kg body weight, every 2 weeks for a maximum of 6 cycles (12 doses). Doses up to 2.4 mg/kg have been evaluated in studies in subjects with CD30-positive hematologic malignancies.

Doxorubicin at 25 mg/m^2 and dacarbazine at 375 mg/m^2 in combination with the above dose of brentuximab vedotin has been studied in the ECHELON-1 trial. This dosing regimen has been established as effective and safe for treatment of subjects with advanced stage HL.

The approved dose for nivolumab as monotherapy for cHL is 240 mg every 2 weeks or 480 mg every 4 weeks (nivolumab approved product labeling)**.** In the CheckMate 205 study, subjects with newly diagnosed cHL were given nivolumab (240 mg every 2 weeks), followed by the combination of NAVD, which resulted in an ORR of 84% (Ramchandren 2019).

After approximately 10 subjects have completed 2 cycles of treatment, the SMC will assess the safety of AN+AD (Section 3.1.2). An additional SMC meeting will occur after approximately 50 subjects in Part C have completed their EOT assessment. Safety will be evaluated separately for Part B and Part C.

3.2.5 Blinding and Unblinding

This is an open-label study.

4 STUDY POPULATION

The subject population to be studied is treatment-naïve subjects with classical HL.

Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection. **As of Amendment 6, Parts A and B were completed.**

4.1 Inclusion Criteria

1. Treatment-naïve, cHL subjects:

    a. Subjects enrolling in Part A of the study must have Ann Arbor Stage III or IV disease.

    b. Subjects enrolling in Part B of the study must have Ann Arbor Stage I or II cHL with bulky mediastinal disease (defined as a single node or nodal mass measuring 10 cm or greater in diameter as determined by CT imaging), or Stage III or IV disease.

    c. Subjects enrolling in Part C of the study must have Ann Arbor Stage I or II cHL without bulky disease.

2. Histologically confirmed cHL according to the current World Health Organization Classification (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, classical HL, or not otherwise specified).

    a. Subjects enrolling in Parts B and C must submit a tumor block for analysis (see Section 7.3.1). Availability of tissue must be confirmed prior to enrollment. If a tumor block is not available, unstained slides (a minimum of 10 unstained slides for Part B and 12 unstained slides for Part C) may be submitted instead of a tumor block.

3. Bidimensional measurable disease as documented by PET/CT or CT imaging. Must have at least one lesion >15 mm (1.5 cm) in the longest diameter on cross-sectional imaging, measurable in 2 perpendicular dimensions on CT (or MRI), and FDG avid by PET.

4. Age 12 years or older in the United States. For regions outside of the United States, subjects must be age 18 years or older.

5. An Eastern Cooperative Oncology Group (ECOG) performance status ≤2

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

7. Subjects of childbearing potential must agree not to breastfeed or donate ova, starting at the time of informed consent and continuing through 7 months after the final dose of study drug.

8. If sexually active in a way that could result in pregnancy, subjects of childbearing potential must agree to use 2 contraception methods (including 1 highly effective) during the study and for 7 months following the last dose of study drug (see Appendix G). Subjects who can father children and have partners of childbearing potential must agree to use 2 contraception methods during the study and for 7 months following the last dose of study drug (see Appendix G). Subjects who can father children must be willing to refrain from sperm donation starting at the time of consent and continuing through the study period and for at least 7 months after the final dose of study drug. Subjects born male who are sexually active with a pregnant or breastfeeding person must use contraceptives outlined in Appendix G to prevent secondary exposure to seminal fluid.

9. The subject or the subject's legally acceptable representative must provide written informed consent. For subjects less than 18 years old, a parent or legally acceptable representative must provide written informed consent; if applicable, the subject should also provide assent per institutional standards.

10. The following baseline laboratory data:

- absolute neutrophil count ≥1500/μL unless there is known bone marrow involvement
- platelet count ≥75,000/μL
- serum bilirubin ≤1.5 x upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease or documented hepatic involvement with lymphoma
- estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation as applicable for subjects ≥18 years old, or bedside Schwartz formula for subjects <18 years old (see Section 7.4.2)
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN or ≤5 x ULN if there is documented hepatic involvement of HL
- hemoglobin ≥8 g/dL

4.2 Exclusion Criteria

1. Nodular lymphocyte predominant HL.
2. History of another malignancy within 3 years 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. Subjects with nonmelanoma skin cancer, localized prostate cancer, or carcinoma in situ of any type are not excluded if they have undergone complete resection.
3. Prior immunosuppressive chemotherapy, therapeutic radiation, or any immunotherapy (e.g., immunoglobulin replacement, other monoclonal antibody therapies) within 4 weeks of first study drug dose.
4. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
5. Active cerebral/meningeal disease related to the underlying malignancy, including signs or symptoms of progressive multifocal leukoencephalopathy (PML) or history of PML. Subjects with a history of cerebral/meningeal disease related to the underlying malignancy are allowed if prior CNS disease has been treated.
6. Any active Grade 3 or higher (per the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study drug. Routine antimicrobial prophylaxis is permitted.
7. Current therapy with other systemic anti-neoplastic or investigational agents.
8. Planned consolidative radiotherapy during the study treatment period (Parts B and C only).

9. Active interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity (Parts B and C only).
10. Grade 3 or higher pulmonary disease unrelated to underlying malignancy.
11. Documented history of idiopathic interstitial pneumonia or diffusing capacity of the lung for carbon monoxide (adjusted for hemoglobin) <50% predicted.
12. 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 (see Appendix E) within 6 months prior to their first dose of brentuximab vedotin.
13. Subjects with Child-Pugh B or C hepatic impairment.
14. Other serious underlying medical condition that, in the opinion of the investigator, would impair the subject's ability to receive or tolerate the planned treatment and follow-up.
15. Neurologic disease compromising at least 1 Activity of Daily Living (total dependence) per Katz Index of Independence in Activities of Daily Living (Appendix H), or poorly controlled by medication per the investigator's assessment.
16. Grade 2 or higher peripheral sensory or motor neuropathy at baseline.
17. Left ventricular ejection fraction <45% or symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), or previous treatment with complete cumulative doses of doxorubicin or other anthracyclines.
18. Subjects with acute or chronic graft-versus-host-disease (GvHD) or receiving immunosuppressive therapy as treatment for or prophylaxis agent against GvHD.
19. Previous treatment with brentuximab vedotin.
20. 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) or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
21. Known to be positive for human immunodeficiency virus (HIV).
22. Subjects who are pregnant or breastfeeding.
23. Known hypersensitivity to any excipient contained in the drug formulation of brentuximab vedotin, any component of AVD, nivolumab, doxorubicin, dacarbazine, filgrastim, or pegfilgrastim.

24. Treatment with botanical preparations (e.g., herbal supplements, traditional Chinese medicines) to treat the disease under study within 2 weeks prior to treatment (Parts B and C only).

25. Subjects who have received a live or attenuated vaccine within 30 days prior to treatment and 100 days after the last dose (Parts B and C only).

26. Subjects with an active autoimmune disease or any other condition requiring systemic treatment with either corticosteroids within 14 days (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 30 days of starting treatment (Parts B and C only). Inhaled, ocular, intra-articular, or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

    a. Subjects 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 to enroll.

4.3 Removal of Subjects From Therapy or Assessment

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

4.3.1 Discontinuation of Study Treatment

A subject's study treatment may be discontinued for any of the following reasons:

- Completed treatment per protocol
- Progressive disease (PD)
- Adverse event (AE)
- Pregnancy
- Investigator decision
- Subject decision, non-AE
- Study termination by sponsor
- Other, non-AE

Subjects who discontinue from study treatment will remain on study for follow-up unless they withdraw consent. CZ only: Subjects who discontinue study treatment due to a lack of clinical benefit following Cycle 2 PET will only remain on study for survival follow-up and subsequent therapy must be recorded.

4.3.2 Subject Withdrawal From Study

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

- Completed study per protocol

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

5 TREATMENTS

5.1 Treatments Administered

For Part A, the treatment regimen A+AVD consists of brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine. For Parts B and C, the treatment regimen AN+AD consists of brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine. Brentuximab vedotin is an ADC consisting of the antibody cAC10, specific for human CD30; the microtubule-disrupting agent MMAE; and a protease-cleavable linker that covalently attaches MMAE to cAC10. Nivolumab is a HuMAb that targets PD-1. Doxorubicin is a cytotoxic anthracycline antibiotic. Vinblastine is a stathmokinetic oncolytic agent. Dacarbazine is an anticancer agent.

Commercially available forms of G-CSF include filgrastim and pegfilgrastim. Both are glycoproteins that regulate production of neutrophils and affect neutrophil proliferation, differentiation, and function.

The study treatments to be administered in Part A are described in summary in Table 2 and in detail in Sections 5.2, 5.3, and 5.4. The study treatments to be administered in Parts B and C are described in summary Table 3 and in detail in Sections 5.2, 5.3, and 5.5. **As of Amendment 6, Parts A and B were completed.**

Table 2: Study treatment – Part A

Drug Administered	Day 1	24–36 hours post A+AVD	Day 15	24–36 hours post A+AVD
Doxorubicin (25 mg/m^2)	X		X	
Vinblastine (6 mg/m^2)	X		X	
Dacarbazine (375 mg/m^2)	X		X	
Brentuximab vedotin (1.2 mg/kg)	X		X	
G-PP[a]		X[a]		X[a]

a G-PP to be administered beginning 24–36 hours post each dose of A+AVD. Dose and length of administration vary depending on type of drug used; see Section 5.4.3

Table 3: Study treatment – Parts B and C

Drug Administered[a]	Day 1	Day 15
Doxorubicin (25 mg/m^2)	X	X
Dacarbazine (375 mg/m^2)	X	X
Brentuximab vedotin (1.2 mg/kg)	X	X
Nivolumab (240 mg)	X	X

a On dosing days, the order of administration will be doxorubicin and dacarbazine, followed by brentuximab vedotin, then nivolumab. Nivolumab will be administered at least 30 minutes after the end of infusion with brentuximab vedotin.

5.2 Brentuximab Vedotin

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

5.2.1 Description

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

5.2.2 Dose and Administration

Brentuximab vedotin 1.2 mg/kg will be administered on days 1 and 15 by IV infusion given over approximately 30 minutes, for up to six 28-day cycles. In the absence of infusion-related reactions, the infusion rate for all subjects 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. Brentuximab vedotin administration should be limited to a maximum of 120 mg q2wk. In Parts B and C, brentuximab vedotin should be administered after the end of the infusion of doxorubicin or dacarbazine, and 30 minutes prior to infusion of nivolumab when administered on the same day.

Weight-based dosing is based on subject actual body weight. Doses must be adjusted for subjects who experience a ≥10% change in weight from baseline. Subject weight must be measured during all relevant assessment windows as described in the schedule of events. Other dose adjustments for changes in body weight are permitted per institutional standard. Rounding is permissible within 5% of the nominal dose. **An exception to weight-based dosing is made for subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose calculated per administration in this study is 120 mg (1.2 mg/kg).**

5.2.3 Method of Procurement

Brentuximab vedotin will be supplied to study sites by Seagen Inc.

5.2.4 Dose Modifications

Table 4 describes the dose modifications for study treatment-associated toxicity. Table 5 describes dose modifications for subjects with impaired renal or hepatic function. Dose reductions of brentuximab vedotin below 0.9 mg/kg are not allowed, and further toxicities are managed with dose delays or permanent discontinuation. If any component of the regimen is discontinued due to AE, subjects may remain on study and continue to receive the remaining treatment components. Subjects who discontinue brentuximab vedotin due to AE after receiving only 1 cycle are ineligible to continue on the study. Refer to Section 6 of the Investigator's Brochure (IB) for additional information on the safety of brentuximab vedotin, and guidance regarding appropriate safety monitoring for subjects.

Table 4: Dose modifications for brentuximab vedotin-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Sensory Neuropathy	Continue at same dose level	Reduce BV dose to 0.9 mg/kg and resume treatment	Withhold BV until PN is ≤ Grade 2, then reduce dose to 0.9 mg/kg and resume treatment; if already at 0.9 mg/kg, continue dosing at that dose.	Discontinue treatment with BV
Motor Neuropathy	Continue at same dose level	Reduce BV dose to 0.9 mg/kg and resume treatment	Discontinue treatment with BV	Discontinue treatment with BV
Non-hematologic (except peripheral neuropathy)	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume treatment at the same dose level[a].	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then reduce dose to 0.9 mg/kg and resume treatment, or discontinue at the discretion of the investigator [a,b].
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[d]. For Grade 3 or 4 neutropenia, growth factor support (G-CSF or GM-CSF) or prophylaxis should be considered for subsequent cycles if not already administered. If Grade 4 neutropenia recurs despite growth factor support, consider discontinuation or dose reduction to 0.9 mg/kg.	

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

b Treatment should be discontinued for subjects who experience Grade 4 infusion-related reactions.

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

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

Table 5: Dose modifications for brentuximab vedotin treatment of subjects with renal or hepatic impairment

Degree of Impairment	Recommended Dose Adjustment
Renal Impairment	
Mild (CrCL ≥50–80 mL/min)	None
Moderate (CrCL ≥30–50 mL/min)	None
Severe (CrCL <30 mL/min)	Avoid use
Hepatic Impairment	
Mild (Child-Pugh A)	Reduce dose to 0.9 mg/kg, up to a maximum of 90 mg every 2 weeks
Moderate (Child-Pugh B)	Avoid use
Severe (Child-Pugh C)	Avoid use

5.2.5 Storage and Handling

Refer to the brentuximab vedotin Pharmacy Binder for more information regarding storage and handling.

5.2.6 Packaging and Labeling

Refer to the brentuximab vedotin Pharmacy Binder for more information regarding packaging and handling.

5.2.7 Preparation

Refer to the brentuximab vedotin Pharmacy Binder for more information regarding preparation.

5.3 Doxorubicin, Vinblastine, and Dacarbazine

5.3.1 Description

All subjects in Part A of this study will be administered AVD: doxorubicin, vinblastine, and dacarbazine. All subjects in Parts B and C of this study will be administered doxorubicin and dacarbazine. Doxorubicin is a cytotoxic anthracycline antibiotic. Vinblastine is a stathmokinetic oncolytic agent. Dacarbazine is an anticancer agent.

5.3.2 Method of Procurement

In the United States, doxorubicin, vinblastine, and dacarbazine will be supplied by the study site from commercial sources, and billed to subjects and/or their third-party payer (insurance, a healthcare provider, or applicable government program).

In regions outside of the United States, doxorubicin and dacarbazine will be provided by Seagen Inc. via a central pharmacy, or will be supplied by the study site from a local source to be reimbursed by Seagen Inc.

5.3.3 Dose and Administration

Part A: AVD will be administered by IV infusion on Days 1 and 15 of each 28-day cycle as follows:

+**A**: Doxorubicin will be administered at 25 mg/m^2

V: Vinblastine will be administered at 6 mg/m^2

D: Dacarbazine will be administered at 375 mg/m^2

AVD is to be administered per institutional standards. Brentuximab vedotin is to be administered as described in Section 5.2.2.

Parts B and C: Doxorubicin and dacarbazine will be administered by IV infusion on Days 1 and 15 of each 28-day cycle as follows:

A: Doxorubicin will be administered at 25 mg/m^2

D: Dacarbazine will be administered at 375 mg/m^2

Each agent is to be administered per institutional standards and the current approved product label. Brentuximab vedotin is to be administered as described in Section 5.2.2, and nivolumab is to be administered as described in Section 5.5.3.

5.3.4 Dose Modifications

Dose modifications of doxorubicin, vinblastine, and dacarbazine due to toxicity are allowed per institutional standards and according to the product's prescribing information at the discretion of the investigator. Permitted dose modifications include discontinuation of a treatment component. Refer to the product's prescribing information for dose modification recommendations.

5.3.5 Storage and Handling

Refer to the product label(s) for more information regarding storage and handling.

5.3.6 Packaging and Labeling

Refer to the product label(s) for more information regarding packaging and labeling.

5.3.7 Preparation

Refer to the product label(s) for more information regarding preparation.

5.4 Granulocyte Colony Stimulating Factor

5.4.1 Description

Filgrastim (including biosimilar) and pegfilgrastim can be used as G-CSF in the study. Both are glycoproteins that regulate production of neutrophils and affect neutrophil proliferation, differentiation, and function.

5.4.2 Method of Procurement

Filgrastim and pegfilgrastim will be supplied by the study site from commercial sources, and billed to subjects and/or their third-party payer (insurance, a healthcare provider, or applicable government program).

5.4.3 Dose and Administration

In Part A, G-CSF will be administered after each dose of A+AVD, following dosing on Days 1 and 15 of every treatment cycle, as follows:

- Pegfilgrastim: 6 mg subcutaneous (SC) 24 to 36 hours after A+AVD per dose
- Filgrastim: 5 mcg/kg (300 to 480 mcg, rounded to the nearest vial) SC daily, beginning 24 to 36 hours after A+AVD per dose, for a minimum of 5 days. Additional doses beyond 5 days are permitted at the discretion of the investigator.

5.4.4 Dose Modifications

Refer to the product label(s) for more information regarding dose modifications.

5.4.5 Storage and Handling

Refer to the product label(s) for more information regarding storage and handling.

5.4.6 Packaging and Labeling

Refer to the product label(s) for more information regarding packaging and labeling.

5.4.7 Preparation

Refer to the product label(s) for more information regarding preparation.

5.5 Nivolumab

5.5.1 Description

All subjects in Parts B and C of this study will be administered the PD-1 checkpoint inhibitor nivolumab. The addition of nivolumab in combination with brentuximab vedotin, doxorubicin, and dacarbazine in newly diagnosed subjects with cHL is considered investigational.

Nivolumab is a sterile, preservative-free, clear to opalescent, colorless to pale-yellow solution supplied by Seagen Inc. in single-use vials for dilution for IV administration. Each single-use vial of the product contains 100 mg/10 mL solution. Detailed information describing the preparation, administration, and storage of nivolumab is located in the Pharmacy Binder.

5.5.2 Method of Procurement

Nivolumab will be provided by Bristol-Myers Squibb and supplied to study sites by Seagen Inc.

5.5.3 Dose and Administration

Nivolumab will be administered by IV infusion on Day 1 and Day 15 of each 28-day treatment cycle. Subjects will receive nivolumab at a dose of 240 mg as a 30-minute infusion. Nivolumab should be administered at a set dose of 240 mg and neither reduced nor increased. Nivolumab should be administered at least 30 minutes after completing treatment with brentuximab vedotin. Nivolumab infusions should be administered through an IV line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Other drugs should not be co-administered through the same IV line (e.g., brentuximab vedotin).

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

5.5.4 Dose Modifications

Nivolumab administration should be withheld or discontinued as described in Table 6. The recommended management of gastrointestinal (GI), renal, pulmonary, hepatic, endocrinopathy, skin, neurological, and myocarditis AEs are provided in Appendix I.

Table 6: Nivolumab Dose Modifications

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/ non-HCC[b]	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[a]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis/ HCC[b]	If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN	Withhold dose[c]

Adverse Reaction	Severity*	Dose Modification
	If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[a]
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction	
	First occurrence	Withhold dose[a]
	Recurrence of same Grade 3 adverse reactions	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

Note: Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

a Resume treatment when adverse reaction improves to Grade 0 or 1.

b HCC: hepatocellular carcinoma.

c Resume treatment when AST/ALT returns to baseline.

5.5.4.1 Resuming Treatment Following Dose Delays

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

See Table 6 in Section 5.5.4 for dose delays and discontinuations.

Subjects may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For subjects with Grade 2 AST, ALT and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Grade ≥3 adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

Prior to re-initiating treatment in a subject with a dosing delay lasting >6 weeks, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per protocol or more frequently if clinically indicated during such dosing delays.

Permitted dose modifications include permanent discontinuation of nivolumab. Subjects may remain on study and continue to receive the remaining treatment components. There are no recommended dose modifications of nivolumab for hyperthyroidism or hypothyroidism.

If nivolumab is held due to AE, once the AE has resolved administration of nivolumab should resume on the same schedule at the next cycle of therapy.

5.5.5 Storage and Handling

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

Drug accountability instructions are provided in the Pharmacy Binder.

5.5.6 Packaging and Labeling

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

5.5.7 Preparation

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

Detailed drug preparation instructions are provided in the Pharmacy Binder.

5.6 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.4.1.3). Any

concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.6.1 Required Concomitant Therapy

There are no required concomitant therapies.

5.6.2 Allowed Concomitant Therapy

Subjects are allowed premedication regimens for anti-emesis purposes and prevention of infusion-related reactions, including corticosteroids, dosing <10 mg daily prednisone equivalent or per local standard of care. Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Doses of >10 mg daily prednisone or prednisone equivalent are allowed for stable adrenal replacement. A brief (<3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed type hypersensitivity reaction caused by a contact allergen) is permitted. Further details are described in Section 5.7.1.

Subjects who are receiving strong Cytochrome P450 (CYP) 3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions.

Growth factor support or prophylaxis (G-CSF or GM-CSF) should be considered for subjects who are at risk for, currently have, or have recently recovered from, neutropenia. CZ only: Primary prophylaxis with G-CSF or GM-CSF from the first dose is recommended for all subjects with previously untreated Hodgkin's lymphoma receiving combination therapy with brentuximab vedotin.

5.6.3 Prohibited Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications (exception: corticosteroid doses of >10 mg daily prednisone, or prednisone equivalent for anti-emesis and prevention of infusion-related reactions are allowed), radiotherapy, or systemic anti-neoplastic therapy from Day 1 through EOT. In addition, other prohibited concomitant therapies should be excluded in accordance with the approved prescribing information for each agent. Exceptions are noted in Section 5.6.2.

5.6.3.1 Prohibited Concomitant Therapy – Parts B and C

The following are prohibited for Parts B and C only:

- Any subject for whom the investigator intends to administer consolidative radiotherapy to any lesions (i.e., large mediastinal masses).
- Immunosuppressive doses of systemic corticosteroids (e.g., prednisone >10 mg/day) (premedication regimens for anti-emesis and prevention of infusion-related reactions are allowed).

- Any 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 or attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose of nivolumab

5.7 Management of Adverse Reactions

Management of AEs should occur per institutional standards. Additional information regarding treatment-emergent AEs (TEAEs) for brentuximab vedotin is available in the brentuximab vedotin IB. Management of immune-mediated AEs (IMAEs) for nivolumab is available in Appendix I.

5.7.1 Management of Infusion Reactions

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

Subjects will be monitored for a period of 2 hours post-infusion of brentuximab vedotin at each visit. Infusion or hypersensitivity reactions may occur within 24 hours or more than 24 hours post-dose, respectively, to either brentuximab vedotin or nivolumab. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

5.7.1.1 Part A

Subjects who have experienced a Grade 1 or Grade 2 infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30–60 minutes prior to each brentuximab vedotin infusion or according to institutional standards.

Subjects who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment per institutional standards.

If anaphylaxis occurs, drug administration should be immediately and permanently discontinued and appropriate medical therapy provided per institutional standards.

5.7.1.2 Parts B and C

If an infusion or hypersensitivity reaction occurs from nivolumab, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as a serious adverse event

(SAE) if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (V4.03) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs):

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their

institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

5.7.2 Management of Tumor Lysis Syndrome

Subjects with rapidly proliferating tumor and high tumor burden may be at risk of tumor lysis syndrome and should be individually evaluated to assess the need for tumor lysis prophylaxis prior to the first dose of brentuximab vedotin. Subjects should receive prophylaxis as appropriate per the institutional standards.

5.7.3 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 prescribing information for further details.

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

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

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

5.7.4 Management of Immune-Adverse Events (Parts B and C only)

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an I-O agent in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue including the following:

- Immune-mediated pneumonitis
- Immune-mediated colitis
- Immune-mediated hepatitis and hepatoxicity
- Immune-mediated endocrinopathies
- Immune-mediated dermatologic adverse reactions
- Immune-mediated nephritis and renal dysfunction

The following groups of AEs should be managed per the algorithms found in Appendix I:

- Gastrointestinal
- Renal

- Pulmonary
- Hepatic, with the following exceptions:
  - Subjects with a baseline LFT level in the Grade 1 range (AST or ALT >ULN to 3.0 x ULN and/or total bilirubin >ULN to 1.5 x ULN) should be managed by AE Grade-specified algorithms as applied to the absolute increase in AE Grade level above base line. For example, management of a Grade 3 AST elevation for a subject who had a baseline AST level in the Grade 1 range would be per the Grade 2 algorithm
- Endocrinopathy
- Skin
- Neurological
- Myocarditis (EU-specific)

See Section 5.6.2 for allowed high-dose corticosteroid treatment

5.7.5 Management of Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Brentuximab vedotin

Weight-based dosing for brentuximab vedotin is based on subject actual body weight (see Section 5.2.2), with the exception of subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. **The maximum dose of brentuximab vedotin calculated per administration in this study is 120 mg.**

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

- Care for and medically stabilize the subject 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, subject weight) and AEs, if any.

Nivolumab

In the event of an overdose of nivolumab, study personnel should:

- Notify the Medical Monitor as soon as they become aware of the overdose
- Closely monitor the subject for AEs, SAEs, and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Doxorubicin, Vinblastine, Dacarbazine

In the event of an overdose of any other study drug (doxorubicin, vinblastine, dacarbazine), the event should be managed according to the product label and/or the institutional standard of care, and promptly reported to the Sponsor.

5.8 Treatment Compliance

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

6 STUDY ACTIVITIES

6.1 Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.4.1.3). Any study protocol-related AE, as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (serum chemistry panel, complete blood count [CBC] with differential [manual differential if clinically indicated, see Section 7.4.2], and weight) may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing per institutional standards. It is recommended that subjects be monitored for renal and hepatic function per the brentuximab vedotin product labeling.

The schedule of events for Part A and Parts B and C are provided in Appendix A and Appendix B, respectively. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7. **As of Amendment 6, Parts A and B were completed.**

6.2 Screening Visit (Day –28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- International prognostic score for Part B only (Appendix D)
- Echocardiogram/multi-gated acquisition (MUGA) scan (can be within the past month for Parts B and C only)
- Electrocardiogram (ECG)
- CT scan (a CT of diagnostic quality of the chest, neck, abdomen, and pelvis is required)
  - CT scans up to 3 days prior to Day -28 (i.e., Day -31) will be accepted
  - To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline
- PET scan (Note: a CT of diagnostic quality may be combined with PET to satisfy the requirements for CT and PET scanning)
  - PET scans up to 3 days prior to Day -28 (i.e., Day -31) will be accepted
- Initiate collection of archived tumor tissue specimen or fresh tumor biopsy (Section 7.3.1) (For Parts B and C only)
- CZ only: HBV and HIV serological testing (positive results will result in subject being considered ineligible for enrollment)

- CZ only: HCV PCR testing (positive results will result in subject being considered ineligible for enrollment)

6.2.1 Baseline Visit (Day –7 to Day 1)

- Height and weight (For subjects <18 years, height must be measured at this visit; for subjects ≥18 years, height measured within 12 months is acceptable)
- Pregnancy test for subjects of childbearing potential
- Physical exam
- ECOG performance status (Appendix C)
- Hemoglobin A1c
- B symptom assessment
- CBC with differential
- Serum chemistry panel (includes thyroid stimulating hormone [TSH], free T3, and free T4; see Section 7.4.27.3.2)
- Estimated glomerular filtration rate (eGFR) calculation per MDRD

6.3 Treatment Period (Day 1 to Day 28)

6.3.1 Part A

6.3.1.1 Part A: Cycles 1–6 Day 1

- Weight
- If Baseline Visit activities occur within 1 day prior to Cycle 1, Day 1, the assessments do not need to be repeated at the Cycle 1 Day 1 visit.
- Results from clinical laboratory assessments must be reviewed prior to study drug administration, including evaluation of hepatic and renal function.
  - CBC with differential
  - Serum chemistry panel
- A+AVD administration
- Pregnancy test for subjects of childbearing potential

6.3.1.2 Part A: Cycles 1–6 Days 2–6

- G-PP administration 24 to 36 hours from the last dose of the A+AVD regimen. See Section 5.4.3.
  - Pegfilgrastim: 6 mg SC
  - Filgrastim: 5 mcg/kg SC daily for a minimum of 5 days.

6.3.1.3 Part A: Cycles 1–6 Day 15

- Weight
- Results from clinical laboratory assessments must be reviewed prior to study drug administration, including evaluation of hepatic and renal function.

- CBC with differential
- Serum chemistry panel

- A+AVD administration

6.3.1.4 Part A: Cycles 1–6 Days 16–20

- G-PP administration 24 to 36 hours from the last dose of the A+AVD regimen. See Section 5.4.3.
  - Pegfilgrastim: 6 mg SC
  - Filgrastim: 5 mcg/kg SC daily for a minimum of 5 days

6.3.2 Parts B and C

6.3.2.1 Parts B and C: Cycle 1 Day 1

- Prior to dosing, confirm subject eligibility per inclusion/exclusion criteria
- If Baseline visit activities occur within 1 day prior to Cycle 1, Day 1, the assessments do not need to be repeated at the Cycle 1 Day 1 visit
- CBC with differential
- Serum chemistry panel (should include amylase and lipase along with TSH, free T3, and free T4; see Section 7.4.2)
- eGFR (Section 7.4.2)
- Peripheral blood collection for biomarker analyses (Part C only; see Section 7.3.3)
- Results from clinical laboratory assessments must be reviewed prior to study drug administration
- Pregnancy test for subjects of childbearing potential
- Physical exam, including weight for dosing
- Doxorubicin and dacarbazine administration (Section 5.3)
- Brentuximab vedotin administration (Section 5.2)
- Nivolumab administration (Section 5.5; approximately 30 minutes after completion of BV administration)
- B symptom assessment (not required if completed at Baseline); Note: Subjects will be monitored for a period of 2 hours post-infusion of brentuximab vedotin at each visit

6.3.2.2 Parts B and C: Cycle 1 Day 15

- ECOG Performance status (Appendix C)
- Results from clinical laboratory assessments must be reviewed prior to study drug administration:
  - Serum chemistry panel (Section 7.4.2)
  - eGFR (Section 7.4.2)
  - CBC with differential (Section 7.4.2)
- Doxorubicin and dacarbazine administration (Section 5.3)

- Brentuximab vedotin administration (Section 5.2)
- Nivolumab administration (Section 5.5; approximately 30 minutes after completion of BV administration)

6.3.2.3 Part B: Cycles 2–6 Day 1; Part C: Cycles 2–4 Day 1

- Results from clinical laboratory assessments must be reviewed and must confirm eligibility prior to study drug administration
- Serum chemistry panel (for Cycle 3 only, must include TSH, free T3, and free T4; see Section 7.4.2)
- eGFR (Section 7.4.2)
- Peripheral blood collection for biomarker analyses (Part C only; Cycles 2 and 4; see Section 7.3.3)
- CBC with differential (Section 7.4.2)
- Physical exam, including weight
- Pregnancy test for subjects of childbearing potential
- B-symptom assessment
- ECOG Performance status (Appendix C)
- Doxorubicin and dacarbazine administration (Section 5.3)
- Brentuximab vedotin administration (Section 5.2)
- Nivolumab administration (Section 5.5; approximately 30 minutes after completion of BV administration)

6.3.2.4 Part B: Cycles 2–6 Day 15; Part C: Cycles 2–4 Day 15

- ECOG Performance status (Appendix C)
- CBC with differential
- Serum chemistry panel
- eGFR (Section 7.4.2)
- Doxorubicin and dacarbazine administration (Section 5.3)
- Brentuximab vedotin administration (Section 5.2)
- Nivolumab administration (Section 5.5; approximately 30 minutes after completion of BV administration)

6.3.2.5 Parts B and C: Cycle 2 Disease Status (Days 25-28)

- CT scan (CT of diagnostic quality of the chest, neck, abdomen, and pelvis is required).
  - To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline.
- PET scan.
  Note: a CT of diagnostic quality may be combined with PET to satisfy the

requirements for CT and PET scanning. Refer to Section 7.2 for further guidance on Deauville scale grading for PET scans.

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

EOT visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the last treatment to assess for AEs.

- Pregnancy test for subjects of childbearing potential (Parts B and C only)
- ECOG performance status (Appendix C)
- Physical exam
- CBC with differential (see Section 7.4.2)
- Serum chemistry panel (for Parts B and C, must include TSH, free T3, and free T4; see Section 7.4.2)
- eGFR (Section 7.4.2)
- Peripheral blood collection for biomarker analyses (Part C only, see Section 7.3.3)
- Hemoglobin A1c
- CT of diagnostic quality of neck, chest, abdomen, and pelvis
  - To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline.
- PET scan (Note: a CT of quality may be combined with PET to satisfy the requirements for CT and PET scanning)
  - No CT or PET scan is required if the subject had CT/PET scans within a week prior to EOT or if the subject discontinued due to radiographically confirmed PD.
- B symptom assessment

6.5 Parts B and C: Safety Visit (100 to 114 days after last dose of nivolumab, or 30 to 37 days after last dose of study medication other than nivolumab, whichever is later)

The final safety visit should occur 100 to 114 days after the last dose of nivolumab or 30 to 37 days post last dose of brentuximab vedotin, doxorubicin, or dacarbazine (concurrent with the EOT visit), whichever is later. The following assessments will be performed:

- Physical exam, including assessment for potential immune-mediated AEs
- Serum chemistry panel (Section 7.4.2)
- eGFR (Section 7.4.2)
- CBC with differential (Section 7.4.2)
- Record disease status, survival status, and any subsequent anticancer therapies received.

6.6 Long-term Follow-up

6.6.1 Part A

Subjects will remain in follow-up until death, withdrawal of consent, or completion of 2 years of long-term follow-up (from EOT visit), whichever occurs first.

Subjects will be followed for disease status assessment per investigator until disease progression; subjects will be followed for survival and subsequent anticancer therapy thereafter.

Follow-up visits will occur every 12 (±1) weeks from the EOT visit.

Subjects who withdraw from study treatment due to PD will not have disease status assessed but will continue to be followed for survival and subsequent anticancer therapy.

6.6.2 Parts B and C

Subjects who do not have confirmed disease progression will have the following assessments every 3 months after the EOT visit for the first year (3 months, 6 months, 9 months, and 1 year), and every 6 months for an additional 2 years:

- Dedicated CT of chest, neck, abdomen, and pelvis; performed at the timepoints above and if progression is suspected based on clinical signs and symptoms
  - To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline
- PET; performed in addition to CT scans if CT is positive at the prior timepoint in PET-negative disease (Refer to Section 7.2 for further guidance on Deauville scale grading for PET scans)
- Physical examination
- Disease status
- SAEs related to treatment

Subjects will then continue in follow-up for 2 additional years (5 years total). For the final 2 years, a physical exam should be performed every 6 months and a dedicated CT of chest, neck, abdomen, and pelvis should be performed every 12 months. CT scans of neck will only be repeated if neck disease is present at Baseline.

All subjects, including those who have progressed and/or have started a subsequent therapy to treat progressive or relapsed cHL, will have the following assessments:

- Survival status and subsequent anticancer therapies received
  Note: 3-month follow-up may be performed with 100-day safety visit
- Resolution of PN, if applicable
- SAEs related to treatment

For Part C only, peripheral blood may be collected at the time of disease progression if the subject has provided additional consent (see Section 7.3.3).

6.7 End of Follow-up

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

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

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

Subject 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.

7.2 Response/Efficacy Assessments

In Part A, the determination of antitumor activity will be based on response assessments made according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014). In Parts B and C, the determination of antitumor activity will be based on objective response assessments made according to Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Appendix F) (Cheson 2016). Treatment decisions by the investigator will be based on these assessments.

Staging will be performed by CT of diagnostic quality and PET scan, with disease involvement determined by focal fluorodeoxyglucose (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. A CT of diagnostic quality may be combined with the PET scan when both are required per protocol. 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.

Progressive metabolic disease (PmD), no metabolic response (NmR), partial metabolic response (PmR), or complete metabolic response (CmR) will be determined using PET-based response at each assessment. If only CT-based assessment is performed, response will be categorized as progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR). In Parts B and C, if tumor flare or pseudo-progression is suspected, a determination should not be made at that time. PmD/PD includes radiological evidence of progression per Lugano classification criteria (Part A); for Parts B and C, incorporate LYRIC. If clinical progression is determined by the investigator, radiographic staging should

also be performed to determine response assessment per Lugano classification criteria. The PET scan metabolic uptake will be graded using the Deauville 5-point scale (Barrington 2010; Biggi 2013) with a score of ≤3 considered to represent a complete metabolic response. 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.

Treatment with checkpoint inhibitors, such as nivolumab in Parts B and C, can result in false positive PET imaging. LYRIC criteria recommends repeat PET imaging and/or biopsy to further evaluate PET-positive (D4 or D5) lesions identified at the EOT response assessment. Repeat PET imaging and/or biopsy is required to further evaluate PET-positive PD.

If tumor flare or pseudo-progression is suspected by the investigator during subject treatment in Parts B or C, then a clinical response of indeterminate response (IR) will be determined until subsequent evaluation of radiographic imaging or biopsy confirms or refutes PD. There are 3 categories of IR, as follows:

1. IR1: An increase in overall tumor burden (as assessed by the sum of the product of the diameters [SPD]) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration;
2. 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
3. IR3: An increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number.

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

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

If a subject has a second determination of IR, then subsequent repeat imaging should be performed between 4 and 8 weeks (or earlier if clinically indicated). Follow-up radiographic assessment for subjects with IR is not required if a follow-up biopsy has been performed that confirms the subject's response. If the subject continues in follow up after confirmation, subsequent follow-up visits should be per the schedule of events.

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

7.3 Biomarker Studies

Biomarker assessments will be performed in tumor tissue as outlined in Section 7.3.2. If a tumor sample is obtained as part of standard of care during the study, a part of that sample should be submitted to the sponsor for biomarker testing.

7.3.1 Tumor Biopsy (Parts B and C)

Subjects in Parts B and C must provide tumor tissue for biomarker analysis. Availability of archival tumor tissue (non-bone sites) must be confirmed prior to enrollment. A formalin fixed paraffin-embedded (FFPE) tumor tissue block is preferred. If a FFPE tumor tissue block is not available, the investigator should consult with the medical monitor. For Part C only, subjects who provide additional consent may provide optional biopsy tissue at the time of progression.

Biomarker assessments will not be used for subject selection. Correlative studies will be conducted to gain a better understanding of target-response relationship, predictive biomarkers, mechanism of action, and possible resistance mechanisms.

7.3.2 Biomarkers in Tumor Tissue (Parts B and C)

To understand the relationship between the biological characteristics of tumors before treatment and subject outcomes, tissue from pre-treatment specimens will be examined. Biopsies will be assessed for specific, predictive, and prognostic biomarkers in the tumor. If tissue is available from a standard of care biopsy collected after enrollment, it may also be examined. Biomarker assessments in tumor tissue may include, but are not limited to, PD-L1, characterization of the tumor microenvironment, tumor subtyping, profiling of somatic mutations or alterations in genes or RNA commonly altered in cancer, and drug effects. Assays may include, but are not limited to, immunohistochemistry and next generation sequencing of RNA and DNA.

7.3.3 Biomarkers in Peripheral Blood (Part C Only)

For Part C only, peripheral blood samples will be taken prior to initiation of study therapy, on-treatment, post-treatment, and at progression (Appendix B). Sample collection at the time of disease progression is optional and will be collected from subjects who give additional consent.

Analysis of peripheral blood samples will include, but are not limited to, peripheral blood mononuclear cells, plasma, serum, circulating tumor-free DNA, and/or RNA/DNA from whole blood. These analyses will assess biomarkers associated with disease or treatment outcomes.

7.4 Safety Assessments

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

In Parts B and C, the safety of AN+AD will be assessed by the SMC. The SMC will review accumulating safety data after approximately 10 subjects have completed Cycle 2. If the SMC determines that the risks outweigh the benefits of AN+AD, the sponsor may choose to halt enrollment in Parts B or C of the study.

7.4.1 Adverse Events

7.4.1.1 Definitions

Adverse Event

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

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

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.4.1.3). 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 an 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 subject 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 resulted in hospitalization or prolonged an existing insubject hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject 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 subject 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 drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.4.1.2 for the definition of potential DILI.)

Adverse Event Severity

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

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

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (A+AVD or AN+AD) 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:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

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

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

7.4.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject 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 SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs Signs or Symptoms

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

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, record as both the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction' and record each sign or symptom as an individual AE. The level of severity for the overall infusion-related reaction and each sign or symptom should be recorded separately.

Recording Serious Adverse Events

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

The following should be considered when recording SAEs:

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

Progression of the Underlying Cancer

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 as AEs or SAEs.

Peripheral Neuropathy

PN TEAEs which are ongoing, newly occurring, or worsen during the safety reporting period will be followed during long-term follow-up and recorded in the electronic case report form (eCRF). These events could include, but are not limited to peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Such events, regardless of seriousness, are to be followed for all changes in severity until the sooner of resolution to baseline or study closure. Brentuximab vedotin dose modification guidelines were provided for PN events higher than Grade 1 as shown in Table 4.

Immune-mediated Adverse Events

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events that are potentially immune-mediated, additional information will be collected on the subject's CRF.

IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's CRF.

Pregnancy

Female subjects are advised to avoid pregnancy during treatment and for at least 7 months after the final dose of study drugs (Appendix G). Male subjects are advised that brentuximab vedotin may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Male subjects with partners of childbearing potential are required to use effective contraception during study treatment and for at least 7 months after the final dose of study drugs.

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 7 months after the last dose of study drug(s), including any pregnancies that occur in the partner of a male study subject. Only report pregnancies that occur in a male subject's partner if the estimated date of conception is after the male subject's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 24 hours of becoming aware of a pregnancy. As part of this 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.

Collection of data on the CRF

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

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.4.1.1) should be reported as SAEs.

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 >3xULN

AND

2. Total bilirubin >2xULN, 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 serious adverse reaction associated with the use of the drug and reported promptly to the Sponsor on an SAE form.

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 >3xULN 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.

7.4.1.3 Reporting Periods for Adverse Events, Serious Adverse Events, and Adverse Events of Clinical Interest

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 drug administration (Part A), 30 days after the last dose of brentuximab vedotin, doxorubicin, dacarbazine or 100 days after the last dose of nivolumab, whichever is later (Parts B and C only). All study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies or withdraws consent. For Parts B and C, any SAEs or TEAEs of PN will be followed until resolution, return to baseline, 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.

7.4.1.4 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 a SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator causality assessment

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

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

7.4.2 Clinical Laboratory Tests

The following laboratory assessment(s) will be performed by local laboratories at scheduled timepoints (see Appendix A for Part A and Appendix B for Parts B and 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, eGFR, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, and uric acid. For Parts B and C, the chemistry panel should also include amylase and lipase; TSH, free T3, and free T4 must also be tested at Cycle 1, Cycle 3, and EOT.
- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.
- Hemoglobin A1c.
- The estimated GFR should be calculated using the MDRD equation as applicable for subjects ≥18 years old, with serum creatinine (Scr) reported in mg/dL.

  GFR (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).
- The estimated GFR should be calculated using the bedside Schwartz formula for subjects <18 years old, with Scr reported in mg/dL.

  eGFR = 0.43 x (height/Scr).
- A serum or urine β-hCG pregnancy test for subjects of childbearing potential.

Except for pregnancy testing, results of clinical laboratory tests are to be submitted to a central repository.

7.4.3 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Vital signs (blood pressure, heart rate, and temperature) will also be assessed. For adult subjects, measurements of height obtained within the prior 12 months may be utilized. Weight should be obtained for accurate dose calculation.

7.4.4 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.4.1.4). The sponsor will report all SAEs, including suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities as required per local legislation or regulatory reporting requirements.

7.5 Appropriateness of Measurements

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

Response will be assessed according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014) in Part A, incorporating LYRIC in Parts B and C, which are standardized criteria for evaluating response in Hodgkin lymphoma. The intervals of evaluation in this protocol are considered appropriate for disease management.

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 subjects at the site, Seagen Inc. 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
- Recording and reporting AEs and SAEs
- 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
- Subject coding and randomization (if applicable)
- 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 Seagen Inc. representative will typically 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 subjects, 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 Seagen Inc. or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

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

8.3 Access to Source Data

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

8.4 Accuracy and Reliability of Data

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

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. 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 Seagen Inc. as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

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

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

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, insubject or office subject records) for the maximum period required by the country and Institution in which the study will be conducted, or for the period specified by Seagen Inc., whichever is longer. The investigator must contact Seagen Inc. 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 Seagen Inc.

9 DATA ANALYSIS METHODS

An overview of study outcome measurements is provided in Table 7.

Table 7: Overview of Study Outcome Measurements – Part A

Primary Objective	Corresponding Primary Endpoint	Corresponding Measurement	Timeframe
• To assess the treatment-emergent febrile neutropenia rate in subjects with previously untreated, advanced stage, cHL treated with A+AVD and G-CSF primary prophylaxis (G-PP)	• The febrile neutropenia rate in subjects treated with A+AVD and G-PP	• Proportion of subjects with treatment-emergent FN.	• EOT
Secondary Objectives	**Corresponding Secondary Endpoints**	**Corresponding Measurements**	**Timeframes**
• To assess the incidence and severity of adverse events of clinical interest	• The rates and severity of each AECI	• Proportion of subjects with treatment-emergent FN.	• Duration of study
• To assess dose intensity, dose reductions, and dose delays related to any component of A+AVD	• Mean dose intensity; the rates of dose reduction and dose delays related to any component of A+AVD	• Mean dose intensity; proportion of subjects with dose reduction; proportion of subjects with dose delays.	• EOT
• To assess primary refractory disease rates	• The rate of primary refractory disease	• Proportion of subjects with primary refractory disease.	• Within 3 months of EOT
• To assess subsequent anticancer therapy utilization	• The rates of each subsequent anticancer therapy taken by subjects	• Proportion of subjects with subsequent anticancer therapies.	• Duration of study
• To assess end of treatment complete response rates	• The complete response rate at EOT	• Proportion of subjects with complete response at EOT.	• EOT
• To assess physician-reported progression-free survival rate at 2 years	• The physician-reported PFS	• PFS rate at 2 years.	• 2 years from treatment start date

Table 8: Overview of Study Outcome Measurements – Parts B and C

Primary Objective	Corresponding Primary Endpoint	Corresponding Measurement	Timeframe
• To assess the complete response (CR) rate at EOT with AN+AD in subjects with previously untreated cHL	• CR rate at EOT	• CR rate	• EOT
Secondary Objectives	**Corresponding Secondary Endpoints**	**Corresponding Measurements**	**Timeframes**
• To assess the safety and tolerability of AN+AD	• The rates of each AE	• Incidence, severity, seriousness, and duration of AEs. • Incidence and severity of lab abnormalities	• Duration of study
• To assess the overall response rate (ORR)	• Estimate the ORR	• ORR at EOT	• EOT
• To assess the duration of response (DOR)	• Assess the DOR	• Time point estimates for DOR	• Duration of study
• To assess the duration of complete response (DOCR)	• Assess the DOCR	• Time point estimates for DOCR	• Duration of study
• To assess the event-free survival (EFS)	• Assess EFS	• Time point estimates for EFS	• Duration of study
• To assess the progression-free survival (PFS)	• Assess PFS	• Time point estimates for PFS	• Duration of study
• To assess the overall survival (OS)	• Assess OS	• Time point estimates for OS	• Duration of study

9.1 Determination of Sample Size

For Part A, approximately 40 subjects will be enrolled in order to provide an adequate level of precision for the estimate of the FN rate. If 4 of 40 subjects experience FN, the FN rate is 10% with 95% CI (2.8%, 23.7%) based on the exact Clopper-Pearson method (Clopper 1934); if 2 of 40 subjects experience FN, the FN rate is 5% (95% CI: 0.6%, 16.9%); if 6 of 40 subjects experience FN, the FN rate is 15% (95% CI: 5.7%, 29.8%).

For Part B, approximately 50 subjects will be enrolled in order to provide an adequate level of precision for the estimate of the CR rate at EOT. If 45 of 50 subjects have a CR at EOT, the CR rate at EOT is 90% with 95% CI (78.2%, 96.7%) based on the exact Clopper-Pearson method (Clopper 1934); if 42 of 50 subjects have a CR at EOT, the CR rate at EOT is 84% (95% CI: 70.9%, 92.8%) ; if 48 of 50 subjects have a CR at EOT, the CR rate at EOT is 96% (95% CI: 86.3%, 99.5%). The 73% CR rate at EOT observed in the A+AVD arm in the ECHELON-1 trial was considered the relevant benchmark when determining an appropriate sample size for Part B (Connors 2018).

For Part C, approximately 150 subjects will be enrolled in order to provide an adequate power to reject the hypothesis that CR rate at EOT is ≤90%. Assuming a CR rate of 95%, 150 subjects would provide approximately 80% power to reject the null hypothesis of a CR rate at EOT ≤90% with a 1-sided alpha = 0.05 and using an empirical variance estimate (East v6.4). This sample size calculation accounts for the interim futility analysis which is further described in Section 9.3.8.

9.2 Study Endpoint Definitions

9.2.1 Part A

9.2.1.1 Febrile Neutropenia Rate

The FN rate is defined as the proportion of subjects who experience treatment-emergent FN.

9.2.1.2 Primary Refractory Disease Rate

The primary refractory disease rate is defined as the proportion of subjects with less than CR or relapse within 3 months of EOT, according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014).

9.2.1.3 Complete Response Rate at EOT

The complete response rate is defined as the proportion of subjects with CR at EOT according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014). Subjects who do not have a post-baseline assessment will be scored as non-responders for calculating the CR.

9.2.1.4 Physician-Reported Progression Free Survival

The physician-reported PFS is defined as the time from start of study treatment to first documentation of progression per investigator or to death due to any cause, whichever comes

first. Subjects without progression or death will be censored; censoring details will be provided in the SAP.

9.2.1.5 End of Treatment PET Negativity Rate

End of treatment PET negativity rate is defined as the proportion of subjects who are PET negative at EOT. Subjects are considered PET negative at EOT if they have a Deauville score ≤3 at EOT.

9.2.2 Parts B and C

9.2.2.1 Complete Response Rate at EOT

CR rate at EOT is defined as the proportion of subjects with CR at EOT, according to the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of LYRIC (Cheson 2016), in subjects with previously untreated cHL. Subjects who do not have a post-baseline assessment will be scored as non-responders for calculating the CR rate at EOT.

9.2.2.2 Objective Response Rate

ORR is defined as the proportion of subjects with CR or partial response (PR) at EOT according to the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of LYRIC (Cheson 2016) in subjects with previously untreated cHL.

9.2.2.3 Duration of Response

Duration of response (DOR) is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression (per the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of LYRIC (Cheson 2016)) or death, whichever comes first. Subjects without progression or death will be censored; details will be provided in the statistical analysis plan (SAP). Duration of response will only be calculated for the subgroup of subjects achieving a CR or PR.

Duration of complete response (DOCR) is defined as the time from start of the first documentation of complete tumor response (CR) to the first documentation of tumor progression (per the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of LYRIC (Cheson 2016)) or death, whichever comes first. DOCR will only be calculated for the subgroup of subjects achieving CR. Censoring will be in a manner similar to DOR.

9.2.2.4 Event-free Survival

Event-free survival (EFS) is defined as the time from the start of study treatment to the first documentation of objective tumor progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease, whichever occurs first.

Subjects without progression, death, or receipt of subsequent anticancer therapy to treat residual or progressive disease will be censored; details are provided in the SAP.

9.2.2.5 Progression-free Survival

PFS is defined as the time from start of study treatment to first documentation of objective tumor progression or death. Subjects without progression or death will be censored; details are provided in the SAP.

9.2.2.6 Overall Survival

Overall survival 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 subject is known to be alive.

9.3 Statistical and Analytical Plan

The statistical and analytical plan presented below summarizes the more complete plan 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 site conduct (e.g., adding baseline assessments to define a subgroup). 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

In general, descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages for categorical variables.

Unless otherwise specified, CIs will be calculated at the 2-sided 95% level.

The 2-sided 95% exact CI using the Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable (e.g., ORR).

For time-to-event endpoints, analyses will be performed using Kaplan-Meier methodology. Kaplan-Meier curves will be presented. KM rates and the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

9.3.1.1 Adjustments for Covariates

No covariate adjustment is planned in the analyses.

9.3.1.2 Handling of Dropouts and Missing Data

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

Subjects who do not have at least 1 post-baseline response assessment as specified in Section 7.2 will be counted as non-responders.

9.3.1.3 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough subjects to warrant an analysis by center. Site-to-site variation will not be adjusted in the analyses.

9.3.1.4 Multiple Comparisons and Multiplicity

No multiple comparisons or multiplicity adjustment is planned for this study. No formal hypothesis test will be performed.

9.3.1.5 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 statistical analyses will be the most recent non-missing measurement prior to the first dose of BV unless otherwise specified in the SAP.

9.3.1.6 Analysis Sets

Full Analysis Set

For Part A, the full analysis set (FAS) includes all subjects who receive at least 1 dose of A+AVD (any of the study drugs in the regimen). The FAS will be used for all safety and efficacy analyses. Subject demographics and baseline disease characteristics will be summarized based on FAS.

For Parts B and C, the full analysis set will include all subjects who are enrolled and receive any amount of the combination therapy in the study. A subject is considered enrolled if he/she has met all criteria for participation in the study and has Seagen Inc. approval as documented in the eCRF. The full analysis set will be used as the primary dataset for efficacy and safety analysis. Subject demographics and baseline disease characteristics will be summarized based on the full analysis set.

Per-protocol Analysis Set

For Part A, the per-protocol analysis set (PPS) includes all FAS subjects who received G-PP and did not have any important protocol deviations. The PPS will be used for the analysis for primary endpoint and may be used for analyses for selected secondary endpoints.

9.3.1.7 Examination of Subgroups

Subgroup analyses may be carried out for some endpoints. Detailed methodology will be provided in the SAP.

9.3.1.8 Timing of Analyses for Part A

The primary analysis will be performed when all subjects in the full analysis set for Part A have completed the safety reporting period.

9.3.1.9 Timing of Analyses for Parts B and C

The primary analysis for each part will be performed when all subjects in the full analysis set for that part have had their status determined for the primary endpoint of CR rate at EOT.

9.3.2 Subject Disposition

The number of subjects enrolled, treated with A+AVD or AN+AD, and completing the study will be summarized. An accounting of study subjects by disposition will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment will be summarized by reason for discontinuation and will be listed with the timing and reason for discontinuation. Subjects who withdraw from the study will be summarized by reason for withdrawal and will be listed with the timing and reason for withdrawal or termination.

9.3.3 Subject Characteristics

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

9.3.4 Treatment Compliance

The dose administered at each cycle/dose for each treatment agent will be assessed and dose intensity will be summarized. For Parts B and C, treatment administration will be summarized for the full analysis set. Summary statistics for duration of therapy (weeks) and the number of cycles per subject will be presented, as well as the number and percentage of subjects who were treated at each cycle and completed each cycle.

Details will be provided in the SAP.

9.3.5 Efficacy Analyses

9.3.5.1 Primary Efficacy Analyses – Part A

For Part A, the rate of FN is the primary endpoint. FN rate and the exact 2-sided 95% CIs using the Clopper-Pearson method (Clopper 1934) will be calculated.

9.3.5.2 Primary Efficacy Analyses – Parts B and C

For Parts B and C, the CR rate at EOT is the primary endpoint. CR rate at EOT will be summarized according to investigator. CR rate at EOT and the exact 2-sided 95% CIs using the Clopper-Pearson method (Clopper 1934) will be calculated.

For Part C a hypothesis test will be performed. The null and alternative hypotheses are:

- Null hypothesis: CR rate at EOT ≤90%
- Alternative hypothesis: CR rate at EOT >90%

The null hypothesis will be tested at a 1-sided alpha of 0.05. The associated p-value will be calculated based on the normal approximation with an empirical estimate of the variance. If $p < 0.05$ is observed, the null hypothesis will be rejected in favor of the alternative hypothesis.

If enrollment in Part C is stopped prior to completion, no hypothesis testing will be performed.

9.3.5.3 Secondary Efficacy Analyses – Part A

For Part A, the primary refractory disease rate, the complete response rate and the EOT PET response rate will be derived and its two-sided 95% exact binomial CI will be presented (Clopper 1934).

The physician-reported PFS rate and OS rate will be based on Kaplan-Meier methodology and Kaplan-Meier plots will be presented. For PFS, the 2 year rate and the associated 95% CI will be presented.

9.3.5.4 Secondary Efficacy Analyses – Parts B and C

For Parts B and C, ORR at EOT and the exact 2-sided 95% CIs using the Clopper-Pearson method (Clopper 1934) will be calculated.

Secondary endpoints of DOR, EFS, PFS, and OS are time-to-event endpoints and will be analyzed using Kaplan-Meier methodology. Kaplan-Meier plots will be presented and event rates at a range of follow-up times and their associated 95% CIs will be presented; EFS and PFS rates at 1 and 2 years and the associated 95% CIs will be presented. Further analysis details will be provided in the SAP.

Detailed methodology will be provided in the SAP.

9.3.6 Pharmacokinetic and Immunogenicity Analyses

No pharmacokinetic or immunogenicity analyses will be performed.

9.3.7 Safety Analyses

9.3.7.1 Extent of Exposure

For Part A, exposure of each treatment agent, including duration of each treatment per cycle, number of cycles, total dose, dose modifications (delays, holds, and reductions), cumulative dose, and dose intensity will be summarized and listed using the FAS.

The number of subjects who received pegylated as well as non-pegylated G-CSF will be summarized by cycle as well as the duration of each. A breakdown of the types of G-CSF medications will be provided.

For Parts B and C, duration of treatment will be summarized and listed.

Duration of treatment, number of cycles, total dose and dose intensity will be summarized. Dose modifications will also be summarized.

Details will be provided in the SAP.

9.3.7.2 Adverse Events

An overview of AEs will be presented, including a tabulation of the incidence of all AEs, TEAEs, treatment-related AEs, grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. Adverse events will be defined as treatment emergent if they are newly occurring or worsen following study treatment.

Adverse events will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) and graded using NCI CTCAE, Version 4.03.

AEs will also be listed and summarized by preferred term, severity, and relationship to study drug. The incidence of AEs will be tabulated by preferred term. AEs leading to premature discontinuation of a study drug will be summarized and listed in the same manner.

For Part A, AEs will be assessed during the study from Day 1 dosing and through 30 days following last dose of study drug. For Parts B and C, AEs will be assessed during the study from Day 1 dosing and through 30 days following the last dose of brentuximab vedotin, doxorubicin, or dacarbazine, or 100 days following the last dose of nivolumab, whichever is later. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

9.3.7.3 Deaths and Serious Adverse Events

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

9.3.7.4 Clinical Laboratory Results

For laboratory results, summary statistics for actual values and for change from baseline may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE Version 4.03 and flagged when values are outside the normal reference range.

9.3.7.5 Pregnancies

Pregnancies in female subjects and in female partners of male subjects will be summarized as well as the outcomes of these pregnancies.

9.3.8 Interim Analyses

The SMC will be responsible for monitoring patient safety in Parts B and C of the study (see Section 7.4).

One interim futility analysis will be performed for Part C after approximately 50 subjects have completed response assessment at EOT. At this interim futility analysis, if the CR rate at EOT is ≤80% (40/50 or fewer subjects with CR at EOT), the sponsor in consultation with the SMC may decide to stop further enrollment of Part C of the trial.

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

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R2); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects 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 subject, or legally acceptable representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

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
- 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.

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

Protocol amendments will be submitted to the IRB/IEC prior to implementing. The investigator is responsible for enrolling subjects 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 subject medical records in the subject 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 subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject 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 subject identities.

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

10.5 Clinical Trial Agreement

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

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APPENDIX A: SCHEDULE OF EVENTS – PART A

		Screening/Baseline[A]		Enrollment	Every 28-day cycle				EOT	F/U[B]
	Day	D –28 to 1	D –7 to 1	Within 7D of 1st dose	D1	D2	D15	D16	Within 30–37D of last dose[C]	Every 12 wks
	Visit window									±1 wk
Screening/ Baseline Assessments	Inclusion/Exclusion	X		Submit eligibility confirmation to Sponsor prior to treatment						
	Informed consent	X								
	Medical history	X								
	Echocardiogram/MUGA scan	X								
	ECG	X								
	Pregnancy test (subjects of childbearing potential)		X		X					
Safety Assessments	Physical exam		X						X	
	Height		X							
	Weight[D]		X		X		X			
	CBC with differential[D]		X		X		X		X	
	Serum chemistry panel[D]		X		X		X		X	
	Hgb A1c		X						X	
	ECOG performance status		X						X	
	Concomitant medications	Related to study procedures[E]			Collect from Day 1 predose through safety reporting period of study drug(s)					
	Adverse event collection									
Treatment	A+AVD administration[F]				X		X			
	Filgrastim administration					X[G]		X[G]		
	Pegfilgrastim administration					X[G]		X[G]		
Response Assessment	CT of chest, neck, abdomen, pelvis	X[K]							X[J]	
	PET scan[H]	X[K]							X[J]	
	B symptom assessment		X						X	
	Disease status									X[I]
	Survival/subsequent anticancer treatment									X

A. If Baseline Visit activities occur within 1 day of Cycle 1 Day 1, they do not need to be repeated.
B. Subjects will remain in follow-up until death, withdrawal of consent, or completion of 2 years of long-term follow-up (from EOT visit), whichever occurs first.
C. EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.
D. Clinical laboratory assessments may be performed 1 day prior to A+AVD administration.
E. From time of informed consent
F. A+AVD should be administered as described in Section 5.
G. Either filgrastim or pegfilgrastim should be started 24–36 hours from the last dose of the A+AVD regimen and administered as described in Section 5.4.3. Filgrastim should be administered for a minimum of 5 days.
H. A CT of diagnostic quality may be combined with the PET scan when both are required per protocol
I. Disease status will be followed until the subject experiences progressive disease
J. Not required if conducted 1 week prior to EOT
K. Scans collected within 3 days prior to Day -28 will be accepted

APPENDIX B: SCHEDULE OF EVENTS – PARTS B AND C

		Screening/ Baseline		Enrollment	Every 28-day cycle		Disease Assessment	EOT	Safety	F/U[A]
	Day	D –28 to 1 (-3 days)	D – 7 to 1	Within 7D of 1st dose	D1	D15	Cycle 2 Day 25	Within 30–37D of last dose[B]	100 days post last dose[C]	Every 12 wks
	Visit window				±2d	±2d	+3d		+2 wk	±1 wk
Screening/ Baseline Assessments	Inclusion/Exclusion, medical history	X	X	Submit eligibility confirmation to Sponsor prior to treatment						
	Informed consent	X								
	International prognostic score (Part B only)	X								
	ECG	X								
	Collection of archived tumor specimen or fresh tumor biopsy[R]	X								
	Pregnancy test (subjects of childbearing potential)		X		X			X		
	CZ only: HBV and HIV serological testing	X[W]								
	CZ only: HCV PCR testing	X[X]								
Safety Assessments	Physical exam[D]		X		X			X	X	X[E]
	CBC with differential		X		X[K]	X		X	X	
	Chemistry panel		X[I]		X[I, J, K]	X[I]		X[I, J]	X[I]	
	eGRF[S]		X		X	X		X	X	
	Peripheral blood collection[F]				X[F, G]			X[F]		X[F, H]
	Hgb A1c		X					X		
	B symptom assessment		X		X[K]			X		
	ECOG performance status		X		X[K]	X		X		
	Echocardiogram/MUGA scan[L]	X								
	Concomitant medications	Related to study procedures[M]			Collect from Day 1 predose through safety reporting period of study drug(s)					
	Adverse event collection[M, N]									
Treatment	Study drug administration				X	X				
Response Assessment	CT of neck, chest, abdomen, pelvis	X[Q, V]					X[V]	X[T, V]		X[P, V]
	PET	X[Q]					X[U]	X[U]		X[O, P]
	Tumor biopsy									X[H]
	Survival and post-treatment therapies								X	X

A. For Parts B and C, disease assessments will be performed during follow-up every 3 months after the EOT visit for the first year, then every 6 months for 2 additional years. Subjects will then continue in follow-up for 2 additional years (5 years total), with physical exams required every 6 months and disease assessments required every 12 months. Timing of follow up visits should be relative to EOT visit and not relative to last dose.

B. EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30-37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

C. The safety visit will be 100-114 days after last dose of nivolumab or 30–37 days post last dose of BV (concurrent with the EOT visit), whichever is later.

D. Physical exam includes vital signs (blood pressure, heart rate, temperature), height (at baseline) and weight

G. Cycles 1, 2, and 4 only

H. Collected only at the time of progression if the subject provides additional consent

I. Must include amylase and lipase (Section 7.4.2)

J. Must include TSH, free T3, T4 at cycles 1, 3, and EOT only (Section 7.4.2)

K. Not required if assessed within 1 day prior to C1D1

L. Performed within 1 month prior to enrollment is acceptable

M. From time of informed consent

N. All PN TEAEs will be followed until resolution, return to baseline, or study closure and entered in the eCRF. Telephone contact is acceptable

O. May discontinue after EOT if negative

P. Parts B and C: PET-CT scan every 3 months post-EOT for one year, then every 6 months for an additional 2 years. For the final 2 years, PET-CT scan every 12 months.

Q. Scans collected within 3 days prior to Day -28 will be accepted.

R. Refer to Section 7.3.1 for details

E. Parts B and C: Physical exam to follow the PET-CT scan schedule for the first 3 years of long-term follow-up. For the final 2 years, a physical exam should occur every 6 months.
F. Part C only
S. eGFR will be calculated per MDRD.
T. No CT or PET scan is required if the subject had CT/PET scans within a week prior to EOT or if the subject discontinued due to radiographically confirmed PD.
U. CT of diagnostic quality may be combined with PET to satisfy the requirements for CT and PET scanning. Refer to Section 7.2 for further guidance on Deauville scale grading for PET scans.
V. To decrease radiation exposure, CT scans of neck will be mandated at Baseline only, restaging imaging will only be repeated if neck disease is present at Baseline.
W. CZ only: Serological testing will be completed, positive results will result in subject being considered ineligible for enrollment.
X. CZ only: PCR testing will be completed, positive results will result in subject being considered ineligible for enrollment.

APPENDIX C: PERFORMANCE STATUS SCALES CONVERSION

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

APPENDIX D: INTERNATIONAL PROGNOSTIC FACTORS SCORING FOR ADVANCED HODGKIN LYMPHOMA

One Point To Be Assigned for Each Prognostic Factor:

Serum albumin <4 g/dL

Hemoglobin <10.5 g/dL

Male sex

Stage IV disease

Age ≥45 years

White cell count ≥15,000 mm^3

Lymphocyte count <600 mm^3 or <8% of white-cell count

Source: (Hasenclever 1998) A Prognostic Score for Advanced Hodgkin's Disease.

APPENDIX E: NEW YORK HEART ASSOCIATION CLASSIFICATION

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

Class I:	subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	subjects with marked limitation of activity; they are comfortable only at rest.
Class IV:	subjects 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 F: OVERVIEW OF LYRIC CRITERIA (PARTS B AND C ONLY)

If tumor flare or pseudo-progression is suspected, then a clinical response of indeterminate response (IR) should be reported based on the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of LYRIC (Cheson 2016).

Definition of Indeterminate Response

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

This pattern may be seen as a consequence of either delayed response or early immune-mediated flare. At least within the context of clinical trials, a biopsy is encouraged in this case because this may help to distinguish the two and, if positive, will confirm the impression of PD. However, if negative for lymphoma, it will support the concept of pseudoprogression and contribute to our understanding of this phenomenon. When such a biopsy is neither safe nor feasible, decisions must be based on a repeat scan 12 weeks after the initial determination of IR.

It is recognized that "clinical deterioration" is subjective. In some cases, the simple growth of a nodal or tumor mass could worsen the symptoms mechanically related to that mass, such as pain at the tumor site or compression of adjacent structures, etc. Such an increase in symptoms that can be directly attributed to the size of the tumor mass may not be considered as clinical deterioration in this context. However, in most cases, subjects should be experiencing clinical stability or improvement by investigator assessment to be considered as having IR, and in all cases, the patient must be considered likely to tolerate continued treatment and not at risk of serious complications should further tumor growth occur.

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

This phenomenon may occur early or late in the treatment course, and therefore, unlike IR1, is not defined by its temporal relationship to treatment initiation. Both within and outside the context of clinical trials, a biopsy is strongly encouraged in such cases. 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 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 progressive disease (PD) with checkpoint inhibitors. 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 of the lesion in question.

While awaiting a better characterization of this phenomenon, we propose that, under the modified response criteria, an increase in FDG avidity of one or more lesions suggestive of lymphoma, without a concomitant increase in size of those lesions meeting PD criteria does not constitute PD.

It is possible that, at a single time point a subject 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 IR2 should take priority (e.g., IR2 in the above example).

These 3 patterns of IR as defined above (IR1, IR2, and IR3) may have very different mechanisms and clinical implications. Therefore, it is critical that data are collected in a consistent manner so that these 3 possible atypical response types occurring within the context of checkpoint inhibitors can be distinguished.

Follow-Up of Indeterminate Response

In subjects categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated, and the subject should be considered to have true PD 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 ≥1 lesion for lesions ≤2 cm, and 10 mm for lesions >2 cm, to be consistent with the Lugano classification (Cheson 2016). The 10% threshold is empiric but designed to account for variability in measurement, especially when taken along with the minimum increase (Oxnard 2011). If the target SPD increase is <10%, the response would still be categorized as IR1, and the subject could continue treatment until a subsequent scan shows either PD (≥10% increase from first IR1 time point and an increase of >5 mm in either dimension of ≥1 lesion) or response (≥50% decrease from baseline). In this situation, it is reasonable to repeat imaging in 4–8 weeks of the original IR1 time point 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 subject should be considered to have PD.
- In the case of IR3, because inflammatory responses may result in an increase in the standardized uptake value of a lesion, the subject 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.

Importantly, if a subject is assessed as having IR and then "true" PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should be subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR. We recognize that these lesions may remain stable during the time of observation, but, even if this is the case, the initial designation of IR should be changed to PD.

APPENDIX G: GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject'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 7 months after the final dose of study drug; see Section 4.1).

Acceptable methods for highly effective birth control (preventing conception)

Subjects who are of childbearing potential[a] or whose partners are of childbearing potential and who are sexually active in a way that could lead to pregnancy may choose to use any TWO of the following methods (please see acceptable combinations below):

- 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 (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b]
  - All male subjects must use a condom (with pregnant/breastfeeding and non-pregnant/non-breastfeeding partners) during treatment and 7 months after the last dose of study drug.

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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

b A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception).

Acceptable combinations of contraceptive methods:

- Hormonal method and vasectomy
- Hormonal method and barrier method
- Intrauterine device and vasectomy
- Intrauterine device and barrier method
- Tubal ligation and vasectomy
- Tubal ligation and barrier method

Acceptable methods for preventing secondary exposure to seminal fluid

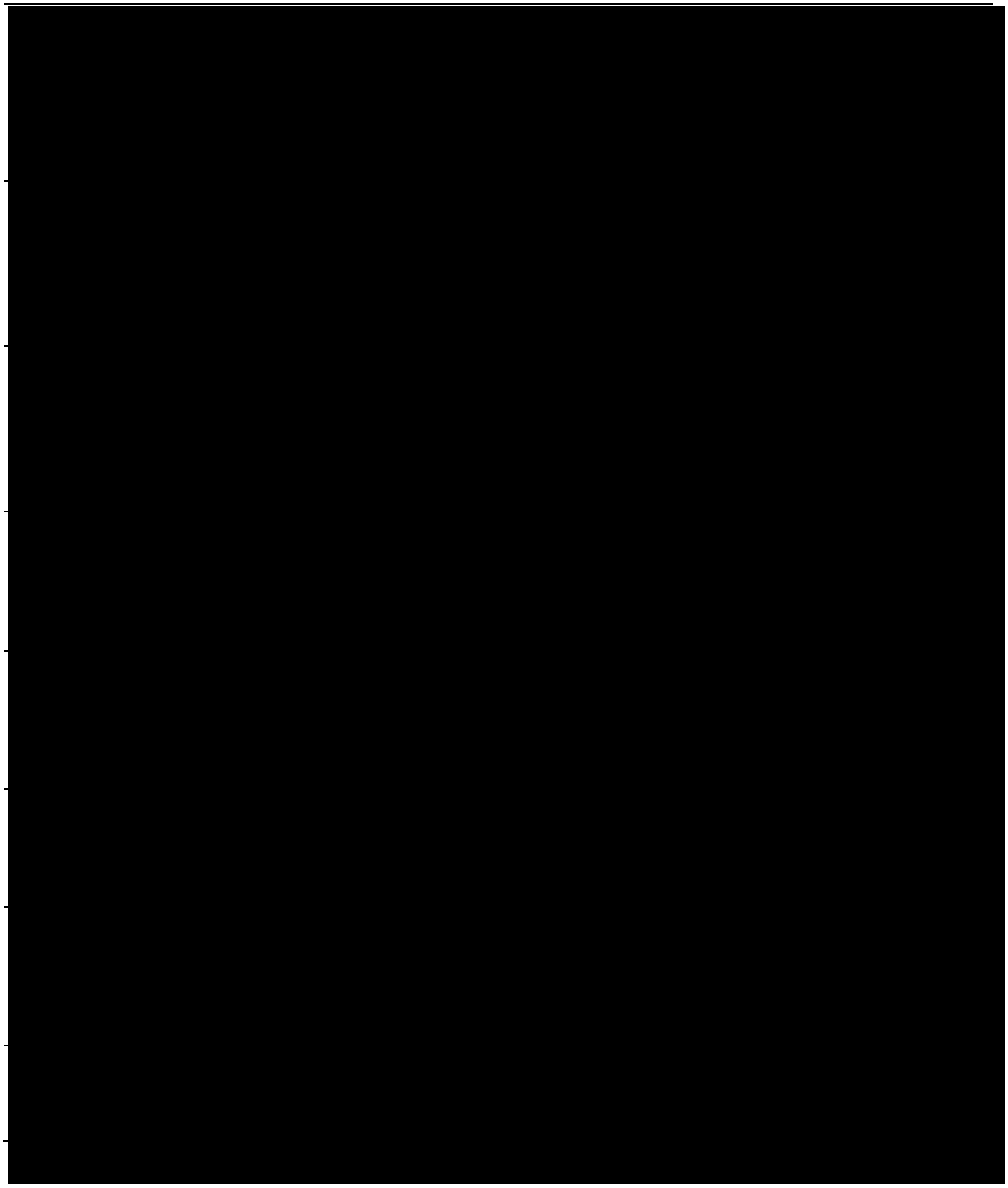
Subjects born male and who are sexually active with a pregnant or breastfeeding person, must use the contraceptives in Option 1 or 2:

- 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
- Barrier methods alone, including double-barrier methods

APPENDIX H: KATZ INDEX OF INDEPENDENCE IN ACTIVITIES OF DAILY LIVING



APPENDIX I: MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patients to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain, blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists >5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists >3-5 days with oral steroids: • Treat as Grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves: • Continue steroids until Grade 1, then taper over at least 1 month If persists >3-5 days, or recurs after improvement:

Grade of Diarrhea/Colitis (NCI CTCAE v4)	Management	Follow-up
≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	• Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine >ULN and > than baseline but ≤1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: • Resume routine creatinine monitoring per protocol If worsens: • Treat as Grade 2 or 3/4
Grade 2-3 Creatinine >1.5x baseline to ≤6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: • Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persists >7 days or worsen: • Treat as Grade 4
Grade 4 Creatinine >6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1: • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3/4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor Symptoms daily, consider hospitalization • 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2.0 to 4.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hrs or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT >ULN to 3.0x ULN and/or T.bili >ULN to 1.5x ULN	• Continue I-O therapy	• Continue LFT monitoring per protocol <u>If worsens:</u> • Treat as Grade 2 or 3/4
Grade 2 AST or ALT >3.0 to ≤5x ULN and/or T.bili >1.5 to ≤3x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	<u>If returns to baseline:</u> • Resume routine monitoring, resume I-O therapy per protocol <u>If elevation persist >5-7 days or worsen:</u> • 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT >5x ULN or T.bili >3x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	<u>If returns to Grade 2:</u> • Taper steroids over at least 1 month <u>If does not improve in >3-5 days, worsens or rebounds</u>: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV. For subjects with HICC, please refer to the protocol for specific details.

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

Asymptomatic TSH elevation	• Continue I-O therapy per protocol If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	• Evaluate endocrine function • Consider pituitary scan <u>Symptomatic with abnormal lab/pituitary scan:</u> • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent • Initiate appropriate hormone therapy <u>No abnormal lab/pituitary MRI scan but symptoms persist:</u> • Repeat labs in 1-3 weeks/MRI in 1 month	<u>If improves (with or without hormone replacement):</u> • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist • If adrenal crisis is ruled out, then treat as above for symptomatic endocrinopathy	

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Rash (NCI CTCAE v4)	Management	Follow-up
Grade 1-2 Covering ≤30% BSA*	• Symptomatic therapy (e.g., antihistamines, topical steroids) • Continue I-O therapy per protocol	<u>If persists >1-2 weeks or recurs:</u> • Consider skin biopsy • Delay I-O therapy per protocol • Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. <u>If worsens</u>: • Treat as Grade 3-4
Grade 3-4 Covering >30% BSA; Life threatening consequences*^	• Delay or discontinue I-O therapy per protocol • Consider skin biopsy • Dermatology consult • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	<u>If improves to Grade 1:</u> • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Refer to NCI CTCAE v4 for term-specific grading criteria.

^ If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	• Continue to monitor patient <u>If worsens</u>: • Treat as Grade2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	<u>If improves to baseline:</u> • Resume I-O therapy per protocol when improved to baseline <u>If worsens</u>: • Treat as Grade 3-4
Grade 3-4	• Discontinue I-O therapy per protocol	<u>If improves to Grade 2:</u>

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Severe Symptoms; Limiting self-care ADL; Life-threatening	• Obtain neurology consult • Treat symptoms per local guidelines • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	• Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Myocarditis Adverse Event Management Algorithm

Grade of Myocarditis (NCI CTCAE v4)	Management	Follow-up

Grade 2
Symptoms with mild to moderate activity or exertion
	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  o Troponin and BNP
	  o ECG ± continuous cardiac monitoring
	  o Echocardiogram
	  o Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Grade 3
Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
 	
Grade 4
Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac monitoring
	• Cardiac evaluation in include:
	  o Troponin and BNP monitoring
	  o ECG ± continuous cardiac monitoring
	  o Echocardiogram
	  o Cardiac MRI
	  o Myocardial biopsy if feasible
	• Immediate initiation of 2.0 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	• Additionally, for Grade 4:
	  o Hospitalize/transfer to institution with expertise
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

Grade of Myocarditis (NCI CTCAE v4)	Management	Follow-up
	in intensive cardiac monitoring o Consider ATG as second agent given its immediate effect	

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

APPENDIX J: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled Multiple Part Clinical Trial of Brentuximab Vedotin in Classical Hodgkin Lymphoma Subjects

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 K: DOCUMENT HISTORY

Version	Date
Original	12-Jul-2018
Amendment 1	09-Nov-2018
Amendment 2	27-Aug-2019
Amendment 3	30-Mar-2020
Amendment 4	11-Nov-2020
Amendment 5	16-Apr-2021
Amendment 6	29-Nov-2021
Amendment 7	xx-July-2023

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Title page	Change of medical monitor to [redacted]	[redacted] will be providing clinical oversight of the study
Title page, 7.4.1.2, and 7.4.1.4	Changed Serious Adverse Event reporting information	To align with current Seagen Inc. practice
6.5	Revised long-term follow-up (LTFU) information to indicate that participants will remain in LTFU for up to 2 years from the End of Treatment visit	To clarify the timeline for LTFU for proper site operations
Appendix C	Replaced the International Prognostic Index (IPI) score sheet with International Prognostic Score (IPS) information.	Correction

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Throughout	Added Part B: Treatment of cHL subjects with brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD)	Exploration of a novel combination treatment to assess safety and the potential for efficacy in this subject population.
Throughout	Various administrative changes were made throughout	To provide clarity when necessary and conform to editorial standards
Section 1	Added information on nivolumab	To provide context for the exploration of nivolumab as part of this novel combination treatment
Section 1.2	Revised section to indicate experience with brentuximab vedotin and A+AVD	To provide context for Part A of the study
Section 1.3	Added information on clinical experience with nivolumab	To provide context for the exploration of nivolumab as part of this novel combination treatment
Section 1.4.2	Added a study rationale for Part B	To provide a rationale for the addition of this novel combination treatment
Section 2	Added objectives for Part B	To provide objectives and the corresponding endpoints for Part B, as this part will be evaluated separately from Part A
Section 3	Added information on the study design for Part B	To provide information regarding the design and execution of Part B and the study rationale for Part B
Section 3.1	Revision of the study population to a total of 90 subjects	To provide the approximate number of subjects for both parts of the study
Section 4.1	Revised inclusion criteria, including the following key points: • Part B to allow subjects with Stage IIA with bulky and Stage IIB cHL • Subjects 12+ years will be allowed to enroll • Subjects must have an ECOG of 1 or 2	To provide an appropriate subject population for testing AN+AD
Section 4.2	Revised exclusion criteria, including the addition of the following: • Planned consolidative radiotherapy (Part B only) • Active interstitial lung disease that is symptomatic or may interfere with management of drug-related pulmonary toxicity (Part B only) • Idiopathic interstitial pneumonia or diffusing capacity of the lung for carbon monoxide <50% predicted • Subjects with acute or chronic graft-versus-host-disease (GvHD) or receiving immunosuppressive therapy as treatment for or prophylaxis agent against GvHD. • Previous treatment with brentuximab vedotin.	To provide an appropriate subject population for testing AN+AD

Section(s)	Change	Rationale
Section 5.1	Provided details for treatment administration for Part B	To provide guidance on administering AN+AD
Section 5.2	Modified to indicate that a pharmacy binder will be provided for brentuximab vedotin	Seagen Inc. will provide brentuximab vedotin (previously commercial supply for Part A)
Section 5.2.3	Added a section to indicate that brentuximab vedotin will be provided by Seagen Inc.	Updated to indicate a switch to clinical rather than commercial supply
Table 4	Updated information for dose modifications for brentuximab vedotin-associated toxicity	To provide management information for specific potential toxicities
Section 5.3.3	Added information on administration of doxorubicin and dacarbazine for Part B	To provide information on administration of these agents
Section 5.5	Added a section to provide information on nivolumab treatment administration	To provide information on administration of nivolumab for Part B
Section 5.6.2.1	Added a section to provide information on allowed concomitant therapy as applies to Part B only	To provide information on allowed concomitant therapy for Part B
Section 5.6.3	Added information indicating that planned consolidative radiotherapy of lesions is exclusionary for Part B	To clarify that investigators must exclude subjects for whom they plan to administer this type of radiotherapy
Section 5.7.1	Added information on infusion or hypersensitivity reactions that may occur in response to either brentuximab vedotin or nivolumab	To provide guidance on common symptoms of these reactions
Section 5.7.4	Added a section with information on the management of immune-adverse events	To provide guidance on these events, which are associated with nivolumab as an immuno-oncology agent
Section 6.3.2	Added a section on procedures for Part B	To provide guidance on study tests and procedures required for Part B
Section 6.4	Revised the EOT visit procedures	To provide guidance on EOT tests or procedures required for Part B and further clarification on the timing of CT/PET scans
Section 6.5	Added a section to detail procedures required at the safety visit for Part B	To provide guidance on the timing of the safety visit and the tests and procedures required at this visit
Section 6.6.2	Added a section to detail long-term follow-up procedures for Part B	To provide guidance on the tests and procedures required during long-term follow-up for Part B
Section 7.2	Added information on response/efficacy assessments for Part B	To provide guidance on determination of antitumor activity in Part B
Section 7.3	Added information to indicate that the safety in Part B will be assessed by a Safety Monitoring Committee	To provide guidance on the timing of this safety analysis and potential subsequent activities
Section 7.3.1	Revised as needed throughout to provide appropriate safety management for the study with the addition of Part B. This includes a longer safety reporting period for Part B, due to safety requirements for nivolumab.	To provide guidance on appropriate identification, reporting, and management of potential adverse events
Section 9	Revised throughout to provide appropriate statistical analysis information for the revised subject population size for Part A, and for the newly added Part B	To provide information on the anticipated statistical analysis for the study

Section(s)	Change	Rationale
Appendix B	Added a schedule of events for Part B	To provide information on the tests and procedures required for Part B during study cycles

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Throughout	Added Part C: Treatment of early stage cHL subjects with brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD)	Exploration of a novel combination treatment to assess safety and the potential for efficacy in an early stage cHL subject population.
Throughout	Various administrative changes were made throughout	To provide clarity when necessary and conform to editorial standards
Section 1.1	Added background information on the impact of bulky mediastinal disease in the cHL population	To provide background information on this specific cHL population
Section 1.2	Added information regarding the clinical experience of combination treatment with brentuximab vedotin, doxorubicin, and dacarbazine, and associated common adverse events	To provide detailed information on the use of these drugs in combination and their expected potential adverse events
Section 1.4.2	Provided information on the use of brentuximab vedotin and nivolumab in combination and clarified that vinblastine may not be required for regimen efficacy	To provide complete information on the rationale for Parts B and C
Section 3.1.1	Added a new section to describe the composition, meeting schedule, and objectives for the Safety Monitoring Committee (SMC) for Parts B and C of the study	To clarify the process and responsibilities associated with the SMC
Section 3.2.3	Added the following sentence to "Method of Assigning Subjects to Treatment Groups": Subjects with Stage II cHL with bulky mediastinal disease will be assigned to Part B. Subjects with Stage I or II cHL with non-bulky mediastinal disease will be assigned to Part C.	To provide direction on enrolling subjects in either Part B or Part C
Section 3.2.4.2	Added the following information to "Rationale for Selection of Doses": Subjects in Part B will receive up to 6 cycles of treatment. Subjects in Part C will receive 4 cycles of treatment.	To provide direction on the number of treatment cycles for subjects in either Part B or Part C
Section 3.2.4.2	Clarified that safety will be evaluated separately for Parts B and C	To clarify the process of SMC oversight of Parts B and C

Section(s)	Change	Rationale
Section 4.1	Modified inclusion criterion 1: Part B will enroll Ann Arbor Stage II cHL with bulky mediastinal disease or Stage III or IV cHL Part C will enroll Ann Arbor Stage I or II with non-bulky mediastinal cHL	To provide enrollment criteria for subjects in either Part B or C
Section 4.1	Modified inclusion criterion 2a to specify that subjects enrolling in Part C must submit a tumor block for analysis	To provide direction on tumor biopsy tissue requested for Part C participation
Section 4.1	Modified inclusion criterion 9 to indicate that serum bilirubin can be ≤3 x ULN for subjects with documented hepatic involvement with lymphoma	To clarify baseline laboratory data requirements for inclusion of these subjects
Table 4	Changed the recommendation for management of Grade 2 sensory neuropathy from "continue at same dose level" to "reduce BV dose to 0.9 mg/kg"	To provide updated guidance on the management of Grade 2 sensory neuropathy
Section 5.2.4	Added text to clarify that dose modifications may include permanent discontinuation of brentuximab vedotin	To provide clear guidance on appropriate dose modifications and the impact on the study treatment regimen
Section 5.2.4	Clarified that subjects who discontinue brentuximab vedotin due to AE after only 1 cycle of treatment may not continue on the study	To provide appropriate safety measures for subjects who have AEs early in treatment
Section 5.5.3	Reduced the duration of nivolumab administration from 60 to 30 minutes	To align with the current recommendation for nivolumab administration
Section 5.5.3	Added the following sentence: Nivolumab should be administered at a set dose of 240 mg and neither reduced nor increased.	To clarify that nivolumab should be neither reduced nor increased in dose
Section 5.5.4.1	Added text to clarify that dose modifications may include permanent discontinuation of nivolumab	To provide clear guidance on appropriate dose modifications and the impact on the study treatment regimen
Section 5.5.4.1	Added the following sentence: If nivolumab is held due to AE, once the AE has resolved administration of nivolumab should resume on the same schedule at the next cycle of therapy.	To clarify the appropriate timing for resuming nivolumab treatment after an AE-related hold
Section 6	Added the following sample collection for Part C only to Cycle 1 Day 1; Cycles 2 and 4, Day 1; the End of Treatment visit, and long-term follow-up (optional):	To provide direction for blood collection used for biomarker analyses in Part C

Section(s)	Change	Rationale
	Peripheral blood collection for biomarker analyses	
Section 6.6.2	Added clarification that PET must be performed in addition to CT scans if CT is positive at the prior time point in PET-negative disease	To clarify the time point when PET/CT may be required
Section 6.6.2	Added the following for Part C: Subjects in Part C who do not have disease progression will continue in long-term follow-up for an additional 2 years. During this period, a physical exam should be performed every 6 months and a dedicated CT of chest, neck, abdomen, and pelvis should be performed every 12 months.	To provide for a 5 year follow-up period for Part C subjects
Section 6.6.2	Added the following sentence: For Part C only, peripheral blood may be collected at the time of disease progression if the subject has provided additional consent	To provide for optional biomarker sample collection during long-term follow-up at the time of disease progression
Section 7.3.1	Added the following sentence: For Part C only, subjects who provide additional consent may provide optional biopsy tissue at the time of progression.	To provide for optional biomarker sample collection during long-term follow-up at the time of disease progression
Section 7.3.3	Added a section to describe collection and analysis of peripheral blood for Part C	To describe the possible analyses that could occur with these samples
Section 7.4.1.3	Extended the safety reporting window for Parts B and C to 100 days	To provide an appropriate window for collection of information regarding AEs that may occur in Parts B or C
Section 9.1	Added information on the statistical determination of sample size for Part C	To provide background information on sample size selection for Part C
Appendix B	Revised as needed to align with operational changes throughout Parts B and C	To align with operational changes as needed
Appendix G	Revised to match current best practices in contraceptive guidance for subjects participating in this clinical trial	To provide clarity on contraceptive expectations and options during subject participation in this clinical trial

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Protocol Synopsis; Section 1; Section 3.2.3; Section 4.1	Part B: Added subjects with Ann Arbor Stage I cHL with bulky mediastinal disease	Early stage bulky mediastinal cHL to include both Stage I with bulky disease and Stage II with bulky disease
Protocol Synopsis; Section 1; Section 3.2.3; Section 4.1	Part C: Changed "non-bulky" to "without bulky" for subjects with Ann Arbor Stage I or II cHL enrolled in Part C	To provide clarification
Throughout	Changed "Seattle Genetics" to "Seagen Inc."	Updated to reflect change in sponsor name
Throughout	Removed USPI references	Updated to global indications
Throughout	Removed FDA references	Updated to meet global regulatory requirements
Throughout	Addition of EMA indications and updated clinical experience for brentuximab vedotin	Updated to add EMA indications
Title Page	Addition of EudraCT Number	Updated to meet EU Regulatory requirements
Title Page	Addition of mobile telephone for medical monitor	To provide additional contact information for medical monitor
Protocol Synopsis	Removed the following text: Subjects are excluded if they have nodular lymphocyte predominant HL ~~or have symptomatic neurologic disease that compromises normal activities of daily living or requires medication~~.	To provide high-level exclusion criteria for synopsis; deleted text is in body of the protocol
Protocol Synopsis	Removed the following text: ~~Prior immunosuppressive chemotherapy, therapeutic radiation, or any immunotherapy (e.g., immunoglobulin replacement, or other monoclonal antibody therapies, including IO agents) must be completed a minimum of 4 weeks prior to the first study dose of any study drug.~~	To align with the treatment-naïve study design of the protocol
Protocol Synopsis	Added the following to efficacy assessments: To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline.	To provide clarification
Protocol Synopsis; Section 1; Section 4.1	Added definition of bulky disease (≥10 cm by CT imaging)	To provide clarity in classifying cHL with or without bulky mediastinal disease
Section 1; Section 1.4.2; Section 7.4	Updated text as follows:	To provide clarity on safety assessment by SMC

	…after approximately 10 subjects have completed ~~treatment~~ **Cycle 2**…	
Section 1.2	Added the following text: The prevalence of neutropenia and FN was mitigated in a sub-set of subjects who received G-PP (29% vs 70% without G-PP, and 11% vs 21% without G-PP, respectively) (Straus 2018a).	Additional rationale for use of G-PP
Section 1.2	Removed the following text: and SMC	To correct previous version; SMC was not part of recommendation of primary prophylaxis
Section 1.4.1	Removed the following text: ~~Further analysis has demonstrated a noted difference in study results in North America when compared to other regions (Connors 2018; Ramchandren 2018). Subjects in the North American intent to treat (ITT) population demonstrated an mPFS by independent review facility at 2 years of 84.3% for A+AVD vs 73.7% for ABVD (hazard ratio (HR)=0.60, 95% CI; 0.40, 0.90). 2-year PFS by investigator in the North American population was 88.1% for A+AVD subjects vs 76.4% for ABVD subjects (HR=0.50, 95% CI; 0.32–0.79).~~	To align with global regulatory updates
Section 1.4.2	Added the following for SMC assessment: If an SMC determines that the risks outweigh the benefits of AN+AD, the sponsor may choose to halt enrollment in Parts B or C of the study.	To provide clarity with other sections of the protocol
Figure 3	Updated Footnote "B" to the following: c d Follow-up period for Parts B and C includes 2 additional years (5 years total).	To clarify that 5-year total follow-up applies to Parts B and C
Section 3.1.1	Definition of End of Study added	Updated to meet EU Regulatory requirements
Section 3.2.4.2	Added the following bolded text: The recommended dose for brentuximab vedotin in combination with chemotherapy for previously untreated Stage III or IV cHL is 1.2 mg/kg up to a maximum of 120 mg **based on 100 kg body weight**	To provide clarity for maximum dose of brentuximab vedotin
Section 4.1	Updated required age for inclusion with the following bolded text: Age 12 years or older **in the United States. For regions outside of the**	Updated to provide clarity on age for inclusion in regions outside of the United States

	United States, subjects must be age 18 years or older.	
Section 4.1	Added the following to inclusion criteria: Subjects of childbearing potential must agree not to breastfeed or donate ova, starting at the time of informed consent and continuing through 7 months after the final dose of study drug.	Updated to align with protocol template updates
Section 4.1	Adjusted the following inclusion criteria: If sexually active in a way that could result in pregnancy, subjects of childbearing potential must agree to use 2 ~~effective~~ contraception methods **(including 1 highly effective)** during the study and for ~~6~~ **7** months following the last dose of study drug (see Appendix G). Subjects who can father children and have partners of childbearing potential must agree to use 2 ~~effective~~ contraception methods during the study and for 7 months following the last dose of study drug **(see Appendix G)**. Subjects who can father children must ~~also~~ be willing to refrain from sperm donation **starting at the time of consent and continuing through the study period and for at least 7 months after the final dose of study drug** ~~during this time~~. **Subjects born male who are sexually active with a pregnant or breastfeeding person must use contraceptives outlined in Appendix G to prevent secondary exposure to seminal fluid.**	Updated to align with protocol template updates and adhere to global regulatory requirements
Section 4.1	Adjusted the following inclusion criteria: …estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73 m2 using the Modification of Diet in Renal Disease (MDRD) study equation as applicable **for subjects ≥18 years old, or bedside Schwartz formula for subjects <18 years old** (see Section 7.4.2).	Added bedside Schwartz formula as this is more appropriate for pediatrics
Section 4.2	Removed the following from Exclusion Criterion #3: ~~unless underlying disease has progressed on treatment~~	To provide clarity since all subjects will be receiving first line treatment in this study

Section 4.2	Updated Exclusion Criterion #15: Neurologic disease compromising at least 1 Activity of Daily Living (total dependence) per Katz Index of Independence in Activities of Daily Living (Appendix H), or poorly controlled by medication per the investigator's assessment.	To include a co-morbidity assessment tool for evaluation of Activities of Daily Living
Section 4.2	Added the following bolded text to Exclusion Criterion #25: Subjects who have received a live or attenuated vaccine within 30 days prior to treatment **and 100 days after the last dose** (Parts B and C only).	Updated to align with text in Section 5.6.3.1
Section 4.2	Added the following bolded text to Exclusion Criterion #26: Inhaled, **ocular, intra-articular,** or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.	To provide clarity for steroids allowed in the absence of active autoimmune disease
Section 5.2.2	Added the following bolded text: The maximum dose calculated per administration in this study is 120 mg **(1.2 mg/kg)**.	To provide clarity for maximum dose of brentuximab vedotin
Section 5.2.4	Moved text describing dose modifications	To better describe information listed in the dose modification tables
Section 5.2.4	Added the following text: Refer to Section 6 of the Investigator's Brochure for additional information on the safety of brentuximab vedotin, and guidance regarding appropriate safety monitoring for subjects.	To provide additional guidance on safety of brentuximab vedotin
Section 5.3.2	Updated with the following bolded text: **In the United States,** doxorubicin, vinblastine, and dacarbazine will be supplied by the study site from commercial sources, and billed to subjects and/or their third-party payer (insurance, a healthcare provider, or applicable government program). **In regions outside of the United States, doxorubicin and dacarbazine will be provided by Seagen Inc. via a central pharmacy, or will be supplied by the study site from a local source to be reimbursed by Seagen Inc.**	To provide clarity for drug procurement methods for regions outside of the United States
Section 5.4.1	Adjusted text describing G-CSF use in the study	To provide clarity on G-CSF

Section 5.6.2	Added the following bolded text: Subjects **are allowed premedications for prevention of infusion-related reactions, including corticosteroids, dosing <10 mg prednisone equivalent or per local standard of care**. … Growth factor support **or prophylaxis** (G-CSF or GM-CSF) should be considered for subjects who **are at risk for, currently** have**,** or ~~who~~ have recently recovered from, neutropenia.	To provide clarity on allowed premedication
Section 5.6.2	Removed the following subheading: ~~5.6.2.1 Allowed Concomitant Therapy – Parts B and C Only~~	To clarify that the allowed concomitant therapies listed are applicable to all parts of the study
Section 5.6.3.1	Added the following bolded text: Immunosuppressive doses of systemic corticosteroids (e.g., prednisone >10 mg/day) **(premedications for prevention of infusion-related reactions are allowed)**.	To provide clarity on allowed premedication
Section 5.7.1	Added the following bolded text: **Subjects will be monitored for a period of 2 hours post-infusion of brentuximab vedotin.** Infusion or hypersensitivity reactions may occur **within 24 hours or more than 24 hours post-dose, respectively,** to either brentuximab or nivolumab.	To provide clarity for infusion/hypersensitivity reactions
Section 5.7.4	Added "Myocarditis (EU-specific)" to AEs	Updated to meet EU Regulatory requirements
Section 6.2	Updated header to "Screening Visit (Day -28 to Day 1)"	To correct a typo in A03
Section 6.2; Appendix B	Changed acceptable window for echocardiogram/multi-gated acquisition scan from within the past 6 months to within the past 1 month	Updated to adhere to global regulatory requirements
Section 6.2	Added the following for Screening Activities: • CT scans up to 3 days prior to Day -28 (i.e., Day -31) will be accepted • PET scans up to 3 days prior to Day -28 (i.e., Day -31) will be accepted	To expand window for allowed Screening scans
Section 6.3.1.1; Section 6.3.2.1; Section 6.3.2.3	Added pregnancy testing to D1 of every cycle	To comply with EU regulations
Section 6.3.2.1	Added "CBC with differential (not required if completed at Baseline	To align with the schedule of events

	visit within 1 day prior to Cycle 1, Day 1)"	
Section 6.3.2.1	Added "B symptom assessment (not required if completed at Baseline)"	To align with the schedule of events
Section 6.3.2.2	Added "ECOG Performance status (Appendix C)"	To align with the schedule of events
Section 6.4	Removed the following bullet point from EOT visit: • ~~International prognostic score (Part A only; Appendix D)~~	This assessment should only occur at baseline and is not useful at EOT.
Section 6.5	Removed "±2 weeks" for nivolumab safety visit window and updated to "100 to 114 days"	To provide clarify that the final safety visit cannot occur 2 weeks *before* the 100-day point post-nivolumab; 2 weeks after the 100-day point has been added to the Schedule of Evaluations
Section 6.5	Added "doxorubicin, or dacarbazine"	To provide clarity for "study medication other than nivolumab"
Section 6.6.2	Added the following for last 2 years of follow-up: Subjects will then continue in follow-up for 2 additional years (5 years total).	To provide clarity on long-term follow-up and clarify this applies to both Parts B and C.
Section 6.7	Removed "End of Study" from heading	End of Study definition added in new Section (Section 3.1.1)
Section 7.3.1	Updated text as follows: Subjects in Parts B and C ~~should~~ **must** provide tumor tissue for biomarker analysis. **Availability of** archival tumor tissue (non-bone sites) **must be confirmed** ~~collected within 3 months of~~ **prior to** enrollment ~~is requested, if available~~.	To provide clarity on tumor tissue collection
Section 7.4.1.2	Updated time to notify Drug Safety Department of pregnancy from 48 hours to 24 hours	Updated to adhere to global regulatory requirements
Section 7.4.1.2	Updated time after final study drug dose to 7 months for pregnancy reporting	Updated to adhere to global regulatory requirements
Section 7.4.1.2	Updated time to avoid pregnancy to 7 months after the final dose of study drugs, and added reference to Appendix G for Pregnancy	To provide additional guidance on Pregnancy
Section 7.4.1.3	Updated text as follows: 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 drug administration (Part A), **30 days after the last dose of brentuximab vedotin, doxorubicin, dacarbazine** or 100 days after the last ~~study drug administration~~ **dose of nivolumab,**	To provide clarity and align with safety visit window

	whichever is later (Parts B and C only).	
Section 7.4.2	Added "Hemoglobin A1c" to clinical laboratory tests	To align with Schedule of Events and provide clarity to sites
Section 7.4.2	Updated the following: • The estimated GFR should be calculated using the MDRD equation as applicable **for subjects ≥18 years old**, with serum creatinine (Scr) reported in mg/dL. GFR (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) • **The estimated GFR should be calculated using the bedside Schwartz formula for subjects <18 years old, with Scr reported in mg/dL.** **eGFR = 0.43 x (height/Scr)**	Added bedside Schwartz formula as this is more appropriate for pediatrics
Section 7.4.3	Added the following text: **Vital signs (blood pressure, heart rate, and temperature) will also be assessed.**	To provide clarity on assessments included in each physical examination
Section 7.4.4	Added Section 7.4.4. Sponsor Safety Reporting to Regulatory Authorities	To provide clarity on safety reporting
Section 9.1	Changed "84.3%" to "94.3%"	To correct typo in version A03
Section 9.3.7.2	Updated time points for AE assessments in Parts B and C	To align with changes made in Section 7.4.1.3
Section 9.3.8	Added the following: An SMC will be responsible for monitoring patient safety in Parts B and C of the study (see Section 7.4). 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 Seagen Inc. Drug Safety Department.	To provide clarity on interim analyses
Section 10.1	Removed the following text: ~~For phase 1 studies, it is preferable for a subject to provide consent themselves.~~	Removed for phase 2 study purposes
Section 10.4	Added the following text: 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	Updated to adhere to global regulatory requirements

	notified by the sponsor in writing that retention is no longer necessary.	
Appendix A	Removed IPS assessment from EOT visit in Part A Schedule of Events	To align with change made in Section 6.4
Appendix A	Added footnote “B” with the following: Subjects will remain in follow-up until death, withdrawal of consent, or completion of 2 years of long-term follow-up (from EOT visit), whichever occurs first.	To align with protocol text
Appendix A	Updated footnote labels	To allow for consistency after insertion of new footnote “B”
Appendix A	Added footnote “K” with the following: Scans collected within 3 days prior to Day -28 will be accepted	To align with changes made in Section 6.3.2.1
Appendix A; Appendix B	Added pregnancy screening on D1 of every cycle	To comply with EU regulations
Appendix B	Added the following for Screening period heading: (-3 days)	To align with changes made in Section 6.3.2.1
Appendix B	Updated 100-day safety visit heading with “+2 weeks”	To align with changes in Section 6.5
Appendix B	Removed thyroid panel from safety assessments	To provide clarity because thyroid panel is already included in the chemistry panel safety assessment
Appendix B	Added “amylase” and “lipase” to footnote “I”	To align with Section 7.4.2 which states that for Parts B and C, the chemistry panel should also include amylase and lipase
Appendix B	Moved “PET” from Baseline time point to Screening time point	To align with Section 6.2 which lists the PET scan during screening, not baseline analysis
Appendix B	Updated footnote “C” as the following: The final safety visit should occur 100-114 days after the last dose of nivolumab or 30–37 days post last dose of BV (concurrent with the EOT visit), whichever is later.	To align with changes in Section 6.5
Appendix B	Updated footnote “A” as the following: For Parts B and C, disease assessments will be performed during follow-up every 3 months after the EOT visit for the first year, then every 6 months for 2 additional years. Subjects will then continue in follow-up for 2 additional years (5	To align with protocol text

	years total), with physical exams required every 6 months and disease assessments required every 12 months. Timing of follow up visits should be relative to EOT visit and not relative to last dose.	
Appendix B	Updated footnote "D" with the following bolded text: Physical exam includes **vital signs (blood pressure, heart rate, temperature),** height (at baseline) and weight	To align with updates made in Section 7.4.3
Appendix B	Added footnote "K" to the following at Baseline: CBC with differential Physical exam Chemistry panel	To clarify that if Baseline Visit activities occur within 1 day prior to Cycle 1, Day 1, the assessments do not need to be repeated at the Cycle 1, Day 1 visit
Appendix B	Added footnote "J" to D1 of every 28-day cycle under chemistry panel safety assessments	To provide clarity to sites that these assessments are only required at Cycles 1 and 3 during treatment cycles
Appendix B	Added footnote "Q" with the following: Scans collected within 3 days prior to Day -28 will be accepted	To align with changes made in Section 6.3.2.1
Appendix B	Added footnote "R" with the following: Refer to Section 7.3.1 for details	To align with updates made in Section 7.3.1
Appendix G	Updated with global guidance on contraception	Updated to adhere to global regulatory requirements
Appendix H	Added Katz Index of Independence in Activities of Daily Living	To provide clarity to Exclusion Criterion #15

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Protocol synopsis	**For Part C, one interim analysis will be performed after approximately 50 subjects have completed response assessment at EOT. At the interim futility analysis, if the CR rate at EOT is ≤80% (40/50 or fewer subjects with CR at EOT), the sponsor in consultation with the SMC may decide to stop further enrollment of the trial.**	In response to MSK research Council comments
Section 1	The components of AN+AD will be administered as described in Section 5. For both Part B and Part C, after approximately 10 subjects have completed Cycle 2, an SMC will assess the safety of AN+AD. Safety will be assessed separately for Part B and Part C. **An additional SMC meeting will occur after approximately 50 subjects in Part C have completed their EOT assessment.**	Clarification
Section 1.4.1	(Straus 2018a). ~~The highest incidence of FN occurred in the ECHELON-1 study during Cycle 1)~~ (Straus 2018a). **The highest incidence of FN occurred in the ECHELON-1 study during Cycle 1** (Connors 2018). When G-PP was administered during Cycle 1 to a sub-set of subjects, the rate of Cycle 1 FN decreased from 11% to 1% (Figure 1), ~~(Straus 2018a). In addition, these subjects experienced fewer infections and Grade 3 or higher AEs (Straus 2018a)~~. **(Straus 2018a). In addition, these subjects experienced fewer infections and Grade 3 or higher AEs (Straus 2018a). Furthermore, subjects who received G-PP in ECHELON-1 had an improved efficacy as demonstrated by 84.6% mPFS at 2 years vs 81.7% without G-PP (Straus 2018a).**	Clarification
Section 1.4.2	The combination of brentuximab vedotin and nivolumab ~~appears to be active and well tolerated in cHL. Each agent has been~~ **as well as each agent** combined separately with doxorubicin, vinblastine, and dacarbazine ~~and also~~ have been shown to be active and well tolerated **in the treatment of cHL**. **Part B will evaluate the combination of AN+AD in advanced stage HL.** Yasenchak et al examined the combination of brentuximab and nivolumab as frontline treatment for subjects ≥60 years with advanced stage	Clarification

Section(s)	Change	Rationale
	HL who were ineligible for or declined conventional chemotherapy. Preliminary results showed an overall response rate (ORR) of 100%, a CR rate of 72%, and a partial response (PR) rate of 28% (Yasenchak 2019). ~~Additionally, preliminary,~~ **The regimen was well-tolerated; the most common treatment related adverse events of any grade were fatigue (48%), peripheral sensory neuropathy (38%), diarrhea, infusion-related reactions, and pyrexia (24% each). Three subjects had immune-related AEs with a maximum severity of Grade 3. Part C will further evaluate the combination of AN+AD in early stage HL.** **The most common treatment-related adverse events of any grade included nausea (79%), peripheral sensory neuropathy (56%), fatigue (50%), constipation (38%), and alopecia (35%). Grade 3 or higher AEs were limited to nausea (3%), neutropenia, (6%), and vomiting (3%).** **An additional SMC meeting will occur after approximately 50 subjects in Part C have completed their EOT assessment. For Part C, one interim analysis will be performed after approximately 50 subjects have completed response assessment at EOT.** If an SMC determines that the risks outweigh the benefits of AN+AD, the sponsor may choose to halt enrollment in Parts B or C of the study.	
Section 1.4.3	**Historical standard of care treatment options for patients with advanced HL have been associated with poor survival (Gordon 2013). In the ECHELON-1 trial, an open-label, international, multicenter, randomized Phase 3 clinical trial in subjects with previously untreated Stage III or IV cHL, the complementary mechanisms of action of brentuximab vedotin with A+AVD, enhanced antitumor activity with significant improvement in mPFS (see Section 1.2).** **The combination of brentuximab vedotin and nivolumab was active and welltolerated in cHL with improved CR rate of 61% in relapsed or refractory cHL (Herrera 2018). The combination of N+AVD as found to have a 67% CR rate in subjects with**	To address Italy Health Authority feedback

Section(s)	Change	Rationale
	newly diagnosed advanced stage cHL (Ramachandren 2019; Section 1.3). In another trial of 11 previously untreated subjects with cHL over 60 years-old and ineligible for or declining conventional combination chemotherapy, the combination of brentuximab vedotin and nivolumab produced a 55% CR rate (Friedberg 2018). Section 1.4.2 provides additional information on the better outcome of this combination therapy. Given the demonstrated activity of brentuximab vedotin as well as nivolumb as treatment of cHL, the evaluation of this regimen is anticipated to provide benefit to these patients with acceptable known toxicity. The toxicity profile of the combination in cHL is expected to be consistent with that of previous studies. Neutropenia and associated complications, including febrile neutropenia and infections, infusion related reactions, and peripheral neuropathy were considered the most clinically important AEs for the combination regimen. Investigators may decide to discontinue study treatment at any time for any of the reasons listed in Section 4.3.1. **The same rationale regarding the use of brentuximab vedotin and nivolumab applies when considered as treatment of early stage cHL. Current accepted therapies for early stage cHL include chemotherapy regimens, radiation, and combined modality therapy of chemotherapy and radiation. These regimens are associated with high cure rates of 85-90% (Meyer 2012) but are also associated with high rates of serious morbidity and mortality in long-term survivors, particularly second primary malignancies and cardiovascular disease (Straus 2018b).** **Recent data in 34 subjects with previously untreated Stage I/II cHL with non-bulky disease, treatment with brentuximab vedotin, doxorubicin, and dacarbazine showed CR, PFS and OS rates of 100% at EOT (Abramson 2018). The promising responses observed with the combination of brentuximab vedotin and nivolumab as treatment of advanced cHL as well as the**	

Section(s)	Change	Rationale
	evidence of activity in earlier stage disease provide a compelling rationale to evaluate the combination of brentuximab vedotin and nivolumab.	
Section 3.1.2	The SMC will meet to evaluate safety after approximately 10 subjects have completed Cycle 2. ~~Additionally~~, ~~the committee will~~ **An additional SMC meeting will be held after approximately 50 subjects in Part C have completed their EOT assessment**. **The committee will also** monitor the safety of participants through regular and/or ad hoc meetings that include review of adverse events and lab abnormalities	In response to MSK research Council comments
Section 3.2.3	Subjects with Stage I or II cHL without bulky ~~medistinal~~ disease will be assigned to Part C**.**	Clarification
Section 4.1	Subjects enrolling in Part C of the study must have Ann Arbor Stage I or II cHL without bulky ~~mediastinal~~ disease.	Clarification
Section 4.2	**Documented history of ~~I~~i**diopathic interstitial pneumonia or diffusing capacity of the lung for carbon monoxide (adjusted for hemoglobin) <50% predicted.	Clarification
Table 4	or prophylaxis should be considered for subsequent cycles **if not already administered**	Clarification
Section 5.7.1	Subjects will be monitored for a period of 2 hours post-infusion of brentuximab vedotin **at each visit**.	Clarification
Section 6.2	• **To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline.** • Initiate collection of archived tumor tissue specimen or fresh tumor biopsy (Section 7.3.1) **(For Parts B and C only)**	Clarification
Section 6.2.1	Height and weight **(For subjects <18 years, height must be measured at this visit; for subjects ≥18 years, height measured within 12 months is acceptable)**	Clarification

Section(s)	Change	Rationale
Section 6.3.2.1	CBC with differential (~~not required if completed at Baseline visit within 1 day prior to Cycle 1, Day 1~~) Serum chemistry panel**, (**~~includes~~ **should include amylase and lipase along with TSH, free T3, and free T4 (**see Section 7.4.2) B symptom assessment (not required if completed at Baseline); **Note: Subjects will be monitored for a period of 2 hours post-infusion of brentuximab vedotin at each visit**	Clarification
Section 6.3.2.5	**To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline**	Clarification
Section 6.4	**To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline**	Clarification
Section 6.6.1	**Follow-up visits will occur every 12 (±1) weeks from the EOT visit**	
Section 6.6.2	• **To decrease radiation exposure, CT scans of neck will be mandated at Baseline only; restaging imaging will only be repeated if neck disease is present at Baseline.** • Disease status • **SAEs related to treatment** Subjects will then continue in follow-up for 2 additional years (5 years total). For the final 2 years, a physical exam should be performed every 6 months and a dedicated CT of chest, neck, abdomen, and pelvis should be performed every 12 months. **CT scans of neck will only be repeated if neck disease is present at Baseline.** • Survival status and subsequent anticancer therapies received Note: 3-month follow-up may be performed with 100-day safety visit • Resolution of PN, if applicable • **SAEs related to treatment**	Clarification
Section 9.1	For Part B, approximately 50 subjects will be enrolled in order to provide an adequate level of precision for the	In response to MSK research Council comments

Section(s)	Change	Rationale
	estimate of the CR rate at EOT. If 45 of 50 subjects have a CR at EOT, the CR rate at EOT is 90% with 95% CI (78.2%, 96.7%) based on the exact Clopper-Pearson method (Clopper 1934); if 42 of 50 subjects have a CR at EOT, the CR rate at EOT is 84% (95% CI: 70.9%, 92.8%) ; if 48 of 50 subjects have a CR at EOT, the CR rate at EOT is 96% (95% CI: 86.3%, 99.5%). **The 73% CR rate at EOT observed in the A+AVD arm in the ECHELON-1 trial was considered the relevant benchmark when determining an appropriate sample size for Part B (Connors 2018).** For Part C, approximately 150 subjects will be enrolled in order to provide ~~an~~ adequate ~~level of precision for the estimate of the CR rate at EOT~~. **power to reject the hypothesis that CR rate at EOT is ≤90%. Assuming a CR rate of 95%, 150 subjects would provide approximately 80% power to reject the null hypothesis of a CR rate at EOT ≤90% with a 1-sided alpha = 0.05 and using an empirical variance estimate (East v6.4). This sample size calculation accounts for the interim futility analysis which is further described in section 9.3.8**~~If 142 of 150 subjects have a CR at EOT, the CR rate at EOT is 95% with 95% CI (89.8%, 97.7%) based on the exact Clopper-Pearson method (Clopper 1934); if 135 of 150 subjects have a CR at EOT, the CR rate at EOT is 90% (95% CI: 84.0%, 94.3%) ; if 146 of 150 subjects have a CR at EOT, the CR rate at EOT is 97% (95% CI: 93.3%, 99.3%)~~.	
Section 9.3.5.2	**CR rate at EOT and the exact 2-sided 95% CIs using the Clopper-Pearson method (Clopper 1934) will be calculated.** **For Part C a hypothesis test will be performed. The null and alternative hypotheses are:** • **Null hypothesis: CR rate at EOT ≤ 90%** • **Alternative hypothesis: CR rate at EOT > 90%** **The null hypothesis will be tested at a 1-sided alpha of 0.05. The associated p-value will be calculated based on the**	In response to MSK research Council comments

Section(s)	Change	Rationale
	normal approximation with an empirical estimate of the variance. If p <0.05 is observed the null hypothesis will be rejected in favor of the alternative hypothesis. **If enrollment in Part C is stopped prior to completion no hypothesis testing will be performed**.	
Section 9.3.8	~~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 Seagen Inc. Drug Safety Department.~~ **One interim futility analysis will be performed for Part C after approximately 50 subjects have completed response assessment at EOT. At this interim futility analysis, if the CR rate at EOT is ≤80% (40/50 or fewer subjects with CR at EOT), the sponsor in consultation with the SMC may decide to stop further enrollment of Part C of the trial.**	In response to MSK research Council comments
Appendix B	~~Confirm availability of archived tumor specimen~~[R] **Collection of archived tumor tissue specimen or fresh tumor biopsy**[R]	Clarification
Appendix B	Updated Footnote I: Must include ~~TSH, free T3, free T4,~~ amylase, and lipase (section 7.4.2) Footnote J: **Must include TSH, free T3, T4 at** cycles 1, 3, **and EOT** only (see **Section** 7.4.2)	To match Section 7.4.2
Appendix B	Added footnotes S, T, U, and V	Clarification

Summary of Changes in Amendment 6

Section(s)	Change	Rationale
Throughout	Various administrative changes were made throughout	To provide clarity when necessary and conform to editorial standards
Protocol Synopsis Study Population	Key eligibility criteria include treatment-naïve subjects (aged ≥12 years **in the US and aged ≥18 years outside of the US**) with classical Hodgkin lymphoma (cHL).	Clarification, updating language to match eligibility criteria.
Protocol Synopsis Study Population	Part B will enroll subjects with Ann Arbor Stage 1 or II cHL with bulky mediastinal disease (defined as **a single node or nodal mass with a diameter** ≥10 cm **on CT imaging**) or Stage III or IV cHL.	Clarification of the definition of bulky mediastinal disease.
Protocol Synopsis Study Design	For Part C, one interim analysis will be performed after approximately 50 subjects have completed response assessment at EOT. ~~At this interim futility analysis, if the CR rate at EOT is ≤80% (40/50 or fewer subjects with CR at EOT), the sponsor in consultation with the Safety Monitoring Committee (SMC) may decide to stop further enrollment of the trial.~~	Clarification
	As of Amendment 6, Parts A and B were completed.	Clarification
Protocol Synopsis Efficacy Assessments	Disease response and progression will be assessed by investigators using the **Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of** Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) ~~modification of Lugano Classification Revised Staging System~~ for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2016).	Clarification
Table of Contents	Updated pagination Inclusion of Appendix I	Administrative
Section 1	Part B is designed to evaluate the combination of brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD) as frontline treatment in subjects with advanced cHL (Stage I/II with bulky mediastinal disease [defined as **a single node or nodal mass with a diameter** ≥10 cm **on CT imaging**], or Stage III or IV).	Clarification of the definition of bulky mediastinal disease.
Section 1.2	Eight of 34 subjects (24%) had neutropenia, but only 2 subjects (6%) had Grade 3 neutropenia; there were no cases of Grade 4 **neutropenia or febrile neutropenia**.	Clarification
Section 1.4.2	For Part C, one interim analysis will be performed after approximately 50	Clarification

Section(s)	Change	Rationale
	subjects have completed response assessment at EOT. ~~If an SMC determines that the risks outweigh the benefits of AN+AD, the sponsor may choose to halt enrollment in Parts B or C of the study.~~	
Sections 3.1, 3.2.3, 4, 5.1 and 6.1	**As of Amendment 6, Parts A and B were completed.**	Clarification
Section 3.2.4.2	After approximately 10 subjects have completed 2 cycles of treatment, an SMC will assess the safety of AN+AD **(Section 3.1.2** ~~Section 3.1.1~~**).**	Administrative, correcting cross-reference link.
Section 4.1	Subjects enrolling in Part B of the study must have Ann Arbor Stage I or II cHL with bulky mediastinal disease (defined as **a single node or nodal mass measuring** 10 cm or greater in diameter as determined by CT imaging) or Stage III or IV disease.	Clarification of the definition of bulky mediastinal disease.
Section 4.1	If a tumor block is not available, ~~contact the medical monitor to discuss alternative specimen arrangments~~ **unstained slides (a minimum of 10 unstained slides for Part B, and 12 unstained slides for Part C) may be submitted instead of a tumor block**.	Clarification
Section 5.2.4	**If any component of the regimen is discontinued due to AE,** ~~S~~subjects may remain on study and continue to receive the remaining treatment components.	Clarification
Section 5.5.4	Nivolumab administration should be withheld or discontinued as described in Table 6. **The recommended management of gastrointestinal (GI), renal, pulmonary, hepatic, endocrinopathy, skin, neurological, and myocarditis adverse events are provided in Appendix I.**	Clarification, to provide reference to guidance regarding the clinical management of common IMAEs that occur with nivolumab.
Section 5.6.2	Subjects are allowed premedications ~~s~~ **regimens** for **anti-emesis purposes and** prevention of infusion-related reactions, including corticosteroids, dosing <10 mg **daily** prednisone equivalent or per local standard of care.	Clarification
	~~Stabel adrenal replacement steroid~~ **D**~~d~~oses of **>10 mg** daily prednisone or prednisone equivalent are **allowed for stable adrenal replacement.**	Clarification
Section 5.6.3	Subjects may not receive other investigational drugs, immunosuppressive medications **(exception: corticosteroid doses of >10 mg daily prednisone, or prednisone equivalent for anti-emesis and** ~~premedications~~ **prevention of infusion-related reactions are**	Clarification

Section(s)	Change	Rationale
	allowed), radiotherapy, or systemic anti-neoplastic therapy from Day 1 through EOT.	
Sections 5.6.3.1	Immunosuppressive doses of systemic corticosteroids (e.g., prednisone >10 mg/day) (premedications **regimens** for **anti-emesis and** prevention of infusion-related reactions are allowed).	Clarification
Section 5.7	Additional information regarding treatment-emergent AEs **(TEAEs)** for brentuximab vedotin is available in the brentuximab vedotin IB**. Management of immune-mediated AEs (IMAEs) for nivolumab is available in Appendix I.**	To provide reference to guidance regarding the clinical management of common IMAEs that occur with nivolumab.
Section 5.7.4	**Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue including** the following ~~groups of AEs should be managed per the algorithms found in Appendix 4 of the nivolumab IB~~**:** • **Immune-mediated pneumonitis** • **Immune-mediated colitis** • **Immune-mediated hepatitis and hepatoxicity** • **Immune-mediated endocrinopathies** • **Immune-mediated dermatologic adverse reactions** • **Immune-mediated nephritis and renal dysfunction** **The following groups of AEs should be managed per the algorithms found in Appendix I**:	To provide provide awareness of common immune-mediated adverse reactions that can occur with nivolumab. To provide reference to guidance regarding the clinical management of common AEs that can occur with nivolumab.
Section 6.2	International prognostic score **for Part B only** (Appendix D)	International prognostic score is applicable to only advanced stage patients
Section 6.2.1	• **Estimated glomerular filtration rate (**eGFR**)** calculation per MDRD	Administrative, defined first use of abbreviation
Sections 6.3.2.1, 6.3.2.2, 6.3.2.3, 6.3.2.4, 6.4, and 6.5	• **eGFR (Section 7.4.2)**	Clarification, to update language to be consistent with eligibility criteria.
Section 6.6.2	• Dedicated CT of chest, neck, abdomen, and pelvis; performed at the timepoints above ~~or~~ **and** if progression is suspected based on clinical signs and symptoms	Clarification that imaging should be conducted at the timepoints and to do additional imaging if progression is suspected (not as a substitute to the timepoints).
Section 7.2	IR1: An increase in overall tumor burden (as assessed by the sum of the product~~s~~ of the ~~largest~~ diameter**s** [SPD]) of ≥50% of up to 6 measurable lesions	Clarification, updated to match LYRIC criteria language.

Section(s)	Change	Rationale
	in the first 12 weeks of therapy, without clinical deterioration;	
	IR3: An increase in FDG uptake ~~using the 5-Point Scale per the Deauville Criteria~~ of 1 or more lesion(s) without a concomitant increase in lesion size or number.	Clarification, updated to match LYRIC criteria language.
Section 7.4.2	● The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, **eGFR**, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, and uric acid.	Clarification, to update language to be consistent with eligibility criteria.
Section 9.2.2.1	CR rate at EOT is defined as the proportion of subjects with CR at EOT, according to the **Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of** ~~Lymphoma Response to Immunomodulatory Therapy Criteria (~~LYRIC~~)~~ (Cheson 2016), in subjects with previously untreated cHL.	Clarification
Section 9.2.2.2	ORR is defined as the proportion of subjects with CR or partial response (PR) at EOT according to the **Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of** ~~Lymphoma Response to Immunomodulatory Therapy Criteria (~~LYRIC~~)~~ (Cheson 2016) in subjects with previously untreated cHL.	Clarification
Section 9.2.2.3	Duration of response (DOR) is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression (per the **Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of** ~~Lymphoma Response to Immunomodulatory Therapy Criteria (~~LYRIC~~)~~ (Cheson 2016)**)** or death, whichever comes first.	Clarification
	Duration of complete response (DOCR) is defined as the time from start of the first documentation of complete tumor response (CR) to the first documentation of tumor progression (per the **Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of** ~~Lymphoma Response to Immunomodulatory Therapy Criteria~~	Clarification

Section(s)	Change	Rationale
	~~(~~LYRIC~~)~~ (Cheson 2016)**)** or death, whichever comes first.	
Appendix A	Removed International prognostic score from Schedule of Events Table	Clarification, International Prognostic Score is applicable to only advanced stage patients
Appendix B	International prognostic score **(Part B only)**	Clarification, International Prognostic Score is applicable to only advanced stage patients
	Added eGFR[S] to Schedule of Events Table. Removed footnote "S" from Day-7 to 1 Screening/Baseline visit for Chemistry panel.	Clarification, updated to match inclusion criteria.
Appendix F	If tumor flare or pseudo-progression is suspected, then a clinical response of indeterminate response (IR) should be reported based on the **Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of** ~~Lymphoma Response to Immunomodulatory Therapy Criteria~~ ~~(~~LYRIC~~)~~ (Cheson 2016).	Clarification
	This pattern may be seen as a consequence of either delayed response or early immune-mediated flare. At least within the context of clinical trials, a biopsy is encouraged in this case because this may help to distinguish the two and, if positive, will confirm the impression of PD. However, if negative for lymphoma, it will support the concept of pseudoprogression and contribute to our understanding of this phenomenon. When such a biopsy is neither safe nor feasible, decisions must be based on a repeat scan 12 weeks after the initial determination of IR. **It is recognized that "clinical deterioration" is subjective.** In ~~general~~ **some cases, the simple growth of a nodal or tumor mass could worsen the symptoms mechanically related to that mass, such as pain at the tumor site or compression of adjacent structures, etc. Such an increase in symptoms that can be directly attributed to the size of the tumor mass may not be considered as clinical deterioration in this context. However, in most cases,** subjects should be experiencing clinical stability or improvement ~~and must be able~~ **by investigator assessment to be considered as having IR, and in all cases, the patient must be considered likely** to tolerate continued treatment	Clarification, updated to match LYRIC criteria language.

Section(s)	Change	Rationale
	and not at risk of serious complications should further tumor growth occur. ~~Symptoms related to tumor growth, such as pain at the tumor site or compression of adjacent structures, may not be considered as clinical deterioration in this context.~~	
	This **phenomenon** may occur early or late in the treatment course**, and therefore, unlike IR1, is not defined by its temporal relationship to treatment initiation. Both within and outside the context of clinical trials,** ~~A~~abiopsy is strongly encouraged ~~when a subject experiences this phenomenon~~ **in such cases**. 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~~ of ~~one~~ 1 or more lesion(s)~~)~~ without a concomitant increase in lesion size or number.	Clarification, updated to match LYRIC criteria language.
Appendix F	Therefore, by itself changes in uptake should not trigger an assignment of progressive disease (PD) **with checkpoint inhibitors**.	Clarification, updated to match LYRIC criteria language.
	It is important to investigate this finding, especially in conjunction with a biopsy ~~(if possible)~~ of the lesion in question. **While awaiting a better characterization of this phenomenon, we propose that, under the modified response criteria,** an increase in FDG avidity of one or more lesions suggestive of lymphoma, without a concomitant increase in size of those lesions meeting PD criteria does not constitute PD. It is possible that, at a single time point a subject could fulfill criteria for both IR1 or **IR**2 AND IR3~~:~~. ~~F~~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 **IR**2 should take priority (e.g., IR2 in the above example). **These 3 patterns of IR as defined above (IR1, IR2, and IR3) may have very different mechanisms and clinical implications. Therefore, it is**	Clarification, updated to match LYRIC criteria language.

Section(s)	Change	Rationale
	critical that data are collected in a consistent manner so that these 3 possible atypical response types occurring within the context of checkpoint inhibitors can be distinguished.	
	~~At~~ **In subjects categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional** 12 weeks (or earlier if clinically indicated). ~~After a response of IR is determined by the Investigator, repeat imaging is mandatory and PD must be confirmed or refuted based on LYRIC follow-up criteria for IR.~~ **At that time, response** should be **re-evaluated, and the subject should be considered to have true PD** 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 **≥1**~~at least one~~ lesion for lesions ≤2 cm, and 10 mm for lesions >2 cm, to be consistent with the Lugano classification (Cheson 2016). **The 10% threshold is empiric but designed to account for variability in measurement, especially when taken along with the minimum increase (Oxnard 2011).** If the target SPD increase is <10%, the response would still be categorized as IR1, and the subject could continue treatment until a subsequent scan shows either PD (≥10% increase from first IR1 time point and an increase of >5 mm in either dimension of **≥1**~~at least one~~ lesion) or response (≥50% decrease from baseline). In this situation, it is reasonable to repeat imaging in 4-8 weeks **of the original IR1 time point** to ensure absence of significant further increase.	Clarification, updated to match LYRIC criteria language.
Appendix F	● In the case of IR3, ~~since~~ **because** inflammatory responses may result in an increase in the standardized uptake value of a lesion, the subject will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the	Clarification, updated to match LYRIC criteria language.

Section(s)	Change	Rationale
	development of new lesions, as noted above. **Importantly, if a subject is assessed as having IR and then "true" PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should be subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR. We recognize that these lesions may remain stable during the time of observation, but, even if this is the case, the initial designation of IR should be changed to PD.**	
Appendix I	**Inclusion of Appendix 4A from Nivolumab IB v21**	To provide guidance regarding the clinical management of common IMAEs that occur with nivolumab.
Appendix J	Renumbered as a result of inclusion of Appendix I above.	Administrative change
Appendix K	Renumbered as a result of inclusion of Appendix I above.	Administrative change

Summary of Changes in Amendment 7

Section(s)	Change	Rationale
Section 4.3.1	Added the following: ● Czechia (CZ) only: Lack of clinical benefit following Cycle 2 PET, at which time consolidative radiotherapy or another established treatment may be indicated, per the discretion of the study investigator CZ only: Subjects who discontinue treatment due to a lack of clinical benefit following Cycle 2 PET will only remain on study for survival follow-up and subsequent therapy must be recorded.	To incorporate CZ-specific changes into global protocol. To provide clarity of discontinuation criteria
Section 5.6.2	Added the following: CZ only: Primary prophylaxis with G-CSF or GM-CSF from the first dose is recommended for all subjects with previously untreated Hodgkin's lymphoma receiving combination therapy with SGN-35.	To incorporate CZ-specific changes into global protocol. To provide clarity on concominant therapy allowed.
Section 6.2	Added the following: ● CZ only: HBV and HIV serological testing (positive results will result in subject being considered ineligible for enrollment) ● CZ only: HCV PCR testing (positive results will result in subject being considered ineligible for enrollment)	To incorporate CZ-specific changes into global protocol. To provide clarity on virologic assessment and eligibility criteria
Appendix B	Added HBV and HIV serological testing during screening (CZ only)	To incorporate CZ-specific changes into global protocol. To align with updates made in Section 6.2
Appendix B	Added HCV PCR testing during screening (CZ only)	To incorporate CZ-specific changes into global protocol. To align with updates made in Section 6.2
Appendix B	Added footnote "W" with the following: Serological testing will be completed, positive results will result in subject being considered ineligible for enrollment.	To incorporate CZ-specific changes into global protocol. To align with updates made in Section 6.2
Appendix B	Added footnote "X" with the following: PCR testing will be completed, positive results will result in subject being considered ineligible for enrollment.	To incorporate CZ-specific changes into global protocol. To align with updates made in Section 6.2