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DEPARTMENT OF HEMATOLOGY

TITLE: A Phase 2 Study of Nivolumab and Brentuximab Vedotin Consolidation After Autologous Stem Cell Transplantation in Patients with High-Risk Classical Hodgkin Lymphoma

CITY OF HOPE PROTOCOL NUMBER: IRB # 16378 Protocol Date: 05/16/22

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MODALITY: Immunotherapy and Drug-Antibody Conjugate
TYPE: Phase 2

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Clinical Trial Protocol

A Phase 2 Study of Nivolumab and Brentuximab Vedotin Consolidation After Autologous Stem Cell Transplantation in Patients with High-Risk Classical Hodgkin Lymphoma

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City of Hope #:	16378
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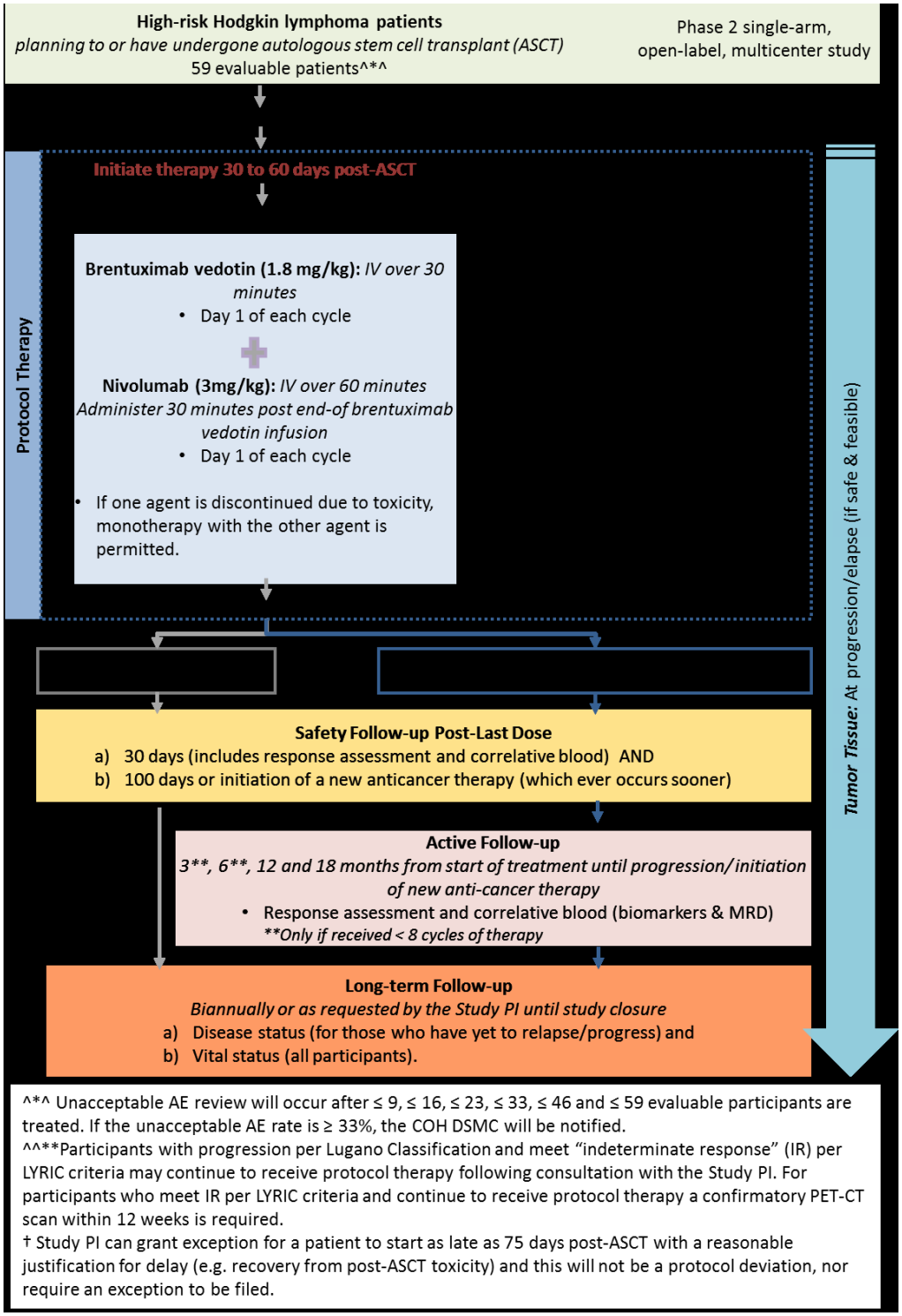
EXPERIMENTAL DESIGN SCHEMA



PROTOCOL SYNOPSIS

Protocol Title:	
A Phase 2 Study of Nivolumab and Brentuximab Vedotin Consolidation After Autologous Stem Cell Transplantation in Patients with High-Risk Classical Hodgkin Lymphoma	
Study Detail	
Indication(s)	Relapsed/ refractory Hodgkin lymphoma post-ASCT
Phase:	2
Number of participants:	59 evaluable; anticipated maximum: 65
Estimated Accrual Duration:	24 months
Estimated Study Duration	42 months
Participant Duration:	Minimum 18 months from start of treatment
Participating Sites:	• City of Hope, Duarte, CA • Fred Hutchinson Cancer Center • MD Anderson Cancer Center • Memorial Sloan Kettering Cancer Center • Hackensack Medical Center • Mayo Clinic
Study Agents:	Nivolumab, Brentuximab Vedotin
Brief Protocol Title for the Lay Public:	Nivolumab and brentuximab vedotin therapy for relapsed/ refractory Hodgkin lymphoma patients after autologous stem cell transplantation.
Sponsor:	City of Hope
Industry Partner:	Bristol Myers Squibb Company
Industry Partner Protocol ID:	CA209-878
Rationale for this Study:	

Classical HL is a lymphoma of B-cell origin that is defined by the presence of Hodgkin-Reed-Sternberg cells in a background of inflammatory cells. Although the majority of patients with Hodgkin Lymphoma (HL) are cured with upfront therapy, as many as 20-40% of patients will have relapsed or refractory (rel/ref) disease. Standard of care treatment for patients with relapsed/refractory HL is salvage chemotherapy followed by autologous stem cell transplantation (ASCT) in chemosensitive patients, but about half of HL patients who undergo ASCT will relapse. HL patients who are refractory to second-line therapy or relapse after ASCT have poor outcomes. Therefore, improved therapies for patients with relapsed/refractory HL are urgently needed.

Brentuximab vedotin (BV) – an antibody-drug conjugate (ADC) of an anti-CD30 monoclonal antibody with the anti-tubulin agent monomethyl auristatin E – is effective in treating relapsed/refractory HL, with an overall response rate (ORR) of 75% and complete response (CR) rate of 34%. Recently, the AETHERA trial demonstrated that BV consolidation treatment following ASCT prolongs PFS in patients with high risk relapsed or refractory classical HL compared to placebo.

The programmed death receptor-1 (PD-1) pathway is an immune checkpoint that normally serves to dampen immune responses in tissues. PD-1 is expressed on activated T-cells and binds its ligands, PD-L1 and PD-L2, on tissue cells or antigen presenting cells to decrease T-cell activation, proliferation, and survival. Tumor cells can co-opt this pathway to evade attack by the host immune system. A wide range of hematologic malignancies express PD-1 or PD-L1, including Hodgkin's lymphoma (HL). In addition, molecular analyses have demonstrated that genetic alterations involving PD-L1 and its overexpression are critical in the pathogenesis of HL. PD-1 inhibitors, including nivolumab, have produced dramatic responses in early-phase studies of patients with

relapsed/refractory HL. An 87% ORR and 100% clinical benefit rate were observed in a phase I study of single-agent nivolumab in patients with relapsed/refractory HL.

Despite the incremental benefit of the addition of post-ASCT BV consolidation, the 2-year PFS in BV-consolidated patients in the AETHERA trial was only 63%. Clearly, there is room for improvement. In addition, with a planned 16 cycles of BV therapy in the AETHERA trial, 23% of patients discontinued BV consolidation therapy and 31% had modification of the BV dose due to peripheral neuropathy. We propose to add nivolumab to the backbone of post-ASCT BV consolidation to improve upon the efficacy of BV post-ASCT consolidation, and to shorten the total duration of consolidation therapy from 16 to 8 cycles to improve tolerability of the combination regimen. Based on the preliminary findings of an ongoing phase 1/2 study, which is evaluating the combination of BV and nivolumab as initial salvage treatment after the failure of frontline therapy, the combination of BV and nivolumab appears safe and well-tolerated. We propose a single-arm phase 2 study to evaluate the efficacy of BV plus nivolumab consolidation therapy in patients with relapsed/refractory HL who have undergone ASCT.

Study Design:

This is a single-arm, open-label Phase 2 study of nivolumab plus BV consolidation for patients with relapsed/ refractory HL who have undergone ASCT. Participant screening can initiate 21 days post-ASCT. Participants must initiate protocol therapy within 30 to 60 days post-ASCT. Study PI can grant exception for a patient to start as late as 75 days post-ASCT with a reasonable justification for delay (e.g. recovery from post-ASCT toxicity) and this will not be a protocol deviation, nor require an exception to be filed. Nivolumab and brentuximab vedotin will be administered in 21-day cycles. BV and nivolumab will be administered on Day 1 of each cycle. Participants will receive up to 8 cycles of protocol therapy, or until unacceptable toxicity or disease progression. Response assessments will occur during screening, Cycle 4 Day 15, 30 days post-last dose, and at 12 and 18 months from start of treatment visits. The primary endpoint is 18-month progression-free survival. Secondary endpoints include overall survival, cumulative incidence of relapse/progression, cumulative incidence of non-relapse mortality, overall response rate, and toxicity.

Objectives:

Primary Objective

- Assess the efficacy of nivolumab plus brentuximab vedotin consolidation after autologous stem cell transplantation (ASCT) in participants with relapsed/refractory classical Hodgkin Lymphoma (HL), as assessed by 18-month progression-free survival (PFS).

Secondary Objective

- Estimate the overall survival (OS), the cumulative incidence of relapse/progression, the cumulative incidence of non-relapse mortality (TRM) in participants with relapsed/ refractory HL who receive nivolumab plus brentuximab vedotin consolidation after ASCT.
- Estimate the overall response rate to nivolumab plus brentuximab vedotin therapy in participants with measurable disease after ASCT.
- Establish the safety and tolerability of nivolumab plus brentuximab vedotin when used as consolidation after ASCT in participants with relapsed/ refractory HL.

Exploratory Objective

- Evaluate the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) definition of indeterminate response to guide the management of patients regarding treatment past progressive disease.
- Explore the impact of nivolumab plus brentuximab vedotin therapy on immune reconstitution after ASCT.
- Explore the prognostic impact of and temporal dynamics of minimal residual disease (MRD) in the peripheral blood as assessed by the next-generation sequencing-based ClonoSEQ platform.

- Explore the prognostic impact of 9p24.1 abnormalities in tumor tissue assessed by FISH on outcomes after ASCT and nivolumab plus brentuximab vedotin post-ASCT consolidation therapy.
- Explore the relationship between immune cells and HRS in tumor samples by 6-color quantitative spatial image analysis using the Vectra system, and correlate with outcome after ASCT and nivolumab plus brentuximab vedotin post-ASCT consolidation therapy.
- Explore whether genetic alterations (e.g. gene expression profiles or genetic mutations) in HL tumor samples are associated with outcome after ASCT and nivolumab plus brentuximab vedotin post-ASCT consolidation therapy.

Evaluation Criteria and Endpoints:

- Response will be assessed per 2014 Lugano Classification.
- Clinical endpoints are as follows:

Endpoint	Patients	Definition
Progression-Free Survival (PFS)	Evaluable patients	Defined as the time from the first dose of study treatment to the first observation of disease relapse/progression or death from any cause, whichever occurs first.
Overall Survival (OS)	Evaluable patients	Defined as the time from the first dose of study treatment to death from any cause.
Cumulative Incidence of Non-Relapse Mortality (NRM)	Evaluable patients	Defined as the time from the first dose of study treatment to non-disease related death.
Cumulative Incidence of Relapse/Progression	Evaluable patients	Defined as the time from the first dose of study treatment to disease relapse/progression.
Overall response rate (ORR)	Evaluable patients with measureable disease post-ASCT	Proportion of patients achieving CR or PR

- Evaluable patients are defined as eligible participants who received at least one dose of the protocol treatment. Eligible participants who did not receive any protocol treatment will be considered in-evaluable, replaced, and excluded from all analyses.
- ***For patients who meet PD per Lugano Classification and also meet IR per LYRIC criteria (Appendix H) [1]:*** In the analysis, patients with PD per Lugano classification and IR per LYRIC criteria who continue study treatment beyond progression per Lugano classification and have confirmation of subsequent PD per LYRIC criteria will be counted as PD at the initial time point of progression per Lugano classification; patients with PD per Luagno classifcation and IR per LYRIC criteria who continue study treatment beyond progression per Lugano classification and do not have confirmation of subsequent PD per LYRIC criteria, with subsequent SD, PR, or CR per Lugano classification, will NOT be counted as PD at the initial time point of progression per Lugano classifcation. Patients with PD per Lugano classification and IR per LYRIC criteria who did NOT continue study treatment beyond progression per Lugano classification will be considered PD at the initial timepoint of progression per Lugano classification.
- Toxicity and adverse events will be recorded using the NCI CTCAE v 4.0. All toxicities/AEs will be recorded from the initiation of protocol therapy through the follow-up period.

Statistical Considerations:

Based on the AETHERA trial, the 18-month PFS rate in patients with relapsed/refractory HL who undergo ASCT followed by BV consolidation is approximately 65% (from the independent assessment data). We hypothesize that adding nivolumab to BV consolidation after ASCT will improve the 18-month PFS rate to 80%. A sample size of 59 evaluable patients will provide approximately 81% power for detecting the increase in 18-month PFS from the baseline of 65% to 80% in this study at 1-sided type I error of 0.05. The power estimation is based on the exact binomial test. Operationally, the study treatment will be considered promising if at least 45 of the 59 evaluable participants are alive and progression-free at 18 months after the first dose of study treatment. The

probability of observing at least 45 surviving and progression-free participants out of a total 59 participants, assuming different PFS rates, is shown in below:

	True 18-month PFS rate			
	65%	**70%**	**75%**	**80%**
The probability of observing at least 45 participants (out of 59 total) being alive and progression-free at 18-months	0.044	0.18	0.48	0.81

To achieve 59 evaluable participants, the maximum study accrual is set to be 65, accounting for up to 10% inevaluable enrollments.

Toxicity Monitoring

Close and continuous monitoring for toxicity will occur throughout the study duration per institutional standards. The COH DSMC will review the AE data quarterly. In the AETHERA trial, 56% of patients who received brentuximab vedotin experienced at least one grade 3-4 adverse event, including 29% with grade 3-4 neutropenia, 10% with grade 3-4 peripheral sensory neuropathy, and 6% with grade 3-4 peripheral motor neuropathy. In this study, the total treatment number of cycles is reduced to 8 but the addition of nivolumab may introduce additional toxicities.

Given the prior toxicity experiences in AETHERA trial and the differences in treatment, in this study we will specifically monitor the occurrence of any "unacceptable AE". Unacceptable AE is defined as any of the following AEs that is at least possibly attributed to protocol therapy during treatment and safety follow-up: Any ≥ Grade 3 immune-related AE; Grade 3 fatigue or non-irAE skin toxicity that does not resolve within 7 days to ≤ Grade 1/baseline; Any other ≥ Grade 3 non-hematologic non-irAE that does not improve within 3 days to ≤ Grade 1/baseline as applicable with supportive care (with the following exception: ≥ Grade 3 laboratory abnormality that is not clinically significant); Grade 4 neutropenia that does not resolve to ≤ Grade 2 within 3 days with supportive care (e.g. GCSF); Grade 3 or 4 thrombocytopenia with bleeding, and Any Grade 5 AE.

This specific monitoring will be performed according to the rule below, which is based on the 50% quartile of the binomial distribution with an unacceptable toxicity rate of 33%.

- 3 or more patients with unacceptable toxicities when ≤ 9 patients have been treated.
- 5 or more patients with unacceptable toxicities when ≤16 patients have been treated.
- 8 or more patients with unacceptable toxicities when ≤23 patients have been treated.
- 11 or more patients with unacceptable toxicities when ≤33 patients have been treated.
- 15 or more patients with unacceptable toxicities when ≤46 patients have been treated.
- 19 or more patients with unacceptable toxicities when ≤ 59 patients have been treated.

If the monitoring rule is met, the study PMT will review and assess the safety of the trial and submit a report outlining the findings and proposed action plans if any to the COH DSMC. The COH DSMC will review and make the decision to continue, modify, or permanently suspend accrual to the trial. At the end of the study with 59 evaluable participants, the 95% exact binomial confidence interval for the rate of such unacceptable AE will have a width of no more than 27%.

Eligibility Criteria

Inclusion Criteria

- Age: ≥ 18 years
- ECOG performance status ≤ 2
- Histologically confirmed diagnosis of classical Hodgkin lymphoma (excluding nodular lymphocyte predominant Hodgkin lymphoma) according to the WHO classification, with hematopathology review at the participating institution.
- Have high-risk relapsed or refractory Hodgkin lymphoma (HL), defined as at least one of the following:

  - Primary refractory disease to front-line therapy.
  - Relapse within 1 year of completing front-line therapy.
  - Extranodal involvement at the time of pre-ASCT relapse.
  - B symptoms at pre-ASCT relapse.
  - More than one type of pre-ASCT salvage therapy required.
- Planning to receive or have received autologous stem cell transplantation (ACST) per institutional standards as part of standard of care.
  - Pre-ASCT participants may consent but will not be eligible to begin treatment until after ASCT, and will have to fulfill all inclusion and exclusion criteria before starting protocol therapy.
  - All participants must initiate Day 1 of protocol therapy within 30-60 days post stem cell reinfusion. Study PI can grant exception for a patient to start as late as 75 days post stem cell reinfusion with a reasonable justification for delay (e.g. recovery from post-ASCT toxicity) and this will not be a protocol deviation, nor require an exception to be filed.
- Recovery from ASCT toxicity as defined as outpatient status , able to drink, eat normally, and do not need intravenous hydration prior to Day 1 of therapy
- Achieved at least stable disease to salvage treatment determined by PET/CT using 2014 Lugano classification prior to ASCT.
- Brentuximab vedotin naïve OR had at least stable disease by Lugano classification to prior brentuximab vedotin treatment
- ANC ≥ 1000/mm^3
- Platelets ≥ 50,000/mm^3
- Hemoglobin ≥ 8 g/dL
- Total bilirubin ≤ 1.5 x ULN OR 3 x ULN for Gilbert's disease
- AST and ALT ≤ 2.5 x ULN
- Creatinine clearance ≥ 40 mL/min per 24 hour urine collection or the Cockcroft-Gault formula
- Forced expiratory volume in one second (FEV1) and carbon monoxide diffusion capacity (DLCO) (adjusted for Hb) ≥ 50% adjusted
- WOCBP only: Negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units o f HCG)
- *Woman of childbearing potential (WOCBP):* use two effective methods of contraception (hormonal or barrier method) or be surgically sterile, or abstain from heterosexual activity for the course of the study through 7 months post last dose of nivolumab. *Male:* use two effective methods of contraception (barrier method) or abstain from heterosexual activity with the first dose of study therapy through 7 months post last dose of nivolumab.

Exclusion Criteria

- Post-ASCT anti-lymphoma or investigational therapy. Immediate post-ASCT consolidative radiation therapy is allowed as long as it occurs prior to initiation of study therapy. Baseline imaging and PFTs must be performed after completion of radiation.
- Previous allogeneic transplant
- Total BCNU dose of > 600 mg/m^2 with prior treatments including transplant conditioning regimen
- Live vaccine within 30 days prior to Day 1 of protocol therapy (e.g. measles, mumps, rubella, varicella, yellow fever, rabies, BCG, oral polio vaccine, and oral typhoid)
- Refractory to prior brentuximab vedotin (i.e. progression while on treatment)
- Refractory to prior anti-PD-1/PD-L agent
- History of prior ≥ Grade 3 hypersensitivity to either brentuximab vedotin or nivolumab
- History of another primary malignancy that has not been in remission for at least 3 years. Exceptions include:
  - Basal cell carcinoma of the skin or
  - Squamous cell carcinoma of the skin that has undergone potentially curative therapy or
  - In situ cervical cancer.

- Known active central nervous system (CNS) involvement by lymphoma, including parenchymal and/or lymphomatous meningitis.
- History of progressive multifocal leukoencephalopathy (PML)
- ≥ Grade 2 peripheral neuropathy
- Prior diagnosis of inherited or acquired immunodeficiency
- Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. Exceptions are:
  - Inhaled or topical steroids and
  - Adrenal replacement doses > 10 mg daily prednisone equivalents in the absence of active autoimmune disease.
  - Uncontrolled illness including ongoing or active infection
- History of active pneumonitis or interstitial lung disease with the following exception:
  - For history of pneumonitis to be an exclusion, patient had to have required supplemental oxygen or corticosteroid treatment. Radiographic changes alone are not an exclusion
- An active, known or suspected autoimmune disease. The following are exceptions:
  - Vitiligo,
  - Type I diabetes mellitus,
  - Residual hypothyroidism due to autoimmune condition only requiring hormone replacement,
  - Psoriasis not requiring systemic treatment, or
  - Conditions not expected to recur in the absence of an external trigger
- Active or known history (standard pre-ASCT assessments) of:
  - Hepatitis B or C infection
  - Human immunodeficiency virus (HIV)
  - Acquired immunodeficiency syndrome (AIDS)
- Pregnant or breastfeeding
- 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 within 6 months prior to Day 1 of protocol therapy
- History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator

Investigational Product Dosage and Administration

Agent	Dose	Route	Schedule	Max. Cycles
Brentuximab Vedotin	1.8 mg/kg	IV over 30 minutes	Day 1 of each 21-day cycle	8
Nivolumab	3 mg/kg	IV over 60 minutes	Day 1 of each 21-day cycle*	
* Nivolumab is administered at least 30 minutes <u>after</u> the brentuximab vedotin infusion has ended.				

Clinical Observations and Tests to be Performed

- Medical history and physical exam
- Safety assessments (CBCs with differential, comprehensive chemistry panel, and thyroid function)
- PET-CT/ CT scans
- Correlative tumor tissue and blood samples

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ABBREVIATIONS

Abbrevation	Meaning
ASCT	Autologous Stem Cell Transplant
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BMS	Bristol Myers-Squibb Company
BV	Brentuximab vedotin
C	Cycle
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HL	Hodgkin Lymphoma
IB	Investigator Brochure
ICF	Informed Consent Form
IND	Investigational New Drug
IR	Indeterminate Response
ir	Immune Related
IRB	Institutional Review Board
IV	Intravenous
LYRIC	LYmphoma Response to Immunomodulatory Therapy Criteria
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
WHO	World Health Organization

1.0 OBJECTIVES

1.1 Primary Objectives

- Assess the efficacy of nivolumab plus brentuximab vedotin consolidation after autologous stem cell transplantation (ASCT) in participants with relapsed/refractory Hodgkin Lymphoma (HL), as assessed by 18-month progression-free survival (PFS).

1.2 Secondary Objectives

- Estimate the overall survival (OS), the cumulative incidence of relapse/progression, the cumulative incidence of non-relapse mortality (TRM) in participants with relapsed/ refractory HL who receive nivolumab plus brentuximab vedotin consolidation after ASCT.
- Estimate the overall response rate to nivolumab plus brentuximab vedotin therapy in participants with measurable disease after ASCT.
- Establish the safety and tolerability of nivolumab plus brentuximab vedotin when used as consolidation after ASCT in participants with relapsed/ refractory HL.

1.3 Exploratory Objectives

- Evaluate the Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) definition of indeterminate response to guide the management of patients regarding treatment past progressive disease.
- Explore the impact of nivolumab plus brentuximab vedotin therapy on immune reconstitution after ASCT.
- Explore the prognostic impact of and temporal dynamics of minimal residual disease (MRD) in the peripheral blood as assessed by the next-generation sequencing-based ClonoSEQ platform.
- Explore the prognostic impact of 9p24.1 abnormalities in tumor tissue assessed by FISH on outcomes after ASCT and nivolumab plus brentuximab vedotin post-ASCT consolidation therapy.
- Explore the relationship between immune cells and HRS in tumor samples by 6-color quantitative spatial image analysis using the Vectra system, and correlate with outcome after ASCT and nivolumab plus brentuximab vedotin post-ASCT consolidation therapy.
- Explore whether genetic alterations (e.g. gene expression profiles or genetic mutations) in HL tumor samples are associated with outcome after ASCT and nivolumab plus brentuximab vedotin post-ASCT consolidation therapy.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 *Classical Hodgkin Lymphoma*

Classical Hodgkin Lymphoma (HL) is a lymphoma of B-cell origin that is defined by the presence of Hodgkin-Reed-Sternberg cells in a background of inflammatory cells. Although the majority of patients with HL are cured with upfront therapy, as many as 20-40% of patients will have relapsed or refractory disease [2, 3]. Standard of care treatment for patients with relapsed/ refractory HL is salvage chemotherapy followed by autologous stem cell transplantation (ASCT) in chemosensitive patients, but about half of HL patients who undergo ASCT will relapse [4, 5]. HL patients who are refractory to second-line therapy or relapse after ASCT have poor outcomes [6]. Therefore, improved therapies to prevent post-ASCT relapse in patients with relapsed/ refractory HL are urgently needed.

2.1.2 *PD-1 in Hodgkin Lymphoma*

The programmed death receptor-1 (PD-1) pathway is an immune checkpoint that normally serves to dampen immune responses in tissues. PD-1 is expressed on activated T-cells and binds its ligands, PD-L1 and PD-L2, on tissue cells or antigen presenting cells to decrease T-cell activation, proliferation, and survival [7]. Tumor cells can co-opt this pathway to evade attack by the host immune system [7]. A wide range of hematologic malignancies express PD-1 or PD-L1, including HL [8, 9], diffuse large B-cell lymphoma (DLBCL) [9], primary mediastinal B-cell lymphoma (PMBCL),[8, 10] follicular lymphoma (FL) [11], chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [12], peripheral T-cell lymphomas (PTCL) [13-17], multiple myeloma (MM),[18] acute myelogenous leukemia (AML) [19, 20], and myelodysplastic syndrome (MDS) [21, 22].

More specifically, the PD-1/PD-L1 pathway appears to play a critical role in the pathogenesis of HL. HL is histologically defined by a small proportion of neoplastic HRS in a polymorphous inflammatory infiltrate, however, it is not clear that the inflammation represents an effective host anti-tumor immune response. In fact, frequent genetic alterations of the 9p24.1 region, which includes the *PD-L1*/*PD-L2* loci, have been identified in HL cell lines and primary HL tissue samples, supporting the concept that the PD-1/PD-L1 pathway plays a key role in host immune evasion that is central to HL pathogenesis [8]. *PD-L1* gene amplification has been linked with increased expression of PD-L1 in HL tumor samples [8]. In addition, the *JAK2* locus is contained within the 9p24.1 region, and JAK2 activation upregulates PD-L1 transcription and expression [8]. Furthermore, Epstein-Barr virus infection, which is frequently observed in HL, has also been identified as a mechanism of PD-L1 upregulation and expression in HL [23]. Based on these findings, it appears that the PD-1/PD-L1 pathway plays a critical role in immune evasion in HL, and supports the use of PD-1 inhibitors for the treatment of HL.

Indeed, inhibitors of PD-1 have produced impressive clinical responses in early-phase studies of these agents in patients with relapsed/ refractory HL. A Phase 1 study of nivolumab demonstrated an 87% ORR and 100% clinical benefit rate in 23 patients with relapsed or refractory HL.[24] A subsequent Phase 2 study of 80 patients who failed ASCT as well as prior brentuximab vedotin confirmed a high ORR of 66% (72% by investigator assessment), with 9% (28% by investigator assessment) of patients having a complete response. Notably, many responders remain in remission (62% of responders at time of censoring), thus a significant proportion of remissions appear to be durable [25]. A Phase 1b study of pembrolizumab in 31 patients with relapsed/ refractory HL who failed prior brentuximab vedotin demonstrated a 65% ORR with 16% of patients achieving CR [26]. A Phase II study of pembrolizumab in patients with relapsed/

refractory HL is ongoing, but interim reports have demonstrated an ORR of 70% in heavily treated patients with advanced HL [27].

2.2 Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes [28]. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVOTM (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014) [29].

2.2.1 *Effects in Humans*

The PK, clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, clear-cell renal cell carcinoma (RCC), and classical Hodgkin Lymphoma (cHL) in addition to other tumor types. This updated Investigator Brochure (IB) references the most recent US Prescribing Information (USPI) and EU Summary of Product Characteristics (SmPC) as the basis for the current state of knowledge on nivolumab for use in humans [29]. See Appendix 1 for USPI and Appendix 2 for SmPC. Nivolumab monotherapy is approved in multiple countries, including the US and EU, for unresectable or metastatic melanoma, previously treated metastatic NSCLC, and previously treated advanced RCC; it is also approved for the treatment of cHL in the US. In addition, nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma in multiple countries, including the US and EU [29].

Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies. Additional clinical activity and safety information presented in this IB focus primarily on data from clinical studies that are relevant to ongoing clinical investigations not in the approved USPI and SmPC (squamous cell carcinoma of the head and neck [SCCHN], small cell lung cancer [SCLC], gastric cancer, urothelial cancer, hepatocellular carcinoma [HCC], colorectal cancer [CRC], and glioblastoma [nivolumab monotherapy]; SCLC, gastric cancer, NSCLC, RCC, and CRC [nivolumab combination therapy]; and Ono Pharmaceutical Co., Ltd. [ONO] studies in Japanese or Korean subjects)[29].

2.2.2 *Clinical Efficacy*

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma. Recently, a Phase 1 trial in relapsed/refractory HL was performed

which showed an ORR of 87% [24]. A Phase 2 trial confirmed the response rate (66%) [25], and this led to accelerated FDA approval of nivolumab in patients who progressed after ASCT and brentuximab vedotin.

2.2.3 *Clinical Safety*

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date.

For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve.

The most advanced combination under development is nivolumab with ipilimumab, which is approved in subjects with unresectable or metastatic melanoma, and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab in combination with ipilimumab is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent when used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

2.3 Brentuximab Vedotin

Brentuximab vedotin, previously known as SGN-35, is an ADC consisting of the chimeric antibody SGN-30 (cAC10) chemically conjugated to a synthetic analog (monomethylauristatin E [MMAE]) of the naturally occurring antitubulin agent, dolastatin10. Brentuximab vedotin is proposed to have a multi-step mechanism of action that is initiated by binding to CD30 on the cell surface and internalization of the ADC. Upon trafficking to lysosomes, MMAE is released from the conjugate through proteolytic degradation of the drug linker [30]. Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis [31].

2.3.1 *Phase 2 Pivotal Study (SG035-0003) in Patients with HL*

SG035-0003 was a Phase 2, single-arm, open-label, multicenter, pivotal study of brentuximab vedotin (1.8 mg/kg IV, every 3 weeks) as a single agent in patients with relapsed or refractory HL. The primary objective was to assess efficacy based on ORR by an IRF. Secondary objectives were to assess duration of tumor control (duration of response and PFS), survival, safety and tolerability, and PK. Patients could remain on treatment for up to 16 cycles (approximately 1 year), or until disease progression, whichever occurred earlier.

There were 102 patients enrolled in the study. The study population was generally balanced with regard to gender (female, 53%) and was primarily white (87%). The median age was 31 years (range 15 to 77); 3 patients were older than 65 years of age and 1 patient was younger than 18 years. Patients entering the study were generally ambulatory and able to perform normal activities without assistance as indicated by an ECOG performance status of 0 (41%) or 1 (59%).

Approximately half of patients (46%) had Stage II disease at initial diagnosis; 26% had Stage III, 20% had Stage IV, 4% had Stage I, and 4% had unknown disease stage. Relative to most recent therapy 58% of patients were relapsed and 42% were refractory. Notably, 71% of patients had primary refractory disease, defined as not achieving a best response of CR with frontline therapy or relapsing within 3 months of completing front-line therapy. All patients had previously received autologous SCT (1 transplant, 89%; 2 transplants, 11%) and all had received at least one prior regimen of systemic chemotherapy (median 3.5 [range, 1 to 13]).

The median time from autologous SCT to relapse was 6.7 months and 71% of patients had experienced relapse within 1 year of autologous SCT. In the intent-to-treat (ITT) analysis set of 102 patients, ORR per IRF was 75% (95% CI [64.9, 82.6]): 33% CR (34 patients) and 41% partial remission (PR) (42 patients). The remaining patients had SD (22 patients), progressive disease (PD) (3 patients), or were not evaluable for response (1 patient). Tumor size reductions were observed in 94% of all patients.

The B symptom resolution rate was 77% (27 of 35 patients with B symptoms at baseline). Median time to resolution of B symptoms was 3.1 weeks (range, 0.4 to 11.9). After a median follow-up period of approximately 3 years for all enrolled patients, the median PFS was 9.3 months (95% CI: 7.1, 12.2 months) and the median OS was 40.5 months (95% CI: 28.7, – months). The estimated 4-year survival rate was 46% (95% CI: 36%, 56%). At the time of study closure, the estimated 5-year overall survival rate was 41% (95% CI: 31 %, 51%) and the median OS was 40.5 months (95% CI: 28.7, 61.9 [range, 1.8 to 72.9+]). The median PFS was 9.3 months overall. Of the 102 enrolled patients, 15 remained in follow-up and in remission at study closure. Among these 15 patients, 6 received consolidative allo-SCT and 9 have received no further therapy since completing brentuximab vedotin.

2.3.2 *Phase 3 Randomized, Placebo-Controlled (SGN35-005) Trial of Post-ASCT Maintenance in Patients with HL*

Study SGN35-005 was a randomized, double-blind, two-arm, placebo-controlled, multicenter, Phase 3 clinical trial designed to evaluate the efficacy and safety of brentuximab vedotin and best standard of care (BSC) compared with placebo and BSC in the treatment of patients at risk of disease progression following ASCT. Patients who had received an ASCT in the previous 30-45 days were randomized in a 1:1 manner to receive study treatment (brentuximab vedotin or placebo), administered as an outpatient IV infusion on Day 1 of each 21 day cycle. Patients were allowed to continue on study treatment for a maximum of 16 cycles, representing approximately 1 year of treatment. The primary objective was to compare the PFS of brentuximab vedotin and BSC versus placebo and BSC. Secondary objectives were to compare overall survival (OS) between the 2 treatment arms, to evaluate the safety and tolerability of brentuximab vedotin compared with placebo, and to characterize the incidence of anti-therapeutic antibodies (ATA). A total of 329 patients were randomized (165 patients to brentuximab vedotin and 164 to placebo). Out of 329 randomized patients, 327 patients received study treatment (167 patients received at least 1 dose of brentuximab vedotin and 160 patients received placebo; 2 patients in the placebo arm withdrew consent before receiving study treatment and 2 additional patients who were randomized to receive placebo each received 1 dose of brentuximab vedotin in error). The overall median age of study patients was 32 years (range, 18 to 76) and the majority of patients (321/329 [98%]) were <65 years of age. The study population was generally balanced with regard to gender (male = 53%) and was primarily white (94%). Patients entering the study were generally ambulatory and able to perform normal activities without assistance as indicated by an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (56%) or 1 (44%). Forty-one percent of patients had Stage II HL at initial diagnosis; 2% had Stage I, 28% had Stage III, 29% had Stage IV, and 1% had unknown disease stage. Patients were considered to be at high risk of residual

HL post ASCT and risk factors at baseline included refractory to frontline therapy (60%), relapsed < 12 months (33%), and extranodal disease at time of pre- ASCT relapse (33%). The median PFS per IRF for patients randomized to receive brentuximab vedotin was 42.9 months [95% CI (30.4, 42.9)] (range, 0.03+ to 42.94) compared with 24.1 months [95% CI (11.5, -)] (range, 0.03+ to 42.35+) for patients who received placebo. The difference between the 2 arms was statistically significant by stratified log-rank test (P=0.001). As assessed by Cox regression analysis, the stratified HR was 0.57 [95% CI (0.40, 0.81)].The estimated 24-month PFS rate was 63% [95% CI (55%, 70%)] for patients in the brentuximab vedotin arm versus 51% [95% CI (43%, 59%)] for patients in the placebo arm.

An additional prespecified analysis per investigator assessment was performed that included clinical lymphoma assessments for defining events and censoring of patients who had not yet progressed. At 24 months (the time of the last protocol-mandated CT scan), there remained a substantial separation between the PFS rate for brentuximab vedotin compared with placebo.

By this analysis, the median PFS for patients who received brentuximab vedotin was not reached (95% CI [-, -]) (range, 0.03+ to 49.05+) compared with 15.8 months (95% CI [8.5,-]) (range, 0.03+ to 48.36+) for patients who received placebo. As assessed by Cox regression analysis, the stratified HR was 0.50 (95% CI [0.36, 0.70]).

By Kaplan-Meier analysis, the estimated 24-month PFS rate was 65% (95% CI [57%, 72%]) for patients in the brentuximab vedotin arm versus 45% (95% CI [37%, 52%]) for patients in the placebo arm.

At the time of the interim OS analysis (a median OS observation time of 30 months [range, 0 to 50]), 53 patients (16%) had died; 28/165 patients (17%) in the brentuximab vedotin arm versus 25/164 patients (15%) in the placebo arm. The OS data are immature and the interpretation of these data is limited by the small number of events observed within a relatively short follow-up period. Interim OS is also confounded by the high rate of crossover to brentuximab vedotin. On the placebo arm, 72 of the 85 (85%) patients who received subsequent therapies received brentuximab vedotin, versus 9 of the 51 (18%) patients on the brentuximab vedotin arm. In part, this was due to a separate companion study that offered brentuximab vedotin only to placebo patients who had progressed. Patients are still on study and being followed for survival.

The median OS was not reached for patients in either treatment arm. There was no significant difference in OS between the treatment arms; the stratified log-rank test P value was 0.62 and the stratified HR was 1.15 [95% CI (0.67, 1.97)].

The estimated 24-month OS rate was 88% [95% CI (82%, 92%)] for brentuximab vedotin and 89% [95% CI (82%, 93%)] for placebo.

2.3.3 Phase 2 Retreatment and Extension Treatment (SGN35-006)

Study SGN35-006 was a Phase 2, open-label study that evaluated the safety and efficacy of brentuximab vedotin as retreatment or extension treatment.

Retreatment

Patients with CD30-positive hematologic malignancies who had experienced CR or PR with brentuximab vedotin on a prior study but who then experienced disease progression or relapse after treatment discontinuation were eligible for brentuximab vedotin retreatment in this study.

There were 32 unique patients enrolled and retreated; these patients had a potential for 35 patient retreatment experiences, as 3 patients re-enrolled and were retreated more than once in the retreatment

arm. Of note, 1 patient did not have any post-baseline efficacy assessments captured and is not included in the efficacy evaluable set; thus, 34 retreatment experiences are summarized for analyses of efficacy. Retreatment arm patients had a median age of 37 years (range, 16 to 72 years). Seventeen patients (53%) were female and 47% were male.

Twenty-seven patients (84%) were white. At retreatment baseline, 38% of patients had an ECOG performance status of 0 and 56% of patients had an ECOG performance status of 1.

The remaining 6% of patients had an ECOG performance status of 2 at retreatment baseline. Of the 32 unique retreatment patients, 21 patients were diagnosed with HL, 8 patients were diagnosed with systemic ALCL (63% were ALK negative), and 3 patients were diagnosed with another disease (2 patients with diffuse large B-cell lymphoma and 1 patient with angioimmunoblastic T-cell lymphoma).

The primary efficacy analysis for this study was performed using the efficacy-evaluable patient set, which includes all retreatment experiences for patients who were retreated at least once on this study and had at least 1 post-baseline restage assessment (N=34).

The ORR was 68% (95% CI, 49.5, 82.6; 60% for HL patients (95% CI, 36.1, 80.9), 91% for systemic ALCL patients (95% CI, 58.7, 99.8), and 33% for patients with other disease diagnoses (95% CI, 0.8, 90.6). Notably, the patient with an “other” disease diagnosis of diffuse large B-cell lymphoma achieved a CR with retreatment.

Of the 23 patients with an objective response, 14 patients had subsequent disease progression or died. The estimated median duration of objective response by Kaplan-Meier analysis was 9.2 months [95% CI (6.6, 12.9 months)]; the range of response duration was 0+ to 28+ months. Of the 13 patients with CR, 9 patients have had subsequent disease progression or died. The estimated median duration of response for patients with CR by Kaplan-Meier analysis was 12.3 months [95% CI (6.2, 14.2 months)]; the range of response duration was 1.7 to 28+ months.

2.3.4 *Summary of Clinical Safety of Post-ASCT BV Therapy*

Exposure was balanced between treatment groups on the AETHERA study (Study SGN35-005, the randomized, double-blind, placebo-controlled Phase 3 study in HL patients who are at risk of disease progression following ASCT) [32]. The median number of cycles was 15 (range, 1 to 16) and the median duration of treatment was approximately 48 weeks, which was higher than the median exposure on the pivotal studies. For the pivotal Phase 2 studies (Studies SG035-0003 and SG035-0004) in HL or systemic ALCL patients, the median number of cycles of treatment with brentuximab vedotin was 7 (range, 1 to 16), a median duration of approximately 24 weeks (range, 3 to 56).

AEs that had a higher relative risk of occurring in patients in the brentuximab vedotin arm compared with patients in the placebo arm (as indicated by a relative risk >1 and CIs that do not include 1) were peripheral motor neuropathy, paresthesia, abdominal pain, constipation, peripheral sensory neuropathy, weight decreased, neutropenia, nausea, myalgia, vomiting, diarrhea, and arthralgia. The most frequently reported Grade 3 or higher AEs included neutropenia, peripheral sensory neuropathy, and peripheral motor neuropathy and the majority of these were considered to be related to treatment with brentuximab vedotin. The most common Grade 4 event across the pivotal studies and StudySGN35-005 was neutropenia. The only other Grade 4 AE reported in more than 1 patient in these studies was thrombocytopenia.

2.4 Overview and Rationale of Study Design

Both brentuximab vedotin and nivolumab have produced high response rates as single-agents in patients with relapsed/ refractory HL. In addition, the AETHERA trial demonstrated that brentuximab vedotin consolidation treatment following ASCT prolongs PFS in patients with high risk relapsed or refractory classical Hodgkin lymphoma (HL) compared to placebo [32]. Despite the incremental benefit of the addition of post-ASCT brentuximab vedotin consolidation, the 2-year PFS in brentuximab vedotin-consolidated patients in the AETHERA trial was only 63%. Clearly, there is room for improvement.

In addition, with a planned 16 cycles of brentuximab vedotin therapy in the AETHERA trial, 23% of patients discontinued brentuximab vedotin consolidation therapy and 31% had modification of the brentuximab vedotin dose due to peripheral neuropathy. We propose to add nivolumab to the backbone of post-ASCT brentuximab vedotin consolidation to improve upon the efficacy of brentuximab vedotin post-ASCT consolidation, and to shorten the total duration of consolidation therapy from 16 to 8 cycles to improve tolerability of the combination regimen.

Based on the preliminary findings of an ongoing Phase 1/2 study, which is evaluating the combination of brentuximab vedotin and nivolumab as initial salvage treatment after the failure of frontline therapy, the combination of brentuximab vedotin and nivolumab appears safe and well-tolerated (Herrera AF et al., ASH 2016, Oral Presentation).

We propose a single-arm Phase 2 study to evaluate the efficacy of brentuximab vedotin plus nivolumab consolidation therapy in patients with brentuximab vedotin-naïve or brentuximab vedotin-responsive (at least SD to prior BV therapy, to prior brentuximab vedotin therapy, no progression while on brentuximab vedotin therapy) relapsed/ refractory HL who have undergone ASCT.

2.4.1 *Rationale for dose and schedule selection*

The recommended dose for brentuximab vedotin per its prescribing information is 1.8 mg/kg via intravenous (IV) infusion administered every 3 weeks. This dose and schedule was evaluated in two pivotal Phase 2 studies (SG035-0003 and SG035-0004) in patients with CD30-positive hematologic malignancies.

The dose for nivolumab for this study is 3 mg/kg via IV infusion administered every 3 weeks. The approved dose for nivolumab as monotherapy is 3 mg/kg every 2 weeks for the treatment of melanoma and metastatic squamous non-small cell lung cancer. However, nivolumab has been studied as monotherapy and in combination treatment in several tumor types with every 3 week dosing. It was recently reported that nivolumab dose levels of 0.3, 2, and 10 mg/kg every 3 weeks yielded similar ORR, PFS, and OS in a Phase 2 trial of patients with metastatic renal cell carcinoma [33]. Moreover, nivolumab dose levels of 0.1, 0.3, 1, 3, and 10 mg/kg every 2 weeks were associated with very similar (median 64%–70%) PD-1 receptor occupancy and comparable ORR and PFS in patients with advanced melanoma [34]. These findings indicate a flat dose-response relationship for nivolumab across a wide dose range for both every 2- and 3-week dosing, suggesting that dosing nivolumab at 3 mg/kg every 3 weeks is appropriate in the current study.

By delivering brentuximab vedotin, a directly cytotoxic agent, together with nivolumab in Cycle 1 it is anticipated that tumor-associated antigens will be released and available for presentation to resident cytotoxic T-cells at the same time that these cells become activated through PD-1 blockade.

Participants will be treated at the doses and schedule deemed safe in the currently ongoing Phase 1/2 study of nivolumab plus brentuximab vedotin as initial treatment of participants with relapsed/ refractory HL after failure of front-line therapy (NCT02572167), except that the drugs will both be given on day 1 of

cycle 1. This change is supported by the safety demonstrated in an ongoing clinical trial (NCT01896999) evaluating the same combination in patients with relapsed or refractory HL in second-line or beyond. In that trial, the rate of infusion reactions was < 10% in that trial, as compared to the 38% infusion-related reaction rate observed in NCT02572167 (both studies presented at ASH 2016). NCT02572167 is being amended to enroll additional patients dosing both medications on Day 1 of Cycle 1.

For this study, we will decrease the number of cycles of post-ASCT consolidation to 8 cycles as compared to 16 cycles in the AETHERA trial [32]. If BV is moved to first line therapy based on the ECHELON-1 trial (NCT01712490), patients will be receiving the equivalent of 6 cycles as a part of induction. Additionally, BV (alone or in combination) as first salvage therapy is being investigated, and patients who receive the agent prior to ASCT typically receive 4 cycles. Most importantly, in the AETHERA trial, the median number of cycles BV completed for patients who completed fewer than 16 cycles was 10.5 cycles [32]. Therefore, since 16 cycles is the maximum number of cycles to be administered in a single patient, many patients will have received 4-6 cycles of BV as part of prior therapy and 10 cycles appeared to be the inflection point for discontinuation of BV for toxicity on the AETHERA trial [32], we chose 8 cycles to stay short of the toxicity inflection point and keep patients from receiving more than 16 total cycles. In addition, other ongoing studies of single-agent PD-1 inhibition as post-ASCT consolidation in HL are employing 8 cycles, therefore, the 8 cycles utilized here will be consistent with the prior experience of anti-PD1 post-ASCT consolidation.

2.4.2 *Rationale for correlative studies*

The correlative analyses that will be performed as part of this clinical trial are exploratory and intended to generate hypotheses that can be validated in a larger study. The rationale for specific proposed correlative studies is included below, though the list of possible correlative studies is not necessarily exhaust, as it is anticipated that the exact nature and type of correlative studies may change as new scientific data emerges during the course of the study.

2.4.2.1 Minimal Residual Disease Assessment

Circulating tumor DNA detection has been examined in lymphoma. Next-generation sequencing (NGS)-based ctDNA detection performed by NGS of the immunoglobulin (Ig) or T-cell receptor genes (Ig-NGS) can identify ctDNA in the peripheral blood mononuclear cells (PBMC) and plasma (cell-free ctDNA) at diagnosis in patients with a range of lymphomas, including classical Hodgkin lymphoma and DLBCL.[35-38] In addition, ctDNA levels (measured by Ig-NGS) track with treatment response in DLBCL, and the persistence or recurrence of ctDNA during and after upfront therapy is associated with subsequent DLBCL relapse.[37, 38] Following allogeneic hematopoietic stem cell transplantation in patients with lymphoma or chronic lymphocytic leukemia (CLL), the presence of ctDNA (Ig-NGS) is associated with a higher risk of subsequent relapse and poorer progression-free survival (PFS).[39-41] Moreover, we have demonstrated that ctDNA assessment is a biomarker of outcome in patients with DLBCL who undergo autologous hematopoietic stem cell transplantation.[42]

2.4.2.2 9p24.1 Abnormalities in HL

Frequent genetic alterations in the 9p24.1 region, which includes the *PD-L1* and *PD-L2* loci, have been observed in HL [8]. *PD-L1* gene amplification has been linked with increased expression of PD-L1 in HL tumor samples [8]. In addition, the *JAK2* locus is contained within the 9p24.1 region, and JAK2 activation upregulates PD-L1 transcription and expression [8]. Furthermore, Epstein-Barr virus infection, which is frequently observed in HL, has also been identified as a mechanism of PD-L1 upregulation and expression

in HL.[23] These findings support the concept that the PD-1/PD-L1 pathway plays a key role in host immune evasion that is central to HL pathogenesis,[8] and provides a strong rationale for the use of PD-1/PD-L1 pathway inhibitors in HL.

Although genetic alterations in the 9p24.1 region are nearly universal in HL patients, inferior outcomes after standard initial treatment are observed in patients with amplification (3 or more copies, 36% of patients at diagnosis) of 9p24.1.[43] While genetic alterations in the 9p24.1 region are commonly observed in patients with HL treated with PD-1 inhibitors [24], the specific types of 9p24.1 alterations have not been examined for association with outcome after PD-1 inhibition.

2.4.2.3 Gene Expression Profiles

In HL patients treated with standard induction chemotherapy, gene expression profiles (GEP) of HL tissue samples, which includes GEP of both the tumor microenvironment (TME) and tumor cells, are associated with outcomes[44-46]. Studies have shown that GEP of genes associated with macrophage activation, the cell cycle, and apoptosis can identify high-risk subsets of patients with poorer survival.[44-46]

Gene expression profiles are associated with outcome after immune checkpoint inhibitor therapy in patients with advanced melanoma. Increased expression of genes that encode for immune-related targets, such as T-cell surface markers, immune receptors, and cytokines/chemokines, in pre-treatment melanoma tumor samples are associated with response to the CTLA4 inhibitor, ipilimumab.[47] In addition, a set of gene expression signatures (upregulation of genes associated with mesenchymal and inflammatory tumor phenotypes, angiogenesis, and wound healing) were enriched in melanoma patients who failed to respond to PD-1 inhibitors (nivolumab and pembrolizumab).[48]

Given the key role of the TME in response to anti-PD-1 therapy as well as in the pathogenesis of HL, we hypothesize that GEP will highlight features of the HL TME in pre-treatment tumor tissue that will be associated with outcome in patients with relapsed or refractory HL treated with PD-1/PD-L1 pathway inhibitors.

2.4.2.4 Multiplexed Immunohistochemistry

The composition and spatial orientation of immune cells and immune checkpoints in and around a tumor is associated with outcome after checkpoint inhibitor therapy. Specifically, the pre-treatment density of CD8+ T-cells, PD-1+ cells, and PD-L1+ cells in melanoma tumors and at the invasive margin is associated with response to pembrolizumab therapy. In addition, the proximity between CD8+ T-cells and PD-L1+ cells in and around melanoma tumors is associated with response to therapy.[49] On treatment biopsies revealed that patients responding to anti-PD-1 therapy had an increase in intratumoral CD8+ T-cells when compared to non-responders. These findings suggest that the melanoma patients who are most likely to respond to PD-1/PD-L1 pathway inhibitors had adaptive immune resistance, an underlying immune response that was shut down by the PD-1/PD-L1 pathway and released by anti-PD-1 therapy.

HL is histologically defined by few Hodgkin Reed-Sternberg (RS) cells surrounded by an ineffective, mixed immune infiltrate. The nearly universal genetic alterations in the *PD-L1* and *PD-L2* loci observed in RS cells, which results in increased expression of PD-L1 on RS cells, suggests that exploitation of the PD-1/PD-L1 pathway to evade the host immune response is fundamental to the pathogenesis of HL.[8] In addition, multispectral imaging-based multiplexed immunohistochemistry has demonstrated that the majority of PD-L1 expressing cells in the HL TME are tumor-associated macrophages, which appear to have PD-L1 expression induced by RS cells (Carey et al., ASH 2015). Despite this underlying dependence on the PD-1/PD-L1 pathway, not all patients respond to PD-1/PD-L1 pathway inhibitors, and some responding

patients have a short duration of response. We hypothesize that there are differences in the TME, specifically the phenotype and spatial orientation of the immune cells in the TME and their proximity to PD-L1 expressing cells and RS cells, which predict response to nivolumab and/or NICE therapy.

2.4.2.5 Impact of Study Treatment on Immune Reconstitution after ASCT

Anti-PD-1 therapy increases the number of cytotoxic T lymphocytes in the peripheral blood, and results in increased IFN-gamma levels and upregulation of IFN-gamma gene target expression. [26, 50] Checkpoint inhibitor therapy, including anti-CTLA4 and anti-PD-1 therapy, also impacts peripheral blood T-cell receptor repertoire (TCR) diversity.[51, 52] Immune reconstitution after autologous stem cell transplantation (ASCT) is well studied, but no there are no data describing immune reconstitution in the setting of ongoing anti-PD-1 therapy. We hypothesize that patients treated with brentuximab vedotin and nivolumab will have earlier and enhanced reconstitution of effector T-cell subsets, and earlier recovery of and broader TCR diversity.

3.0 ELIGIBILITY CRITERIA

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent

__2. Agreement to allow the use of archival tissue from pre-ASCT tumor biopsies (See Section 9.2 for details)

- If unavailable, exceptions may be granted with Study PI approval.

Age Criteria and Performance Status

__3. Age: ≥ 18 years

__4. ECOG performance status ≤ 2 (See Appendix A)

Nature of Illness and Treatment History

__5. Histologically confirmed diagnosis of classical Hodgkin lymphoma (excluding nodular lymphocyte predominant Hodgkin lymphoma) according to the WHO classification, with hematopathology review at the participating institution.

__6. Have high-risk relapsed or refractory Hodgkin lymphoma (HL), defined as at least one of the following:

- Primary refractory disease to front-line therapy.
- Relapse within 1 year of completing front-line therapy.
- Extranodal involvement at the time of pre-ASCT relapse.
- B symptoms at pre-ASCT relapse.
- More than one type of pre-ASCT salvage therapy required.

__7. Planning to receive or have received autologous stem cell transplantation (ACST) per institutional standards as part of standard of care.

- **Pre-ASCT participants** may consent but will not be eligible to begin treatment until after ASCT, and will have to fulfill all inclusion and exclusion criteria before starting protocol therapy.
- **All participants** must initiate Day 1 of protocol therapy **within 30-60 days post stem cell reinfusion**. Study PI can grant exception for a patient to start as late as 75 days post stem cell reinfusion with a reasonable justification for delay (e.g. recovery from post-ASCT toxicity) and this will not be a protocol deviation, nor require an exception to be filed.

__8. Recovery from ASCT toxicity as defined as outpatient status , able to drink, eat normally, and do not need intravenous hydration prior to Day 1 of therapy

__9. Achieved at least stable disease to salvage treatment determined by PET/CT using 2014 Lugano Classification [2] prior to ASCT.

__10. Brentuximab vedotin naïve OR had at least stable disease by Lugano Classification to prior brentuximab vedotin treatment

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

Organ Function Criteria and Pregnancy

__11. ANC ≥ 1000/mm^3	ANC:	Date:
__12. Platelets ≥ 50,000/mm^3	Plts:	Date:
__13. Hemoglobin ≥ 8 g/dL	Hgb:	Date:
__14. Total bilirubin ≤ 1.5 x ULN OR 3 x ULN for Gilbert's disease	ULN: Bil:	Date:
__15. AST and ALT ≤ 2.5 x ULN	ULN: ALT: ULN: AST:	Date: Date:
__16. Creatinine clearance* ≥ 40 mL/min per 24 hour urine collection or the Cockcroft-Gault formula * Calculated per institutional standard	ULN: Serum Cr: Cr Cl:	Date:

$$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for females})$$

Or

$$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}} \quad (\times 0.85 \text{ for females})$$

__17. Forced expiratory volume in one second (FEV1) and carbon monoxide diffusion capacity (DLCO) (adjusted for Hb) ≥ 50% adjusted	FEV1: DLCO:	Date:
__18. *WOCBP only*: Negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) • If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	Urine test: Serum test:	Date:

Contraception

__19. *Woman of childbearing potential (WOCBP)*: use two effective methods of contraception (hormonal or barrier method) or be surgically sterile, or abstain from heterosexual activity for the course of the study through 7 months post last dose of nivolumab.

- WOCBP defined as not being surgically sterilized or have not been free from menses for > 1 year.

Male: use two effective methods of contraception (barrier method) or abstain from heterosexual activity with the first dose of study therapy through 7 months post last dose of nivolumab.

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

3.2 Exclusion Criteria

Prospective participants who meet any of the following criteria will not be eligible to participate in the study:

Prior Therapy/ Procedures

__1. Post-ASCT anti-lymphoma or investigational therapy. Immediate post-ASCT consolidative radiation therapy is allowed as long as it occurs prior to initiation of study therapy. Baseline imaging and PFTs must be performed after completion of radiation.

__2. Previous allogeneic transplant

__3. Total BCNU dose of > 600 mg/m^2 with prior treatments including transplant conditioning regimen

__4. Live vaccine within 30 days prior to Day 1 of protocol therapy (e.g. measles, mumps, rubella, varicella, yellow fever, rabies, BCG, oral polio vaccine, and oral typhoid)

Other Illnesses and Conditions

__5. Refractory to prior brentuximab vedotin (i.e. progression while on treatment)

__6. Refractory to prior anti-PD-1/PD-L1 agent

__7. History of prior ≥ Grade 3 hypersensitivity to either brentuximab vedotin or nivolumab

__8. History of another primary malignancy that has not been in remission for at least 3 years. Exceptions include:

- Basal cell carcinoma of the skin or
- Squamous cell carcinoma of the skin that has undergone potentially curative therapy or
- In situ cervical cancer.

__9. Known active central nervous system (CNS) involvement by lymphoma, including parenchymal and/or lymphomatous meningitis.

__10. History of progressive multifocal leukoencephalopathy (PML)

__11. Grade ≥ 2 peripheral neuropathy at the present time

__12. Prior diagnosis of inherited or acquired immunodeficiency

__13. Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. Exceptions are:

- Inhaled or topical steroids and
- Adrenal replacement doses > 10 mg daily prednisone equivalents in the absence of active autoimmune disease.

Participant MRN (COH Only):	Participant Initials (F, M, L):
Institution:	

__14. Uncontrolled illness including ongoing or active infection

__15. History of or active pneumonitis or interstitial lung disease:
- For history of pneumonitis to be an exclusion, patient had to have required supplemental oxygen or corticosteroid treatment. Radiographic changes alone are not an exclusion.

__16. An active, known or suspected autoimmune disease. The following are exceptions:
- Vitiligo,
- Hemolytic anemia associated with the lymphoma (history of or at the present time)
- Type I diabetes mellitus,
- Residual hypothyroidism due to autoimmune condition only requiring hormone replacement,
- Psoriasis not requiring systemic treatment, or
- Conditions not expected to recur in the absence of an external trigger

__17. Active or known history (standard pre-ASCT assessments) of:
- Hepatitis B or C infection
- Human immunodeficiency virus (HIV)
- Acquired immunodeficiency syndrome (AIDS)

__18. Women who are pregnant or lactating

__19. 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 within 6 months prior to Day 1 of protocol therapy

__20. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator

Noncompliance

__21. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ **Site PI**			
☐ **Authorized study MD**			
☐ **Study Nurse**			
☐ **Study CRA/ CRC**			
☐ **Other:_____**			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT

NOTE: Sites must meet activation requirements prior to enrolling participants.

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see Section 16.4), and the prospective participant must receive a copy of the signed informed consent document.

Screening can initiate **21 days after ASCT** and screening assessments are listed in Section 10.0.

Participants who signed informed consent prior to ASCT must have completed ASCT and have recovered from ASCT toxicities to be eligible per Section 3.0 to receive protocol therapy.

4.2 Participant Enrollment

4.2.1 *COH DCC Availability and Contact Information*

Eligible participants will be registered on the study centrally by the DCC at City of Hope. DCC staff are available **between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays).** DCC contact information is as follows:

- phone: (626)-218-7904
- e-mail: DCC@coh.org

4.2.2 *Slot verification and reservation*

Designated study staff should call the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.3 *Registration Process*

To register a participant, the subsequent procedure is to be followed.

1. The participating site's data manager/coordinator/research nurse should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The data manager/coordinator/research nurse should then e-mail copies to DCC@coh.org of the following documents to the DCC:
   - Registration Cover Sheet (Appendix B)
   - Completed Eligibility Criteria List (printed from Section 3.0 of the protocol)
   - Source documentation to support eligibility criteria**
   - Signed informed consent document
   - Signed HIPAA authorization form (if separate from the informed consent document)
   - Signed subject's Bill of Rights (COH only)

**For COH participants, provide copies of source documentation only if not readily available as a finalized record in the COH Electronic Medical Record (EMR).

3. After having received all transferred documentation, the DCC will complete the review the documents to verify eligibility, working with the participating site as needed to resolve any missing required source elements. A participant failing to meet all protocol eligibility requirements will not be registered.
4. Once eligibility has been confirmed, DCC staff will register the participant by: assigning a subject accession number, register the subject on study centrally into a COH clinical trials management system for non-COH participants, and enter the subject into the eCRF system, Medidata RAVE.
5. Once registration has been completed, DCC staff will send a Confirmation of Registration Form, including the participant study number to:
   - the site study team: Site Lead Investigator, treating physician, protocol nurse, CRC and pharmacy
   - the COH sponsor team designees

4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

The DCC is to be notified of all participants who sign consent but do not meet eligibility criteria or do not initiate protocol therapy. For non-COH sites, the reason for screen failure will be documented in registration coversheet (see Appendix B) and submitted to the DCC.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a multi-center, open-label, Phase 2 clinical trial for participants with relapsed or refractory Hodgkin lymphoma who have undergone autologous stem cell transplant (ASCT). Participants will initiate protocol therapy within 30 to 60 days post stem cell reinfusion. Study PI can grant exception for a patient to start as late as 75 days post stem cell reinfusion with a reasonable justification for delay (e.g. recovery from post-ASCT toxicity) and this will not be a protocol deviation, nor require an exception to be filed. Nivolumab and brentuximab vedotin will be administered in an outpatient setting in each 21-day cycle.

Participants will receive up to 8 cycles of protocol therapy. If one agent is discontinued due to toxicity, then the participant may continue to receive single agent monotherapy.

Participants who complete protocol therapy (Section 5.6) will undergo follow-up (Section 5.7). Windows for all assessments and treatments are detailed in Section 10.0.

5.2 Treatment Cycle Definition

In the absence of treatment-related delay, a cycle of therapy is defined as 21 days with a ± 3 day window.

Day 1 of a cycle is defined as the administration of brentuximab vedotin (Section 5.3); the only exception to this will be if brentuximab vedotin is held or discontinued in which case Day 1 of a cycle will be defined as the adminitration of nivolumab.

5.3 Treatment Plan

Table 5.3 describes the combination regimen. The starting dose for brentuximab vedotin will be 1.8 mg/kg. Protocol therapy must be initiated within 30 to 60 days post stem cell reinfusion. Study PI can

grant exception for a patient to start as late as 75 days post stem cell reinfusion with a reasonable justification for delay (e.g. recovery from post-ASCT toxicity) and this will not be a protocol deviation, nor require an exception to be filed.

Table 5.3 Dosing regimen and schedule

Agent	Dose	Route	Schedule	Max. Cycles
Brentuximab Vedotin	1.8 mg/kg	IV over 30 minutes	Day 1 of each 21-day cycle	8
Nivolumab	3 mg/kg	IV over 60 minutes	Day 1 of each 21-day cycle	

5.4 Agent Administration

Mandatory prophylaxis for infusion related reaction must be initiated **at least 30 minutes** prior to agent administration.

- For participants **without** history of infusion reaction to brentuximab vedotin or nivolumab. Recommended pre-medication to include, per institutional standard:
  - Acetaminophen/paracetamol
  - Anti-histamine (e.g. diphenhydramine)
- For participants **who have experienced** an infusion related reaction to brentuximab vedotin or nivolumab (prior to this study, or on this study while not taking corticosteroid prophylaxis). Recommended pre-medication to include (and modifiable per institutional standard):
  - Acetaminophen/paracetamol 325 to 1000 mg
  - Anti-histamine: Diphenhydramine 25–50 mg (or equivalent)
  - Corticosteroid: Hydrocortisone IV no more than 100 mg (or equivalent)
  - Ranitidine may be considered
- For participants **who experience** infusion related reaction to study agents **while taking prophylactic corticosteroids**.
  - Premedication to follow above, but increase corticosteroids:
    - Methylprednisolone 40 mg IV (or equivalent e.g. hydrocortisone IV 200 mg).

For supportive care during infusion reaction, see Section 5.9.2.

5.4.1 *Brentuximab Vedotin*

Brentuximab vedotin will be administered as a 30 minute IV infusion on Day 1.

When both agents are administered sequentially, brentuximab vedotin will be administered first. The infusion must have ended at least 30 minutes prior to the nivolumab infusion.

Dosing is based on participant actual body weight. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight from baseline. Other dose adjustments for changes in body weight are permitted per institutional standard. An exception to weight-based dosing is made for participants weighing > 100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

Management and dose reductions associated with brentuximab vedotin AEs are outlined in Section 6.2.

5.4.2 *Nivolumab*

Nivolumab will be administered as a 60 minute (± 5 minute) IV infusion on Day 1.

Nivolumab should be administered at least 30 minutes after completing treatment with brentuximab vedotin on Day 1.

The nivolumab dose is fixed at 3 mg/kg. Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Refer to Section 8.1.9 for additional administration information.

The dosing calculations for nivolumab should be based on the actual body weight at baseline. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

Management and dose delays associated with nivolumab AEs are outlined in Section 6.2.

5.5 Assessments and Special Monitoring

Refer to Section 10.0 for schedule of assessments. **Note:** on days when agent(s) is/are administered, assessments are to be completed (and results reviewed if a safety or response assessment) prior to administration of agent(s).

5.5.1 *Special Monitoring*

- *Infusion reactions*
  - Infusion or hypersensitivity reactions may occur to either brentuximab vedotin or nivolumab.
  - Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions.
  - 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.
  - Refer to Section 5.9.2 for management guidelines.
- *Immune-related Adverse Events (AEs)*
  - Nivolumab is associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes.
  - Early recognition and management of AEs associated with nivolumab may mitigate severe toxicity.
  - Refer to Section 5.9.2 for management guidelines.

5.6 Duration of Therapy and Criteria for Removal from Study Treatment

Participants will receive protocol therapy until one of the below criteria are met:

- Disease progression
  - **Note:** Following consultation with the Study PI, participants who meet progression per 2014 Lugano classification [53] but who meet the criteria of "indeterminate response" (IR) according to the provisional modification to the 2014 Lugano Classification, the LYRIC

criteria [1] (Appendix H), and are deriving clinical benefit may continue to receive protocol therapy beyond progression as long as they meet the following criteria:

- Continue to meet treatment criteria
- Investigator-assessed clinical benefit and subject is tolerating study drug.
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

- *If the patient has IR per LYRIC criteria and is receiving therapy beyond progression*:
  - A confirmatory PET-CT should be performed within 12 weeks after initial progression to determine whether the patient meets PD criteria according to the LYRIC criteria [1].
  - Further progression is defined according to the LYRIC criteria
  - Protocol therapy should be discontinued permanently upon documentation of PD per the LYRIC criteria

- Participant receives 8 cycles (~ 6 months) of protocol therapy
- Unacceptable toxicity related to protocol therapy despite dose delay/ modification
  - **Note:** If one agent is delayed due to toxicity, then participants many continue with monotherapy for the other agent.
- General or specific changes in the participant's condition (including intercurrent illness) which render the participant unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy by the participant (See Section 16.5)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to Follow-up.

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the medical record and appropriate eCRF. The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.7 Follow-Up

Following completion of protocol therapy, participant will enter follow-up. Note, the safety follow-up visits may occur concurrently with other follow-up visits:

- **Safety Follow-up** - All participants will undergo safety follow-up visits, typically at 30 days and 100 days following the end of treatment.
- **Active Response Follow-Up** – for participants who have yet to progress/relapse. These visits also involves the collection of research samples. This period has a maximum of 18 months from start of treatment.
- **Long Term Follow-Up** – for all participants who have progressed/relapsed OR completed Active Response Follow-Up. This follow-up will be performed typically via medical record review. It will entail (a) Disease status (for those who have yet to relapse/progress) (b) Vital status (all participants). The long-term follow-up period will have a maximum duration of 5 years (from start of treatment).

See Section 10.0 for details and windows.

5.8 Duration of Participation and Criteria for End of Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and follow-up)
- Participant withdrawal (see Section 16.5).
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for reasons including but not limited to study termination, behavioral or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the medical record and appropriate eCRF. The COH DCC should be promptly notified of the change in participant status.

5.9 Supportive care, Prohibited and Concomitant Medications/ Therapies

Participants must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator.

5.9.1 *Prohibited medications/ therapies*

The following medications/ therapies are **prohibited** from Day 1 of protocol therapy until end of protocol therapy (last day of study agent or decision to end study agent(s) whichever occurs later):

- Co-medication that may interfere with study results; e.g. immuno-suppressive agents other than corticosteroids used for treatment of an IrAE are prohibited during the treatment period, unless discussed with the Study PI and felt to be of low clinical risk to the participant.
- Live attenuated vaccines
- Herbal and natural remedies

The following medications/therapies are prohibited any time after ASCT, active protocol treatment, or follow-up. If the patient receives one of these therapies in the absence of disease progression, the patient will be censored at the time of initiation.

- Other investigational therapy
- Concurrent anti-cancer therapy: chemotherapy, biological response modifiers, hormone therapy, surgery, palliative radiation therapy, or immunotherapy).

5.9.2 *Supportive care and permitted medications/ therapies*

With the exception of prohibited therapies (see Section 5.9.1), participants should receive prophylactic or supportive care as clinically indicated per institutional policies and suspected immune-related AEs (irAE) guidelines stated below.

Blood products

- *Platelet and/or red blood cell supportive growth factors or transfusions*
  - Permitted when applicable
- *Colony stimulating factors (CSFs)*
  - Permitted for treatment of neutropenia per institutional practice.

Corticosteroids

- *Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption)*
  - Permitted
- *Systemic corticosteroids*
  - Physiologic replacement doses permitted even if > 10 mg/day prednisone or equivalent.
- *Brief course of corticosteroids (< 3 weeks)*
  - Permitted for prophylaxis (e.g. contrast dye allergy)
  - Permitted for treatment of non-autoimmune conditions (e.g, delayed-type hypersensitivity reaction caused by contact allergen)

Strong CYP3A4/5 inhibitors

Closely monitor for AEs when administered concomitantly with brentuximab vedotin.

Required prophylaxis

Standard international guidelines for infection prophylaxis for herpes simplex virus (HSV), varicella-zoster virus (VZV), and Pneumocystis jiroveci (PCP) after ASCT must be followed. Per international guidelines, Herpes virus prophylaxis with acyclovir or similar agent and pneumocystis jiroveci (PCP) prophylaxis is required for all patients on this study. Administer prophylaxis from the time of engraftment (or the time of first study treatment dosing) for at least 9 months after ASCT. If herpes virus or PCP prophylaxis is held, the reasoning (e.g. renal dysfunction) must be documented.

- *First Choice*
  - Trimethoprim-sulfamethoxazole: 1 double-strength (DS) tablet (160/800 mg) orally 3 times/week; 1 DS tablet orally daily; 1 single-strength (80/400 mg) tablet orally daily; or 1 DS tablet two times a day 2 days a week.

- *First Alternative*
  - Atovaquone: 750 mg twice daily or 1500 mg once daily, orally

- *Other Alternatives*
  - Dapsone: 50 mg orally 2 times/day; or 100 mg orally daily
  - Pentamidine: 300 mg every 3-4 weeks by Respirgard II™ nebulizer

Management of infusion reactions

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

Grade 2 infusion reactions

- If the onset of a reaction occurs during an infusion,
  - The infusion may be interrupted for treatment of the infusion-related reaction, **and/or**
  - The infusion time may be extended.
  - Recommended treatments include: antihistamines, corticosteroids, and/or bronchodilator therapy, as appropriate.

Grade 3 or 4 infusion reactions

- If the onset of a reaction occurs during infusion, the infusion must be interrupted.
- Begin an IV infusion of normal saline
- Recommend treatments include:
  - bronchodilators,
  - epinephrine 0.2 to 1 mg of a 1:1,000 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.
- Monitor until the investigator is comfortable that the symptoms will not recur.
- Follow institutional guidelines for anaphylaxis.
- *For late-occurring hypersensitivity symptoms* (e.g. appearance of a localized or generalized pruritus within 7 days post-treatment):
  - Symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids)

Management of immune-related AEs

The following immune-related AEs (irAEs) related to nivolumab should be managed as outlined below.

5.9.2.1 Hepatic

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

For patients with baseline LFT that are within normal limits:

Grade 1: AST or ALT > ULN – 3.0 x ULN and/or Total bilirubin > ULN -1.5X ULN

- Continue liver function tests (LFT) monitoring per protocol
- If worsens treat as Grade 2 or 3-4

Grade 2: AST or ALT > 3.0 to ≤ 5 x ULN and/or Total bilirubin >1.5 to ≤ 3 x ULN

- Increase frequency of monitoring to every 3 days
- If returns to baseline: Resume routine monitoring, resume therapy per protocol
- If elevations persist > 5-7 days or worsen :
  - 0.5-1 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 nivolumab per protocol

Grade 3-4: AST or ALT > 5 x ULN and /or Total bilirubin >3 x ULN

- Increase frequency of monitoring to every 1-2 days
- Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

- Add prophylactic antibiotics for opportunistic infections
- Consult gastroenterologist
- If returns to grade 2:
  - Taper steroids over at least 1 month
- If does not improve in >3-5 days, worsens or rebounds:
  - Add mycophenolate mofetil 1 gram (g) twice daily (BID)
  - If no response within an additional 3-5 days, consider other immunosuppressants

For patients with baseline LFTs (transaminases or bilirubin) 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 according to the hepatic algorithm as applied to the absolute increase in AE grade level above baseline. Therefore, for these patients, management of a Grade 3 LFT abnormality would be per the Grade 2 algorithm, and management of a Grade 4 LFT abnormality would be per the Grade 3 algorithm.

5.9.2.2 Renal

Grade 1: Creatinine > ULN and > than baseline but ≤ 1.5x baseline

- 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

- Monitor creatinine every 2-3 days
- Administer 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent
- Consider renal biopsy
- If returns to Grade 1:
  - Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume nivolumab and routine creatinine monitoring per protocol
- If elevations persist > 7 days or worsen:
  - Treat as Grade 4

Grade 4: Creatinine > 6x ULN

- Monitor creatinine daily
- Administer 1.0-2.0 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

5.9.2.3 Diarrhea/Colitis

- 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 1 Diarrhea/ Colitis

- Symptomatic treatment
- Close monitoring for worsening symptoms.
- Educate patient to report worsening immediately
- If worsens:
  - Treat as Grade (G) 2 or 3/4

Grade 2 Diarrhea/ Colitis

- Symptomatic treatment
- If persists > 5-7 days or recur:
  - Administer 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
- If worsens or persists > 3-5 days with oral steroids:
  - Treat as grade 3/4

Grade 3-4 Diarrhea/ Colitis

- Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent
- Add prophylactic antibiotics for opportunistic infections
- Consider lower endoscopy
- If improves:
  - Continue steroids until grade 1, then taper over at least 1 month
- If persists > 3-5 days, or recurs after improvement:
  - 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.

5.9.2.4 Endocrinopathy

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

Asymptomatic thyroid stimulating hormone (TSH) elevation

- If TSH < 0.5 x lower limit of normal (LLN), or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include free thyroxine (fT4) at subsequent cycles as clinically indicated; consider endocrinology consult

Symptomatic endocrinopathy

- Evaluate endocrine function
- Consider pituitary scan
- Symptomatic with abnormal lab/pituitary scan:
  - 1-2 mg/kg/day methylprednisolone IV or by mouth (PO) equivalent
  - Initiate appropriate hormone therapy
- No abnormal lab/pituitary MRI scan but symptoms persist:
  - Repeat labs in 1-3 weeks /MRI in 1 month
- If improves (with or without hormone replacement):
  - Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
  - 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)

- Rule out sepsis
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids
- Consult endocrinologist

5.9.2.5 Neurological

- 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.

Grade 1: Asymptomatic or mild symptoms; Intervention not indicated

- Continue to monitor the patient

Grade 2: Moderate symptoms; instrumental ADL

- Treat symptoms per local guidelines
- Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent
- If worsens:
  - Treat as Grade 3-4

Grade 3-4: Severe symptoms; Limiting self-care ADL; Life-threatening

- Obtain neurology consult
- Treat symptoms per local guidelines
- 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent

- Add prophylactic antibiotics for opportunistic infections
- If improves to Grade 2:
  - Taper steroids over at least 1 month
- If worsens or atypical presentation:
  - Consider IVIG or other immunosuppressive therapies per local guidelines

5.9.2.6 Pulmonary

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

Grade 1: Radiographic changes only

- Monitor for symptoms every 2-3 days
- Consider Pulmonary and Infectious Disease (ID) consults

Grade 2: Mild to moderate new symptoms

- 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 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

- Hospitalize
- Pulmonary and ID consults
- 2-4 mg/kg/day methylprednisolone IV or IV equivalent
- Add prophylactic antibiotics for opportunistic infections
- Consider bronchoscopy, lung biopsy

5.9.2.7 Skin

Grade 1-2 Covering ≤ 30% body surface area (BSA)

- Symptomatic therapy (e.g. antihistamines, topical steroids)
- If persists > 1-2 weeks or recurs:
  - Consider skin biopsy

  - 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
- If worsens:
  - Treat as Grade 3-4

Grade 3-4: Covering >30% BSA; Life threatening consequences

- Consider skin biopsy
- Dermatology consult
- 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent
- If improves to Grade 1:
  - Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infection

6.0 ANTICIPATED TOXICITIES AND DOSE DELAY/MODIFICATIONS

6.1 Anticipated Toxicities

6.1.1 *Brentuximab vedotin*

Per the IB the expected toxicities for brentuximab vedotin are as follows:

System Organ Class	Adverse Reactions
Infections and infestations	
Very common	Infection[a], upper respiratory tract infection
Common	Herpes zoster, pneumonia, herpes simplex, oral candidiasis
Uncommon	Pneumocystis jiroveci pneumonia, staphylococcal bacteremia, cytomegalovirus infection or reactivation, sepsis/septic shock
Frequency not known	Progressive multifocal leukoencephalopathy
Blood and lymphatic system disorders	
Very common	Neutropenia
Common	Anamia, thrombocytopenia
Uncommon	Febrile neutropenia
Immune system disorders	
Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	
Common	Hyperglycemia
Uncommon	Tumor lysis syndrome
Nervous system disorders	
Very common	Peripheral sensory neuropathy, peripheral motor neuropathy
Common	Dizziness
Uncommon	Demyelinating polyneuropathy
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnea
Gastro-intestinal disorders	
Very common	Nausea, diarrhea, vomiting, constipation, abdominal pain
Uncommon	Pancreatitis acute
Hepatobiliary disorders	
Common	Alanine aminotransferase/aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	
Very common	Rash[a], pruritus
Common	Alopecia
Uncommon	Stevens-Johnson syndrome/toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, myalgia
Common	Back pain
General disorders and administration site conditions	

System Organ Class	Adverse Reactions
Very common	Fatigue, pyrexia, infusion-related reactions[a]
Common	Chills
Investigations	
Very common	Weight decreased

a Represents pooling of preferred terms

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data).

6.1.2 *Nivolumab*

Per the IB (version 17, June 2018) the expected toxicities for nivolumab are as follows:

System Organ Class	Adverse Reactions
Infections and infestations	
Common	Upper respiratory tract infection
Uncommon	Pneumonia[a], bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare	Histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)
Blood and lymphatic system disorders	
Very common	Neutropenia[a,b], lymphopenia, leucopenia, thrombocytopenia, anemia
Uncommon	Eosinophilia
Immune system disorders	
Common	Infusion related reaction[c], hypersensitivity[c]
Rare	Anaphylactic reaction[c]
Not known	Solid organ transplant rejection
Endocrine disorders	
Common	Hypothyroidism, hyperthyroidism
Uncommon	Adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus
Rare	Diabetic ketoacidosis
Metabolism and nutrition disorders	
Common	Decreased appetite
Uncommon	Dehydration, metabolic acidosis
Hepatobiliary disorders	
Uncommon	Hepatitis[c]
Rare	Cholestasis
Nervous system disorders	
Common	Peripheral neuropathy, headache, dizziness
Uncommon	Polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c]

System Organ Class	Adverse Reactions
Eye disorders	
Uncommon	Uveitis, blurred vision, dry eye
Not known	Vogt-Koyanagi-Harada syndrome[g]
Cardiac disorders	
Uncommon	Tachycardia
Rare	Arrhythmia (including ventricular arrhythmia), atrial fibrillation, myocarditis[a,e]
Vascular disorders	
Common	Hypertension
Rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Common	Pneumonitis[a,c], dyspnea[a], cough
Uncommon	Pleural effusion
Rare	Lung infiltration
Gastro-intestinal disorders	
Very common	Diarrhea, nausea
Common	Colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth
Uncommon	Pancreatitis, gastritis
Rare	Duodenal ulcer
Skin and subcutaneous tissue disorders	
Very common	Rash[d], pruritus
Common	Vitiligo, dry skin, erythema, alopecia
Uncommon	Erythema multiforme, psoriasis, rosacea, urticaria
Rare	Toxic epidermal necrolysis[a,e], Stevens-Johnson syndrome[a,e]
Musculoskeletal and connective tissue disorders	
Common	Musculoskeletal pain[f], arthralgia
Uncommon	Polymyalgia rheumatica, arthritis
Rare	Sjogrengia rheumatica, arthritis myositis (including polymyositis)[a,e], rhabdomyolysis[a,e]
Renal and urinary disorders	
Uncommon	Tubulointerstitial nephritis, renal failure (including acute kidney injury)[a,c]
General disorders and administration site conditions	
Very common	Fatigue
Common	Pyrexia, oedema (including peripheral oedema)
Uncommon	Pain, chest pain
Investigations	
Very common	Increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcemia, increased creatinine, hyperglycemia[c], hypercalcemia, hyperkalemia, hypokalemia, hypomagnesemia, hyponatremia

System Organ Class	Adverse Reactions
Common	Increased total bilirubin, hypoglycemia, hypermagnesemia, hypernatremia, weight decreased

a Fatal cases have been reported in completed or ongoing clinical studies
b Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements.
c Life-threatening cases have been reported in completed or ongoing clinical studies.
d Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.
e Reported also in studies outside the pooled dataset.
f Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
g Post-marketing event

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 2578). These reactions are presented by system organ class and by frequency.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

6.2 Dose Modification/Delays

- Toxicities will be graded using the NCI CTCAE v 4.0.
- Baseline values are from the last values obtained prior to treatment.
- If one agent is held due to toxicity for a given cycle, administration of the delayed agent should resume once the toxicity is resolved on the same schedule with the next cycle of combination therapy.
- If one agent is permanently discontinued, then the participant may continue monotherapy with the other agent.
- If both agents are held together and the toxicity lasts > 6 weeks, then protocol therapy will be discontinued.
- **Nivolumab dose management guidelines** are described in Table 6.2.1.
  - Management algorithms for nivolumab have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological. The algorithms have been incorporated into Table 6.2.1 and can also be found in the Nivolumab IB. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.
  - Dose reductions or dose escalations are not permitted for nivolumab.
  - Asterisk (*) in Table 6.2.1: Following consultation with the Study PI, treatment delay > 6 weeks due to prolonged steroid taper is permissible.
  - Dosing interruptions or delays lasting > 6 weeks that occur for non-nivolumab-related reasons may be allowed if approved by the Study PI. Prior to re-initiating treatment in a participant with a dosing interruption lasting > 6 weeks, the Study PI must be consulted.

- **Brentuximab vedotin dose modification/ delay** are described in Table 6.2.2.
  - Doses reduced for brentuximab vedotin-related toxicity should not be re-escalated without discussion with the Study PI.

Table 6.2.1 Dose management guidelines for Nivolumab

Toxicity	Nivolumab Dose Management Guidelines
Hematological Toxicity	
Anemia or thrombocytopenia Grade 3 *Platelets: < 50,000 - 25,000/mm³*	Continue nivolumab
Anemia or thrombocytopenia Grade 4 *Platelets <25,000/mm³*	• Hold nivolumab • Once toxicity resolves ≤ Grade 2 resume nivolumab per protocol • Permanently discontinue if there is a treatment delay > 6 weeks.
Neutropenia Grade 3 *ANC <1000 - 500/mm³*	Continue nivolumab • Consider growth factor (G-CSF) support
Neutropenia Grade 4 *ANC < 500/mm³*	• Hold the nivolumab dose • Once toxicity resolves to ≤ Grade 2 or baseline, resume treatment with nivolumab per protocol • Growth factor support should be instituted. • A repeat blood draw to evaluate the grade of neutropenia should be performed within 3 days. • Consider growth factor support (G-CSF or GMCSF) for subsequent cycles. • If toxicity recurs despite growth factor support, consider nivolumab discontinuation. • Permanently discontinue if there is a treatment delay > 6 weeks.
Eye (Blurred Vision, Eye Pain, Uveitis)	
Eye pain, blurred vision Grade 2	Discontinue nivolumab if toxicity does not respond to topical therapy and does not improve to Grade 1 within 6 weeks or requires systemic treatment.
Uveitis Grade 2	Discontinue nivolumab if toxicity does not respond to topical therapy and does not improve to Grade 1 within 6 weeks or requires systemic treatment.
Uveitis Grade 3	Discontinue nivolumab

Toxicity	Nivolumab Dose Management Guidelines
Hepatic (AST, ALT, Total bilirubin) – *when baseline LFTs are within normal limits*	
Note: for participants with Grade 1 baseline LFTs, hepatic dose management guidelines below should be followed.	
Grade 1 *AST or ALT > ULN- 3.0 xULN and/or Total bilirubin > ULN -1.5 x ULN*	• Continue nivolumab per protocol • See *Section 5.9.2.1* for supportive care.
Grade 2 *AST or ALT > 3.0 to ≤ 5 x ULN **OR** T. bili > 1.5 to ≤ 3 x ULN*	• Hold the dose of nivolumab • See *Section 5.9.2.1* for supportive care. • If toxicity resolves within 5 days to baseline resume nivolumab per protocol • If elevations persist > 5-7 days or worsen – Resume therapy per protocol when LFT returns to Grade ≤ 1 or baseline and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period.
Low Grade 3 *AST or ALT > 5-≤ 8 x ULN x ULN **OR** total bilirubin >3-≤ 5 x ULN*	• Per investigator discretion the nivolumab dose may be delayed rather than discontinued.
High Grade 3 and Grade 4 *AST or ALT > 8 x ULN **OR** total bilirubin >5 x ULN*	• Discontinue nivolumab therapy • See *Section 5.9.2.1* for supportive care.
Concurrent ≥ Grade 2 AST or ALT (> 3 x ULN) **AND** total bilirubin > 2 x ULN	• Discontinue nivolumab therapy • See *Section 5.9.2.1* for supportive care.
Hepatic (AST, ALT, Total bilirubin) – *when baseline LFTs are Grade 1*	
Note: for participants with baseline LFTs that are within normal limits, hepatic dose management guidelines above should be followed.	
Grade 1 and 2 *G1: AST or ALT > ULN- 3.0 xULN and/or Total bilirubin > ULN -1.5 x ULN* *G2: AST or ALT > 3.0 to ≤ 5 x ULN **OR** T. bili > 1.5 to ≤ 3 x ULN*	• Continue nivolumab per protocol • See *Section 5.9.2.1* for supportive care.
Low Grade 3 *AST or ALT > 5-≤ 8 x ULN x ULN OR total bilirubin >3-≤ 5 x ULN*	• Hold the dose of nivolumab • See *Section 5.9.2.1* for supportive care. • If toxicity resolves within 5 days to baseline resume nivolumab per protocol • If elevations persist > 5-7 days or worsen – Resume therapy per protocol when LFT returns to Grade ≤ 2 or baseline and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period.

Toxicity	Nivolumab Dose Management Guidelines
High Grade 3 and Grade 4 *AST or ALT > 8 x ULN **OR** total bilirubin >5 x ULN*	• Discontinue nivolumab therapy • See *Section 5.9.2.1* for supportive care.
Concurrent ≥ Grade 2 AST or ALT (> 3 x ULN) **AND** total bilirubin > 2 x ULN	• Discontinue nivolumab therapy • See *Section 5.9.2.1* for supportive care.
Renal (Creatinine)	
Grade 1 *Creatinine > ULN and > than baseline but ≤ 1.5x baseline*	• Continue nivolumab per protocol • See *Section 5.9.2.2* for supportive care. • If worsens: – Treat as Grade 2 or 3/4
Grade 2-3 *Creatinine > 1.5x baseline to ≤ 6x ULN*	• Hold the dose of nivolumab • See *Section 5.9.2.2* for supportive care. • Resume therapy per protocol once the toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period. • If elevations persist > 7 days or worsen: – Treat as Grade 4
Grade 4 *Creatinine > 6x ULN*	• Discontinue nivolumab • See *Section 5.9.2.2* for supportive care.
Gastrointestinal (Diarrhea/ Colitis) Toxicity	
Diarrhea/Colitis Grade 1 *Diarrhea:< 4 stools/day over baseline;* *Colitis: asymptomatic*	• Continue nivolumab. – See *Section 5.9.2.3* for supportive care. • If worsens: – Treat as Grade (G) 2 or 3/4
Diarrhea/Colitis Grade 2 *Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL* *Colitis: abdominal pain; blood in stool*	• Hold the dose of nivolumab • See *Section 5.9.2.3* for supportive care. • If toxicity resolves to Grade ≤ 1 within 5 days resume therapy with study regimen • If persists > 5-7 days or recur: – Resume study regimen per protocol once the toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period. • *If worsens or persists > 3-5 days with oral steroids*: – Treat as Grade 3-4

Toxicity	Nivolumab Dose Management Guidelines
Diarrhea/Colitis Grade 3-4 *Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL)* *Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs* *G4: life-threatening, perforation*	• Discontinue study regimen • See *Section 5.9.2.3* for supportive care.
Endocrinopathy	
Asymptomatic thyroid stimulating hormone (TSH) elevation	• Continue nivolumab per protocol • See *Section 5.9.2.4* for supportive care.
Symptomatic endocrinopathy	*Symptomatic with abnormal lab/pituitary scan*: • Hold the dose of nivolumab • See *Section 5.9.2.4* for supportive care. • If toxicity improves (with or without hormone replacement): – Resume therapy per protocol when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period. – **Note:** Grade 3 endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)	• Hold or discontinue nivolumab per investigator discretion – **Note:** Grade 4 endocrinopathy AEs, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Study PI. • See *Section 5.9.2.4* for supportive care. • If adrenal crisis was ruled out, then treat as above for Symptomatic Endocrinopathy.
Neurological	
Grade 1 *Asymptomatic or mild symptoms; Intervention not indicated*	• Continue nivolumab per protocol • See *Section 5.9.2.5* for supportive care. • If worsens: – Treat as Grade 2 or 3-4

Toxicity	Nivolumab Dose Management Guidelines
Grade 2 *Moderate symptoms; Limiting instrumental ADL*	• Hold the nivolumab dose • See *Section 5.9.2.5* for supportive care. • Resume therapy per protocol once the toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period. • If worsens: – Treat as Grade 3-4
Grade 3-4 *G3:Severe symptoms; Limiting self-care ADL* *G4:Life-threatening consequences; urgent intervention indicated*	• Discontinue nivolumab • See *Section 5.9.2.5* for supportive care.
Pulmonary	
Pulmonary Grade 1 *Radiographic changes only*	• Consider holding nivolumab • See *Section 5.9.2.6* for supportive care.
Pulmonary Grade 2 *Mild to moderate new symptoms*	• Hold nivolumab • See *Section 5.9.2.6* for supportive care. • Resume therapy per protocol once the toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period. • If not improving after 2 weeks or worsening: – Treat as Grade 3-4
Pulmonary Grade 3-4 *Severe new symptoms; New or worsening hypoxia; Life-threatening*	• Discontinue nivolumab • See *Section 5.9.2.6* for supportive care.
Skin	
Skin Grade 1-2 *Covering ≤ 30% body surface area (BSA) (refer to CTCAE v4.0 for term specific criteria)*	• Continue nivolumab per protocol – **Note:** Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity. • See *Section 5.9.2.7* for supportive care. • If persists > 1-2 weeks or recurs: – Hold nivolumab – Once improving , taper steroids over at least 1 month*, and resume study regimen per protocol. (* See exception in Section 6.2.) • If worsens: – Treat as Grade 3-4

Toxicity	Nivolumab Dose Management Guidelines
Skin Grade 3 *Covering >30% BSA; Life threatening consequences (refer to CTCAE v4.0 for term specific criteria)*	• Hold nivolumab • See *Section 5.9.2.7* for supportive care. • Resume study regimen per protocol once toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period.
Skin: Grade 4 *(refer to CTCAE v4.0 for term specific criteria)*	• Discontinue nivolumab • See *Section 5.9.2.7* for supportive care.
Fatigue	
Grade 2	Continue nivolumab per protocol
Grade 3	• Hold study agents • Resume study regimen per protocol once toxicity returns to Grade ≤ 2 • Discontinue treatment if toxicity lasts for > 6 weeks
Grade 4	Discontinue nivolumab
Amylase or Lipase elevation	
Grade 2	Continue nivolumab per protocol
Lipase or amylase Grade 3 *Asymptomatic or not associated with clinical manifestations of pancreatitis*	• Continue nivolumab per protocol • Consult the Study PI
Isolated Grade 4 amylase or lipase *Asymptomatic or not associated with clinical manifestations of pancreatitis*	• Delay the dose of nivolumab until resolution to < Grade 2 • Consult the Study PI • If toxicity > 7 days from onset, discontinue therapy.
Lipase or amylase Grade 4 *Symptomatic or associated with clinical manifestations of pancreatitis*	• Discontinue nivolumab
Laboratory abnormalities	
NOTE: Follow guidelines above for hematologic, hepatic (ALT, AST, total bilirubin), creatinine or amylase/lipase.	
Grade 2	Continue nivolumab per protocol
Grade 3	• Delay the dose of nivolumab until resolution to ≤ Grade 1 • Discontinue treatment if toxicity lasts for > 6 weeks
Grade 4	Discontinue nivolumab if not an isolated Grade 4 event and is associated with clinical sequelae and are not corrected with supplementation/appropriate management within 72 hours of their onset.

Toxicity	Nivolumab Dose Management Guidelines
Immune-related (ir) AEs related to Nivolumab (Other than irAEs specified above)	
Note: See above sections for **specific orientation** regarding the following ir-related toxicities: eye related toxicities, ALT/AST/total bilirubin, creatinine, diarrhea/colitis, endocrinopathies, neurological, pulmonary, and skin.	
Grade 2	• Hold nivolumab dose • Resume study regimen per protocol once toxicity returns to Grade ≤ 1 or baseline and if applicable, when steroid taper (≥ 1 month*) is complete. (* See exception in Section 6.2.) • Discontinue treatment if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period.
Grade 3 or 4	Discontinue nivolumab
Non-hematologic non-immune related toxicities related to Nivolumab (except fatigue and laboratory abnormalities)	
Grade 2	If persistent > 3 days despite supportive measures, delay the dose of nivolumab until resolution to ≤ Grade 1 or baseline
Grade 3	• Delay the dose of nivolumab until resolution to ≤ Grade 1 or baseline • Discontinue if toxicity lasts > 7 days.
Grade 4	Discontinue nivolumab

Table 6.2.2 Dose modifications for brentuximab vedotin associated toxicity

Toxicity	Brentixumab vedotin Dose Management Guidelines
Peripheral Neuropathy	
Grade 1	Continue at same dose level
Grade 2	Reduce dose to 1.2 mg/kg and resume treatment
Grade 3	Withhold until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at 1.2 mg/kg^ ^ Dose reductions below 1.2 mg/kg are not allowed, and toxicities should be managed with dose delays.
Grade 4	Discontinue brentuximab vedotin
Non-hematologic (except peripheral neuropathy)	
Grade 1	Continue at same dose level
Grade 2	Continue at same dose level
Grade 3	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume treatment at the same dose level. – **Note:** Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.
Grade 4	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the investigator [a,b,c] a. Dose reductions below 1.2 mg/kg are not allowed, and toxicities should be managed with dose delays. b. Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption. c. Treatment should be discontinued for patients who experience Grade 4 infusion-related reactions. *See Section 5.9.2 for supportive care.*

Toxicity	Brentixumab vedotin Dose Management Guidelines
Hematologic	
Grades 1-3	Continue at same dose level
Grade 4	• Withhold until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at the same dose level. – **NOTE:** Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption • In case of grade 4 neutropenia, growth factor support should be instituted and a repeat blood draw to evaluate the grade of neutropenia should be performed within 3 days. • Growth factor support (G-CSF or GMCSF) should be considered for subsequent cycles. If Grade 4 neutropenia recurs despite growth factor support, consider discontinuation or dose reduction to 1.2 mg/kg.

7.0 ADVERSE EVENT AND UNANTICIPATED PROBLEM REPORTING

The authorized investigator will be responsible for determining the event name, assessing the severity (i.e., grade), expectedness, and attribution of all adverse events.

7.1 Definitions

- **Adverse Event (AE)** - [Modified from the definition of adverse event in 21 CFR 312.32] An adverse event is any untoward medical experience or change of an existing condition that occurs during or after protocol intervention, whether or not it is considered to be related to the protocol intervention.
- **Serious Adverse Event (SAE)** [per 21 CFR 312.32] - defined as any *expected or unexpected adverse events* that result in any of the following outcomes:
  - Death
  - Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
  - Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
  - A persistent or significant disability/incapacity
  - A congenital anomaly/birth defect
  - Secondary malignancy*
  - Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).
    *Modified from 21 CFR 312.32
- **Adverse Event Description and Grade**
  - The description and grading scales found in the most recent version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized to characterize AEs. AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE v 4.0. All appropriate treatment areas should have access to a copy of the CTCAE v. 4.0. A copy can be downloaded from the NCI/ CTEP web site.
- **Unexpected Adverse Event** – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event. Modified from 21 CFR 312.32 (a)
- **Expected Adverse Event** – An adverse event is expected if it does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.
- **Adverse Event Attribution-** The following definitions will be used to determine the causality (attribution) of the event to the study agent(s) or study procedure.

- **Unrelated –** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is doubtfully related to the investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.
- **Definite –** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs, AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

- **Unanticipated Problem (UP)** – Any incident, experience, or outcome that **meets all three** of the following criteria:
  - Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
  - Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
  - Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

7.2 Definition of Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

The investigator must immediately notify the **Study PI/ DCC** via an **expedited report** (see Section 7.8).

7.3 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 to the **Study PI/ DCC** (see Section 7.8).

7.4 Pregnancy

If, following initiation of protocol therapy, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the protocol therapy will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify the **Study PI/ DCC** via an **expedited report**; the Study PI or designee will subsequently inform BMS (see Section 7.8).

The Investigator should make every effort to follow the female participant until completion of the pregnancy per institutional policies, and should notify the Study PI/ DCC.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported via an **expedited report**.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Study PI/DCC **expeditiously;** the Study PI or designee will subsequently inform BMS (see Section 7.8)**.**

7.5 Laboratory Test Abnormalities

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Potential drug induced liver injury requires an **expedited report** and should be reported as an Important medical event (see Section 7.8).

7.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug requires an **expedited report** (see Section 7.8).

7.7 Routine AE Reporting Guidelines

Routine AE reporting will occur via data entry into the study eCRF.

AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

All AEs will be recorded from the initiation of protocol therapy through the follow-up period. The highest grade for any toxicity plus Grade 3 or 4 event for the same toxicity (if not the highest grade) will be reported during each cycle and during the safety follow-up period.

AE information recorded in the CRF include: Attribution to protocol therapy, grade and seriousness.

The collection of nonserious AE information should begin at initiation of protocol therapy up to a minimum of 100 days following the last dose of protocol therapy. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

7.8 Expedited AE Reporting Guidelines

Each AE will be assessed to determine if it meets the criteria for expedited reporting. Adverse event reporting is to occur according to the site's specific IRB guidelines, and as outlined in this Section.

7.8.1 *Expedited Adverse Event Reporting to Local IRB*

Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the DCC copies of the IRB submission and corresponding IRB response.

7.8.2 *Expedited Adverse Event Reporting to DCC/ Study PI*

- Adverse events that meet the specified guidelines below are to be reported to the DCC and Study PI within the timelines and per the procedures in the sections that follow.
- Report the following per Table 7.8.2 to the DCC /Study PI **within 24 hours** of being aware that the event met reporting criteria:

Table 7.8.2 Expedited Reporting Guidelines

Time point	What to report expeditiously
From the signing of the consent to study completion	All unanticipated problems
From time of signing of the consent to Day 1 of protocol therapy	All SAEs related to protocol procedures
From Day 1 of protocol therapy through (i) 30 days post-last dose visit **AND** (ii) 100 days post last dose visit or until initiation of a new anticancer therapy.	• All SAEs regardless of relationship to protocol therapy, study procedure, underlying disease or concomitant treatment. • AEs that meet the definition of an unanticipated problem • Potential drug induced liver injury • Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug • Secondary malignancy • Pregnancy and lactation • Overdose • Grade 3/4 infusion reactions • Discontinuation of protocol therapy due to unusual or unusually severe AE considered related to study agents.
After the 100 days post last dose visit (i.e. follow-up)	• All SAEs that are considered possibly, probably, or definitely related to therapy. • Pregnancy and lactation (up to 7 months post last dose of nivolumab)
Note: All reportable events will require follow up until stabilization or resolution per the agreement of the Study PI.	

- Reportable adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator; for ongoing reportable AEs that are unrelated to protocol therapy, the follow-up period may end at the 100 days post-last dose of protocol therapy assessment. The DCC and Study PI should be consulted prior to ending the follow-up of events that have stabilized.

7.8.3 *Expedited reporting to the DCC/Study PI – Non COH Sites*

1. Document/describe AE/UP on each of the following:
   a. MedWatch 3500A or local IRB submission document*
      i. MedWatch 3500A is downloadable form at http://www.fda.gov/medwatch/getforms.htm
      ii. *The local IRB submission document may be used if the document template is approved by the DCC
   b. Expedited Reporting Coversheet
      i. The Expedited Reporting Coversheet is found in Appendix G. A modifiable Microsoft Word document is also available from the DCC. An electronic signature on the document will be accepted.
2. Scan and email above documents to DCC@coh.org with the subject title as "Herrera Nivolumab SAE".
   a. All expedited reports received at this account are forwarded immediately to the Study PI, and to DCC personnel.
   b. While not required, if available and applicable, please also include the local IRB submission for this event in the submission.
3. If an email receipt from DCC personnel is not received within one working day, please call (626)-218-7904 and/or email DCC@coh.org.

7.8.4 *Expedited reporting to the DCC/Study PI –COH Only*

1. Email the following information to DCC@coh.org and the Study PI.
   a. Participant ID, date the event met criteria for reporting, whether the event meets the definition of serious, whether the event is an unanticipated problem, grade of event, attribution of event, whether the event is a known expected toxicity to study agent.
2. Complete the iRIS AE/UP reporting form per COH reporting timeline.

7.9 Reporting of AE/UP by the Study PI

The Study PI (or designee) will:

- Report to COH IRB and DSMC all reportable AEs that meet COH IRB and DSMC reporting criteria and occur at non-COH sites according to City of Hope's Institutional policy on reporting AE/UP and indicate whether or not a protocol and/or consent form change is required.
- Report all expedited reportable AEs to participating investigators as an IND Safety Report occurring within 15 calendar days of receipt of sponsor (lead site) notification, and indicate

whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed, and, for non-COH sites, a statement that the report should be submitted to their local IRB for review as an IND safety report if applicable per local IRB policy.

- For IND Sponsor reporting purposes only: using a MedWatch 3500A form, report to the FDA, (via COH Office of IND Development and Regulatory Affairs (OIDRA)) regardless of the site of occurrence, any SAE that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA:

  Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

  The criteria that require reporting using the MedWatch 3500A are:

  - Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
  - Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
  - Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

  The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy.

- Report to Global Pharmacovigilance & Epidemiology at Bristol-Myers Squibb Company (BMS), regardless of the site of occurrence, any expedited AEs within 24 hours of being aware of the event via email or facsimile. On all correspondence to BMS also include the BMS protocol ID: **CA209-878**.

  SAE Email Address: Worldwide.Safety@BMS.com

  SAE Facsimile Number: 609-818-3804

  - The initial report will be as complete as possible and include an assessment of the causal relationship between the event and the study agent(s). Information not available at the time of the initial report will be documented on a follow-up report.
  - If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.
  - All pregnancy related events, including pregnancy that occurs in a female partner of a male study participant perinatal and neonatal outcome and, where applicable, offspring information will be submitted on the BMS Pregnancy Surveillance Form [provided upon request from BMS]

- Submit annually within 60 days (via COH OIDRA) of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report adverse drug experiences, history of actions taken since the last report because of adverse drug experiences.

- Report every 3 months to the COH DSMC a Protocol Management Team (PMT) report, to include aggregate analysis of safety information, accrual and participant status.
- Circulate to all participating sites for submission to their IRBs the COH DSMC report and DSMC recommendation, in accordance with NIH guidance.
- Report to BMS aggregate safety information (including nonserious events) at time of COH PMT report.
- Report all reportable serious adverse events to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed, and, for non-COH sites, a statement that the report should be submitted to their local IRB for review as an IND safety report if applicable per local IRB policy.
- Forward to participating sites all safety reports received from BMS for nivolumab, that have not occurred directly on this protocol, indicating whether a consent form or protocol change is required within 30 calendar days of notification to Study PI.

8.0 AGENT INFORMATION

8.1 Nivolumab

Nivolumab has been FDA approved for the treatment of patients with classical HL that has relapsed or progressed after ASCT and post-transplantation brentuximab vedotin.

Additionally nivolumab is approved for:

- Patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
- Patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy

For additional information refer to the IB.

8.1.1 *Other Names*

BMS-936558-01, MDX1106, ONO-4538, anti-PD-1, OPDIVO™.

8.1.2 *Description*

Type	IgG4 monoclonal
Source:	Human
Target:	PD-1
Molecular weight:	146 kDa

8.1.3 *Mechanism of Action*

Nivolumab blocks the interaction between human PD-1 receptor and its ligands (PD-L1 and PD-L2). This promotes immune responses and antigen specific T-cell responses to both foreign and self-antigens.

8.1.4 *Pharmacokinetics*

Half-life:	~26 days
Steady state clearance (CLss):	8.2 mL/h
Volume of distribution (Vss):	6.8 L
Steady-state concentration:	~ 12 weeks when 3 mg/kg is administered every 14 days

8.1.5 *Human Toxicity*

See Section 6.1.2.

8.1.6 *Formulation*

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Appearance
Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100 mg/Vial (10 mg/mL).	Carton of 5 or 10 vials	Clear to opalescent, colorless to pale yellow liquid. May contain particles
* Nivolumab may be labeled as BMS-936558-01 Solution for Injection			

8.1.7 *Storage*

- *Injection 100 mg/10 mL*: Vials for nivolumab injection must be stored at 2-8°C and protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.
- *Undiluted and Diluted Injection in the IV Container*: The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2-8 °C) for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20-25 °C) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

  For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions"

8.1.8 *Handling and Dispensing*

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects.

The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

8.1.9 *Preparation and Administration*

Please refer to the most recent investigator's brochure for nivolumab.

Do not administer nivolumab as an IV push or bolus injection.

For additional administration details refer to Section 5.4.2.

8.1.10 *Supplier*

The investigational agent will be supplied free of charge by Bristol-Myers Squibb Company.

8.1.11 *Ordering*

- Initial Orders

  Following submission and approval of the required regulatory documents, a supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial. The first request may take place upon screening of the first patient
  The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time.
  It is imperative that only drug product designated for this protocol number be used for this study.
  Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing

- Re-Supply
  - Drug re-supply request form should be submitted electronically business days before the expected delivery date. Deliveries will be made Tuesday through Friday.
  - When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

8.1.12 *Drug Excursions*

Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form.

8.1.13 *Accountability*

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using a drug accountability log.

8.1.14 *Destruction and Return*

The investigator is responsible for keeping accurate records of the clinical supplies received from Bristol-Myers Squibb Company or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures.

Prior to the destruction of nivolumab, the DCC should be notified and an acknowledgement to proceed from the DCC should be received.

Destruction will be documented in a drug accountability log.

8.2 Brentuximab vedotin

Please refer to the package insert for a detailed description. Brentuximab vedotin has been FDA approved for the treatment of patients with classical HL after failure of autologous hematopoietic stem cell

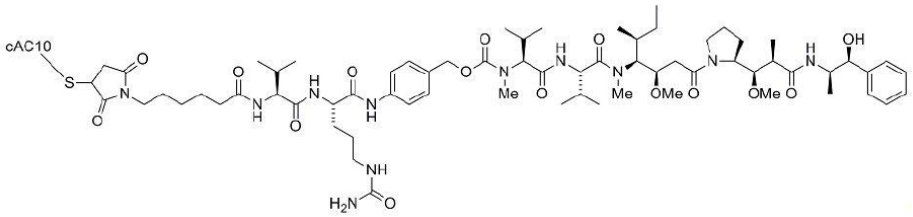
transplantation (auto-HSCT), after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, and treatment of patients with classical HL at high risk of relapse or progression as post-auto-HSCT consolidation.

8.2.1 *Other Names*

ADCETRIS®

8.2.2 *Description*

Structural Formula:



Empirical Formula: $C_{6476}H_{9930}N_{1690}O_{2030}S_{40}$ $(C_{68}H_{105}N_{11}O_{15})_{3–5}$

Type:	Antibody-drug conjugate (ADC). The chimeric monoclonal IgG1 antibody cAC10 is covalently linked to the monomethyl auristatin E (MMAE) via a protease-cleavable linker. About 4 molecules of MMAE are attached to each antibody molecule.
Source:	Mouse-human chimera
Target:	CD30
Molecular weight:	153 kDa

8.2.3 *Mechanism of Action*

Brentuximab vedotin targets the cell surface receptor CD30 which is expressed in Hodgkin's lymphoma (HL). Nonclinical data suggest that the binding of the ADC to CD30-expressing cells leads to the internalization of the ADC-CD30 complex. Proteolytic cleavage of ADC within the cell results in the release of the MMAE. Free MMAE binds to the microtubule network and subsequently leads to cell cycle arrest and apoptosis.

8.2.4 *Pharmacokinetics*

MMAE Tmax:	1 to 3 days
MMAE Steady-State	21 days with every 3-week dosing
ADC Vd:	6 to 10 L
MMAE protein binding:	68-82%
MMAE Metabolism:	Metabolized via CYP3A4/5; inhibits CYP3A4/5
MMAE Excretion:	renal excretion up to 24% and in feces 72%
ADC Elimination half-life:	4-6 days

8.2.5 *Human Toxicity*

See Section 6.1.1.

8.2.6 *Formulation*

For injection: 50 mg of brentuximab vedotin will be supplied as sterile, white to off-white lyophilized, preservative-free cake or powder in a single-use vial for reconstitution.

8.2.7 *Storage*

Store at 2-8°C in the original carton to protect from light. DO NOT FREEZE.

8.2.8 *Handling*

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent.

8.2.9 *Preparation*

Follow package label instructions for reconstituting the lyophilized powder and diluting into 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection for infusion.

8.2.10 *Dose and Administration*

Administer brentuximab vedotin as an intravenous infusion only over 30 minutes.

Do not mix brentuximab vedotin with, or administer as an infusion with, other medicinal products.

See Section 5.4.1 for dosing and additional administration guidelines.

8.2.11 *Supplier*

Brentuximab vedotin is available commercially.

9.0 CORRELATIVE & SPECIAL STUDIES

9.1 Correlative Study Plan

The correlative analyses that will be performed as part of this clinical trial are exploratory and intended to generate hypotheses that can be validated in a larger study. The list of correlative studies below is not meant to be exhaustive, as it is anticipated that the exact nature and type of correlative studies may change as new scientific data emerges during the course of the study.

Table 9.1 Correlative Study Plan

Tissue type	Planned correlative anlysis
Tumor tissue	• FISH of the 9p24.1 region will be performed by the COH Cytogenetics Core Laboratory in HL tumor samples to assess the relationship between 9p24.1 abnormalities and outcome after study therapy. • Gene expression profiling of HL tumor specimens to determine whether there are profiles associated with outcome after study therapy. • Quantitative spatial image analysis of immune and tumor cells in tumor samples via 8-color histology using the Vectra system to assess the presence of and spatial relationships between tumor infiltrating lymphocytes/immune cell populations (e.g., CD8+ T-cells, tumor-associated macrophages) and immune checkpoint ligands/receptors (e.g., PD-L1).
Blood	• Peripheral blood flow cytometry of immune cell subsets (including PD-L1 and PD-L2 bearing lymphocytes) at baseline, during treatment, and at 12 and 18 months after ASCT to determine the impact of study therapy on post-ASCT immune reconstitution • Next-generation sequencing-based minimal residual disease (MRD) assessment using the Adaptive Biotechnologies ClonoSEQ assay (previously Sequenta, Inc LymphoSIGHT assay), which is able to detect MRD in the peripheral blood of patients with HL[36]. We will assess MRD at baseline, during treatment, and at 12 and 18 months after ASCT. These sequential samples will allow us to track the temporal dynamics of MRD after brentuximab vedotin plus nivolumab consolidation therapy, and to determine whether study therapy can eradicate MRD in patients who are MRD+ after ASCT

9.2 Tumor Tissue Studies

9.2.1 *Timepoints of Collection*

1. *Baseline tissue*: Archival tissue from pre-ASCT tumor biopsies will be retrieved and submitted post-enrollment. **Preferred time point**: Post-relapse biopsy or biopsy performed to confirm refractory disease after first-line therapy but if this is not available the diagnostic biopsy will be used instead.

- **NOTE:** If unavailable, exceptions may be granted with Study PI approval.

2. *From participants who progress/ relapse during study (strongly encouraged, but not mandatory)*: If safe and feasible, submission of a tumor lesion core or excisional.

9.2.2 *Guidelines for archival specimens*

Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:

- If tissue block is available submit:
  - 6 paraffin scrolls measuring 10 μm thick placed into a Nunc tube and frozen at -80° C AND
  - 10 x 5 micron unstained slides
- If tissue block is unavailable submit 20 x 5 μm unstained slides

9.2.3 *Guidelines for fresh tumor tissue processing*

9.2.3.1 Non-COH sites

Tumor lesion core or excisional biopsies should be flash frozen and kept at -80 ^{o}C until batch shipment.

9.2.3.2 COH only

Three core biopsies OR excisional biopsies should be submitted. If fewer than 3 core biopsies are available because of safety, then 1 or 2 cores may be submitted.

Core biopsies:

- Three core biopsies will be obtained for diagnostic purposes and 3 similar additional cores will be obtained for research.
  1. One core biopsy will snap frozen in OCT fixative, and an additional half of a core will be snap frozen without OCT fixative.
  2. Half of a core will be finely minced in a 10cm petri dish and frozen at -80° C in a Nunc tube in 1 ml of RPMI-1640 medium containing 20% fetal calf serum and 10% DMSO, then will be transferred to liquid nitrogen.
  3. Half of a core will be processed for DNA and RNA extraction according to the manufacturer's recommendation.
  4. The final half of a core biopsy will be processed to dissociate the cells, with the cell suspension cryopreserved in liquid nitrogen.

For excisional biopsies:

- An approximately 1cm x 1cm tumor sample will be divided into 5 equal portions and processed as described for core biopsies.

The diagnostic portion of the specimen:

- Process in a routine fashion by hematopathology. Using the formalin-fixed paraffin embedded (FFPE) tissue block, 15 x 5 micron unstained slides will be obtained

9.2.4 *Labeling of samples*

Samples will labeled with the study number, institution (for non-COH sites), subject ID (issued by COH), date, timepoint of collection (i.e. baseline or progression) and if applicable patient initials.

9.2.5 *Sample shipment and receiving lab*

Tissue specimens collected at the above indicated timepoints will either be taken to (COH only) or batch-shipped (non-COH sites) to COH Pathology Core. For all sites, please include the **Correlative Tissue form (Appendix I)** with your shipment.

Please note that samples should be **batch shipped from non-COH sites on Monday to Wednesday** in time for receipt Tuesday to Friday. Refer to Appendix C for shipping details.

9.3 Blood samples

Table 9.3 provides an overview of correlative blood studies.

Table 9.3 Overview of correlative blood studies

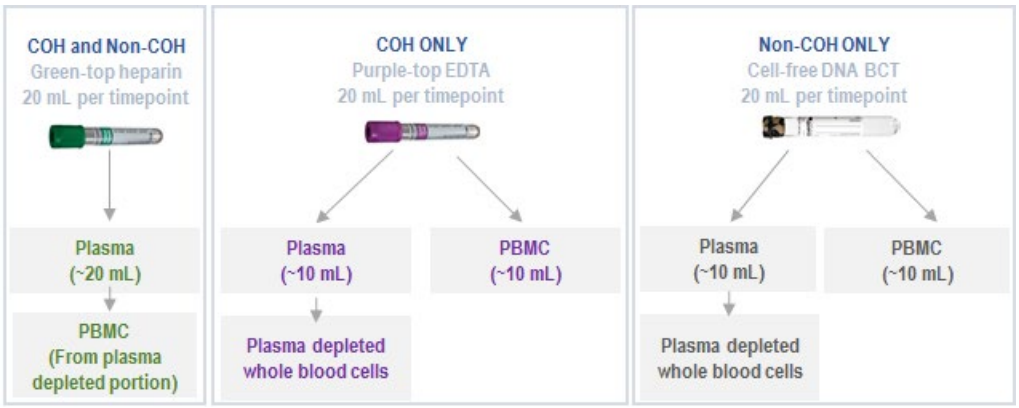
Timepoint of collection	Total volume per timepoint	Tube Type	Processing/ Receiving Laboratory	Type of Laboratory Analysis
Timepoints for <u>all blood studies</u> except where noted: • Cycle 1 Day 1 (baseline) • **Green-top ONLY:** Cycle 2 Day 1 • Cycle 5 Day 1 (OR 3 months^ if off treatment but yet to progress), • 30 days post last dose visit • 6 months^ if off treatment but yet to progress • 12 month from start of treatment follow up visit (if yet to progress) • 18 month from start of treatment follow up visit (if yet to progress)	~20 mL	Green-top (sodium or lithium heparin)	Analytical Pharmacology Core Facility (APCF) at COH	**Dr. Peter Lee/ Dr. Tim Synold (COH)** • PBMC isolation to assess immune reconstitution • Plasma for cytokine analysis
	~20 mL	**COH only**: Purple-top (K+EDTA)	APCF at COH	Minimal residual disease (MRD) assessment using next-generation sequencing (NGS)
	~20 mL	**Non-COH**: Cell-free BCT® DNA tubes		
^ Collect during Active Follow-up assessment visit(s) if received < 8 cycles of therapy				

Whole blood will be separated into peripheral blood mononuclear cells (PBMCs) and plasma and subjected to NGS for ctDNA assessment. ctDNA will be measured in the plasma fraction and PBMCs will provide germline sequences. Samples will be shipped to and NGS/ctDNA assessment performed in collaboration with Dr. Margaret Shipp at the Dana-Farber Cancer Institute.

9.3.1 *Notification to APCF, Blood sample collection and Labeling*

Notification to COH APCF of Pending Collection	Site	Tube Type	Labeling and Collection Details	Post-collection Instructions
• Notify **at least one** day in advance) • **Send calendar invite via e-mail**: Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org)	COH	• Green-top • Purple-top	1. Label tubes with COH protocol #, subject ID (issued by DCC), institution (for non-COH sites), date and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials. 2. Timepoints of collection are stated in Table 9.3. 3. Blood samples will be collected from an indwelling venous catheter or by venipuncture 4. Invert tubes eight times after collection. 5. **Immediately** place the tubes **on ice**.	**Promptly** deliver the blood samples on ice to the APCF, Shapiro room 1042 for processing **within 4 hours.**
	Non-COH	Green-top		• Peripheral blood samples will be **shipped overnight at ~+4°C** to APCF laboratory. • **Include** with shipment: - Blood sample collection form (Appendix D) - Copy of the latest CBC results (with differential) and the date of the test
	Non-COH	Cell free DNA BCT® tubes	1. Label tubes with COH protocol #, subject ID, institution (for non-COH sites), date and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials. 2. Timepoints of collection are stated in Table 9.3. 3. Fill in sample collection form in Appendix D. 4. If applicable, follow recommendations for order of draw outlined in Clinical and Laboratory Standards Institute (CLSI) H3-A6. a. BCT® tubes may not be drawn immediately following a heparin tube; if necessary collect a non-additive or EDTA tube as "waste tube" prior to collection in the BCT® tube. 5. Blood samples will be collected from an indwelling venous catheter or by venipuncture. 6. Below guidelines to **avoid possible backflow** from the tube should be followed since BCT® tubes contain a formaldehyde-free preservative: a. Keep patient's arm in the downward position during collection. b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection. c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of aapplication. 7. Completely fill the tube. 8. Remove tube from adapter and immediately invert the tubes 8 to 10 times. 9. **DO NOT FREEZE** samples. Store samples at **18-25 °C** until shipment.	See Appendix E for shipment details.

9.3.2 *Sample Processing by APCF*



COH samples only: Blood samples will be kept on a rocker set at low speed to mimic circulation and avoid clot formation until processing.

Tube Type and Volume	Processing Details		Downstream assay
Green-top (~20 mL)	Plasma	1. Centrifuge for 10 minutes at 1800 x g at 4 °C. 2. The resulting upper plasma layer from each tube will be drawn up sequentially into a sterile 5 mL syringe and pushed through a sterile 0.2/0.8 micron disposable filter. a. **Save** the plasma-depleted portion **for isolation of PBMC**. 3. The filtered plasma will then be transferred in 500 µL aliquots into multiple appropriately-labeled Starstedt microfuge tubes. 4. To **one aliquot**, add 0.5 mL glycerol/0.02% sodium azide solution to dilute the plasma 50/50 v/v. Keep the diluted plasma sample at -20˚C and do not freeze. 5. All the remaining plasma aliquots will be stored frozen at -80˚C until use.	Cytokine analysis
	Peripheral blood mononuclear cells (PBMC)	6. Any blood remaining in the two green-top tubes used to prepare plasma above will be diluted 1:1 with Hank's Balanced Salt Solution (HBSS) in a sterile 50 mL conical centrifuge tube. 7. PBMC will then be isolated from the combined whole blood sample by Ficoll-gradient per COH APCF procedures. 8. Isolated PBMC will be stored in liquid nitrogen until use.	FACS

Tube Type and Volume	Processing Details		Downstream assay
Purple-top (~10 mL)	Plasma and Plasma depleted whole blood cells (PDWB)	1. Centrifuge for 10 minutes at 1800 x g at 4 °C. 2. Remove the tubes from the centrifuge. Do not disturb the cellular layer. 3. Extract plasma carefully. a. **Do not disturb** the **buffy coat** while pipetting plasma; leave ~3-4mm of plasma behind to ensure the buffy coat is undisturbed. 4. Freeze plasma at -80°C in 1-2mL aliquots. Do not fill tubes beyond 70% capacity. 5. Mix the remaining PDWB. 6. Freeze PDWB at -80°C in 1-2mL aliquots.	Sequencing-cell free circulating tumor DNA and germline DNA
Purple-top (~10 mL)	PBMC	1. Dilute whole blood with 1:1 with Hank's Balanced Salt Solution (HBSS) in a sterile 50 mL conical centrifuge tube. 2. PBMC will then be isolated from the combined whole blood sample by Ficoll-gradient **per COH APCF procedures**. 3. Isolated PBMC will be stored at -80°C until use.	Sequencing
Cell free DNA BCT® (~10 mL)	Plasma and Plasma depleted whole blood cells (PDWB)	1. Centrifuge for 10 minutes at 1600 x g at **room temperature.** 2. Remove the upper plasma layer and transfer to a new conical tube. a. **Save** the PDWB portion (see below). 3. Centrifuge the plasma at 16000 x g for 10 minutes. 4. Collect the plasma. 5. Freeze plasma at -80°C in 1-2mL aliquots. Do not fill tubes beyond 70% capacity. 6. Mix the remaining PDWB. 7. Freeze at -80°C in 1-2mL aliquots.	Sequencing-cell free circulating tumor DNA and germline DNA
Cell free DNA BCT® (~10 mL)	PBMC	1. Dilute whole blood with 1:1 with Hank's Balanced Salt Solution (HBSS) in a sterile 50 mL conical centrifuge tube. 2. PBMC will then be isolated from the combined whole blood sample by Ficoll-gradient **per COH APCF procedures**. 3. Isolated PBMC will be stored at -80°C until use.	Sequencing

10.0 STUDY CALENDAR

All procedures may increase in frequency if clinically indicated.

Table 10.0 Study Activity Calendar

							Safety visits may be combined with Active Follow-up visits if the windows for the two visits overlap					
Protocol Activity	**Screening[a]**	**Protocol Therapy [b,c]**					**Safety Visits[i]**		**Active Follow-up [h,i]**			**Long-term Follow-up[l]**
		Cycle 1	**Cycle 2**	**Cycle 3**	**Cycles 4-7**	**Cycle 8**	**Time from last dose**		**Time from start of treatment**			
		D1 [d,e]	**D1[e]**	**D1[e]**	**D1[e]**	**D1[e]**	**30 days[f]**	**100 days[g]**	**3 months[j]**	**6 months[k]**	**12 months**	**18 months**
Informed consent [m]	X											
Eligibility [n]	X											
Registration [o]	X											
Medical history [p]	X											
Physical exam [q]	X	X	X	X	X	X	X					
Vital signs [r]	X	X	X	X	X	X	X					
ECOG status (Appx. A)	X	X	X	X	X	X	X					
Con-meds [s]	X	X	X	X	X	X	X					
Adverse Events [t]	X [t]	----------X [u]----------										
Pregnancy[v]	X[w]	X[d]										
EKG	X											
Pulmonary [x]	X											
Thyroid [y]	X[w]			X	C6 only		X					
CBC w/diff, plts	X[w]	X	X	X	X	X	X					
Serum chemistry [z]	X[w]	X	X	X	X	X	X					
Amylase, lipase	X[w]	X	X	X	X	X	X					
Immunoprofiling blood [aa]		X	X		C5 only		X		X		X	
MRD blood [aa]		X			C5 only		X		X		X	
Tumor tissue	X[bb]						----------X[cc]----------					
CT [dd]	X [dd]				C4 D15 [ee,gg]		X [ee,hh]		X[ee]		X [ee]	X[ee,ii]
PET-CT [dd]	X [dd]				C4 D15 [ee,gg]		X [ee,hh]		X[ee]		X [ee]	X[ee,ii]
Response [ff]					C4 D15 [gg]		X		X		X	
Nivolumab [jj]		X	D1 of each cycle									
Brentuximab vedotin[jj]		X	D1 of each cycle									
Long-term[l]												X

a. Screening can initiate 21 days post-ASCT. Screening evaluations will be performed within 28 days from Day 1 of protocol therapy (including cardiac and pulmonary function tests), **except** laboratory assessments to be performed within 14 days prior to Day 1 of protocol therapy.
b. Protocol therapy must initiate within 30-60 days post-ASCT. Study PI can grant exception for a patient to start as late as 75 days post-ASCT with a reasonable justification for delay (e.g. recovery from post-ASCT toxicity) and this will not be a protocol deviation, nor require an exception to be filed. Protocol therapy may last up to 8 cycles (~ 6 months), until unacceptable toxicity or disease progression (see Section 5.6 for more comprehensive list).
c. In the absence of treatment delay, each treatment cycle lasts 21 days ± 3 days.
d. Day 1 of Cycle 1 is defined as the day of first administration of brentuximab vedotin. Screening evaluations performed within 14 days prior to start of protocol therapy may serve as Day 1 baseline evaluations, **except** for pregnancy test which must be performed within 24 hours prior to Day 1 of protocol therapy.
e. Activities (**except** imaging and response assessment) and safety assessment review to be performed within 72 hours prior to initiation of the new cycle.
f. The 30 days post-last dose assessments to occur 30 (-2/+7) days post-last dose or, if > 30 days elapsed since last dose, within 7 days after decision to end treatment. Expedited reporting will occur during this period (see Section 7.8).
g. The 100 days post-last dose assessments to occur 100 (-7/+28) days post-last dose or at initiation of a new anticancer therapy. Expedited reporting will occur during this period (see Section 7.8). Safety follow-up may be extended until resolution/ stabilization of reportable AEs.
h. For participants who ended protocol therapy and have yet to progress/relapse, Active follow-up visit to occur at 3 months (± 14 days), 6 months (± 14 days), 12 months (± 28 days) and 18 months (± 28 days) from start of treatment until progression or initiation of new anticancer therapy.
i. The Safety assessments/activities may be joint with Active Follow-up assessments/activities if the windows for the two visits overlap.
j. The 3 month Active Follow-up activities to occur if the participant ended protocol therapy prior to the Cycle 4 Day 15 scan.
k. The 6 month Active Follow-up activities to occur if the participant ended protocol therapy prior to Cycle 8.
l. Long-term follow-up for those for all participants who have progressed/relapsed OR completed Active Response Follow-Up. Assessment to occur biannually or as requested by the Study PI via medical record review, review of social security registry/ public records, and/or telephone call.
m. Informed consent process to be fully documented (see Section 16.4). Informed consent must occur prior to any research only (non-SOC) screening procedures.
n. Eligibility criteria are detailed in Section 3.0.
o. Registration in a COH clinical trial management system (CTMS).
p. Medical history to include a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
q. Standard physical exam with skin analysis.
r. Vital signs: Weight, heart rate, temperature, respiratory rate, blood pressure and oxygen saturation. Height will be measured at screening only.
s. *Concomitant medications:* All medications taken within 28 days of start of protocol therapy should be recorded in source documents. All concomitant medications and blood products administered or changed during the patient's participation in the study until the Safety follow up visit and the reason for administration must be recorded in the source documents and in eCRFs. See Section 5.9 for restrictions and guidelines.
t. Adverse events (AE) will be assessed using CTCAE v.4.0. SAEs related to study procedures will be recorded and reported from time of informed consent until Day 1 of protocol therapy.
u. AE recording and reporting will continue until the completion of the Safety follow-up or until resolution or stabilization of any reportable AEs during Safety follow-up.
v. Serum or urine pregnancy test for WOCBP.

w. Laboratory assessments (pregnancy, thyroid, blood counts, serum chemistry and amylase/lipase) to be performed within 14 days prior to start of protocol therapy.

x. Pulmonary function tests to include spirometry, lung volume measurements and diffusion capacity measurement.

y. Thyroid stimulating hormone (TSH) and free T4 at baseline, and Day 1 of Cycles 3 and 6.

z. Chemistry panel to include: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, and phosphorus.

aa. Correlative blood will be collected as follows. See Section 9.3 for details for notifying APCF, processing and non-COH site shipment.

- **All sites for immunoprofiling studies:** 20 mL into green-top tubes per timepoint
- **COH only for MRD studies**: 20 mL into purple-top tubes per timepoint, and
- **Non-COH only for MRD studies**: 20 mL into cell free DNA BCT tubes per timepoint

bb. Archival tumor tissue to be submitted post-enrollment. **Note:** If unavailable, exceptions may be granted by the Study PI. Refer to Section 9.2.1.

cc. If safe and feasible, submission of a research tumor biopsy (fresh core or excisional biopsy) from participants who progress/relapse during study is encouraged. Refer to Section 9.2.1.

dd. PET-CT or CT of neck, chest, abdomen and pelvis can be performed at screening. If there is evidence of neck involvement by lymphoma at baseline, neck CT should be continued at subsequent tumor evaluation.

ee. If prior response was CR perform CT for subsequent timepoints; if prior response was PR perform CT or PET-CT. **NOTE**: Conversions from PR to CR should be confirmed with a PET-CT scan.

ff. Response assessments per 2014 Lugano Classification (See Section 11.1) [53]. **Note:** Participants who meet progression per 2014 Lugano Classification but meet "indeterminate response" per LYRIC criteria [1] may continue to receive protocol therapy beyond progression (Refer to Section 5.6 and Appendix H for details).

gg. Imaging and response assessment to occur at Cycle 4 Day 15 (+7 days). **NOTE:** *If receiving therapy beyond progression per IR LYRIC criteria*: A confirmatory PET-CT should be performed within 12 weeks after initial progression per Lugano criteria (Refer to Section 5.6).

hh. For participants who progressed or completed 8 cycles of planned therapy.

ii. Every effort should be made to perform PET-CT at '18-months from start of treatment' visit (especially if the participant never achieved CR after ASCT). However, if a PET-CT is not possible, a diagnostic quality CT will be acceptable.

jj. The dosing plan for the agents is described in Section 5.3; recommended supportive care is described in Section 5.9. Refer to Section 6.2 for dose delay/ modification guidelines.

11.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

11.1 Response, Clinical Endpoints and Toxicity

11.1.1 *Response/Progression*

HL response/progression will be evaluated using 2014 Lugano Classification (see Table 11.1) [53, 54]. Participants who meet the definition of progressive disease per Lugano Classification should be evaluated using the LYRIC criteria (see Appendix H).

PET-CT or diagnostic quality CT of the neck, chest, abdomen, and pelvis (N/C/A/P) with IV contrast will be performed at baseline and the pre-specified time points in the study calendar. PET and CT may be co-acquired or acquired separately. Additional necessary restaging studies including dedicated CT scans, MRI, or bone marrow biopsies, are permitted at the investigator's discretion. Although diagnostic quality CT is acceptable, PET-CT is the preferred disease assessment method throughout the study, particularly for patients not in CR. Since 18-month PFS is the primary endpoint, every effort should be made to perform PET-CT at the "18-month from start of treatment" time point (particularly if the patient never achieved CR after ASCT), but if not possible, diagnostic quality CT will be acceptable. PET-CT and CT results will be read by a radiologist at each study site and investigator response based on radiology reading will be performed.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy be obtained whenever possible. Note that an FDG-negative PET scan will only be considered complete remission in patients whose tumor was FDG-avid at baseline.

A disc copy of the study-required images, including post-salvage/pre-ASCT PET scan should be sent to the Study PI upon request. Per institutional practices, the images should be de-identified (coded) and the disc should be labeled with Subject ID, COH Protocol # and institution name.

Table 11.1 2014 Lugano Classification Response Criteria

Response	Site	CT-Based Response	PET-CT Based Response
Complete Response		Complete radiologic response (all of the following)	Complete metabolic response (even with a persistent mass)
	Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤1.5 cm in longest diameter (LDi). No extralymphatic sites of disease.	Score ≤ 3* with or without a residual mass on 5-point scale†. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue

Response	Site	CT-Based Response	PET-CT Based Response
			even if the tissue has high physiologic uptake.
	Nonmeasured lesion	Absent	Not applicable
	Organ enlargement	Regress to normal	Not applicable
	New lesions	None	None
	Bone marrow	Normal by morphology; if indeterminate, IHC negative	No evidence of FDG-avid disease in marrow
Partial Response		Partial remission (all of the following)	Partial metabolic response
	Lymph nodes and extralymphatic sites	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease
	Nonmeasured lesion	Absent/normal, regressed, but no increase	Not applicable
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No response or stable disease		Stable disease	No metabolic response
	Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasured lesion	No increase consistent with progression	Not applicable

Response	Site	CT-Based Response	PET-CT Based Response
	Organ enlargement	No increase consistent with progression	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	No change from baseline
Progressive disease		Progressive disease requires at least 1 of the following	Progressive metabolic disease
	Individual target nodes/nodal masses	PPD progression:	Score 4 or 5† with an increase in intensity of uptake from baseline and/or
	Extranodal lesions	An individual node/lesion must be abnormal with: • Longest diameter (LDi) > 1.5 cm and • Increase by ≥ 50% from PPD nadir and • An increase in LDi or shortest diameter (SDi) from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly	• New FDG-avid foci consistent with lymphoma at interim OR end-of-treatment assessment
	Nonmeasured lesion	New or clear progression of preexisting nonmeasured lesions	None
	New lesions	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma	• New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). • If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
	Bone marrow	New or recurrent involvement	New or recurrent FDG-avid foci

Measured dominant lesions:
Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.

Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

Nonmeasured lesions:
Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

†*PET 5-point scale*:
1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Abbreviations:
CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

11.1.2 *Clinical Endpoints*

Evaluable patients are defined as eligible participants who received at least one dose of the protocol treatment. Eligible participants who did not receive any protocol treatment will be considered in-evaluable, replaced, and excluded from all analyses.

Endpoint	Patients	Definition
*Progression-Free Survival (PFS)**	Evaluable patients	Defined as the time from the first dose of study treatment to the first observation of disease relapse/progression or death from any cause, whichever occurs first. For patients who are alive and have not had disease relapse/progression at the last follow-up, it is censored at the time of last follow-up. If a patient receives non-protocol anti-HL treatment prior to disease relapse/progression, the patient will be censored at the time of non-protocol anti-HL treatment.

Endpoint	Patients	Definition
Overall Survival (OS)	Evaluable patients	Defined as the time from the first dose of study treatment to death from any cause. For patients alive at the last follow-up, it is censored at the time of last follow-up.
*Cumulative Incidence of Non-Relapse Mortality (NRM)**	Evaluable patients	Defined as the time from the first dose of study treatment to non-disease related death. Disease relapse or progression is considered a competing risk. For surviving patients without disease relapse/progression at the last follow-up, it is censored at the time of last follow-up. If a patient receives non-protocol anti-HL treatment prior to disease relapse/progression, the patient will be censored at the time of non-protocol anti-HL treatment.
*Cumulative Incidence of Relapse/Progression**	Evaluable patients	Defined as the time from the first dose of study treatment to disease relapse/progression. Death without relapse/progression is considered a competing risk. For surviving patients without relapse/progression at the last follow-up, it is censored at the time of last follow-up. If a patient receives non-protocol anti-HL treatment prior to disease relapse/progression, the patient will be censored at the time of non-protocol anti-HL treatment.
Overall response rate (ORR)	Evaluable patients with measureable disease post-ASCT	Proportion of patients achieving CR or PR [53]

* ***For patients who meet PD per Lugano Classification and also meet IR per LYRIC criteria (Appendix H) [1]:*** In the analysis, patients with PD per Lugano classification and IR per LYRIC criteria who continue study treatment beyond progression per Lugano classification and have confirmation of subsequent PD per LYRIC criteria will be counted as PD at the initial time point of progression per Lugano classification; patients with PD per Luagno classifcation and IR per LYRIC criteria who continue study treatment beyond progression per Lugano classification and do not have confirmation of subsequent PD per LYRIC criteria, with subsequent SD, PR, or CR per Lugano classification, will NOT be counted as PD at the initial time point of progression per Lugano classifcation. Patients with PD per Lugano classification and IR per LYRIC criteria who did NOT continue study treatment beyond progression per Lugano classification will be considered PD at the initial timepoint of progression per Lugano classification.

11.1.3 *Toxicity*

Toxicity and adverse events will be recorded using the NCI CTCAE v 4.0. All toxicities/AEs will be recorded from the initiation of protocol therapy through the follow-up period. The highest grade for any toxicity plus Grade 3 or 4 event for the same toxicity (if not the highest grade) will be reported during each cycle and during the safety follow-up period.

Eligible participants who did not receive any protocol treatment will be considered in-evaluable, replaced, and excluded from all analyses on toxicity.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a single-arm, open-label Phase 2 study of nivolumab plus BV consolidation following ASCT in patients with relapsed/ refractory HL who have undergone ASCT. Participants will receive protocol treatment consisting of 21-day cycles, for up to 8 cycles. The primary endpoint is 18-month progression-free survival. Secondary endpoints include overall survival, cumulative incidence of relapse/progression, cumulative incidence of non-relapse mortality, overall response rate, and toxicity. The target sample size is 59 eligible participants who received at least one dose of the protocol treatment. Eligible participants who did not receive any protocol treatment will be considered in-evaluable and replaced. The total study accrual may be increased slightly beyond 59 patients in order to achieve 59 evaluable participants with at least one dose. To account for up to 10% inevaluable enrollments, the maximum study accrual is set to be 65 participants. The projected study accrual duration is 24 months at the estimated accrual rate of 2-3 patients per month. With a planned follow-up until 18 months from the first dose of study treatment for the last accrued patient, the projected total study duration for accrual and follow-up is approximately 42 months.

12.2 Sample Size Accrual Rate

The target sample size is 59 participants with at least one dose of the protocol treatment, with the study total accrual potentially slightly larger to accommodate some eligible participants who did not receive any protocol treatment due to various reasons. City of Hope performs approximately 20-30 ASCT in patients with HL each year. Table 12.2 below describes the number of patients with HL evaluated at COH each year, as well as the number of ASCT for HL performed between 2011 and 2015. Based on this estimate, we expect to accrue 15-20 patients per year at COH. This will be a multicenter study with 6 total sites. We expect a total accrual of 2-3 patients per month across all sites. Therefore, accrual is expected to be completed in 24 months. With a planned follow-up until 18 months from the first dose of study treatment for the last accrued patient, the total anticipated study duration will be approximately 42 months.

Table 12.2 City of Hope Patient Availability

Disease Site	2011	2012	2013	2014	2015
Hodgkin Lymphoma (HL)	388	392	361	425	394
HL patients undergoing ASCT	21	33	22	33	30

12.3 Statistical Analysis Plan

12.3.1 *Power Estimation*

The primary endpoint is 18-month PFS, as defined in Section 11.0. Eligible participants who received at least one dose of the protocol treatment will be evaluable for the primary endpoint; eligible participants who did not receive any protocol treatment will be considered in-evaluable and excluded from all analyses.

Based on the AETHERA trial, the 18-month PFS rate in patients with relapsed/refractory HL who undergo ASCT followed by BV consolidation is approximately 65% (from the independent assessment data) [32]. We hypothesize that adding nivolumab to BV consolidation after ASCT will improve the 18-month PFS rate to 80%. A sample size of 59 evaluable patients will provide approximately 81% power for detecting the

increase in 18-month PFS from the baseline of 65% to 80% in this study at 1-sided type I error of 0.05. The power estimation is based on the exact binomial test. Operationally, the study treatment will be considered promising if at least 45 of the 59 evaluable participants are alive and progression-free at 18 months after the first dose of study treatment. The probability of observing at least 45 surviving and progression-free participants out of a total 59 participants, assuming different PFS rates, is shown in Table 12.3.1.

Table 12.3.1 The probability of declaring the trial a success assuming different PFS rates

	True 18-month PFS rate			
	65%	**70%**	**75%**	**80%**
The probability of observing at least 45 participants (out of 59 total) being alive and progression-free at 18-month	0.044	0.18	0.48	0.81

12.3.2 *Analysis Plans*

Patient demographics and baseline disease characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics such as number, mean, standard deviation, standard error, median (range) etc. will be provided. For categorical variables, patient counts and percentages will be provided.

For all analyses, only eligible participants who received at least one dose of protocol treatment will be considered evaluable and included in the analyses. Eligible participants who did not receive any protocol treatment will be considered in-evaluable and excluded from all analyses.

PFS will be estimated using the product-limit method of Kaplan and Meier along with the Greenwood estimator of standard error. When there is no censoring in PFS prior to 18 months after the first dose of study treatment, the observed 18-month PFS will be compared to the baseline of 65% by one-sided exact test of binomial proportion. In case of censoring in PFS prior to 18 months after the first dose of study treatment (which are expected to be rare), the Kaplan-Meier estimate for 18-month PFS along with the Greenwood standard error estimator will be used for the testing of null hypothesis at 65%.

OS will be estimated using the product-limit method of Kaplan and Meier along with the Greenwood estimator of standard error. Cumulative incidence of relapse/progression and cumulative incidence of non-relapse mortality, as well as their confidence intervals will be estimated using competing risk methodology, treating the other event as a competing risk. Overall response rate will be estimated by the proportion of patients achieving either CR or PR among participants with measurable disease after ASCT, along with the exact binomial confidence interval.

Observed toxicities will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v4.0 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.

For the exploratory objects, descriptive statistics will be used to summarize the responses and outcomes for patients who receive protocol treatment past disease progression and the correlative study measures. For continuous variables, number, mean, standard deviation, standard error, median (range) etc., will be provided. For categorical variables, patient counts and percentages will be provided. Changes in these measures before, during, and after treatment (when measured) will also be summarized by descriptive statistics and tables/plots. Various statistical analyses will be used to explore the association between

these correlative endpoint measures (at different time points and the associated changes over time, when measured) with clinical outcomes such as PFS/OS and response. For the exploratory correlation of these endpoints with survival outcomes, survival analysis techniques such as Log rank test and Cox proportional hazard models will be considered. For the exploratory correlation of these endpoints with response, analyses comparing groups of participants defined by response may be conducted by various two sample tests such as two-sample t-test or Wilcoxon rank sum test for the continuous correlative endpoints, or Chi-square test/Fisher's exact test for the categorical correlative endpoints. Appropriate regression models will also be considered, such as logistic regression for analyses on response and Cox proportional hazards models for survival outcomes. All these analyses are exploratory in nature and no multiple comparison adjustments will be made in these exploratory analyses

12.3.3 *Toxicity Monitoring*

Close and continuous monitoring for toxicity will occur throughout the study duration per institutional standards. The COH DSMC will review the AE data quarterly. In the AETHERA trial [32], 56% of patients who received brentuximab vedotin experienced at least one Grade 3-4 adverse event, including 29% with Grade 3-4 neutropenia, 10% with Grade 3-4 peripheral sensory neuropathy, and 6% with Grade 3-4 peripheral motor neuropathy.

In this study, the total treatment number of cycles is reduced to 8 but the addition of nivolumab may introduce additional toxicities.

Given the prior toxicity experiences in AETHERA trial and the differences in treatment [32], in this study we will specifically monitor the occurrence of any **"unacceptable AE". Unacceptable AE** is defined as any of the following AEs that is at least **possibly attributed** to protocol therapy during treatment and safety follow-up:

- Any ≥ Grade 3 immune-related AE
- Grade 3 fatigue or non-irAE skin toxicity that does not resolve within 7 days to ≤ Grade 1/baseline
- Any other ≥ Grade 3 non-hematologic non-irAE that does not improve within 3 days to ≤ Grade 1/baseline as applicable with supportive care with the following **exception**:
  - ≥ Grade 3 laboratory abnormality that is not clinically significant
- Grade 4 neutropenia that does not resolve to ≤ Grade 2 within 3 days with supportive care (e.g. GCSF)
- Grade 3 or 4 thrombocytopenia with bleeding
- Any Grade 5 AE

This specific monitoring will be performed according to the rule below, which is based on the 50% quartile of the binomial distribution with an unacceptable toxicity rate of 33%.

- 3 or more patients with unacceptable toxicities when ≤ 9 patients have been treated.
- 5 or more patients with unacceptable toxicities when ≤ 16 patients have been treated.
- 8 or more patients with unacceptable toxicities when ≤ 23 patients have been treated.
- 11 or more patients with unacceptable toxicities when ≤ 33 patients have been treated.
- 15 or more patients with unacceptable toxicities when ≤ 46 patients have been treated.

- 19 or more patients with unacceptable toxicities when ≤ 59 patients have been treated.

If the monitoring rule is met, the study PMT will review and assess the safety of the trial and submit a report outlining the findings and proposed action plans if any to the COH DSMC. The COH DSMC will review and make the decision to continue, modify, or permanently suspend accrual to the trial. At the end of the study with 59 evaluable participants, the 95% exact binomial confidence interval for the rate of such unacceptable AE will have a width of no more than 27%.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using Medidata RAVE, City of Hope's electronic capture system. Medidata RAVE is a web based, password protected system that is fully compliant with global regulatory requirements, including 21CRF Part 11 compliant.

13.3 Case Report Forms/ Data Submission Schedule

Study personnel at each site will enter data from source documents corresponding to a participant's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

All data will be collected using electronic data collection system described in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 14 calendar days of treatment administration
Adverse Event Report Forms	Within 10 calendar days of the assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of completing treatment or being taken off study for any reason
Follow up/ Survival Forms	Within 14 calendar days of the protocol defined follow up visit date or call

13.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 ADHERENCE TO THE PROTOCOL

A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval.

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Protocol deviations may be on the part of the participant, the investigator, or study staff.

All deviations from the protocol must be documented in study participant source documents and promptly reported to the Study PI and to the local IRB according to its policies requirements. The Study PI will report the deviation according to City of Hope's deviation policy for reporting deviations.

14.1 Emergency Modifications

Investigators may implement a deviation from the protocol to eliminate an immediate hazard(s) for the protection, safety, and well-being of the study patient to trial participants without prior IRB or Sponsor approval.

For any such emergency modification implemented:

- The local IRB and/or DSMC must be notified according to local institutional policies.
- The Study PI must be notified as soon as practicable (within 24 hours) via email to the Study PI and dcc@coh.org. This email should provide input on the following:
  - Description of the event
  - Impact on participant safety or the safety to others
  - Impact on the study design

14.2 Planned Non-Emergency Deviations

All non-emergency planned deviations from the protocol must have prior approval by the Study PI, the Site Lead Investigator and the local IRB, and if applicable the COH IRB.

14.3 Unplanned Deviations – Deviations Discovered After They Have Occurred.

For deviations to the protocol discovered after they have occurred:

- The local IRB and/or DSMC must be notified according to local institutional policies.
- The Study PI must be notified as soon as practicable (within 24 hours of awareness of event) via email to the Study PI and dcc@coh.org. This email should provide input on the following:
  - Description of the event
  - Impact on participant safety or the safety to others
  - Impact on the study design
  - A corrective and preventative action plan

A list of deviations from all participating sites will be submitted along with the Protocol Management Team (PMT) progress report to the COH DSMC.

14.4 Single Subject Exceptions

An SSE is a planned deviation, meaning that it involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives prior approval by the PI and the IRB.

COH only: Reporting SSEs: the SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

15.0 STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

15.1 Site Lead Investigator Responsibilities

The Site Lead Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations (CFR). The Site Lead Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

It is the responsibility of the Site Lead Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events, deviations, and unanticipated problems.

The Site Lead Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms at his/her site. For remote or onsite monitoring and auditing, the Site Lead Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Site Lead Investigator and will require his/her final signature to verify the accuracy of the data.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of participants under the investigator's care; and for the control of drugs under investigation.

15.2 All Investigator Responsibilities

All investigators agrees to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

15.3 Study PI Responsibilities

The Study PI is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312.

15.4 Protocol Management Team (PMT)

The PMT minimally consisting of the Study Principal Investigator, Site Lead Investigator(s), collaborating investigators, the research nurse, the clinical research associate/coordinator, and the study biostatistician is responsible for ongoing monitoring of the data and safety of this study.

The PMT will meet (in person or via teleconference) at least monthly, and will meet at least quarterly with the study biostatistician, to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed, including the implementation of stopping rules.

15.5 Monitoring/ Auditing

Clinical site auditing/ monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

The site Investigator/Institution will permit the study monitors and appropriate regulatory authorities direct access to the study data and to the corresponding source data and documents to verify the accuracy of this data. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Details of clinical site monitoring are documented in the OCTAM SOP that is provided as a supplement to this document. This document specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Staff from OCTAM will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SOP. Documentation of monitoring activities and findings will be provided to the site study team, the site PI, study PI, and the COH DSMC.

15.6 Quality Assurance

The City of Hope Clinical Research Information Support will provide quality assurance.

An additional level of quality assurance of the study-required images will be performed by the Study PI (see Section 11.1.1 for details).

15.7 City of Hope Data and Safety Monitoring Committee (DSMC)

This is a Risk Level 4 study, as defined in the City of Hope Data and Safety Monitoring Plan because the trial involves a COH IND.

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The COH DSMC will review and monitor toxicity and accrual data from this trial. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team. The COH DSMC Charter is a supplement to this protocol.

The DSMC will review the study's status every 3 months and/or more frequently if necessary. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.

Data and safety will be reported to the COH DSMC using the PMT report and submitted every 3 months from the date of activation.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

16.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects

- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

16.3 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federal wide Assurance issued by and registered with the Office for Human Research Protections (OHRP). Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent document will be in the possession of the Investigator, and, for sites external to COH, the possession of the coordinating center, before the study is initiated. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

The IRB will be informed of revisions to other documents originally submitted for review; serious unexpected or unanticipated adverse experiences occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Any amendment to the protocol document and accompanying informed consent document/template, as developed and provided by the Study PI, will require review and approval by the IRB before the changes are implemented in the study. The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

16.4 Informed Consent

For a multi-site study, each participating institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the patient or the patient's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the Site Investigator and available for inspection sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

16.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and follow-up procedures.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and follow-up procedures.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

16.6 Special and Vulnerable Populations

16.6.1 *Inclusion of Women and Minorities*

The study is open anyone regardless of gender or ethnicity. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of maternal toxicity have been reported. Findings in monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy [29]. The effects of brentuximab vedotin on embryogenesis, reproduction, and spermatogenesis in humans are unknown.

16.6.2 *Exclusion of Children*

Children/ adolescents (< 18 years old of age) are excluded from this study because the historical comparator trials were conducted in adults. Future studies may be planned to include children/ adolescents.

16.6.3 *Inclusion of HIV Positive Individuals*

Participants with a history of HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

16.6.4 *Vulnerable Populations*

45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, or economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and COH IRB approval.

16.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed participant authorization informing the participant of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, ant the rights of a research participant to revoke their authorization for use of their PHI. In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of participants will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. Source documents provided to coordinating center for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring/ auditing, IRB reviews, and FDA/regulatory authority inspections. The participant's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject ID, institution and timepoint of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

16.8 Future Use of Stored Specimens and Other Identifiable Data

Samples will be stored for up to 10 years following the end of the study. The Study PI will be the administrator. Identifiable data analysis will cease following analysis of samples and the results have been published.

16.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

16.10 Financial Obligations, Compensation, and Reimbursement of Participants

Nivolumab will be provided by the manufacturer free of charge to study participants.

The research participant nor the insurance carrier will be responsible for the research procedures related to this study.

The research participant will be responsible for the cost of purchasing brentuximab vedotin, all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope or at the non-COH site to the injured research participant, however, financial compensation will not be available. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

16.11 Publication/Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among City of Hope and BMS. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov and results will be reported on ClinicalTrials.gov within 12 months of the estimated or actual completion date of the trial, whichever date is earlier.

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APPENDIX A: ECOG PERFORMANCE STATUS

ECOG Performance Status Scale [55]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: REGISTRATION COVERSHEET

COH IRB# 16378: A Phase 2 Study of Nivolumab and Brentuximab Vedotin Consolidation After Autologous Stem Cell Transplantation in Patients with High-Risk Classical Hodgkin Lymphoma

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: (626)-218-7904
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:
Address:

Phone:
Fax:
e-mail:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
Medical Record No:	Investigator/Treating Physician:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
☐	Black	☐	Hispanic	Codes:	
☐	Caucasian	☐	Non-Hispanic	**01** Private	**06** Military or Veterans Adm. sponsored
☐	Asian	☐	Other_____	**02** Medicare	**07** Self-pay (no insurance)
☐	American Indian			**03** Medicare & private ins.	**08** No means of payment (no insurance)
☐	Native Hawaiian/Pacific Islander			**04** Medicaid	**09** Unknown
☐	Other_____ _____			**05** Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX C: TISSUE SHIPPING GUIDELINES FOR EXTERNAL NON-COH SITES

*These guidelines apply to **non-COH sites** only.*

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).

2. Notify City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org) of impending shipment. To request a FedEx shipping label, email DCC@coh.org and indicate the planned shipment date.

3. **Slides/ Blocks:** Batch ship at room temperature via FedEx. During extreme heat, include refrigerated (not frozen) gel packs or gel insulators.

   It is recommended to ship samples via FedEx overnight (for a delivery by 3 pm or earlier the next day) or FedEx 2-day (with a morning delivery). During extreme heat, ship via FedEx overnight (for a delivery ideally by 10.30 am, or 3 pm the next day).

4. **Frozen samples** should be batch shipped on dry ice via FedEx overnight (for a delivery by 10.30 am the next day). The shipment should contain enough dry ice to last at least 72 hours.

5. On the day of shipment, email the sample shipment information to City of Hope Pathology Core (DL-PATHCORE-BiospecimenSupport@COH.org).

6. Ship samples with a **copy of the correlative tissue form (Appendix I)** and a **copy of the pathology report** to:

Karen Miller
COH Pathology Core
City of Hope National Medical Center
1500 E. Duarte Road
Familian Science (Building 084), Room 1207
Duarte, CA 91010
Telephone: 626-218-8408
Email: DL-PATHCORE-BiospecimenSupport@COH.org

APPENDIX D: CORRELATIVE BLOOD COLLECTION FORM (NON-COH SITES ONLY)

Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	

Blood samples will be collected from an indwelling venous catheter or by venipuncture. Refer to Section 9.3 for collection details.

Before scheduled blood collection (at least one day in advance) send calendar invite via email to Leslie Smith-Powell (LSmith-Powell@coh.org) and Stephanie Lee (stlee@coh.org) or their designee at the Analytical Pharmacology Core Facility (APCF) to inform them of a pending collection.

Sample #	Timepoint of Collection	Expected Volume	Tube Type Used (Select One)	Collected Volume	Time of Collection	Date of Collection
1.	Cycle 1 Day 1 (C1D1)-Baseline	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
		20 mL	BCT tube	_____ mL	____:____ AM/ PM	____/____/____
2.	Cycle 2 Day 1 (C2D1)	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
3.	Cycle 5 Day 1 (C5D1) (OR 3 months *^)	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
		20 mL	BCT tube	_____ mL	____:____ AM/ PM	____/____/____
4.	30 days post-last dose	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
		20 mL	BCT tube	_____ mL	____:____ AM/ PM	____/____/____
5.	6 months *^	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
		20 mL	BCT tube	_____ mL	____:____ AM/ PM	____/____/____
6.	12 months from start of treatment (if yet to progress)	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
		20 mL	BCT tube	_____ mL	____:____ AM/ PM	____/____/____
7.	18 months from start of treatment (if yet to progress)	20 mL	Green-top	_____ mL	____:____ AM/ PM	____/____/____
		20 mL	BCT tube	_____ mL	____:____ AM/ PM	____/____/____

* If off treatment (i.e. < 8 cycles of treatment) but yet to progress
^ Collect during Active Follow-up assessment per Section 10.0.

A copy of this form should accompany the sample shipments to COH APCF. **Refer to Appendix E for shipping instructions COH APCF.**

CRA/Study Coordinator/ Nurse:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

APPENDIX E: BLOOD SHIPPING GUIDELINES FOR EXTERNAL NON-COH SITES

Follow the requirements for the proper packaging and shipping of biomedical material found in 42 CFR Part 72 - Interstate Shipment of Etiologic Agents Centers for Disease Control and Prevention, Office of Health and Safety Biosafety Branch.

When to ship and temperature of shipment:	**BCT tubes:** Via overnight courier at **ambient temperature**. **Green-tops:** On the day of collection overnight at **around +4 °C with a refrigerated cool pack** in an appropriate container via FedEx
Days to ship:	**Monday-Wednesday** for receipt Tuesday-Friday by the laboratory. If this is not feasible, advance arrangements should be made with Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) or their representative.
Notification on the day of shipment	Email the FedEx shipment # with a copy of Appendix D. • Leslie Smith-Powell (LSmith-Powell@coh.org) or • Stephanie Lee (stlee@coh.org) or their representative
*What to include **with** the shipment*	• Copy of Appendix D • Copy of the latest CBC results (with differential) and the date of the test
Shipment address	Dr. Tim Synold Analytical Pharmacology Core Facility Shapiro 1042 City of Hope National Medical Center 1500 E. Duarte Road Duarte, CA 91010

APPENDIX G: EXPEDITED REPORTING COVERSHEET

NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT

For Use by Participating Institutions Only

THIS FORM ALONG WITH A COPY OF THE MEDWATCH 3500 OR IRB REPORTING FORM MUST BE **EMAILED** TO DCC@COH.ORG WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT OR UNANCTICIPATED PROBLEM

COH IRB #16378- Participating Site IRB # _____

From:	Date:
Phone No.:	Email:
Reporting Investigator:	
Event:	
Participant ID:	Institution:
Date Event Met Reporting Criteria (as defined in protocol):	

Type of Report:	☐ Initial ☐ Follow-up
CTCAE Grade:	☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5
Attribution to **nivolumab:**	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Attribution to **brentuximab vedotin**:	☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite
Historical/Known Correlation to **nivolumab**:	☐ Expected ☐ Unexpected
Historical/Known Correlation to **brentuximab vedotin**:	☐ Expected ☐ Unexpected
Meets Definition of Serious AE:	☐ Serious ☐ Non-serious
Meets Definition of Unanticipated Problem:	☐ UP ☐ Not a UP
Has the event been reported to the following institution's IRB?	☐ No ☐ Yes; Date:_____/____/_____

Authorized Investigator Signature:	Date:____/____/____

APPENDIX H: LYRIC CRITERIA

Lugano Classification was developed based on treatment with cytotoxic agents [53]. Immunotherapeutic drugs, may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as clinical responses after initial increases in tumor burden or even the appearance of new lesions. Thus, the 2014 Lugano Classification may not provide an accurate assessment of response to immunotherapeutic agents. Provisional modification of the Lugano criteria (LYRIC Criteria) may be used to assess participants who meet progressive disease per Lugano Classification [1, 53].

Complete Response	Partial Response	Progressive Disease
Same as Lugano	Same as Lugano	As with Lugano with the following **exceptions**: **Indeterminate response (IR)** • IR1: ≥50% increase in SPD of up to 6 measurable lesions in first 12 weeks of therapy without clinical deterioration • IR2: <50% increase in the overall SPD with a. Appearance of a new lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment • IR(3): Increase in FDG uptake without a concomitant increase in lesion size or number Patients with IR should continue on therapy and have repeat imaging after an additional 12 weeks (or sooner if clinically indicated). Progressive disease criteria in these patients will be met if: • IR1: An additional increase in the target SPD of ≥ 10% between the first IR1 timepoint and the SPD being assessed; or an increase in ≥ 5mm in either dimension of at least one lesion for lesions ≤ 2cm and 10mm for lesions > 2cm. • IR2: the new or growing lesion(s) should be added to the target lesions (total of no more than 6) and there is PD if the SPD if the newly defined set of target lesions has increased ≥50% from their nadir value (which may precede the IR time point). • IR3: There is evidence of PD by an increase in lesion size or the development of new lesions.
Abbreviations: SPD, sum of the product of the diameters; PPD, product of the perpendicular diameters.		

APPENDIX I: CORRELATIVE TISSUE FORM (FOR ALL SITES)

A copy of this form should <u>accompany the sample shipments</u> to COH Pathology Core.
Non-COH sites: refer to Appendix C for shipping instructions to COH Pathology Core.

COH IRB number: 16378	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

CRA/Study Coordinator/Nurse Printed Name:
CRA/Study Coordinator/Nurse Signature:
Contact Number: