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DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A Phase 2 Front-Line PET/CT-2 Response-Adapted Brentuximab Vedotin and Nivolumab Incorporated and Radiation-Free Management of Early Stage Classical Hodgkin Lymphoma (cHL)

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB #18157 **PROTOCOL DATE: 03/21/2023**

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DISEASE SITE: Hodgkin Lymphoma

STAGE: Early Stage

MODALITY(IES):

TYPE: Phase 2

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Clinical Trial Protocol

A Phase 2 Front-Line PET/CT-2 Response-Adapted Brentuximab Vedotin and Nivolumab Incorporated and Radiation-Free Management of Early Stage Classical Hodgkin Lymphoma (cHL)

Version Date:	03/21/2023
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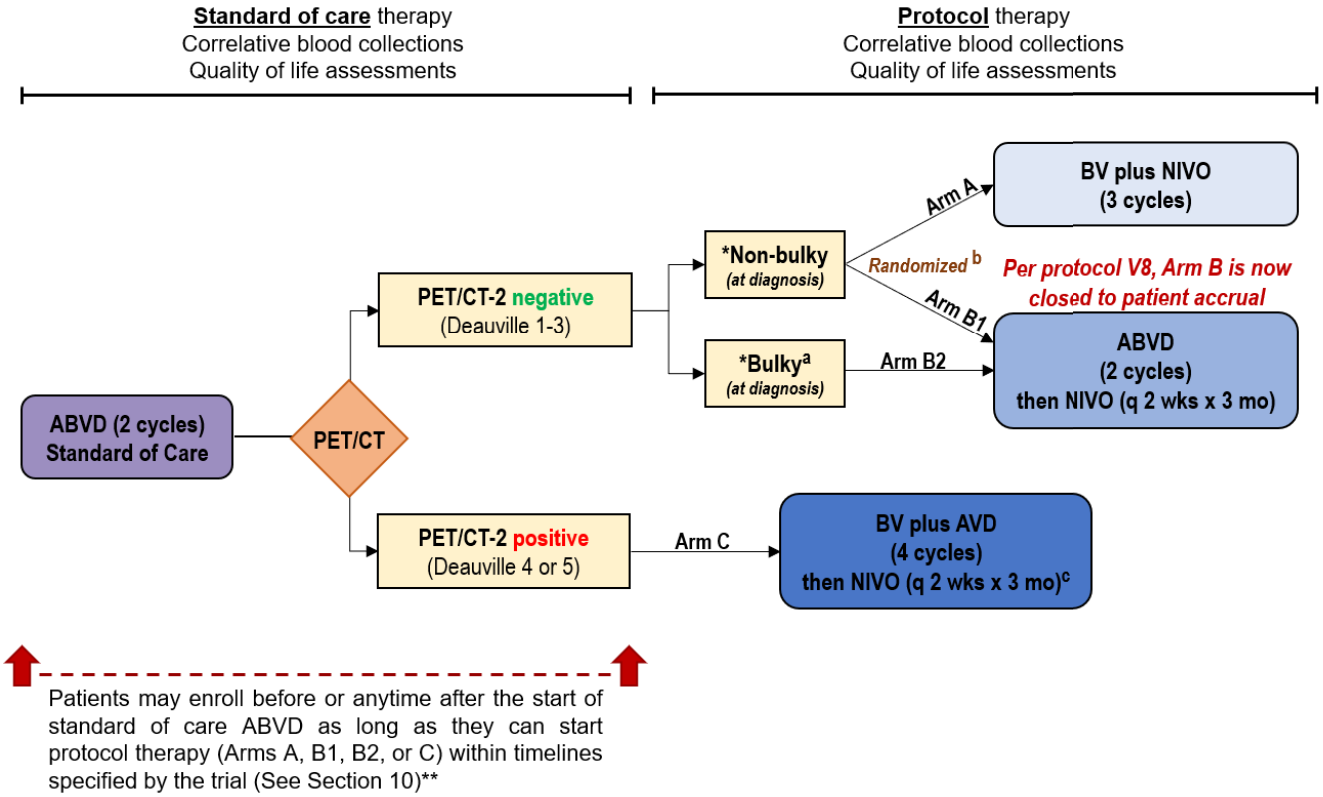
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STUDY SCHEMA

Favorable and unfavorable risk early stage cHL patients who are planning, undergoing, or have just completed 2 cycles of standard of care ABVD will be enrolled in this study.

Per protocol version 08, dated 09/09/22, the study design is revised so that all patients with negative PET/CT-2 will be assigned to Arm A. Arm B (B1/B2) is now closed to patient accrual. Patients with positive PET/CT-2 will be assigned to Arm C (same as before).



* Determination of bulky vs. non bulky disease is based on assessment prior to any treatment (baseline PET/CT).
**Patients must meet study eligibility criteria to enroll in the study, and will need to meet an additional set of criteria to be able to start protocol therapy (see Section 3).

The DCC will:
- register participants who are eligible to enter the study
- assign treatment arm for **all** arms (randomized and non-randomized) of the trial.
(See Section 4 for additional details)

a. Bulky is defined by mediastinal mass ≥ 7.5 cm on baseline PET/CT (prior to SOC ABVD treatment).

b. Patients will be randomized equally with stratification for balance between arms for baseline factors of stage I vs II, and A vs B symptoms.

c. Patients in Arm C must be PET-CT negative at the end of the 4 cycles of BV+AVD in order to receive nivolumab. (Refer to Section 5.2.5 for additional details and exceptions).

No adverse event data will be collected during standard of care ABVD. Adverse event data collection will begin on Cycle 1, Day 1 of protocol therapy.

PROTOCOL SYNOPSIS

Protocol Title

A Phase 2 Front-Line PET/CT-2 Response-Adapted Brentuximab Vedotin and Nivolumab Incorporated and Radiation Free Management of Early Stage Classical Hodgkin Lymphoma (cHL)

Study Detail

Population/Indication(s):	Early Stage Classical Hodgkin Lymphoma (cHL)
Phase:	2
Sample Size:	162 patients maximum (at least 150 evaluable)
Estimated Accrual Duration:	56 months
Estimated Study Duration	7 years
Participant Duration:	Up to 45 months
Participating Sites:	Refer to Protocol team Section
Study Agents:	Brentuximab vedotin, nivolumab, doxorubicin, bleomycin, vinblastine, dacarbazine
Sponsor:	City of Hope, NAHLC
Industry Partner:	Bristol-Myers Squibb, Seattle Genetics

Rationale for this Study

The goals for early stage cHL patients are to develop, through clinical trials, methods of care that decrease long term toxicities while preserving excellent outcomes for patients with PET/CT-2 negativity. Conversely, for patients with PET/CT-2 positivity, the goals are to improve outcomes and minimize needs for future salvage therapies. One of the challenges is that, while there is significant agreement that Deauville 4 and 5 represent a positive PET/CT scan, the Deauville 3 scans with uptake greater than mediastinum but less than or equal to the liver can be defined as PET/CT positive versus negative depending on the publication or trial, as evidenced by the trials reviewed above. For the RAPID and EORTC H10 trials PET-negativity was defined as Deauville 1 or 2, whereas the CALGB/Alliance 50604 defined PET-negativity as Deauville 1 to 3. Non-inferiority was not met for either the RAPID or the EORTC H10 trials for omission of radiation therapy for the interim PET-negative patients, but the losses of PFS were small of 3 to 10%. By comparison the CALGB/Alliance 50604 trial showed that if interim PET positivity is defined as Deauville 4 or 5, even change of therapy to escalated BEACOPP with its associated toxicities did not significantly impact outcomes with a 3-year PFS of only 66% and the authors concluded that alternative strategies needed to be considered.

Given the predictive power of an interim PET/CT scan, the NAHLC designed a trial that stratifies treatment for early stage cHL patients utilizing this result, rather than the risk factors as defined by GHSG from favorable to bulky mediastinal.

This trial seeks to evaluate the incorporation of the recently approved targeted agents brentuximab vedotin and/or nivolumab to allow interim PET/CT-2 negative patients, defined as Deauville 1 to 3, to have radiation therapy omitted, but with the goal of retaining PFS through the addition of these novel therapies. For patients with interim PET/CT-2 positive scans, defined as Deauville 4 and 5, the incorporation of BV and nivolumab aims at improving PFS and thus minimizes the chances of ultimately needing salvage therapies and autologous stem cell transplant, without switching to a regimen such a escalated BEACOPP, which has been shown to still have relatively low PFS in this patient population and a high side effect profile including infertility. Data supporting the addition of BV and/or nivolumab come from the trials reported above, including monotherapy activity of these drugs and combination data for BV plus AVD.

Objectives

Primary Objective

- Determine the 18-month progression free survival (PFS) for each arm of therapy stratified by PET/CT-2 response.

Secondary Objectives

- Assess safety, tolerability, and quality of life (QOL) for each arm of therapy.
- Measure PET/CT-2 negativity rate after 2 lead-in cycles of standard of care ABVD.
- Evaluate the 3-year PFS and overall survival (OS) for each arm of treatment.

Exploratory Objectives

- Evaluate if a baseline antitumor immune response, as assessed by a Nanostring gene panel, correlates with PFS.
- Evaluate if minimal residual disease (MRD) status, as monitored by cancer personalized profiling by deep sequencing (CAPP-Seq) of ctDNA, can be correlated with PFS.

Study Design

This is a multi-arm phase 2 study of a front-line, radiation-free, PET/CT-2 response-adapted therapy incorporating brentuximab vedotin (BV) and/or nivolumab in patients with early stage classical Hodgkin lymphoma. After having received 2 lead-in cycles of standard of care ABVD, patients will be evaluated and classified according to their PET/CT (PET/CT-2) scan results:

- PET/CT-2 negative patients (Deauville 1-3) without bulky disease (bulky disease is defined by mediastinal mass ≥ 7.5 cm at diagnosis) will be randomized equally to receive either 3 cycles of BV+nivolumab (Arm A), or 2 cycles of ABVD followed by nivolumab maintenance q2w for 3 months (Arm B). Randomization will be done with stratification for balance between arms for baseline factors of stage I vs II, and A vs B symptoms. PET/CT-2 negative patients with bulky mediastinal mass ≥ 7.5 cm at diagnosis will not be randomized and will be treated on Arm B.
- PET/CT-2 positive patients (Deauville 4 or 5) will all receive 4 cycles of BV plus AVD followed by nivolumab maintenance q2w for 3 months (PET/CT-2 positive patients will **not** be divided into bulky and non-bulky cohorts).

Response will be evaluated using the 2014 Lugano Classification. The primary efficacy endpoint is progression-free survival rate (PFS).

Per protocol version 08, dated 09/09/22, the study design is revised so that all patients with negative PET/CT-2 will be assigned to Arm A. Arm B is now closed to patient accrual. Patients with positive PET/CT-2 will be assigned to Arm C (same as before).

Evaluation Criteria and Endpoints

Primary Endpoint(s):

- Progression-free survival (PFS) at 18 months.

Secondary Endpoints:

- Toxicities and quality of life.
- PET/CT-2 negativity rate after the 2 lead-in cycles of standard of care ABVD.
- Progression-free survival (PFS) at 3 year, Overall survival (OS).

Statistical Considerations

This is a multi-arm phase II study for patients with newly diagnosed early stage (ES) cHL. After 2 cycles of standard of care ABVD, patients will be evaluated and classified by their PET scan results (PET/CT-2): negative if Deauville score is in the range of 1-3; positive if Deauville score is in the range of 4-5. Patients without PET/CT-2 results are not evaluable and will be replaced.

Revised design per protocol version 08:

Given the slower rate of patient accrual and a lower proportion of patients with negative PET/CT-2 and initial non-bulky disease (i.e., those eligible for randomization), the study is being revised to close the randomization and close Arm B. Arm B1/B2 will be closed for further patient enrollment and patients will only be accrued to Arm A and Arm C instead. Starting with protocol version 08, patients who are PET/CT-2 negative (regardless of bulky disease status at diagnosis) will be assigned to Arm A (3 cycles of BV plus Nivolumab); patients who are PET/CT-2 positive will be assigned to Arm C (4 cycles of BV plus AVD, then nivolumab maintenance q2w for 3 months). The projected final patient numbers are: ~53 Arm A, ~65 Arm B (Arm B1/B2 combined), and ~36 Arm C.

The goal is to still reach a PFS18 rate of 90% for Arm A (which will now include ~7 patients with negative PET/CT-2 and initial bulky disease who would have been assigned to Arm B2 on the original design). With n=~53, the 2-sided 95% confidence interval for PFS18 will have a width of approximately 16% at target PFS18 of 90%. The goal for Arm C is not changed as there is no change to this subgroup or its treatment. With ~36 patients, the 95% confidence interval for PFS18 will have a width of approximately 30% at target PFS18 of 70%. With the revised design patients enrolled to Arm B1/B2 will be analyzed as one group which will include approximately half patients with bulky disease and half without bulky disease; therefore, the target PFS18 is 85% which is the middle of Arm B1 and Arm B2 targets. With~65 patients, the 95% confidential interval for PFS18 will have a width of approximately 17%. Futility and toxicity monitoring are to be performed per Bayesian designs. The monitoring boundaries for Arm B1 and B2 will be followed until the point these arms are closed. The monitoring boundary for Arm A will continue until the entire study accrual is complete. The monitoring for Arm C will be performed as initially planned.

Abbreviated Eligibility Criteria

Main Inclusion Criteria

- Histologically confirmed diagnosis of classical Hodgkin lymphoma. Nodular Lymphocyte-Predominant Hodgkin Lymphoma is excluded.
- Stage IA, IB, IIA, or IIB cHL by Cotswold modified Ann Arbor staging.
- Measurable disease.
- Eastern Cooperative Oncology Group performance status of ≤ 2.
- Age ≥ 16 years.
- Patients or their legally authorized representative must provide written informed consent.

Main Exclusion Criteria

- History of another primary malignancy that has not been in remission for at least 3 years.
- Known cerebral/ meningeal disease.
- History of progressive multifocal leukoencephalopathy (PML).
- Known history of pancreatitis.
- Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV within 6 months prior to start of protocol therapy.
- Symptomatic cardiac disease.
- Known hypersensitivity to investigational agents.
- Known active infection with hepatitis B or hepatitis C or uncontrolled HIV.
- Previous therapy for Hodgkin lymphoma, with the exception of ABVD (patients may have received up to 2 cycles of ABVD as standard of care therapy, as long as they can start subsequent therapy [therapy administered in Arms A, B1/B2, or C] within timelines specified by the trial [refer to Section 10]).
- Sensory > grade 1 or any peripheral motor neuropathy.
- Women whom are pregnant or lactating.
- Subjects with active interstitial pneumonitis.
- Subjects with active, known or suspected autoimmune disease.

Criteria to start protocol therapy
• Adequate hematological, renal, pulmonary, cardiac, and hepatic function. • Subjects with a non-lymphoma-related condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalents) or other immunosuppressive medications within 14 days of start of protocol therapy are excluded. See exception in Section 3.2. • No sensory > grade 1 peripheral neuropathy, and no peripheral motor neuropathy (any grade). • No active systemic viral, bacterial, or fungal infection requiring IV treatment within 1 week of start of protocol therapy. • Females of childbearing potential must have a negative serum or urine β-hCG pregnancy. • Both females of childbearing potential and males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last doses of study drugs.

Investigational Product Dosage and Administration

BV plus Nivo Regimen (Arm A):

Drug (Abbreviation)	Dose	Method
Brentuximab Vedotin (BV)	1.8 mg/kg *(Dose level -1 is 1.2 mg/kg)*	IV on Days 1
Nivolumab (Nivo)	3 mg/kg	IV on Days 1

ABVD Regimen (Arm B1/B2**): (Closed to accrual starting with protocol version 08)**

Drug (Abbreviation)	Dose	Method
Doxorubicin (A)	25 mg/m^2	IV on Days 1 and 15
Bleomycin (B)	10 units/m^2	IV on Days 1 and 15
Vinblastine (V)	6 mg/m^2	IV on Days 1 and 15
Dacarbazine (D)	375 mg/m^2	IV on Days 1 and 15

BV plus AVD Regimen (Arm C):

Drug (Abbreviation)	Dose	Method
Doxorubicin (A)	25 mg/m^2	IV on Days 1 and 15
Vinblastine (V)	6 mg/m^2	IV on Days 1 and 15
Dacarbazine (D)	375 mg/m^2	IV on Days 1 and 15
Brentuximab Vedotin (BV)	1.2 mg/kg *(Dose level -1 is 0.9 mg/kg*)	IV on Days 1 and 15
G-CSF as supportive care	Refer to Section 5.2.4	

Nivolumab Maintenance Regimen (Arm B1/B2/C):

Drug (Abbreviation)	Dose	Method
Nivolumab (Nivo)	3 mg/kg	IV on Days 1

Clinical Observations and Tests to be Performed

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

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ABBREVIATIONS

Abbreviation	Meaning
ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
AE	Adverse Event
AVD	Doxorubicin, Vinblastine, Dacarbazine
BV	Brentuximab Vedotin
CAPP-Seq	Cancer Personalized Profiling by deep Sequencing
CFR	Code of Federal Regulations
cHL	Classical Hodgkin Lymphoma
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Coordinator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DLT	Dose Limiting Toxicity
DSMC	Data & Safety Monitoring Committee
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GHSG	German Hodgkin Study Group
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MRD	Minimal Residual Disease
NCI	National Cancer Institute
OIDRA	Office of IND Development and Regulatory Affairs
OS	Overall Survival
PD	Progressive Disease
PET/CT	Positron Emission Tomography/Computed Tomography
PFS	Progression free survival
PFT	Pulmonary function test
PI	Principal Investigator
PMT	Protocol Management Team
PR	Partial Response
QOL	Quality of Life
SAE	Serious Adverse Event
SD	Stable disease
SOC	Standard of care

1.0 OBJECTIVES

1.1 Primary Objective

- Determine the 18-month progression free survival (PFS) for each arm of therapy stratified by PET/CT-2 response.

1.2 Secondary Objectives

- Assess safety, tolerability, and quality of life (QOL) for each arm of therapy.
- Measure PET/CT-2 negativity rate after 2 lead-in cycles of standard of care ABVD.
- Evaluate the 3-year PFS and overall survival (OS) for each arm of treatment.

1.3 Exploratory Objectives

- Evaluate if a baseline antitumor immune response, as assessed by a Nanostring gene panel, correlates with PFS.
- Evaluate if minimal residual disease (MRD) status, as monitored by cancer personalized profiling by deep sequencing (CAPP-Seq) of ctDNA, can be correlated with PFS.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 Classical Hodgkin lymphoma incidence, pathophysiology, staging, and risk factor categorization

According to the American Cancer Society (ACS), there will be about 80,500 new cases of lymphoma in 2017 in the US, including 8,260 cases of Hodgkin Lymphoma (HL) with 95% anticipated to be classical HL and 72,240 cases of non-Hodgkin lymphoma. According to this same source, about 1,070 patients will die of Hodgkin Lymphoma in 2017.[1] In the European Union, the crude incidence of HL is 2.3 and the mortality is 0.4 cases/100,000/year.[2] cHL is slightly more common in males and has a bimodal age distribution curve. In the US, the first peak arises for patients around 20 years and a second one arises for patients around 65 years.[3]

The World Health Organization (WHO) 2016 classification of lymphoid neoplasms kept the same classification for HL as in 2008, id est classical HL (cHL, which encompasses nodular sclerosis classical Hodgkin lymphoma, lymphocyte-rich classical Hodgkin lymphoma, mixed cellularity classical Hodgkin lymphoma and lymphocyte-depleted classical Hodgkin lymphoma) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).[4]

Although the etiology of cHL is unknown, according to a Scandinavian (Denmark and Sweden) study, the standardized incidence ratio (SIR) of cHL is of 2.55 among patients who had infectious mononucleosis (IM) caused by Epstein-Barr virus (EBV). The SIR remained elevated up to two decades after the occurrence of IM, but decreased with time thereafter.[5] Furthermore, the incidence of cHL is increased as well in settings associated with immunodeficiency such as hematopoietic cell transplantation, therapy with immunosuppressive drugs and HIV infection.[6-9]

Histologically, the presence of malignant multinucleated giant Reed-Sternberg cells within the characteristic reactive cellular background is the pathologic hallmark of classical HL.[10] The characteristic surface antigen expressed on Reed-Sternberg cells is CD30.

The Ann Arbor staging system (AASS, or clinical stage (CS)) with Cotswolds modifications is the current system used for patients with cHL[11] and different prognostic factors such as GHSG (German Hodgkin Study Group), EORTC (European Organization for Research and Treatment of Cancer) or NCCN (National Comprehensive Cancer Network) have been proposed to further classify cHL into favorable or unfavorable risk groups.[2, 12] To illustrate, the GHSG defines as unfavorable risk factors a large mediastinal mass (ratio ≥ 1/3), ≥1 extranodal lesion, ESR (erythrocyte sedimentation rate) ≥ 50 without B-symptoms or ≥ 30 with B-symptoms, ≥3 nodal areas (out of 11

GHSG areas).[13] The GHSG has further classified the cHL patients into 3 groups, early-favorable stages (CS IA, IIA, IIB without risk factors), early-unfavorable or intermediate stages (CS I, IIA, and IIB with risk factors such as large mediastinal mass, extranodal involvement, high ESR, ≥ 3 lymph nodes) and advanced stages (CS IIB, IIIA with risk factors; CS IIIA + splenic involvement; CS IIIB; CS IV).[14] These three groups have a prognostic significance and have been used to personalize the treatment of frontline cHL, as it will be described below in further details. While in Europe often patients who otherwise fit criteria for early stage cHL disease but who have bulky mediastinal masses are often treated on advanced stage protocols in North America these patients are still generally grouped with other early stage unfavorable risk patients.

2.1.2 Predictive role of interim PET response in long-term outcomes

18F-FDG (Fludeoxyglucose) Positron Emission Tomography/Computed Tomography (PET/CT) has been recommended by different societies as initial staging imaging.[2, 15]. The 5-point scale (1: no uptake; 2: uptake ≤mediastinum; 3: uptake >mediastinum but ≤liver; 4: uptake moderately more than liver uptake, at any site; 5: markedly increased uptake at any site and new sites of disease) was proposed as a consensus at an international workshop, under the auspices of Groupe d'Etude des Lymphomes de l'Adulte (GELA) which took place in Deauville, France, in April 2009 and has been called the Deauville criteria ever since.[16] Furthermore, Milgrom et al showed that a model incorporating the Deauville score and soft tissue volume (STV) reduction predicted freedom from progression (FFP) more accurately than either measurement alone in the Deauville 1 to 4 subset, which might improve risk stratification and contribute to response-adapted individualization of therapy.[17]

Moreover, interim PET/CT performed after two chemotherapy cycles has been shown to be a reliable predictor of treatment outcome in ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine)-treated cHL patients.[18, 19] Gallamini et al have even showed that early interim PET/CT was prognostically superior to international prognostic score (IPS) in advanced-stage cHL.[20] Besides, Oki et al showed in a retrospective study with 229 patients, that in early stage non-bulky disease, bulky stage II disease, advanced stage low International Prognostic Score (IPS ≤2) and advanced stage (IPS ≥3), the 3-year progression-free survival rates in PET2-negative (Deauville score <4) vs. PET2-positive (Deauville score ≥4) groups were 95·9% vs. 76·9%, 83·3% vs. 20·0%, 77·0% vs. 30·0% and 71·0% vs. 44·4%, respectively.[19]

Furthermore, Gallamini et al showed in a retrospective study with 260 patients (53 with early unfavorable cHL and 207 advanced stage cHL) with newly diagnosed cHL treated with ABVD ± IFRT, that the 3-year PFS was 28% for patients with interim positive scans and 95% for patients with interim negative scans. The sensitivity, specificity, and negative and positive predictive values of interim positron emission tomography scans for predicting treatment outcome were 0.73, 0.94, 0.94 and 0.73, respectively, which confirmed the prognostic role and validity of the Deauville five-point scale for interpretation of interim positron emission tomography scans.[21]

2.1.3 Concern of late term toxicities in survivors

Indeed, even if the majority of cHL patients achieve complete remission and cure with current treatment paradigms, a minority of patients will experience relapse and death. In addition, given the young age at diagnosis and overall high survival rates, serious acute and long-term treatment-related toxicities remain a concern.

As a matter of fact, long-term survivors of cHL experience several late adverse effects of treatment (such as pulmonary dysfunction, endocrinopathies (thyroid dysfunction, infertility), neck muscle atrophy, and persistent fatigue), with second malignant neoplasms (SMNs) and cardiovascular diseases (CVDs) being the leading causes of death in these patients. In fact, cHL survivors have 2-4 fold increased risks to develop SMNs related to radiotherapy and alkylating agents such as solid tumors (breast, gastrointestinal cancers, lung cancer, thyroid cancer, soft tissue and bone sarcomas) and acute leukemias and CVD related to radiotherapy and anthracycline-containing chemotherapy compared to the general population.[22] In a retrospective study of Aleman et al with 1261 patients treated for cHL before age 41 between 1965 and 1987, deaths from other causes exceeded those due to cHL after 20 years from start of treatment, SMNs followed by CVDs were also the most common causes of deaths not due to cHL.[23]

Subsequently, attempts have been made to maintain a high survival rate while reducing toxicities, notably by reducing the radiation field size and the dose of radiation, especially in early-stage disease, and by reducing the of use of alkylating agents.[24] Certainly, there remains an unmet need for predictive tools to help guide individualized treatment decisions for patients. This includes the identification of high-risk cHL patients where more intensive therapy may be indicated, and conversely, the attenuation of treatment in lower risk patients in an attempt to decrease acute and late toxicities.[25] In this regard, many trials have studied and are currently using treatment guided by interim PET/CT, as further described below.[26-29]

2.1.4 Evolution of Standard Chemotherapy for Early Stage cHL

In 1992 Canellos et al published a phase 3 trial comparing MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) versus MOPP alternating with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and ABVD alone with 361 patients with cHL stage III-IV. It was shown that ABVD for 6-8 months was as effective as MOPP alternating with ABVD and superior to MOPP alone and less toxic than MOPP/MOPP alternating with ABVD, thus establishing ABVD as standard of care for cHL.[30] It is to be noted that the risks of secondary leukemias and myelodysplastic syndromes have been decreased with ABVD compared with MOPP.[31]

Engert et al showed in the 4-arm (four cycles of ABVD followed by 30 Gy of radiation therapy (group 1), four cycles of ABVD followed by 20 Gy of radiation therapy (group 2), two cycles of ABVD followed by 30 Gy of radiation therapy (group 3), or two cycles of ABVD followed by 20 Gy of radiation therapy (group 4)) phase III study HD10 of the GHSG with 1370 patients with newly diagnosed early stage cHL with a favorable prognosis, that two cycles of ABVD followed by 20 Gy of involved-field radiation therapy was as effective and less toxic than four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. Indeed, at 5 years, the rates of freedom from treatment failure (FFTF) were 93.0% with the four-cycle ABVD regimen and 91.1% with the two-cycle regimen. Furthermore, there were no significance of FFTF when the effects of 20-Gy and 30-Gy doses of radiation therapy were compared. Besides, adverse events and acute toxic effects of treatment were most common in the patients who received four cycles of ABVD and 30 Gy of radiation therapy (group 1).[32] Following this study, 2 cycles of ABVD and 20-Gy of IFRT (involved-field radiation therapy) became the new standard of care for newly diagnosed early stage cHL with a favorable prognosis.

With the aim at preventing late toxicity, Eghbali et al designed the EORTC-GELA H9-F with 783 patients with supradiaphragmatic stage I-II cHL and favorable features (age < 50, and CS I-II$^{2-3}$, and A + ESR < 50 or B + ESR < 30, and MT (mediastinal tumor) ratio < 0.35). After 6 cycles of EBVP (epirubicin, bleomycin, vinblastine, prednisone), CR (complete response)/CRu (complete response unknown) patients were randomized between 36 Gy IFRT (group 1), 20 Gy IFRT (group 2) and no RT (group 3). At July 2005, the 4-year EFS and OS rates were as follows: Group 1 88% and 98%, group 2 85% and 100% and group 3 69% and 98%. In conclusion, in favorable early stage cHL patients who achieved CR(u) after 6 cycles of EBVP, omission of IFRT lead to an unacceptable failure rate, however, with the current follow-up, IFRT 20Gy provides results equivalent to those of IFRT 36 Gy.[33]

Moreover, Engert et al of the University of Cologne designed the phase III 2-arm GHSG HD16 (NCT00736320) trial for patients with untreated early stage favorable cHL. This study compares 2 cycles of ABVD followed by 20 Gy IFRT irrespective of FDG-PET results after chemotherapy versus 2 cycles ABVD followed by 20 Gy IFRT if FDG-PET is positive after chemotherapy; 2 cycles ABVD and treatment stop if FDG-PET is negative after chemotherapy. This study is ongoing, but not recruiting participants, the primary outcome is the 5-year PFS (progression free survival) and the estimated completion date is expected for May 2020.[34]

Eich et al of the GHSG designed the trial HD11 for patients with newly diagnosed early unfavorable cHL. In this 4-arm (four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) + 30 Gy of IFRT; four cycles of ABVD + 20 Gy of IFRT; four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP$_{baseline}$) + 30 Gy of IFRT; or four cycles of BEACOPP$_{baseline}$ + 20 Gy of IFRT) study with 1,395 patients, the data showed that moderate dose escalation using BEACOPP$_{baseline}$ did not significantly improve outcome in early unfavorable cHL. In fact, there was no difference between BEACOPP$_{baseline}$ and ABVD when followed by 30 Gy of IFRT (5-year FFTF difference, 1.6%) and after four cycles of BEACOPP$_{baseline}$, 20 Gy was not inferior to 30 Gy (5-year FFTF difference, −0.8%), whereas inferiority of 20 Gy cannot be excluded

after four cycles of ABVD (5-year FFTF difference, −4.7%). Treatment-related toxicity occurred more often in the arms with more intensive therapy.[35] In conclusion, HD11 set 4 cycles of ABVD and 30-Gy IFRT as standard of care for newly diagnosed early unfavorable cHL.

Nevertheless, practitioners often recommend 6 cycles followed by RT, especially for bulky disease for early unfavorable cHL patients. However, Gunther, Fanale et al confirmed in a retrospective study with 128 patients with early unfavorable cHL that six cycles of ABVD followed by ISRT does not appear superior to four cycles of ABVD followed by ISRT for disease control, even for bulky disease. Moreover, more patients experienced bleomycin pulmonary toxicity in the 6-cycle group (20% vs 31%).[36]

Besides, Ferme et al designed the phase III EORTC-GELA H9-U trial with stage I and II cHL with unfavorable risk factors. The trial compared ABVD x 6 cycles and IFRT 36–40 Gy (group 1) *vs* ABVD x 4 cycles and IFRT (group 2) *vs* BEACOPP baseline x 4 cycles and IF-RT (group 3). In total, 808 patients were enrolled and at July 2005, the 4-year event-free survival (EFS) and overall survival (OS) rates are as follows: 91% and 95% for group 1, 87% and 94% for group 2 and 90% and 93% for group 3. These preliminary results indicated that a combination of 4 cycles of ABVD and IFRT 30 Gy is sufficient to cure a large majority of cHL patients with unfavorable early stage disease and that BEACOPP baseline has no advantage over ABVD in these patients.[37] The regimen with 4 cycles of ABVD and IFRT 30 Gy became the new standard of care for patients with early stage unfavorable cHL.

In addition, Von Tresckow et al of the GSHG designed the phase III HD14 trial aiming at improving long-term tumor control in untreated early unfavorable cHL patients. 1,528 patients were randomly assigned to either four cycles of ABVD or an intensified treatment consisting of two cycles of escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) followed by two cycles of ABVD (2 + 2). Chemotherapy was followed by 30 Gy IFRT in both arms. The 2 + 2 regimen demonstrated superior FFTF compared with four cycles of ABVD, with a difference of 7.2% at 5 years and the difference in 5-year PFS was 6.2%. There was more acute toxicity associated with 2 + 2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies. In conclusion, intensified chemotherapy with two cycles of BEACOPP escalated followed by two cycles of ABVD followed by IFRT significantly improves tumor control in patients with early unfavorable cHL.[38] However, the 2 + 2 regimen is not uniformly used because of the increased toxicity without long term overall survival improvement.

Finally, Engert et al of the University of Cologne designed the phase III GHSG HD17 (NCT01356680) trial for patients with untreated early stage unfavorable cHL. In this trial, cHL patients receive two cycles of $BEACOPP_{escalated}$ followed by two cycles of ABVD. Then, interim PET is performed and further treatment is stratified according to the PET result. Patients with a positive PET are randomized between 30 Gy INRT (involved-node radiotherapy) and 30 Gy IFRT. Patients with a negative PET are randomized between 30 Gy IFRT and follow up. This study is ongoing, but not recruiting participants, the primary outcome is the 3-year PFS and the estimated completion date is expected for December 2019.[39]

Straus et al designed the phase II CALGB (Cancer and Leukemia Group B) 50203 trial aim at reducing ABVD toxicity. In this trial, ninety-nine assessable patients with newly diagnosed, no bulky stages I and II Hodgkin lymphoma received 6 cycles of doxorubicin, vinblastine, and gemcitabine (AVG). The progression-free survival (PFS) at 3 years was 77%, the relapse rate was less than 10% for patients with favorable prognostic factors. The 2-year PFS for cycle 2 PET-negative and -positive patients was 88% and 54%, respectively, compared with 89% and 27% for cycle 6 PET-negative and -positive patients.[40] Although the AVG results were inferior to those achievable with ABVD, this regimen has never been to date compared in a phase III randomized trial with ABVD.

Meyer et al designed the phase III trial NCIC/ECOG HD.6 for patients with untreated stage IA or IIA non bulky cHL. 405 patients were randomly assigned to treatment with ABVD alone or to treatment with subtotal nodal radiation therapy, with or without ABVD therapy. Patients in the ABVD-only group, both those with a favorable risk profile and those with an unfavorable risk profile, received four to six cycles of ABVD. Among those assigned to subtotal nodal radiation therapy, patients with a favorable risk profile received subtotal nodal radiation therapy alone and patients with an unfavorable risk profile received two cycles of ABVD plus subtotal nodal radiation therapy. At 12 years, the rate of overall survival was 94% among those receiving ABVD alone, as compared with 87% among those receiving subtotal nodal radiation; the rates of freedom from disease progression were 87% and 92% in the

two groups, respectively and the rates of event-free survival were 85% and 80%, respectively. To summarize, among patients with Hodgkin's lymphoma, ABVD therapy alone, as compared with treatment that included subtotal nodal radiation therapy, was associated with a higher rate of overall survival owing to a lower rate of death from other causes.[41] This study raised questions regarding change of practice (indication/site) for radiation therapy.

2.1.5 First steps of integration of interim PET response into early stage trials

The advent of data supporting the predictive power of an interim PET scan led to the goals of both trying to de-escalate therapy to minimize risk for patients with interim negative PET scans, while escalating therapy for patients who have interim PET positive scans. These efforts aim to minimize the need for future 2nd line chemotherapy with a consolidative autologous stem cell transplant (ASCT) for interim PET positive patients while decreasing late toxicities for patients with interim PET negative scans. However, one of the challenges that emerged was how success was defined and also whether a Deauville 3 PET/CT scan should be considered to a negative vs positive interim PET scan result.

Radford et al designed the phase III UK Rapid trial with newly diagnosed stage IA or stage IIA cHL patients. After 3 cycles of ABVD, 571 patients underwent PET scanning. Patients with negative PET (Deauville score <3) findings were randomly assigned to receive IFRT or no further treatment; patients with positive PET (Deauville score >2) findings received a fourth cycle of ABVD and radiotherapy. The 3-year progression-free survival rate was 94.6% in the radiotherapy group and 90.8% in the group that received no further therapy, with an absolute risk difference of −3.8 percentage points. Therefore, the results of this study did not show the non-inferiority of the strategy of no further treatment after chemotherapy with regard to progression-free survival.[42]

Equally important, the phase III EORTC/LYSA/FIL H10 trial was designed to evaluate treatment adaptation on the basis of early PET (ePET) after two cycles of ABVD in previously untreated favorable (F) and unfavorable (U) (EORTC risk factors criteria: U: at least one of the following criteria: age ≥ 50 years or more than three nodal areas or mediastinal-thoracic ratio ≥ 0.35 or no B symptoms and erythrocyte sedimentation rate [ESR] ≥ 50 or B symptoms and ESR ≥ 30; F: all others) stage I and II cHL. The standard arm consisted of ABVD followed by involved-node radiotherapy (INRT), regardless of ePET result and the experimental arm consisted of ePET-negative (images were scored according to International Harmonization Project criteria[43]: mediastinal blood pool activity is recommended as reference background activity to define PET positivity of a residual mass ≥ 2 cm in greatest transverse diameter, regardless of its location. A smaller residual mass or a normal-sized lymph node is considered positive if its activity is above that of the surrounding background) patients who received ABVD only, whereas ePET-positive patients switched to two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP$_{esc}$) and INRT. André, Raemaekers et al showed that of 1,925 patients who received an ePET, 361 patients (18.8%) were positive. In ePET-positive patients, 5-year PFS improved from 77.4% for standard ABVD + INRT to 90.6% for intensification to BEACOPP$_{esc}$ + INRT. In ePET-negative patients, 5-year PFS rates in the F group were 99.0% versus 87.1% in favor of ABVD + INRT; the U group, 92.1% versus 89.6% in favor of ABVD + INRT. In conclusion, in stage I and II cHL, PET response after two cycles of ABVD allows for early treatment adaptation. When ePET is positive after two cycles of ABVD, switching to BEACOPP$_{esc}$ + INRT significantly improved 5-year PFS. In ePET-negative patients, non-inferiority of ABVD only could not be demonstrated and the risk of relapse is increased when INRT is omitted, especially in patients in the F group.[44, 45]

Finally, Straus et al designed the CALGB/Alliance 50604 trial of response-adapted chemotherapy or chemotherapy/radiation therapy based on PET for non-bulky stage I and II cHL patients, in order to minimize treatment for the majority of pts who are interim PET negative (Deauville scores 1-3) and only intensify treatment for those who are PET positive (Deauville scores 4-5). 164 patients were included and received 2 cycles of ABVD followed by PET. PET- pts received 2 more cycles of ABVD, and PET+ pts received 2 cycles of BEACOPP$_{escalated}$ + 3060 cGy IFRT. At a median follow-up time of 2 years, 6% of PET- pts relapsed or progressed with an estimated 3-year progression-free-survival (PFS) of 92% and 31% of PET+ patients failed with an estimated 3-year PFS of 66%. By Cox model, observed hazard ratio comparing PET- and PET+ PFS for patients is 6.04 (1.82, 20.08). It is likely that the trial will meet the primary objective of 3-year PFS of at least 85% for PET- patients treated with 2 additional

cycles of ABVD, but it is unlikely that the results will meet secondary objective of improving the 3-year PFS of PET+ patients treated with 2 cycles of escalated BEACOPP + IFRT. In conclusion, more intensive treatment with 2 cycles of $BEACOPP_{escalated}$ and IFRT for the 9% of patients who are interim PET+ will unlikely improve the 3-year PFS to the level considered to be of clinical interest in this trial.[46]

2.1.6 Novel therapies

2.1.6.1 Brentuximab vedotin

Classical HL is characterized by the presence of malignant Hodgkin's Reed-Sternberg (HRS) cells, and CD30 expression is a hallmark of this disease [47]. Brentuximab vedotin (BV) is an anti CD30 antibody conjugated by a protease-cleavable linker to the microtubule-disrupting agent, monomethyl auristatin E (MMAE) and selectively delivers MMAE to the CD30 expressing cells [48].

BV in Relapsed/ Refractory Management

Younes *et al*. reported a phase I dose escalation trial (BV given at dose of 0.1-3.6mg/kg q3week) in 45 patients with relapsed CD30 positive lymphomas, 42 had cHL) [49]. Maximum tolerated dose (MTD) on study was 1.8mg/kg. Tumor regression was seen in 86% with complete response rate of 25% (50% ORR in 1.8mg/kg cohort) and these responses were durable (duration of response 9.7 months). Fanale *el al*. conducted another phase I dose escalation study where BV was administered more frequently on days 1, 8, 15 of each 28-day cycle (doses ranging from 0.4-1.4mg/kg) and enrolled 44 patients with relapsed/refractory (RR) hematological malignancies (38/44 had cHL) [50]. MTD was 1.2mg/kg. Tumor regression was seen in 85% and ORR was 59% with 34% CR with median duration of response (DOR) not reached at median follow up of 45 weeks on study. It is important to note that ORR was same but CR rate was better with q week dose as compared to q3week dosing schedule [49] although more patients developed peripheral sensory neuropathy with frequent dosing (all grades: 66%, grade II/IV: 6%).

A phase II trial established its efficacy and safety in relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and led to its successful approval by the Federal Drug Administration (FDA) in 2011 and by Health Canada in 2013 for 3rd line management of cHL [51]. A total of 102 patients were enrolled and 71% had primary refractory disease (did not respond to first line or relapsed within first 3 months of first line therapy). Patients received 1.8mg/kg intravenous infusion every 3 weeks up to 16 cycles or until disease progression or toxicity. ORR was 75% with CR up to 34% with median DOR up to 20.5 months for those in CR. Most of these response were durable as long term follow up of this study reported 5 years overall survival rate of 41% and PFS of 22% [52]. The most common (≥10%) treatment related adverse events were: peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), neutropenia (19%), diarrhea (18%), pyrexia (14%), vomiting (13%), arthralgia (12%), pruritus (12%), myalgia (11%), peripheral motor neuropathy (11%) and alopecia (10%). A total of 55% patients experienced adverse events of grade 3 or greater which included peripheral sensory neuropathy (8%) and laboratory abnormalities [neutropenia (20%), thrombocytopenia (8%) and anemia (6%)]. Of the patients who experienced treatment-related peripheral neuropathy, 88% experienced either resolution (73%) or improvement (14%) in symptoms. No deaths were attributed to study drug. BV has also been studied as consolidation after autologous stem cell transplant in cHL in a randomized double blind phase III trial [53]. Patients (n=329) in this study had high risk disease (primary refractory cHL, relapsed cHL within 1 year of initial treatment or extranodal disease) and received BV (1.8mg/kg q3week for 16 cycles). Median PFS in treatment group was 43 months compared to 24 months in placebo group (hazard ratio 0.57, 95% CI 0.40-0.81; p=0.0013). Additional 1 year follow up of this study showed sustained separation of curve [54].

BV in Front-Line Management

Advanced Stage Disease

Based on promising efficacy in relapsed/refractory disease, BV has been brought to the frontline setting with the goals of improving cures in cHL. BV combination with standard (ABVD) or modified (AVD) was studied in frontline setting in a phase I trial [55]. Fifty one patients with stage IIA bulky disease or stage IIB-IV disease were enrolled.

BV was given every 2 weeks and MTD was 1.2mg/kg in both groups. Results were promising: 95% in BV+ABVD group achieved CR as did 95% in BV+AVD group. However, 44% of patients in BV+ABVD group developed pulmonary toxicity (which exceeded historical reports with ABVD alone). Given the high pulmonary toxicity rate for BV plus bleomycin the phase I trial was modified and bleomycin was removed with continued enrollment with BV plus AVD and no patients in the BV+AVD group developed pulmonary toxicity. Most common grade ≥ 3 adverse events in BV+ABVD group vs BV+AVD group were neutropenia (80% vs 77%), anemia (20% vs 12%), febrile neutropenia (20% vs 8%), pulmonary toxicity (20% vs 0) and pulmonary embolism (12% vs 0). Combination of BV+AVD has shown high level of efficacy with a 5-year failure-free-survival (FFS) of 92% and an 5-year overall survival of 79%.[56] Given the very high levels of efficacy as well as safety this regimen was studied in a phase III trial in advanced stage cHL (NCT01712490) which enrolled 1,334 stage III and IV cHL patients to BV+ AVD vs ABVD therapy. Initial two-year modified PFS (mPFS) rate for patients in the BV + AVD arm was 82.1% compared to 77.2% in the control arm.[57] Modified PFS included as an event patients who had a final treatment PET/CT after the 6th cycle of chemotherapy with a Deauville score of 3 or higher and subsequent treatment.[58]

Early Stage Disease

ABVD plus radiation is standard therapy for limited stage cHL but there remains a risk of radiation toxicity as well as bleomycin induced pulmonary toxicity. The rationale behind combining BV+AVD in limited stage disease is to reduce these toxicities while maintaining efficacy. This combination was studied in a phase II study in stage I-II cHL (non-bulky disease) in which radiation was eliminated [59]. Thirty four patients were enrolled and BV was given on days 1 and 15 followed by PET scan and then BV+AVD for 4-6 cycles. After BV monotherapy 53% were in CR and at the end of treatment 88% were in CR while PFS at a median follow up of 14 months was 90% with 97% OS. A follow-up study will investigate the combination of brentuximab vedotin plus doxorubicin and dacarbazine, with the goal of eliminating toxicities associated with vinblastine. Safety of combination of BV with AVD followed by radiation in unfavorable risk disease (stage I-II) was established by a phase II trial in which patients were treated with 4 cycles of BV and AVD followed by 30Gy involved site radiation for those who achieved negative PET scan (defined by Deauville score 1-3) [60]. Twenty nine were treated with BV+AVD and twenty five received radiation. Treatment was well tolerated; only four patients had grade ≥ 3 AEs and included febrile neutropenia, peripheral neuropathy and hypertension. 93% had negative PET scan after 4 cycles and 1 year PFS was 93.3% with 47% of the enrolled patients meeting GHSG criteria for bulky mediastinal disease.

Over 60 Years Patients

Elderly patients with cHL tolerate chemotherapy poorly, have inferior outcomes and salvage therapies in relapsed/refractory patients can be challenging [61] . Addition of BV to frontline therapies in this population potentially can improve efficacy. A phase II study examined efficacy and safety of BV monotherapy vs BV+bendamustine vs BV+dacarbazine in frontline setting in patients aged ≥ 60 years [62]. ORR in 60 treated patients (n=27 BV monotherapy, 22 BV+dacarbazine, 11 BV+bendamustine) was 100% (with 62% CR in BV+dacarbazine group, 78% CR in BV+bendamustine group). Treatment-related AEs ≥ grade 3 occurred in 43% of pts overall. Ongoing follow-up will define durability, and ultimately the potential role of these combinations as standard options for elderly patients with cHL. Another phase II trial looked at sequential BV and AVD in elderly patients with advanced stage cHL in frontline setting [63]. In this trial patients received initial 2 cycles of BV monotherapy followed by PET scan and 6 cycles of AVD in all patients and then 4 cycles of BV consolidation in those who achieved with CR or PR. Twenty evaluable patients had ORR of 85% and CR of 30% after first 2 cycles of BV monotherapy and ORR as well as CR increased to 95% after 6 cycles of AVD. Early reports showed more AEs in this population (grade ≥ 3 in 77% including a grade 5 pancreatitis).

2.1.6.2 PD-1 Inhibitors

Preclinical studies demonstrated that RS cells have copy number alterations involving chromosome 9p24.1 [64, 65], which leads to increased PD-1 ligand expression and evasion of host immune system [66]. Both PD-1 inhibitors nivolumab and pembrolizumab were recently approved for management of relapsed cHL respectively in 2016 and 2017.

Nivolumab in Management of Relapsed/Refractory HL

A phase I study established substantial therapeutic efficacy of nivolumab in lymphoid malignancies with ORR of 87% (17% CR) [67]. This was followed by phase II trial that enrolled patients with cHL who are either refractory to autologous stem cell transplant or relapsed after or failed to respond to brentuximab vedotin [68]. Patients received nivolumab intravenously at 3mg/g every 2 weeks until progression or unacceptable toxicity. Eighty patients were recruited and at a median follow up of 8.9 months, 66.3% achieved an objective response. The most common (≥15%) drug-related adverse events included fatigue (25%), infusion reactions (20%) and rash (16%). The most common grade 3 or 4 adverse events were neutropenia (5%) and increased lipase levels (5%). No deaths were attributed to the study drug. These encouraging results led to ongoing early phase clinical trials in which nivolumab is studied with AVD both in early stage (NCT03004833) as well as advanced stage cHL (NCT02181738, NCT03033914) in frontline setting with the sponsored advanced stage trial. Nivolumab monotherapy followed by N-AVD was well tolerated in patients with newly diagnosed, untreated, advanced-stage cHL. At the end of therapy, N-AVD was associated with an ORR per investigator of 84% and a CR per investigator in 80% of patients [69].

Nivolumab plus BV

The rationale behind combining nivolumab with BV is that the immune checkpoint inhibitor leads to activation of the immune cells in the tumor microenvironment, while concurrently targeting HRS cells with the CD30 antibody-drug conjugate BV, to overcome tumor cell resistance. In a phase I trial patients with relapsed refractory cHL received nivolumab + BV for 16 cycles[70]. Nivolumab was given at 3 mg/kg and BV at 1.2 mg/kg or 1.8 mg/kg. Only one patient had dose limiting toxicity (pneumonitis: recovered fully). The only additional grade 3 AEs noted were one each grade 3 rash and pruritus. The most common grade 1-2 treatment related adverse events were: transaminitis (9%), peripheral sensory neuropathy (6%), and rash (3%). Other AEs of interest included: diarrhea (3%), blurry vision (2%), and myalgias (2%). Results are impressive; ORR was 100%, with CR rate of 62.5% (two patients were resistant to previous BV and achieved CR with combination). Optimization of this combination strategy is planned with ongoing accrual to cohorts receiving BV + nivolumab, and BV + ipilimumab (monoclonal antibody that targets CTLA-4) + nivolumab. This promising non cytotoxic based drug combination was investigated as first salvage therapy in a phase I/II study (this study excluded patients who received ≥ 1 line of therapy, prior brentuximab vedotin, or prior stem cell transplant) [71]. Patients were treated in 21-day cycles for up to 4 cycles, (schedule: 1.8 mg/kg of BV on day 1 and 3 mg/kg of nivolumab on day 8 of each cycle), followed by stem cell transplant. Preliminary results reported in 29 patients with ORR of 90% and 62% had a complete response. The overall safety profile was manageable, with no dose reductions or discontinuations due to adverse events. Infusion-related reactions occurred in 38% overall, most commonly flushing, nausea (14% each); chest discomfort, dyspnea, urticaria (12% each); cough and pruritus (10% each). Nine patients proceed to ASCT. Investigators noted that the combination of BV and nivolumab appeared to have no impact on stem cell mobilization or engraftment. An ongoing phase I is evaluating this combination in elderly patients with cHL (not eligible for ABVD) in frontline setting (NCT02758).

2.2 Overview and Rationale of Study Design

2.2.1 Overview

This is a multi-arm phase 2 study of a front-line, radiation-free, PET/CT-2 response-adapted therapy incorporating brentuximab vedotin (BV) and/or nivolumab in patients with early stage classical Hodgkin lymphoma. After 2 lead-in cycles of standard of care ABVD, patients will be evaluated and classified according to their PET/CT (PET/CT-2) scan results:

- PET/CT-2 negative patients (Deauville 1-3) without bulky disease (bulky disease is defined by mediastinal mass ≥ 7.5 cm at diagnosis) will be randomized equally to receive either 3 cycles of BV+nivolumab (Arm A), or 2 cycles of ABVD followed by nivolumab maintenance q2w for 3 months (Arm B). Randomization will be done with stratification for balance between arms for baseline factors of stage I vs II, and A vs B symptoms. PET/CT-

2 negative patients with bulky mediastinal mass ≥ 7.5 cm at diagnosis will not be randomized and will be treated on Arm B.

- PET/CT-2 positive patients (Deauville 4 or 5) will all receive BV plus 4 cycles of AVD followed by nivolumab maintenance q2w for 3 months (PET/CT-2 positive patients will **not** be divided into bulky and non-bulky cohorts).

Response will be evaluated using the 2014 Lugano Classification. The primary efficacy endpoint is progression-free survival rate (PFS) at 18 months.

Per protocol version 08, dated 09/09/22, the study design is revised so that all patients with negative PET/CT-2 will be assigned to Arm A. Arm B (B1/B2) is now closed to patient accrual. Patients with positive PET/CT-2 will be assigned to Arm C (same as before).

2.2.2 Rationale

The goals for early stage cHL patients are to develop, through clinical trials, methods of care that decrease long term toxicities while preserving excellent outcomes for patients with PET/CT-2 negativity. Conversely, for patients with PET/CT-2 positivity, the goals are to improve outcomes and minimize needs for future salvage therapies. One of the challenges is that, while there is significant agreement that Deauville 4 and 5 represent a positive PET/CT scan, the Deauville 3 scans with uptake greater than mediastinum but less than or equal to the liver can be defined as PET/CT positive versus negative depending on the publication or trial, as evidenced by the trials reviewed above. For the RAPID and EORTC H10 trials PET-negativity was defined as Deauville 1 or 2, whereas the CALGB/Alliance 50604 defined PET-negativity as Deauville 1 to 3. Non-inferiority was not met for either the RAPID or the EORTC H10 trials for omission of radiation therapy for the interim PET-negative patients, but the losses of PFS were small of 3 to 10%. By comparison the CALGB/Alliance 50604 trial showed that if interim PET positivity is defined as Deauville 4 or 5, even change of therapy to escalated BEACOPP with its associated toxicities did not significantly impact outcomes with a 3-year PFS of only 66% and the authors concluded that alternative strategies needed to be considered.

Given the predictive power of an interim PET/CT scan, the NAHLC designed a trial that stratifies treatment for early stage cHL patients utilizing this result, rather than the risk factors as defined by GHSG from favorable to bulky mediastinal.

This trial seeks to evaluate the incorporation of the recently approved targeted agents brentuximab vedotin and/or nivolumab to allow interim PET/CT-2 negative patients, defined as Deauville 1 to 3, to have radiation therapy omitted, but with the goal of retaining PFS through the addition of these novel therapies. For patients with interim PET/CT-2 positive scans, defined as Deauville 4 and 5, the incorporation of BV and nivolumab aims at improving PFS and thus minimizes the chances of ultimately needing salvage therapies and autologous stem cell transplant, without switching to a regimen such a escalated BEACOPP, which has been shown to still have relatively low PFS in this patient population and a high side effect profile including infertility. Data supporting the addition of BV and/or nivolumab come from the trials reported above, including monotherapy activity of these drugs and combination data for BV plus AVD.

2.2.2.1 Rationale for choice of treatment plans

Arm B: Among the PET-negative patients, non-bulky patients randomized to Arm B will receive in total ABVD x 4 followed by nivolumab, which represents the closest treatment plan to standard of care (which is ABVD x 2-4 followed by radiation therapy, depending on favorable/unfavorable). Arm B also includes patients with bulky disease (who would typically receive ABVD x 4-6 followed by radiation therapy or ABVD x 6 without radiation [at least 4 cycles of ABVD either way]). In Arm B, nivolumab substitutes for radiation therapy; ABVD x 4 followed by nivolumab rather than ABVD x 4 followed by radiation.

Arm A: The treatment plan in Arm A is evaluating the substitution of radiation therapy with BV plus nivolumab. In the RAPID study, omission of radiation was studied in PET-negative patients and was found to yield a PFS of > 90% after just 3 cycles of ABVD alone.[41] Because of the many treatment regimens that have been studied in early

stage HL (ABVD x 2 and radiation, ABVD x 3 alone in RAPID, ABVD x 3 and radiation, ABVD x 4 and radiation), and because we are including all patients with early stage HL including favorable and unfavorable patients, ABVD x 2 followed by 3 cycles of BV-nivolumab was seen as the lowest acceptable common denominator in terms of standard chemotherapy but also provides 3 cycles of proven effective therapy in HL[72, 73] as a potent substitute for radiation.

Arm C: Arm C represents an escalation of therapy in patients who are PET-positive, with escalation from ABVD to BV plus AVD, and then substitution of radiation with nivolumab. BV plus AVD was found to be superior to ABVD alone in stage III-IV HL.[58] In addition, similar outcomes were observed in stage III-IV patients who received BV plus AVD and had PET-positive disease after 2 cycles of therapy in the ECHELON-1 study[58] compared to stage III-IV patients who were escalated to BEACOPP after a positive interim PET scan following ABVD x 2 in the RATHL and S0816 studies.[26, 74]

2.2.2.2 Rationale for randomization between Arm A and Arm B1

An important feature of this study is that it allows any early stage HL patient, favorable or unfavorable, including patients with bulky disease, in an effort to harmonize the treatment of early stage HL across risk groups, with the incorporation of novel agents and dynamic risk stratification using PET scans.

Among the PET-negative patients, because the standard of care treatment varies widely across studies (Favorable: ABVD x 2 with radiation, ABVD x 3 with radiation, ABVD x 4 with radiation, ABVD x 3 no radiation in RAPID vs Unfavorable: ABVD x 4 with radiation, ABVD x 6 with radiation, A(B)VD x 6 without radiation) the study seeks to strike a balance between providing a “standard” arm with an accepted standard of care for favorable and unfavorable patients with simple substitution of radiation with the novel agents (Arm B: ABVD x 4 followed by nivolumab) and an “experimental” arm which provides the lowest end of the range of standard chemotherapy but replaces radiation with the novel potent agents for the most favorable patients who are PET-negative (Arm A: ABVD x 2 followed by BV plus nivolumab). As mentioned in the previous section, standard of care for patients with bulky disease would include at least 4 cycles of ABVD, therefore these patients are not randomized and will receive 4 cycles of ABVD.

3.0 ELIGIBILITY CRITERIA AND CRITERIA TO START PROTOCOL THERAPY

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

Participants must meet all of the **eligibility criteria listed in Section 3.1** on screening examination to be eligible to participate in the study, and must meet all the **criteria listed in Section 3.2** within the specified timelines to be able to start protocol therapy.

3.1 Eligibility criteria

3.1.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent of the participant and/or legally authorized representative

- Assent, when appropriate, will be obtained per institutional guidelines.

__2. Be willing to provide archival tissue of a biopsy that was performed prior to standard of care ABVD treatment.

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

Age Criteria, Performance status, Language

__3. Age: ≥ 16 years

__4. ECOG ≤ 2 (see Appendix A)

Nature of Illness and Illness-Related Criteria

__5. Histologically confirmed diagnosis of classical Hodgkin lymphoma (cHL) by current World Health Organization classification (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted, or classical Hodgkin lymphoma, NOS [not otherwise specified]) at local enrolling center. Nodular Lymphocyte-Predominant Hodgkin Lymphoma is excluded.

__6. Stage IA, IB, IIA, or IIB cHL by Cotswold modified Ann Arbor staging done prior to any treatment with ABVD.

__7. Must have prior to standard of care ABVD treatment at least one lesion that is > 1.5 cm in the longest diameter on cross-sectional imaging and measureable in two perpendicular dimensions on CT and FDG avid by PET.

3.1.2 Exclusion Criteria

Prior and concomitant therapies

__1. Patients must be naïve in terms of any prior therapy for Hodgkin lymphoma (including immunotherapy, chemotherapy or radiation therapy) with the exception that they may have received up to 2 cycles of ABVD as standard of care therapy prior to enrollment, as long as they can start protocol therapy (therapy administered in Arms A, B1/B2, or C) within timelines specified by the trial (See Section 10).

__2. 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 or conditions

__3. Peripheral sensory neuropathy > grade 1 or any peripheral motor neuropathy.

__4. History of another primary malignancy that has not been in remission for at least 3 years. (The following are exempt from the 3-year limit: nonmelanoma skin cancer, fully excised melanoma in situ [Stage 0], curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear).

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

__5. Known active central nervous system (CNS) involvement by lymphoma, including parenchymal and/or lymphomatous meningitis.

__6. History of progressive multifocal leukoencephalopathy (PML).

__7. Known history of pancreatitis.

__8. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV within 6 months prior to enrollment.

__9. Uncontrolled cardiac disease including ventricular dysfunction, left ventricular ejection fraction <45%, coronary artery disease, or arrhythmias.

__10. Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin, nivolumab, or any component of ABVD.

__11. Known active infection with hepatitis B or hepatitis C. Patients who are hepatitis B carriers can enroll if have a negative hepatitis B PCR DNA test and are on hepatitis B suppressive medication management with entecavir or lamivudine. Patients with past active HCV infection are eligible if they are PCR negative after curative therapy. Testing to be done only in patients suspected of having infections or exposures.

__12. Known active infection with HIV. Patients who are HIV positive can enroll if CD4 count is > 200/μL and have an undetectable or unquantifiable HIV viral load within 28 days of enrollment, have concurrent management with infectious disease specialists, and are on stable combination antiretroviral therapy. Participants are required to be on antiretroviral regimens that are in accordance with the current International AIDS Society guidelines concurrently with chemotherapy. The specific agents are at the discretion of the Investigator and the use of investigational agents currently available on an expanded access basis is allowed. Use of experimental antiretroviral agents or those containing zidovudine (including Combivir and Trizivir) or ritonavir (includes Norvir® or Kaletra®), Cobicistat, Didanosine (Videx® or Videx EC®), or similar potent CYP3 inhibitors are prohibited. In order to be eligible, participants taking zidovudine or ritonavir, Cobicistat, Didanosine, or other CYP3 inhibitors must change to a different regimen 7 days prior to therapy initiation. Changes to HAART therapy during the study may be made if medically necessary (toxicity, failure of regimen, etc.). Participants must be on HAART for at least 7 days prior to therapy. HIV testing to be done only in patients suspected of having infections or exposures.

__13. Subjects with active interstitial pneumonitis.

__14. Subjects with active, known or suspected autoimmune disease. Subjects with 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 are permitted to enroll.

__15. *Females only*: Pregnant or breastfeeding

__16. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__17. 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).

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

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.			

3.2 Criteria to start protocol therapy

Clinical Laboratory and Organ Function Criteria to start protocol therapy must be met within 28 days after standard of care ABVD C2D15, except for MUGA/ECHO and PFT (see Section 10).

Note: ANC and platelets counts will be checked on C1D1 of each BV-containing cycle in Arms A and C (see Section 10) independently of these criteria.

Clinical Laboratory and Organ Function Criteria

__1. Total bilirubin ≤ 1.5 x ULN OR 3 x ULN for Gilbert's syndrome)	ULN: Bil:	Date:
__2. AST ≤ 2.5 x ULN	ULN: AST:	Date:
__3. ALT ≤ 2.5 x ULN	ULN: ALT:	Date:
__4. Creatinine clearance* ≥ 30 mL/min per 24 hour urine collection or the Cockcroft-Gault formula *Calculated per institutional standard $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ (x 0.85 for females) **Or** $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}}$ (x 0.85 for females)	ULN: Serum Cr: Cr Cl:	Date:
__5. Left ventricular ejection fraction (LVEF) ≥ 45%	LVEF:	Date:
__6. Carbon monoxide diffusion capacity (DLCO) (adjusted for Hb) ≥ 60%.	DLCO:	Date:
__7. **Women of childbearing potential (WOCBP)**: negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required	Urine: Serum:	Date:

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

Contraception

__8. Agreement by females **and** males of childbearing potential* to use an effective method of birth control or abstain from heterosexual activity for the course of the study through at least 6 months after the last dose of brentuximab vedotin (for both women and men), and through at least 5 months after the last dose of nivolumab (for women only).

* Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 1 year (women only).

Prior and concomitant therapies

__1. Subjects with a non-lymphoma-related condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalents) or other immunosuppressive medications within 14 days of start of protocol therapy are excluded. Exceptions: -inhaled or topical steroids, -adrenal replacement doses > 10 mg daily prednisone or equivalents in the absence of active autoimmune disease.

Other illnesses or conditions

__2. No sensory > grade 1 peripheral neuropathy, and no peripheral motor neuropathy (any grade).

__3. No active systemic viral, bacterial, or fungal infection requiring treatment with IV antimicrobial therapy within 1 week prior to start of protocol therapy.

__4. Any condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

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

4.0 PARTICIPANT ENROLLMENT AND RANDOMIZATION

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 17.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0 (Study Calendar).

4.2 Participant Enrollment

4.2.1 COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

- E-mail: DCC@coh.org

4.2.2 Slot verification and reservation

Issues that would cause treatment delays should be discussed with the Study PI.

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

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

4.2.3 Registration Process

- **Registration can occur before or anytime after the start of standard of care ABVD therapy as long as protocol therapy can be started within timelines specified by the trial (See Section 10).**
- **Start of protocol therapy can only occur after criteria listed in Section 3.2 and requirements listed in Section 4.3 are met, and after DCC sends treatment confirmation and arm information.**
- **Information required to start protocol therapy (Section 4.3) will be submitted to the DCC as a complete packet as soon as it is available (could be submitted at time of registration or later).**

Allow up to 24 hours for the DCC to review. To register a participant the subsequent procedure is to be followed:

1. The study team should contact the DCC via 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 study team will email a Complete Registration Packet to the DCC, which consists of a copy of the following documents:
   a. Completed Registration Cover Sheet (Appendix B)*
   b. Completed Eligibility Criteria List** (printed from Section 3.1) with signature of appropriate staff personnel as detailed on document.
   c. Signed informed consent document that has been approved by the local institutional review board (IRB) for the enrolling center.
   d. Signed HIPAA authorization form (if separate from the informed consent document).

e. Signed subject's Bill of Rights (California only).

* **Note:** If the results of PET/CT-2 are not yet known at that time, complete only Section A of the Registration Cover Sheet. However, Section B will need to be completed and provided to the DCC before the patient can start protocol therapy (See Section 4.3).
** **Note:** Completed Eligibility Criteria (Section 3.1) is required to enroll a patient on the study. Another set of Complete Eligibility Criteria (Section 3.2) will need to be met and provided to the DCC before the patient can start protocol therapy (See Section 4.3).

3. In some cases, the DCC may request additional documentation prior to registration. Please refer to the Work Instruction – Reviewing Packets and Registering Subjects for more information. A copy of this work instruction can be provided by the DCC, upon request.
4. When all documents are received, the DCC will review and work with the study team to resolve any missing elements. Any missing documents may delay registration. A participant failing to meet all requirements will not be registered and the study team will be immediately notified.
5. The DCC will send a Confirmation of Registration Form, including the Subject Study Number to:
    - The study team: Site Lead Investigator, treating physician/ sub-investigator, protocol nurse, CRC, and pharmacy (as needed).
    - The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
6. Upon receipt of the Confirmation of Registration email from the DCC, COH study team will register the patient in OnCore. DCC will register non-COH patients in OnCore.

4.3 Requirements for starting protocol therapy.

To be able to start protocol therapy, the subsequent procedure is to be followed:

1. The study team must email a copy of the following documents to the DCC:
    a. Completed Criteria list from Section 3.2 (printed from Section 3.2) with signature of appropriate staff personnel as detailed on document.
    b. Completed Section B of the Registration Cover Sheet (Appendix B). If Section A was completed and provided to the DCC at an earlier time, complete only the following fields in Section A: CRA/Study Coordinator, Contact Number, Patient's Initials, Medical Record No, Patient's DOB and Sex. If the patient is not yet enrolled on the study, complete both Sections A and B and follow the guidelines in Section 4.2.3.

    Please allow sufficient time for DCC review, as patients must start protocol therapy (administered in Arms A, B1, B2, and C) **within timelines specified by the trial** (see Section 10).
2. When all documents are received, the DCC will complete the review of the documents to verify compliance, and work with the study team as needed to resolve any missing elements.
3. Once compliance is confirmed, DCC staff will send within 24 hours a Confirmation that the patient can start protocol therapy and the randomized or assigned treatment arm to:
    - The study team: Site Lead Investigator, treating physician/ sub-investigator, protocol nurse, CRC, and pharmacy (as needed).
    - The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
4. Upon receipt of this confirmation email from the DCC, COH study team will update the patient information in OnCore. DCC will update the information in OnCore for non-COH patients.

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

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment. For non-COH sites, the reason for screen failure will be documented in the registration coversheet (see Appendix B) and submitted to the DCC.

4.5 Treatment arm assignment

Treatment arm assignment for **all** arms (randomized and non-randomized) will be **centrally done by the DCC.**

Randomization:

For patients without bulky disease (on baseline PET/CT) who are PET/CT-2 negative after the first 2 lead-in cycles of ABVD, the DCC staff will use a computer-generated randomization table, prepared by the trial Biostatistician, to assign subjects to receive either BV+nivolumab (Arm A) or ABVD followed by nivolumab maintenance (Arm B1). The study design consists of randomization in a 1:1 ratio.

Patients will be randomized with stratification for balance between arms for baseline factors of stage I vs II, and A vs B symptoms.

Non-random treatment arm assignment:

All patients who are PET/CT-2 negative with bulky mediastinal mass ≥ 7.5 cm at diagnosis will be treated on Arm B2. All patients who are PET/CT-2 positive will be treated on Arm C.

Per protocol version 08, dated 09/09/22, the study design is revised so that all patients with negative PET/CT-2 will be assigned to Arm A. Arm B (B1/B2) is now closed to patient accrual. Patients with positive PET/CT-2 will be assigned to Arm C (same as before).

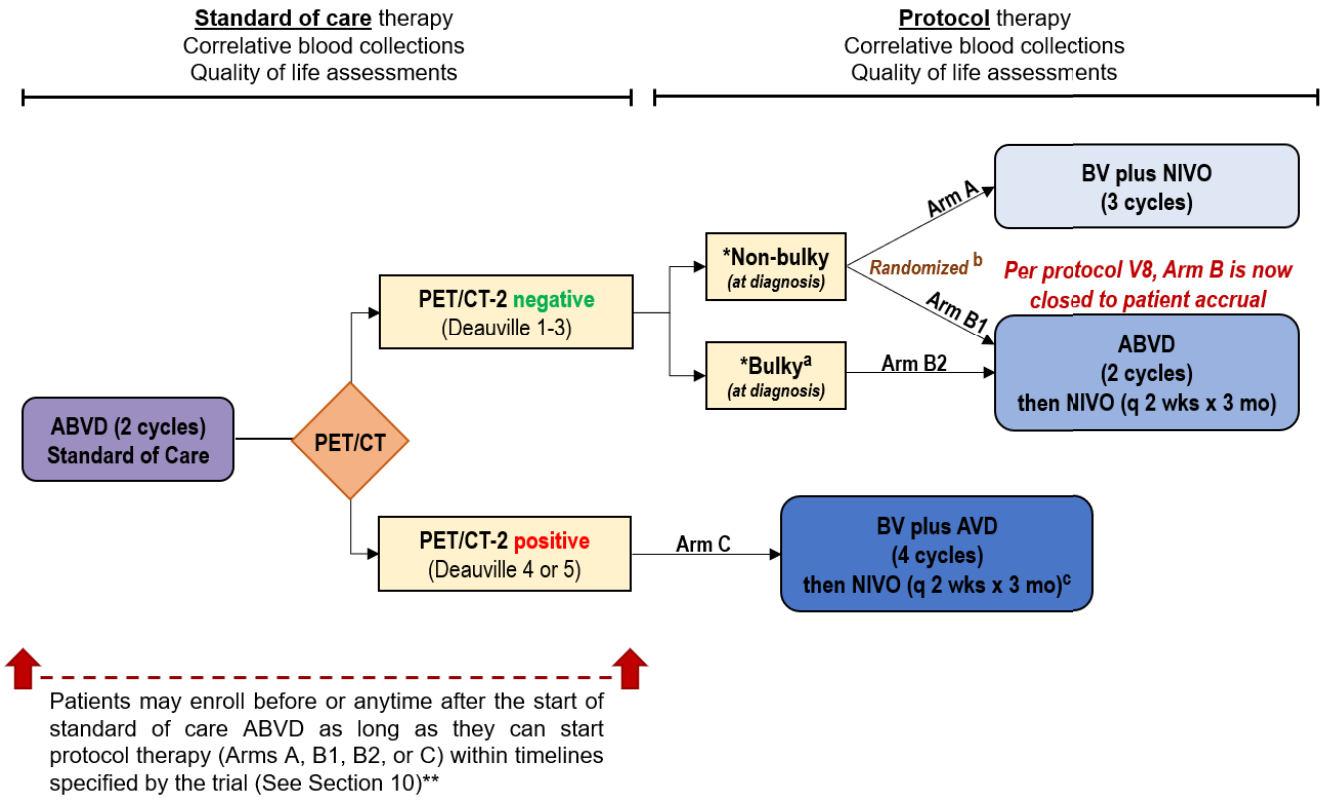
5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

Favorable and unfavorable risk early stage cHL patients who are planning, undergoing, or have just completed 2 cycles of standard of care ABVD will be enrolled in this study.

All criteria listed in Section 3.2 and requirements listed in Section 4.3 must be met **prior to starting protocol therapy**.

Per protocol version 08, dated 09/09/22, the study design is revised so that all patients with negative PET/CT-2 will be assigned to Arm A. Arm B (B1/B2) is now closed to patient accrual. Patients with positive PET/CT-2 will be assigned to Arm C (same as before).



* Determination of bulky vs. non bulky disease is based on assessment prior to any treatment (baseline PET/CT).
**Patients must meet study eligibility criteria to enroll in the study, and will need to meet an additional set of criteria to be able to start protocol therapy (see Section 3).

The DCC will:
- register participants who are eligible to enter the study
- assign treatment arm for **all** arms (randomized and non-randomized) of the trial.

(See Section 4 for additional details)

a. Bulky is defined by mediastinal mass ≥ 7.5 cm on baseline PET/CT (prior to SOC ABVD treatment).

b. Patients will be randomized equally with stratification for balance between arms for baseline factors of stage I vs II, and A vs B symptoms.

c. Patients in Arm C must be PET-CT negative at the end of the 4 cycles of BV+AVD in order to receive nivolumab. (Refer to Section 5.2.5)

No adverse event data will be collected during standard of care ABVD. Adverse event data collection will begin on Cycle 1, Day 1 of protocol therapy.

5.2 Treatment Plan

All criteria listed in Section 3.2 and requirements listed in Section 4.3 **must be met prior to starting protocol therapy.**

Baseline weight refers to the patient weight prior to start of protocol therapy (C1D1 pre-dose).

5.2.1 Prophylaxis guidelines for infusion related reactions with **brentuximab vedotin or nivolumab**

Premedication for infusion related reactions as listed below is **mandatory**, and must be initiated at least 30 minutes prior to agent administration.

○ For participants **without** history of infusion reaction to brentuximab vedotin or nivolumab:

Patients receiving BV and nivolumab: Premedicate. Recommended premedication includes, per institutional standard:

- Acetaminophen/paracetamol
- Anti-histamine (e.g. diphenhydramine).

Patients receiving only BV or only nivolumab: No premedication is required, however premedications are allowed per institutional standard).

○ For participants **who have experienced** an infusion related reaction to brentuximab vedotin or nivolumab on this study while not taking corticosteroid prophylaxis. Pre-medication should include (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 brentuximab vedotin or nivolumab **while taking prophylactic corticosteroids**.

- Premedication as above, but increase corticosteroids:

– Methylprednisolone 40 mg IV (or equivalent e.g. hydrocortisone IV 200 mg).

For supportive care during infusion reaction, see Section 5.8.1.

5.2.2 -Brentuximab Vedotin plus Nivolumab- Maintenance: Regimen and Administration (Arm A)

Table 5.2.2 BV plus Nivo Regimen (Arm A)

Drug (Abbreviation)	Dose	Method	Schedule*
Brentuximab Vedotin (BV)	1.8 mg/kg *(Dose level -1 is 1.2 mg/kg)*	IV on Days 1	Every cycle x 3 cycles
Nivolumab (Nivo)	3 mg/kg	IV on Days 1	Every cycle x 3 cycles

*Cycle is 21 days

Treatment may be administered up to 3 days before or after the protocol-specified days due to administrative reasons.

Patients must have an **ANC ≥ 500/mm^3 and platelets ≥ 75,000 cells/mm^3** to be eligible for **day 1 of all cycles** on labs assessed within 3 days.

Premedication is required for all infusions, refer to guidelines in Section 5.2.1

Treatment should start within 21 to 28 days after completion of C2D15 of standard of care ABVD for patients who are PET/CT-2 negative and who do not have a bulky mediastinal mass of ≥ 7.5 cm at diagnosis and who are randomized to this arm (Arm A). Drugs should be given in the stated order. Brentuximab vedotin will be administered as an IV infusion over 30 min (+10 min). BV will be dosed based on baseline weight (C1D1 pre-dose). Subsequent doses will be adjusted for participants who experience a ≥ 10% change in weight from baseline. It is acceptable but not necessary to re-calculate subsequent doses for participants who experience a ≤ 10% change in weight from baseline. For patients weighing greater than 100 kg, the dose will be calculated based on 100 kg. BV dose rounding is permissible within 5% of the nominal dose. Nivolumab will be dosed based on baseline weight (C1D1 pre-dose) and administered as an IV infusion over 30 min (+10 min), and should be given within 2 hours of the BV infusion. Nivolumab dose may be rounded according to institutional practice. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight from baseline. For management of adverse events and toxicities associated with brentuximab vedotin and nivolumab see sections 5.8, 7.1.1, and 7.2.

BV plus nivolumab maintenance can be delayed because of AE for up to 6 weeks. For patients with grade 4 neutropenia, growth factor support with filgrastim is recommended to be provided to improve neutropenia to grade ≤ 3 for continued dosing. Patients with occurrence of grade 4 neutropenia should receive prophylactic growth factor support with filgrastim or pegfilgrastim or similar for subsequent cycles.

If BV must be held, Nivo should be held for up to 2 weeks to see if both drugs can be dosed together. However, if administration is delayed for more than 2 weeks, Nivo will be administered and BV added back once appropriate according to AE management guidelines.

If Nivo must be held, BV should be held for up to 2 weeks to see if both drugs can be dosed together. However, if administration is delayed for more than 2 weeks, BV will be administered and Nivo added back once appropriate according to AE management guidelines.

5.2.3 ABVD: Regimen and Administration (Arms B1 and B2)

Cycle 1 of ABVD protocol regimen should start within 14-28 days post-C2D15 of standard of care ABVD.

Table 5.2.3 ABVD Regimen (Arms B1 and B2) – CLOSED to accrual starting with protocol version 08

Drug (Abbreviation)	Dose	Method	Schedule*
Doxorubicin (A)	25 mg/m^2	IV on Days 1 and 15	Every cycle x 2 cycles
Bleomycin (B)	10 units/m^2	IV on Days 1 and 15	Every cycle x 2 cycles
Vinblastine (V)	6 mg/m^2	IV on Days 1 and 15	Every cycle x 2 cycles
Dacarbazine (D)	375 mg/m^2	IV on Days 1 and 15	Every cycle x 2 cycles

*Cycle is 28 days

Treatment may be administered up to 3 days before or after the protocol-specified days due to administrative reasons.

ABVD drugs are to be administered per institutional guidelines. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight from baseline. For management of adverse events and toxicities associated with ABVD see sections 5.8 and 7.3.

If a patient has a component of ABVD omitted due to toxicity (e.g. bleomycin omitted or discontinued for pulmonary toxicity), the patient remains eligible for protocol therapy and should receive the remaining components of ABVD.

ABVD treatment can be delayed because of AE other than neutropenia alone for up to 3 weeks. For patients with cytopenias alone (not to be confused with febrile neutropenia), ABVD should be dosed on schedule.

5.2.4 Brentuximab Vedotin plus AVD: Regimen and Administration (Arm C)

Table 5.2.4 BV plus AVD Regimen (Arm C)

Drug (Abbreviation)	Dose	Route	Day	Schedule*
Doxorubicin (A)	25 mg/m^2	IV	Days 1 and 15	Every cycle x 4 cycles
Vinblastine (V)	6 mg/m^2	IV	Days 1 and 15	Every cycle x 4 cycles
Dacarbazine (D)	375 mg/m^2	IV	Days 1 and 15	Every cycle x 4 cycles
Brentuximab Vedotin (BV)	1.2 mg/kg *(Dose level -1 is 0.9 mg/kg*)	IV	Days 1 and 15	Every cycle x 4 cycles
[a]G-CSF: Pegfilgrastim OR Filgrastim	**Pegfilgrastim:** Adults or pediatric patients ≥ 45 kg: 6 mg. Pediatric patients < 45 kg: 0.1 mg/kg OR **Filgrastim:** 5 mcg/kg	**Pegfilgrastim:** SubQ OR **Filgrastim:** SubQ or IV For patients age 16-17: SubQ is preferred	**Pegfilgrastim:** All patients: **Days 2 & Days 16** On-body injector kit is allowable OR **Filgrastim:** For patients age ≥ 18: Suggested to administer for 5 days (e.g.: Days 6-10 and Days 21-25) but can be adjusted if more or less is needed, should be no less than 2 days between study treatment days. For patients age 16-17: See Footnote b	Every cycle x 4 cycles **Pegfilgrastim:** All patients: no sooner than 24 hrs after completion of chemo **Filgrastim:** Age ≥ 18: no sooner than 24 hours after completion of chemo

a. For pegfilgrastim, biosimilars are also allowable. For filgrastim: biosimilar forms of recombinant filgrastim (tbo-filgrastim or filgrastim-sndz) are permitted at institutional discretion.

b. For age 16-17: Daily, beginning Day 4, 5, 6, 7, 8, or Day 9 inclusive, per institutional policy, and continuing until ANC > 1000 µL post nadir. Filgrastim should be stopped 24 hours prior to Day 15 treatment and may resume 24 hours after the Day 15 treatment.

*Cycle is 28 days

Treatment may be administered up to 3 days before or after the protocol-specified days due to administrative reasons.

Patients must have **platelets ≥75,000 cells/mm^3** to be eligible for day 1 of all BV+AVD cycles on labs assessed within 3 days.

Prophylaxis guidelines for infusion related reactions are provided in Section 5.2.1.

Treatment should start within 21 to 28 days after completion of C2D15 of standard of care ABVD for patients who are PET/CT-2 positive (Arm C). AVD will be administered per institutional guidelines. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight from baseline.

Brentuximab vedotin will be administered as an IV infusion over 30 min (+10 min). BV will be dosed based on baseline weight (C1D1 pre-dose). Subsequent doses will be adjusted for participants who experience a ≥ 10% change in weight from baseline. It is acceptable but not necessary to re-calculate subsequent doses for participants who experience a ≤ 10% change in weight from baseline. For patients weighing greater than 100 kg, the dose will be calculated based on 100 kg. BV dose rounding is permissible within 5% of the nominal dose. BV should be administered within approximately 1 hour after AVD infusion on days 1 and 15. All patients receiving BV plus AVD must receive prophylactic growth factor support with G-CSF given the risks of febrile neutropenia. The schedule and the G-CSF formulation are indicated in Table 5.2.4. For management of adverse events and toxicities associated with brentuximab vedotin and AVD see sections 5.8 and 7.1.2. Patients must have a negative PET/CT defined as Deauville score of 1 to 3 to move to nivolumab maintenance.

BV+AVD treatment can be delayed because of AE other than neutropenia alone for up to 3 weeks. For patients with neutropenia alone (not to be confused with febrile neutropenia), BV+AVD should be dosed on schedule.

If BV must be held, AVD should be given if possible.

5.2.5 Nivolumab Maintenance: Regimen and Administration (Arms B1, B2, and C)

Table 5.2.5 Nivolumab Maintenance Regimen (Arms B1, B2, and C)

Drug (Abbreviation)	Dose	Method	Schedule*
Nivolumab (Nivo)	3 mg/kg	IV on Days 1	Every cycle x 6 cycles

*Cycle is 14 days

Treatment may be administered up to 3 days before or after the protocol-specified days due to administrative reasons.

Prophylaxis guidelines for infusion related reactions are provided in Section 5.2.1.

Treatment should start within 14 to 28 days after C2D15 of protocol therapy ABVD for Arms B1/B2, and within 14 to 45 days after C4D15 of BV plus AVD for Arm C. Patients with PET/CT-2 negativity treated on Arms B1/B2 and those with PET/CT-2 positivity treated on Arm C will receive 3 months (6 cycles) of nivolumab maintenance. Patients on Arm C will need to have a PET/CT after the conclusion of 4 cycles of BV plus AVD that shows negativity (Deauville 1-3) to proceed onto nivolumab maintenance; patients on Arm C with a positive PET/CT after 4 cycles of BV plus AVD will go off protocol therapy (Section 5.4). Note: a patient who is PET/CT positive after 4 cycles of BV plus AVD but has a negative biopsy at the end of BV plus AVD treatment and whom the investigator considers to be in remission may receive nivolumab maintenance with Study PI approval. Nivolumab will be dosed based on baseline weight (C1D1 pre-dose), and administered as an IV infusion over 30 min (+10 min). Nivolumab dose may be rounded according to institutional practice. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight from baseline. For management of adverse events and toxicities associated with nivolumab see sections 5.8 and 7.2.

Nivolumab maintenance can be delayed because of AE for up to 6 weeks.

5.3 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see Section 10.0.

It may be necessary to perform study procedures at unscheduled time points if deemed clinically necessary by the investigator.

Note: Initiate a new cycle after all procedures/safety assessments have been completed.

5.4 Duration of Therapy and Criteria for Removal from Protocol Therapy

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

- Confirmed disease progression per 2014 Lugano criteria.[75]
- Patient with PET/CT-2 positive findings who receives 4 cycles of BV plus AVD and continues to have PET/CT positive disease.
- Completed protocol therapy
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
- **Note:** If one agent is discontinued due to toxicity, then the participant may continue to receive the other study agents. Refer to Section 5.2 for additional details for each arm.
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy (Refer to Section 17.5)

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

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.5 Follow-up

Patients will undergo follow-up for 3 years after end of treatment.

Exception: Patients who enrolled in the study before PET/CT-2 but who did not start protocol therapy will **not** undergo any follow-up.

- **Response Follow-up**- for those who have yet to have disease progression.

Follow-up visits will be conducted at 6-month intervals from end of treatment for a total of 3 in person follow-up visits.

- **Survival Follow-up**- for participants who have progressed OR completed Response Follow-Up.

Patients can either be seen in person or followed-up by phone for documentation of disease status and survival every 6 months (+/- 1 month) until 3 years post-completion of therapy. Subsequent therapies will be collected when available.

Assessment time points and windows are detailed in Section 10.0.

The COH DCC and the Study PI should be promptly notified of any change in participant follow-up status.

5.6 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and 3 years of follow-up after protocol treatment)
- Withdrawal of consent (Refer to Section 17.5)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- Participant enrolled in the study but did not start protocol therapy.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.7 Prohibited and Concomitant Therapies/Medications

5.7.1 Allowed concomitant medications

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

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded in the eCRF and documented in the Electronic Health Record/medical record.

5.7.2 Prohibited medications and therapies

Prohibited from Day 1 of protocol therapy until end of protocol therapy:

a. Herbal or natural remedies
b. Other investigational therapy
c. Other concurrent systemic anti-cancer therapy for management of the cHL including: chemotherapy, biologic response modifiers, hormone therapy, surgery, palliative radiation, or immunotherapy.
d. 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.
e. Live attenuated vaccines

Doxorubicin is a major substrate of cytochrome P450 CYP3A4, and CYP 2D6, and P-glycoprotein (P-gp). Interactions have been reported with inhibitors of these enzymes which can result in increased concentration and exposure to doxorubicin. Conversely, inducers such as certain anti-epileptic agents may decrease the concentration of doxorubicin. Avoid concurrent use of doxorubicin with inhibitors and inducers of CYP3A4, CYP 2D6, and/or P-gp.

5.8 Supportive care

Prophylaxis or supportive care can be given as clinically indicated per institutional policies.

For all patients receiving nivolumab, following suspected immune-related AEs (irAE), follow guidelines stated in **Section 5.8.2**.

a. Routine anti-emetic prophylaxis should be administered per institutional standards with chemotherapy with ABVD and BV plus AVD.

b. Prophylaxis guidelines for infusion related reactions are provided in Section 5.2.1.

c. Given low rates of tumor lysis syndrome for cHL routine tumor lysis prophylaxis is not recommended.

d. Blood and growth factors

i. Platelet and/or red blood cell supportive growth factors or transfusions: Per institutional standard of care.

ii. Colony stimulating factors: Permitted for treatment of neutropenia per institutional standard of care.

In addition, all patients receiving BV plus AVD should receive prophylactic growth factor support with G-CSF given risks of febrile neutropenia. The schedule and the G-CSF formulation are indicated in Table 5.2.4.

e. 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).

f. Strong CYP3A4/5 inhibitors:
Closely monitor for AEs when administered concomitantly with brentuximab vedotin.

5.8.1 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)

5.8.2 Management of immune-related AEs

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

Note that the recommendations below are intended as guidelines, and may be superseded by the judgment of the treating clinician. In addition, clinicians are encouraged to refer to the latest version of the investigational brochure for the most up-to-date recommendations, which may also supersede the guidelines below.

5.8.2.1 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 to 3.0 x ULN and/or Total bilirubin > ULN to 1.5X ULN

- Consider increasing frequency of monitoring, then continue liver function tests (LFT) monitoring per protocol
- If worsens treat as below

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
- If elevations persist > 5-7 days or worsen:
  - 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when AST and ALT returns to < 3x ULN and bilirubin < 1.5x ULN, taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections

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 AST or ALT > 20 x ULN or bilirubin > 10 x ULN is 2 mg/kg/day methylprednisolone IV.
- Add prophylactic antibiotics for opportunistic infections
- Consult gastroenterologist or hepatologist
- If AST and ALT return to < 5 x ULN and bilirubin < 3 x ULN:
  - 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 tacrolimus or other immunosuppressants per local guidelines
  - Note: avoid infliximab due to potential risk of liver failure

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.

5.8.2.2 Renal

- Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
- 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: 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 to Grade 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 with nephrology consult
- If returns to Grade 1:
  - Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume 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
- If no improvement or worsening:
  - Add additional immunosuppression

5.8.2.3 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
- 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 – Diarrhea: <4 stools/day over baseline – Colitis: asymptomatic

- 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: 4-6 stools/day over baseline; IV fluids indicated < 24 hrs; limiting instrumental ADL – Colitis: abdominal pain; blood in stool

- Symptomatic treatment
- If persists > 5-7 days or recurs:
  - 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 (G3): ≥ 7 stools per day over baseline; IV fluids ≥ 24 hrs; limiting self care ADL – Colitis (G3): severe abdominal pain; peritoneal signs; Colitis (G4): life-threatening, perforation

- 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) or other immunosuppressants
  - Consider testing CMV for steroid refractory colitis
  - Note: Infliximab should not be used in cases of perforation or sepsis

5.8.2.4 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) abnormality or Hyperglycemia requiring no medical intervention

- 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
- Monitor TSH as per protocol
- Monitor blood sugar
- If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below

Symptomatic endocrinopathy or Hyperglycemia requiring initiation of treatment or change in daily management or work up

- Evaluate endocrine function; consider endocrinology consult
- Consider pituitary scan
- Symptomatic with abnormal lab/pituitary scan:
  - 1-2 mg/kg/day methylprednisolone IV or by mouth (PO) equivalent for hypophysitis
  - Initiate appropriate hormone/medical therapy
- No abnormal lab/pituitary MRI scan but symptoms persist:
  - Repeat labs in 1-3 weeks /MRI in 1 month
- Hyperglycemia:
  - Screen for Diabetic Ketoacidosis (DKA). If negative, treat diabetes. If DKA, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia
- 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
- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

5.8.2.5 Neurological

- Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
- 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
- If worsens:
  - Treat as Grade 2 or Grade 3-4

Grade 2: Moderate symptoms; Limiting instrumental ADL

- Consider neurology consult
- 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

5.8.2.6 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 Pneumonitis: Radiographic changes only

- Monitor for symptoms every 2-3 days
- Consider Pulmonary and Infectious Disease (ID) consults
- Re-image at least every 3 weeks
- If worsens:
  - Treat as Grade 2 or 3-4

Grade 2 Pneumonitis: 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
- Frequent imaging at clinically appropriate time points is recommended
- If persists > 5-7 days or recurs:
  - 0.5 - 1 mg/kg/day methylprednisolone IV or oral equivalent
  - When symptoms improve to Grade 1, taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
- If worsens or persists > 3-5 days with oral steroids:
  - Treat as Grade 3-4

Grade 3-4 Pneumonitis: 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
- If improves to baseline:
  - Taper steroids over at least 6 weeks
- If not improving after 48h or worsening:
  - Add additional immunosuppression

5.8.2.7 Skin

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

Rash Covering ≤ 30% body surface area (BSA) (refer to NCI CTCAE v5 for term-specific grading criteria)

- 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 > 30% BSA

Rash Covering >30% BSA (with or without symptoms); Life threatening consequences (refer to NCI CTCAE v5 for term-specific grading criteria)*

- Consider skin biopsy
- Dermatology consult
- 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent
- If improves to < 10% BSA:
  - Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infection

  * If Steven-Johnson Syndrome (SJS), toxic epidermal necrosis (TEN), Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, refer patient for specialized care for assessment and treatment

5.8.2.8 Myocarditis

- Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
- Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
- Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression

Grade 2: Symptoms with mild to moderate activity or exertion

- Hospitalization with cardiac monitoring
- Urgent cardiology consultation for evaluation and management
  - Troponin and BNP (B-type natriuretic peptide)
  - ECG ± continuous cardiac monitoring
  - Echocardiogram
  - Cardiac MRI
- Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
- If worsens, intensify treatment according to grade
- Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms.
- Repeat cardiac MRI for post treatment assessment and cardiology follow-up

Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated, or:

Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)

- Hospitalize to intensive cardiac monitoring
- Cardiac evaluation to include:
  - Troponin and BNP monitoring
  - ECG ± continuous cardiac monitoring
  - Echocardiogram
  - Cardiac MRI
  - Myocardial biopsy if feasible
- Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
- Consider adding a second immunosuppressive agent
- Additionally, for life threatening (Grade 4) myocarditis:
  - Hospitalize/transfer to institution with expertise in intensive cardiac monitoring

  - Consider ATG (anti-thymocyte globulin) as second agent given its immediate effect
- If no improvement, consider additional immunosuppression
- Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms.
- Repeat cardiac MRI for post treatment assessment and cardiology follow-up

6.0 ANTICIPATED ADVERSE EVENT LIST

6.1 Doxorubicin

- Adverse reactions
  - Include nausea/vomiting, alopecia, fatigue, mucositis, urine discoloration, infertility, leukopenia, neutropenia, thrombocytopenia, and acute cardiotoxicity (atrioventricular block, bradycardia, bundle branch block, ECG abnormality, extrasystoles [atrial or ventricular], nonspecific ST or T wave changes on ECG, sinus tachycardia, supraventricular tachycardia, tachyarrthythmia, ventricular tachycardia) as well as delayed cardiotoxicity (cardiac failure, decreased left ventricular ejection fraction, myocarditis, pericarditis)
- Warnings and precautions
  - Bone marrow suppression
  - Cardiomyopathy
  - Extravasation
  - Radiation sensitization and radiation recall
  - Secondary malignancy
  - Tumor lysis syndrome

6.2 Bleomycin

- Adverse effects
  - Phlebitis, tumor pain, hyperpigmentation, atrophic striae, exfoliation of skin, hyperkeratosis, localized vesiculation, skin rash, skin sclerosis, alopecia, nail bed changes, stomatitis, mucositis, anaphylactoid reaction , scleroderma, tachypnea, rales, interstitial pneumonitis, pulmonary fibrosis, hypoxia
- Warnings and precautions
  - Pulmonary toxicity - may occur in up to 10% of patients, ranging from pneumonitis to pulmonary fibrosis. More common in patients over 70 years of age and dose exceeding 400 units (cumulative). Risk may be increased with concurrent use of GCSF.
  - Idiosyncratic reaction – hypotension, altered mental status, fever, chills, wheezing
  - Hepatotoxicity

6.3 Vinblastine

- Adverse events
  - Common adverse events include fatigue, bone pain, alopecia, hypertension, leukopenia, anemia, thrombocytopenia, and constipation. Cardiovascular events (myocardial infarction, angina pectoris, ECG abnormalities), Raynaud's phenomenon, have also been reported.
- Warnings and precautions
  - Bone marrow suppression
  - Extravasation
  - Stomatitis (rare)
  - Neurotoxicity

- Pulmonary toxicity

6.4 Dacarbazine

- Adverse reactions
  - Nausea/vomiting, anorexia, diarrhea, myalgias, malaise, alopecia, facial flushing or paresthesia, leukopenia, anemia, thrombocytopenia, skin rash, photosensitivity, hepatotoxicity
- Warnings and precautions
  - Anaphylaxis
  - Bone marrow suppression
  - Teratogenicity
  - Extravasation
  - Hepatic necrosis

6.5 Brentuximab Vedotin

Per the IB (version 19, October 2021) the expected toxicities for brentuximab vedotin (monotherapy) are as follows:

System Organ Class	Adverse Reactions	N=1421 N (%)
Blood and lymphatic system disorders	Anemia	2 (0.12)
	Febrile neutropenia	9 (0.54)
	Neutropenia	9 (0.54)
	Thrombocytopenia	4 (0.24)
Gastrointestinal disorders	Abdominal pain	4 (0.24)
	Diarrhea	10 (0.60)
	Nausea	10 (0.60)
	Vomiting	10 (0.60)
General disorders and administration site conditions	Fatigue	3 (0.18)
	Pyrexia	20 (1.21)
Immune system disorders	Anaphylactic reaction	6 (0.36)
Infections and infestations	Diverticulitis	2 (0.12)
	Influenza	2 (0.12)
	Pneumocystis jirovecii pneumonia	3 (0.18)
	Pneumonia	22 (1.39)
	Sepsis	2 (0.12)
	Septic shock	3 (0.24)
	Urinary tract infection	3 (0.18)
Metabolism and nutrition disorders	Hyperglycemia	8 (0.48)
Nervous system disorders	Demyelinating polyneuropathy	4 (0.24)
	Peripheral motor neuropathy	9 (0.54)
	Peripheral sensory neuropathy	9 (0.54)
Respiratory, thoracic and mediastinal disorders	Dyspnea	8 (0.48)
Skin and subcutaneous tissue disorders	Rash erythematous	2 (0.12)
	Rash maculo-papular	2 (0.12)

6.6 Nivolumab

Per the IB (version 20, July 2021) the expected toxicities for nivolumab are as follows:

System Organ Class	Adverse Reactions
Cardiac disorders	
Rare	Atrial fibrillation, myocarditis, pericardial effusion, pericarditis, arrhythmia
Very rare	Immune-mediated myocarditis[a], ventricular arrhythmia
Endocrine disorders	
Uncommon	Adrenal insufficiency, hyperglycemia, hypophysitis, hypothyroidism
Rare	Diabetes mellitus, hyperthyroidism, hypopituitarism, diabetic ketoacidosis, Type 1 diabetes mellitus, fulminant type 1 diabetes mellitus, autoimmune thyroiditis, thyroiditis
Very rare	Autoimmune hypothyroidism, immune-mediated hyperthyroidism[a]
Eye disorders	
Rare	Iridocyclitis, uveitis
Gastrointestinal disorders	
Uncommon	Diarrhea, colitis, nausea, pancreatitis, vomiting, immune-mediated enterocolitis
Rare	Abdominal pain, gastritis, autoimmune colitis, stomatitis, enterocolitis, pancreatitis acute, enteritis, autoimmune pancreatitis
Very rare	Constipation, immune-mediated pancreatitis[a]
General disorders and administration site conditions	
Uncommon	Pyrexia, fatigue
Rare	Asthenia, mucosal inflammation, oedema peripheral, chills
Hepatobiliary disorders	
Uncommon	Autoimmune hepatitis, hepatitis
Rare	Drug-induced liver injury, immune-mediated hepatitis, hepatitis acute, hyperbilirubinemia, hypertransaminasemia
Immune system disorders	
Uncommon	Infusion-related reaction
Rare	Hypersensitivity, anaphylactic reaction, sarcoidosis
Infections and infestations	
Rare	Bronchitis, upper respiratory tract infection
Investigations	
Uncommon	ALT increased, AST increased
Rare	Lipase increased, transaminases increased, liver function test increased, blood bilirubin increased, amylase increased, blood creatinine increased, hepatic enzyme increased, blood alkaline phosphatase increased, blood glucose increased
Metabolism and nutrition disorders	
Uncommon	Hyponatremia
Rare	Dehydration, decreased appetite
Musculoskeletal and connective tissue disorders	

System Organ Class	Adverse Reactions
Rare	Myositis, arthritis, polyarthritis, arthralgia, myalgia, polymyalgia rheumatica, polymyositis, rhabdomyolysis
Nervous system disorders	
Rare	Headache, encephalitis, myasthenia gravis, peripheral motor neuropathy, dizziness, Guillain-Barre syndrome, demyelination, myasthenic syndrome, peripheral neuropathy, peripheral sensory neuropathy
Very rare	Polyneuropathy
Renal and urinary disorders	
Uncommon	Acute kidney injury
Rare	Tubulointerstitial nephritis, renal failure, autoimmune nephritis, immune-mediated nephritis, nephritis
Respiratory, thoracic and mediastinal disorders	
Common	Pneumonitis
Uncommon	Interstitial lung disease, dyspnea
Rare	Immune-mediated lung disease[a], respiratory failure, organising pneumonia, cough
Skin and subcutaneous tissue disorders	
Rare	Rash, rash maculo-papular, pemphigoid, Stevens-Johnson syndrome, erythema multiforme, psoriasis, dermatitis, drug eruption, pruritus, rash pustular, rash papular, toxic epidermal necrolysis
Very rare	Rash macular, rash pruritic
Vascular disorders	
Rare	Hypotension

[a] Adverse reactions not included in previous IB (version 19).

Adverse reactions reported for patients treated with nivolumab monotherapy (N = 15,217).

Frequency is defined using the following convention: 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).

7.0 DOSE DELAY/ MODIFICATION GUIDELINES

A study drug can be discontinued at the discretion of the investigator for the safety of a patient, even if it does not meet the criteria for discontinuation provided in this section.

- Toxicities will be graded using the NCI CTCAE v 5.0.
- **Baseline values** are from the last values obtained prior to protocol therapy.
- Dose interruption or delay is permitted for toxicity or administrative reasons. If toxicity is deemed attributable to any single agent, then dose delay or missed dose of any single agent is allowable (ie, BV, nivolumab, A, B, V, or D alone may be delayed or missed or the entire regimen (BV-Nivo or BV-AVD) may be delayed or missed at the discretion of the treating investigator).
- 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.

- Any dose delays/deviations due to COVID-19 should be documented. Treatments for COVID-19 (e.g. Paxlovid) and prophylactic monoclonal antibody therapy (e.g. Evusheld) are allowable per protocol.

NOTE: For Arm A only (brentuximab vedotin and nivolumab combination):

- If one agent is permanently discontinued, 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.

7.1 Brentuximab vedotin

Specific guidelines for Arm A and for Arm C are presented in Sections 7.1.1 and 7.1.2, respectively.

7.1.1 **Arm A** [combination with nivolumab] **ONLY**

Dose modification/ delay guidelines for brentuximab vedotin for **Arm A** (combination with nivolumab), are described in Table 7.1.1.

Doses reduced for brentuximab vedotin-related toxicity should not be re-escalated without discussion with the Study PI.

Table 7.1.1 Dose modifications for brentuximab vedotin associated toxicity (Arm A only)

The guidelines below apply to brentuximab only. In cases where the treating investigator feels that the toxicity is CLEARLY unrelated to brentuximab, exceptions to these guidelines may be considered, in discussion with the Study PI.

Toxicity	Brentuximab 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	If no prior dose reduction, withhold until toxicity resolves to ≤ Grade 2, then resume treatment at 1.2 mg/kg If prior dose reduction, permanently discontinue brentuximab vedotin
Grade 4	Permanently 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, then resume brentuximab vedotin at the same dose level [a,b] a. Patients who develop asymptomatic Grade 3 or 4 electrolyte laboratory abnormalities may continue brentuximab vedotin without interruption. b. In case of Grade 3 infusion-related reactions, once toxicity resolves to ≤ Grade 2: - Consult Study PI to continue to administer brentuximab vedotin during subsequent cycle(s) at the same dose level with prophylaxis premedication - Otherwise, permanently discontinue brentuximab vedotin. *See Section 5.8.1 for supportive care.*
Grade 4	Withhold dose until toxicity is ≤ Grade 2, then reduce dose to 1.2 mg/kg and resume brentuximab vedotin, 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 asymptomatic Grade 3 or 4 electrolyte laboratory abnormalities may continue brentuximab vedotin without interruption.

Toxicity	Brentuximab vedotin Dose Management Guidelines
	c. Brentuximab vedotin should be discontinued for patients who experience Grade 4 infusion-related reactions. *See Section 5.8.1 for supportive care.*
Hematologic	
Grades 1-3	Continue at same dose level
Grade 4	• Withhold brentuximab vedotin until toxicity resolves to ≤ Grade 3, then resume treatment at the same dose level. - **NOTE:** Patients who develop Grade 3 or 4 lymphopenia may continue brentuximab vedotin without interruption. • For Grade 4 neutropenia: - Growth factor support (G-CSF or GMCSF) should be considered for subsequent cycles. - If Grade 4 neutropenia recurs despite growth factor support, reduce dose to 1.2 mg/kg. - If Grade 4 neutropenia recurs despite growth factor support and dose reduction to 1.2 mg/kg, permanently discontinue brentuximab vedotin (unless continuing therapy is discussed with and approved by study PI).
Suspected progressive multifocal leukoencephalopathy (PML)	
Any Grade	If PML is suspected, hold brentuximab vedotin, and perform a diagnostic work-up. The workup may include, but is not limited to the following: • Neurologic examinations and neurology consultation, as warranted. · • Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically nonenhancing and do not have mass effect. • PCR analysis. John Cunningham virus (JCV) DNA, detectable in CSF or in a brain biopsy, is suggestive of PML. If PML is confirmed, brentuximab vedotin should be permanently discontinued.

For any other adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication the main study PI should be notified.

7.1.2 **Arm C** [combination with AVD] **ONLY**

- Dose delay or modification is allowable for toxicities related to brentuximab therapy if it is determined by the treating physician that it is in the best interest of the patient for safety reasons taking into consideration the overall clinical status of the subject. In the event of a BV-related AE that requires hold or discontinuation of BV, AVD may be continued (dose reductions may be necessary).
- If both BV and AVD are held together and the toxicity lasts > 6 weeks, then protocol therapy will be discontinued.
- Dose modification/ delay guidelines for brentuximab vedotin for **Arm C** (combination with AVD), are described in Table 7.1.2.
- Doses reduced for brentuximab vedotin-related toxicity should not be re-escalated without discussion with the Study PI.

For toxicities that can be treated or prevented, such as nausea, vomiting, diarrhea and neutropenia, treatment may be resumed at the previous dose once supportive measures have been instituted and toxicity recovers to Grade ≤2.

Table 7.1.2. Dose modifications for brentuximab vedotin associated toxicity (Arm C only)

In cases where the treating investigator feels that the toxicity is CLEARLY unrelated to brentuximab, exceptions to these guidelines may be considered, in discussion with the Study PI.

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
Peripheral Neuropathy	Grade 1	No change.
	Grade 2	• Reduce brentuximab vedotin dose to 0.9mg/kg (max 90 mg) and resume treatment; if already at 0.9mg/kg continue dosing at that level.
	Grade 3	• Brentuximab vedotin should be delayed until neuropathy improves to Grade 2 or lower. • Once improved to grade 2 or lower, brentuximab vedotin should be restarted at the reduced dose of 0.9mg/kg. • Patients who develop grade 3 neuropathy after dose reduction of brentuximab vedotin to 0.9mg/kg should have brentuximab vedotin discontinued. • In the setting of Grade 3 peripheral neuropathy (e.g., obstipation, weakness), that persists/occurs despite discontinuation of brentuximab vedotin, the dose of vinblastine will be reduced by 50% for all further cycles of AVD
	Grade 4	• Discontinue brentuximab vedotin. • In the setting of Grade 4 peripheral neuropathy (e.g., obstipation, weakness), that persists/occurs despite discontinuation of brentuximab vedotin, vinblastine will be omitted from all future cycles of AVD.
Pneumonitis	Grade 1	No change.
	Grade 2	If suspected, strongly consider administration of 100 mg of oral or intravenous prednisolone in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. Upon occurrence of pneumonitis, brentuximab vedotin should be held, and notify the Study PI within 48 hours.
	Grade 3-4	If suspected, strongly consider administration of 100 mg of oral prednisone or intravenous methylprednisolone (1 mg/kg IV every 12 hours) in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. **Discontinue brentuximab vedotin.** Upon occurrence of pneumonitis, brentuximab vedotin should be held, and notify the Study PI within 48 hours.
	≤ Grade 1	No change.

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
Abnormal liver function (AST/ALT, Total bilirubin, immune-related hepatitis)	Grade 2	• If the bilirubin rises to > 2 x ULN (but ≤ 5 x ULN), the doxorubicin and vinblastine doses must be reduced by 50% of last dose received to avoid undue hepatic toxicity. Full doses should be given once the bilirubin is ≤ 2 x ULN.
	Grade 3-4	• Hold doxorubicin and vinblastine • Withhold brentuximab vedotin until ≤ Grade 2 • Dose reduction of brentuximab vedotin to 0.9mg/kg can be considered. • If recurs after BV dose reduction, discontinuation of brentuximab vedotin can be considered.
Progressive Multifocal Leukoencephalopathy (PML)	Any Grade	If PML is suspected, hold brentuximab vedotin, and perform a diagnostic work-up. The workup may include, but is not limited to the following: • Neurologic examinations and neurology consultation, as warranted. · • Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically nonenhancing and do not have mass effect. • PCR analysis. John Cunningham virus (JCV) DNA, detectable in CSF or in a brain biopsy, is suggestive of PML. If PML is confirmed, brentuximab vedotin should be permanently discontinued.
Febrile Neutropenia, Sepsis, Infections or infestations	Grade 1-2 (only pertains to infection/infestation)	No change.
	Grade 3	• Hold all protocol therapy until ≤ Grade 2. • If using daily filgrastim (rather than pegfilgrastim), additional doses beyond days 5-10 should be administered in subsequent cycles. • Consider prophylaxis with antibacterial therapy for subsequent cycles. • First occurrence - continue at same dose level. • Second occurrence – Consider dose reduction to 0.9mg/kg (max 90 mg) of brentuximab vedotin. • Additional occurrence – If brentuximab vedotin has already been dose reduced, consider discontinuation of brentuximab vedotin. • If febrile neutropenia recurs despite brentuximab vedotin dose reduction or discontinuation, it is allowable to decrease the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician.
	Grade 4	• Hold all protocol therapy until ≤ Grade 2. • If using daily filgrastim (rather than pegfilgrastim), additional doses beyond days 5-10 should be administered. • Consider prophylaxis with antibacterial therapy for subsequent cycles.

Treatment-related Adverse Event	Grade of Event	Management for Brentuximab vedotin
		• First occurrence - consider dose reduction to 0.9mg/kg (max 90 mg) of brentuximab vedotin. • Second/repeated occurrence – if brentuximab vedotin has already been dose reduced, discontinuation of brentuximab vedotin is recommended. • If febrile neutropenia recurs despite brentuximab vedotin dose reduction or discontinuation, it is allowable to decrease the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician.
Hematologic (excluding lymphopenia)	Grade 1-2	No change.
	Grade 3-4	• No change required. • For neutropenia, if using daily filgrastim (rather than pegfilgrastim), additional doses beyond days 5-10 and 20-25 can be considered. • For Grade 4 neutropenia, withhold brentuximab vedotin until toxicity resolves to ≤ Grade 3. Continued therapy with aggressive G-CSF management can be considered in discussion with the Study PI. • For anemia, manage per institutional guidelines. Erythrocyte transfusion is allowable. • For thrombocytopenia, consider platelet transfusion and/or manage per institutional guidelines. Delay of brentuximab vedotin for Grade 4 thrombocytopenia may be considered at the investigator's discretion.
Non-hematologic events (not including electrolyte abnormalities or others not specifically outline above, e.g. neuropathy)	Grade 1-2	No change.
	Grade 3-4	• Withhold brentuximab vedotin until toxicity is ≤ Grade 2. • Dose reduction of brentuximab vedotin to 0.9mg/kg (max 90 mg) can be considered. • If non-hematological Grade 3-4 toxicity recurs after one dose reduction, discontinuation of brentuximab vedotin should be considered.
Electrolyte abnormalities	Grade 1-4	• Continue at same dose level, provided electrolyte toxicity is not medically consequential and has been readily corrected. • If electrolyte abnormality is medically consequential, refer to guidelines above for non-hematologic events. Patients who develop asymptomatic Grade 3 or 4 electrolyte laboratory abnormalities may continue all study treatment without interruption but should receive appropriate medical therapy.

For any other adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication the main study PI should be notified.

7.2 Nivolumab

These guidelines apply to all arms.

Nivolumab dose management guidelines are described in Table 7.2.

- 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, Neurological, and Myocarditis. The algorithms have been incorporated into Table 7.2 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 7.2: 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.

Table 7.2 Nivolumab Dose Management Guidelines

The guidelines below apply to nivolumab only. In cases where the treating investigator feels that the toxicity is CLEARLY unrelated to nivolumab, exceptions to these guidelines may be considered, in discussion with the study chair.

Toxicity	Nivolumab Dose Management Guidelines
Hematological Toxicity	
Anemia or thrombocytopenia Grade 3 *Platelets: < 50,000 - 25,000/mm^3*	Continue nivolumab
Anemia or thrombocytopenia Grade 4 *Platelets <25,000/mm^3*	• Hold nivolumab • Supportive transfusions as needed • Consider corticosteroids if AIHA or ITP suspected • Once toxicity resolves ≤ Grade 2 resume nivolumab per protocol • Permanently discontinue nivolumab if toxicity lasts > 6 weeks.
Neutropenia Grade 3 *ANC <1000 - 500/mm^3*	Continue nivolumab • Consider growth factor (G-CSF) support
Neutropenia Grade 4 *ANC < 500/mm^3*	• Hold the nivolumab dose • Growth factor support should be instituted. • Consider growth factor support (G-CSF or GMCSF) for subsequent cycles. • Consider corticosteroids if an autoimmune cause is suspected. • Once toxicity resolves to ≤ Grade 2, resume treatment with nivolumab per protocol. • If toxicity recurs despite growth factor support, consider nivolumab discontinuation. • Permanently discontinue nivolumab if toxicity lasts > 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
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 5.8.2.1* 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 5.8.2.1* for supportive care. • If toxicity resolves within 5 days to baseline resume nivolumab per protocol • If elevations persist > 5-7 days or worsen – Resume nivolumab per protocol when LFT returns to Grade ≤ 1 or baseline and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab 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 5.8.2.1* for supportive care.
Concurrent ≥ Grade 2 AST or ALT (> 3 x ULN) **AND** total bilirubin > 2 x ULN	• Discontinue nivolumab therapy • See *Section 5.8.2.1* 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 5.8.2.1* 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 5.8.2.1* for supportive care. • If toxicity resolves within 5 days to baseline resume nivolumab per protocol • If elevations persist > 5-7 days or worsen – Resume nivolumab per protocol when LFT returns to Grade ≤ 2 or baseline and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period.
High Grade 3 and Grade 4	• Discontinue nivolumab therapy

*AST or ALT > 8 x ULN **OR** total bilirubin >5 x ULN*	• See *Section 5.8.2.1* for supportive care.
Concurrent ≥ Grade 2 AST or ALT (> 3 x ULN) **AND** total bilirubin > 2 x ULN	• Discontinue nivolumab therapy • See *Section 5.8.2.1* for supportive care.
Renal (Creatinine)	
Grade 1 *Creatinine > ULN and > than baseline but ≤ 1.5x baseline*	• Continue nivolumab per protocol • See *Section 5.8.2.2* 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 5.8.2.2* for supportive care. • Resume nivolumab per protocol once the toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab 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 5.8.2.2* for supportive care.
Gastrointestinal (Diarrhea/ Colitis) Toxicity	
Diarrhea/Colitis Grade 1 *Diarrhea:< 4 stools/day over baseline;* *Colitis: asymptomatic*	• Continue nivolumab. – See *Section 5.8.2.3* 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 5.8.2.3* for supportive care. • If toxicity resolves to Grade ≤ 1 within 5 days resume nivolumab • If persists > 5-7 days or recur: – Resume nivolumab per protocol once the toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab 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
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 nivolumab • See *Section 5.8.2.3* for supportive care. • For grade 3 diarrhea that improves to grade ≤1 or baseline with appropriate management within 6 weeks, nivolumab may be resumed after discussion with the study PI.
Endocrinopathy	
Asymptomatic thyroid	• Continue nivolumab per protocol

stimulating hormone (TSH) elevation	• See *Section 5.8.2.4* for supportive care.
Symptomatic endocrinopathy	*Symptomatic with abnormal lab/pituitary scan*: • Hold the dose of nivolumab • See *Section 5.8.2.4* for supportive care. • If toxicity improves (with or without hormone replacement): – Resume nivolumab per protocol when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab 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 5.8.2.4* 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 5.8.2.5* for supportive care. • If worsens: – Treat as Grade 2 or 3-4
Grade 2 *Moderate symptoms; Limiting instrumental ADL*	• Hold the nivolumab dose • See *Section 5.8.2.5* for supportive care. • Resume nivolumab per protocol once the toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab 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 5.8.2.5* for supportive care.
Pulmonary	
Pulmonary Grade 1 *Radiographic changes only*	• Consider holding nivolumab • See *Section 5.8.2.6* for supportive care.
Pulmonary Grade 2 *Mild to moderate new symptoms*	• Hold nivolumab • See *Section 5.8.2.6* for supportive care. • Resume nivolumab per protocol once the toxicity returns to Grade ≤ 1

	and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab 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 5.8.2.6* for supportive care.
Skin	
Skin Grade 1-2 *Covering ≤ 30% body surface area (BSA) (refer to CTCAE v5.0 for term specific criteria)*	• Continue nivolumab per protocol – **Note:** Subjects who have not experienced a Grade 3 drug-related skin AE may resume nivolumab in the presence of Grade 2 skin toxicity. • See *Section 5.8.2.7* for supportive care. • If persists > 1-2 weeks or recurs: – Hold nivolumab – Once improving , taper steroids over at least 1 month*, and resume nivolumab per protocol. (* See exception in Section 7.2) • If worsens: – Treat as Grade 3-4
Skin Grade 3 *Covering >30% BSA; Life threatening consequences (refer to CTCAE v5.0 for term specific criteria)*	• Hold nivolumab • See *Section 5.8.2.7* for supportive care. • Resume nivolumab per protocol once toxicity returns to Grade ≤ 1 and when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period.
Skin: Grade 4 *(refer to CTCAE v5.0 for term specific criteria)*	• Discontinue nivolumab • See *Section 5.8.2.7* for supportive care.
Myocarditis	
Grade 1 *Laboratory or imaging abnormality only, asymptomatic*	• Hold nivolumab. Can resume when toxicity resolve.
Grade 2-4 *G2: Symptoms with mild to moderate activity or exertion* *G3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated* *G4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic*	• Discontinue nivolumab • See *Section 5.8.2.8* for supportive care.

support)	
Fatigue	
Grade 2	Continue nivolumab per protocol
Grade 3	• Hold nivolumab • Resume nivolumab per protocol once toxicity returns to Grade ≤ 2 • Discontinue nivolumab 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 lasts > 7 days from onset, discontinue nivolumab.
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 or 4	Patients who develop asymptomatic Grade 3 or 4 electrolyte laboratory abnormalities may continue nivolumab without interruption.
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, skin, and myocarditis.	
Grade 2	• Hold nivolumab dose • Resume nivolumab per protocol once toxicity returns to Grade ≤ 1 and if applicable, when steroid taper (≥ 1 month*) is complete. (* See exception in Section 7.2) • Discontinue nivolumab if toxicity lasts for > 6 weeks or unable to initiate steroid taper within a 6 week period.
Grade 3 or 4	Discontinue nivolumab. In cases of grade 3 toxicities, exceptions may be made after discussion with the study PI.
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.
Grade 3	• Delay the dose of nivolumab until resolution to ≤ Grade 1. • Discontinue nivolumab if toxicity lasts > 7 days.
Grade 4	Discontinue nivolumab

For any other adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication the main study PI should be notified.

7.3 ABVD

These guidelines apply to Arms B1 and B2.

Dose modifications/ discontinuation of ABVD due to adverse events are permitted at the investigator's discretion/ per institutional standards.

Although it has been common practice in adult oncology settings in the United States to attenuate doses or delay treatment due to cytopenias alone, recent studies have shown that this policy is unnecessary and inadvisable for patients receiving ABVD and results in suboptimal treatment outcomes.[76, 77] Patients should receive full doses of ABVD on schedule on Days 1 and 15 of each 28 day cycle without treatment delays, **unless neutropenic fever or documented infections are present**. In nearly all cases, counts will recover despite administration of the next course of full dose chemotherapy administered on time.[76, 77]

8.0 AGENT INFORMATION

8.1 Doxorubicin

Drug information summarized below.[71]

- Mechanism of action: intercalation between base pairs by inhibiting topoisomerase II, inhibits DNA and RNA synthesis; formation of iron-doxorubicin complexes can bind DNA and cell membranes, producing free radicals that cleave DNA.
- Preparation, storage: Refer to institutional standards or prescribing information.
- Administration: Refer to institutional standards or prescribing information and Section 5.2.
- Pharmacokinetics/Pharmacodynamics
    - Distribution: 809 to 1,214 L/m^2. Doxorubicin does not cross the blood-brain barrier.
    - Metabolism: primarily hepatic to doxorubicinol (active), then to inactive aglycones, sulfates, and glucuronides.
    - Excretion: ~40% as unchanged drug in feces, less than 12% as unchanged drug and metabolites in urine.
- Human toxicity: See Section 6.1 for details.
- Standard dose adjustment considerations
    - ***Hepatic impairment:***
        - ***Reduction of 50% if serum bilirubin 1.2 to 3 mg/dL, reduction of 75% if 3.1 to 5 mg/dL.***
        - ***Do not initiate doxorubicin if serum bilirubin greater than 5 mg/dL.***
- Drug Interactions
    - Doxorubicin is a major substrate of cytochrome P450 CYP3A4, and CYP 2D6, and P-glycoprotein (P-gp). Interactions have been reported with inhibitors of these enzymes which can result in increased concentration and exposure to doxorubicin. Conversely, inducers such as certain anti-epileptic agents may decrease the concentration of doxorubicin.

- Supplier
    - Commercial supply will be used.

8.2 Bleomycin

Drug information summarized below.[75]

- Mechanism of action: inhibits DNA, RNA, and protein synthesis; binds DNA to induce strand breaks. Preparation, storage: Refer to institutional standards or prescribing information.
- Administration: Refer to institutional standards or prescribing information and Section 5.2.
- Pharmacokinetics/Pharmacodynamics
    - Distribution: Vd 16.5 L/m2.
    - Metabolism: enzymatic inactivation by bleomycin hydrolase.
    - Excretion: urine (~65%), lower percentage (~40%) for intrapleural administration.
- Human toxicity: See Section 6.2 for details.
- Standard dose adjustment considerations
    - ***Renal impairment***
        - ***CrCl 40 to 50 (ml/min): 70% of normal dose***
        - ***CrCl 30 to 40: 60% of normal dose***
        - ***CrCl 20 to 30: 55% of normal dose***
        - ***CrCl 10 to 20: 45% of normal dose***
        - ***CrCl 5 to 10: 40% of normal dose***
- Drug Interactions
    - Nephrotoxic drugs may affect bleomycin renal clearance.
    - Concomitant administration of bleomycin and brentuximab vedotin is contraindicated due to increased risk of pulmonary toxicity.
- Contraindications: hypersensitivity to bleomycin.
- Supplier
    - Commercial supply will be used.

8.3 Vinblastine

Drug information summarized below.[78]

- Mechanism of action: binds to tubulin to inhibit microtubule formation, leading to arrest of cell cycle in metaphase; may interfere with nucleic acid and protein synthesis by blocking glutamic acid utilization.
- Preparation, storage: Refer to institutional standards or prescribing information.
- Administration: Refer to institutional standards or prescribing information and Section 5.2.
- Pharmacokinetics/Pharmacodynamics
    - Distribution: 70% of body weight; widely distributed throughout, with 50% of dose binding to platelets, RBC, and WBC. Vinblastine does not cross the blood-brain barrier.
    - Metabolism: via CYP 3A enzymes to active metabolite.
    - Excretion: feces 10%, urine 14%.
- Human toxicity: See Section 6.3 for details.
- Standard dose adjustment considerations
    - ***Hepatic impairment***
        - ***Reduction of 50% if serum bilirubin greater than 3 mg/dL.***
- Drug Interactions
    - Cytochrome P450 inhibitors or inducers should be used with caution in combination with vinblastine.

- Contraindications
    - Significant granulocytopenia or presence of bacterial infection.
- Supplier
    - Commercial supply will be used.

8.4 Dacarbazine

Drug information summarized below.[79]

- Mechanism of action: conversion to active metabolite (methyl-triazine-1-yl)-imidazole-4-carboxamide (MTIC), an alkylator compound, leads to DNA strand breaks and apoptosis.
- Preparation, storage: Refer to institutional standards or prescribing information.
- Administration: Refer to institutional standards or prescribing information and Section 5.2.
- Pharmacokinetics/Pharmacodynamics
    - Distribution: 1.49 L/kg.
    - Metabolism: extensive metabolism to active form, (methyl-triazine-1-yl)-imidazole-4-carboxamide (MTIC).
    - Excretion: urine 40%, as unchanged drug.
- Human toxicity: See Section 6.4 for details.
- Dose adjustments: no dosage adjustments provided in prescribing information.
- Drug Interactions
    - Dacarbazine is a substrate of CYP 2E1 and 1A2. Inhibitors and inducers may alter the metabolism of dacarbazine.
- Contraindication: patients who have demonstrated hypersensitivity to dacarbazine.
- Supplier
    - Commercial supply will be used.

8.5 Brentuximab Vedotin

Product information summarized below.[80]

Please refer to the investigator brochure 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) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, - treatment of patients with classical HL at high risk of relapse or progression as post-auto-HSCT consolidation, and - first-line treatment of classical HL stage III or IV disease in combination with doxorubicin, vinblastine and dacarbazine.

8.5.1 Mechanism of action

Brentuximab vedotin is a CD30 chimeric IgG1 antibody conjugated to monomethyl auristatin E (MMAE) by a cleavable dipeptide linker. MMAE binds to tubulin to disrupt the microtubule network and induce cell cycle arrest in G2/M phase

8.5.2 Pharmacokinetics

- Absorption: Concentrations are dose proportional from 1.2 to 2.7 mg/kg dosing. Minimal to no accumulation of drug is observed with repeated dosing. Tmax of MMAE is 1 to 3 days.
- Distribution: MMAE is 68 to 82% bound to human plasma proteins. The volume of distribution at steady state is 6 to 10 L.

- Metabolism: MMAE undergoes minimal metabolism. The primary route is oxidation by CYP 3A4/5, and MMAE can inhibit these CYP isoforms, but not others.
- Excretion: up to 24% of MMAE is excreted in urine and 72% is excreted in feces, primarily unchanged drug.

8.5.3 Human toxicity

See Section 6.5 for details.

8.5.4 Standard dose adjustments considered

- **Renal impairment:**
  - ***Mild (Crcl >50-80 ml/min) or moderate (Crcl 30-50 ml/min): No adjustment.***
  - ***Severe (<30 ml/min): Avoid use***
- **Hepatic impairment:**
  - ***Mild (Child-Pugh A): 1.2 mg/kg (up to 120 mg)***
  - ***Moderate (Child-Pugh B) or severe (Child-Pugh C): Avoid use***

8.5.5 Drug Interactions

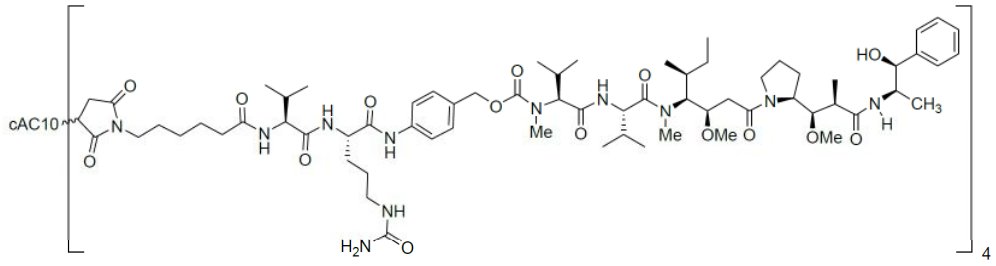
Patients receiving strong CYP3A4 inhibitors and/or P-glycoprotein inhibitors should be monitored for adverse reactions as these agents may increase exposure to MMAE.

8.5.6 Contraindications

Concomitant bleomycin administration (due to pulmonary toxicity)

The information provided below is based on BV Pharmacy manual V11, dated 24-May-2018 (Seattle Genetics):

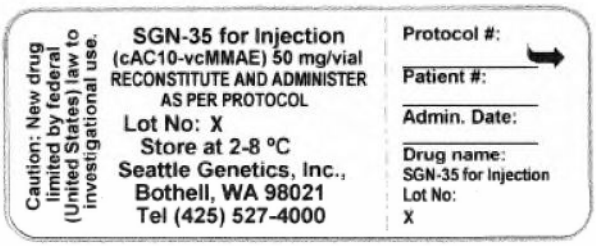
8.5.7 Structural formula



8.5.8 Pharmaceutical properties

- Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder, supplied in single-use vials. Brentuximab vedotin drug product is reconstituted with water for injection (WFI), USP, or equivalent. The reconstituted brentuximab vedotin drug product is a clear to slightly opalescent, colorless solution with no visible particulate matter. The reconstituted solution is subsequently diluted in sterile 0.9% Sodium Chloride for Injection, 5% Dextrose Injection, or Lactated Ringer's Injection for intravenous (IV) administration. The diluents should be USP grade or equivalent.
- Brentuximab vedotin is the United States Adopted Name (USAN) and the International Nonproprietary Name (INN) assigned to SGN-35. Drug product vials may be labeled as SGN-35 or as brentuximab vedotin; the 2 names can be used interchangeably. The clinical supplies for open-label studies are labeled as follows:

50 mg vial



8.5.9 Formulation

- Each vial contains 55 mg SGN-35 for Injection (brentuximab vedotin), trehalose, sodium citrate, and polysorbate 80. The 5 mg overfill in each vial is to ensure that the labeled quantity of 50 mg SGN-35 may be withdrawn. The drug product vial is reconstituted with the appropriate amount of Sterile Water for Injection. The pH of reconstituted product is approximately 6.6.

8.5.10 Vial storage and handling

- Vials and solutions containing brentuximab vedotin must be stored under refrigeration at 2-8°C.
- Chemical and physical stability of the reconstituted brentuximab vedotin drug product has been demonstrated for 24 hours at 2–8°C and 25°C. However, brentuximab vedotin does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use. Do not freeze.
- Please use the investigational product complaint form to report any findings upon inspection of the drug product. Drug product observed to have a potential irregularity should be quarantined until the Sponsor provides further instructions.
- Recommended safety measures for the handling and preparation of brentuximab vedotin for Injection include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

8.5.11 Reconstitution

1. Reconstitute lyophilized brentuximab vedotin by adding 10.5 mL Sterile Water for Injection, USP, or equivalent to the 50 mg vial, directing the stream to the side of the vial. The concentration of reconstituted brentuximab vedotin is 5 mg/mL with a total volume of 11 mL.

2. Closed System Transfer Devices (CSTDs) can be used for brentuximab vedotin.
    a. Known incompatible products: none.

3. Gently swirl the vial until contents are completely dissolved. The vial must not be shaken. Slight “bubbling” of the solution upon reconstitution may be observed.

4. Allow the reconstituted vial to settle for a minute to allow bubbles to dissipate. The reconstituted product should be a colorless, clear to slightly opalescent solution with no visible particulates.

5. Reconstituted vials must be stored under refrigeration (2-8°C) and must be administered within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

8.5.12 Dose Preparation

1. Transfer the required volume of reconstituted product to an infusion bag (A glass, sterile bottle may be used instead of an infusion bag.) It is recommended that the infusion bag be labeled with the patient number or name, and the drug name and lot number. The infusion bag size should allow enough diluent to achieve a concentration of 0.4–1.8 mg/mL. The following bag types are compatible with brentuximab vedotin: polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, polypropylene, or polyethylene. Discard any remaining reconstituted product.

2. Dilute reconstituted product in either 0.9% Sodium Chloride Injection, Lactated Ringer's solution, or dextrose 5% in water (D5W). The diluents should be USP grade or equivalent. The final concentration of brentuximab vedotin in infusion bag should be in the range of 0.4–1.8 mg/mL. See examples calculations in Table 8.5.12 below.

   - Total dose = patient weight x dose level. Note that for patients weighing more than 100 kg, total dose will be calculated using 100 kg.
   - Volume of reconstituted product required = total dose/5 mg per mL
   - Final concentration = total dose/total volume of infusion

Table 8.5.12 Examples of BV dose preparation calculations

Pt weight (kg)	Dose level (mg/kg)	Total dose (mg)	Volume of reconstituted product required (mL)	Volume of diluent (mL)	Total volume of infusion (mL)	Concentration[a] (mg/mL)
45	1.2	54	10.8 (requires 2 vials[b])	100	110.8	0.49
70	1.8	126	25.2 (requires 3 vials[b])	150 or 250	175.2 or 275.2	0.72 or 0.46
120	1.8	180[c]	36 (requires 4 vials[b])	150 or 250	186 or 286	0.97 or 0.63

a Must be between 0.4 and 1.8 mg/mL
b Approximately 10 mL can be withdrawn from each vial.
c For patients weighing more than 100 kg, total dose will be calculated using 100 kg.

3. Gently invert the infusion bag. DO NOT SHAKE or expose the prepared dosing solution to excess vibration at any time when transferring or transporting the reconstituted product. Pneumatic tube systems are not recommended.

4. Prior to administration, inspect the prepared dosing solution (in infusion bag) for any particulate matter or discoloration.

5. Do not prepare a single dose of brentuximab vedotin using vials from different lots. Use vials from the same lot number for a given dose.

6. The prepared dosing solution must be stored under refrigeration (2-8°C) and must be used within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

8.5.13 Dose Administration

- **Per protocol**, brentuximab vedotin dose rounding is permissible within 5% of the nominal dose.
- **BRENTUXIMAB VEDOTIN MUST NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS.** Brentuximab vedotin should be administered over 30 min (+10 min) and cannot be mixed with other medications. In-line filters should not be used during the IV administration.
- For additional administration details refer to Section 5.2.

8.5.14 Temperature Excursions and Quality Issues

Brentuximab vedotin drug product that is affected by a temperature excursion or a quality issue must be quarantined and stored at the labeled storage conditions. Quality issues may occur in transit, during storage, or reconstitution. Quality issues include visual defects, Brentuximab vedotin drug product between the vial neck and stopper, or particulates in the reconstituted/diluted solution.

As soon as a temperature excursion or quality issue is identified, pharmacy staff must complete the Investigational Product Quality Complaints and Temperature Excursions Form and submit to Seattle Genetics. Sites can use their own temperature excursion logs.

Under no circumstance should drug product being evaluated for a temperature excursion or quality issue be dispensed for administration to a patient.

After evaluating the information provided, Seattle Genetics will inform the pharmacy about the final disposition of the affected drug product and provide documentation to be retained in the pharmacy. The documentation may provide additional instructions prior to allowing the affected drug product to be destroyed according to institutional drug disposal procedures.

Note: If applicable, include details of patient(s) treated with affected brentuximab vedotin drug product on the Investigational Product Quality Complaints and Temperature Excursions Form for notification to Seattle Genetics Drug Safety in a timely manner.

8.5.15 Supplier

Brentuximab vedotin will be provided free of charge by Seattle Genetics for investigational use.

8.5.16 Ordering

Sites will place orders for brentuximab vedotin via the Seattle Genetics Investigational Drug Request Form; the Seattle Genetics Protocol ID 35-IST-046 must also be stated in the form. Seattle Genetics will require a copy of the participating site's initial IRB approval in order to approve the initial shipment. The timing for initial shipment will be about 3 weeks and resupply will be about 1 week.

Sites should place orders a week in advance of the shipment.

8.5.17 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.

8.5.18 Destruction

Any partially used vials or prepared dosing solutions may be discarded according to institutional drug disposal procedures. Partially used vials may not be used to provide treatment for a different patient.

The investigator is responsible for keeping accurate records of the clinical supplies received from Seattle Genetics 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.

Destruction will be documented in a drug accountability log.

8.6 Nivolumab

Product information summarized below.[81]

Please refer to the investigator brochure for a detailed description.

Nivolumab has been FDA approved for the treatment of patients with classical HL that has relapsed or progressed after auto-HSCT and post-transplantation brentuximab vedotin, or after 3 or more lines of systemic therapy that includes ASCT.

8.6.1 Mechanism of action

Nivolumab is a fully human IgG4 antibody that inhibits programmed cell death-1 (PD-1) activity by binding the PD-1 receptor and preventing binding of ligands PD-L1 and PD-L2, leading to T cell activation and proliferation.

8.6.2 Pharmacokinetics/Pharmacodynamics

Distribution: Vd 6.8L

8.6.3 Human toxicity

See Section 6.6 for details.

8.6.4 Drug Interactions

No formal drug-drug interaction studies have been conducted.
Immunosuppressants and corticosteroids may diminish therapeutic effect.

8.6.5 **Formulation**

Product Description and Dosage Form	Potency	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).	Clear to opalescent, colorless to pale yellow liquid. May contain particles

[contains in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80].

8.6.6 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 (protect from light and freezing), and a maximum of 8 hours of the total 24 hours can be at room temperature (20-25 °C) and room light. The maximum 8-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".

8.6.7 Preparation and administration

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

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

For additional administration details refer to Section 5.2.

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

8.6.8 Supplier

Nivolumab will be provided free of charge by Bristol Myers Squibb for investigational use.

8.6.9 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 may 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. 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.

8.6.10 Accountability

Will be done according to institutional guidelines at each site. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent.

8.6.11 Destruction

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. BMS will not be responsible for any drug destruction or accept any drug return.

Destruction will be documented in a drug accountability log.

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Immune Gene Signatures

Immune profiling will be performed on the FFPE tumor samples obtained at baseline using a custom Nanostring gene panel consisting of ~1,500 genes to identify immune gene signatures predictive of clinical outcome. Our underlying hypothesis is that the magnitude of the pre-existing antitumor immune response correlates with PFS after the combination therapy outlined in this protocol.

9.1.1 Time points of Collection

Baseline tissue: Archival tissue from diagnostic tumor biopsies will be retrieved and submitted post-enrollment.

NOTE: If unavailable, exceptions may be granted with the lead study PI approval.

9.1.2 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 tube and frozen at -80° C
    - AND
  - 10 x 5 μm thick unstained slides
- If tissue block is unavailable submit:
  - 20 x 5 μm thick unstained slides

9.1.3 Labeling of samples

Samples will be labeled with the study number, institution, subject ID (issued by DCC), subject initials, date, time point of collection, and if applicable patient initials.

9.1.4 Sample shipment and receiving lab

Samples 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 C)** 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 D for tissue shipping details.**

9.2 Circulating Tumor DNA

Genomic profiling will also be performed on circulating tumor DNA (ctDNA) isolated from plasma to characterize the mutation profile and association with clinical outcome. This will be performed using Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq), an established method for genotyping and monitoring B-cell lymphomas from circulating tumor DNA.[82] Samples will be assessed for somatic events including single nucleotide variants (SNVs), copy number alterations (CNAs), and translocations; their association with clinical outcomes will be studied. In addition, ctDNA levels will be quantified to assess minimal residual disease (MRD) throughout the course of therapy.
ctDNA testing is being done throughout the study for MRD monitoring and association with PFS. ctDNA testing is strongly recommended, unless not feasible.

9.2.1 Blood Samples

Blood samples will be collected from an indwelling venous catheter or by venipuncture.

NOTES:

- **For patients who enrolled on the study but who end up not starting protocol therapy, any correlative blood sample collected during SOC ABVD will be destroyed.**
- **For patients who started SOC ABVD prior to study enrollment, and who therefore did not have a correlative blood collection performed at baseline (prior to SOC ABVD cycle 1, day 1), their first correlative blood collection will occur at time of PET/CT-2. No correlative blood will be collected at SOC ABVD cycle 1, day 15 and SOC ABVD cycle 2, day 1 in patients who did not have a correlative blood collection performed at baseline.**

Table 9.2.1.1 Overview of Correlative Blood Samples

Treatment Arm	Timepoint of collection	Total volume per time point	Tube Type	Processing / Receiving Laboratory	Type of Laboratory Analysis
Arms A, B1, and B2	**1. Baseline (prior to SOC ABVD cycle 1, day 1)** **2. SOC ABVD cycle 1, day 15** **3. SOC ABVD cycle 2, day 1** **4. At time of PET/CT-2*** **5. At end of therapy**	~20 mL **(2 tubes of 10 ml)**	Cell-free DNA BCT® (Streck) tubes***	APCF† (COH)	Genomic profiling and Minimal residual disease (MRD) assessment
Arm C	**1. Baseline (prior to SOC ABVD cycle 1, day 1)** **2. SOC ABVD cycle 1, day 15** **3. SOC ABVD cycle 2, day 1** **4. At time of PET/CT-2*** **5. At C2D1 of BV+AVD therapy** **6. At end of BV+AVD therapy**** **7. At end of therapy** **8. At 12 months post-therapy** **9. At 18 months post-therapy**				

***** Anytime **after C2D15** of SOC ABVD cycle 2 and **prior** to start of protocol therapy.

****** Anytime **after** C4D15 of BV+AVD and **prior** to start of nivolumab.

*******Cell-Free DNA BCT® (glass, 10 mL volume) tubes from Streck. Cat. No, as of April 2019, for a box of 100 tubes is: 218962.

† APCF = Analytical Pharmacology Core Facility (COH).

SOC: Standard of care.

Table 9.2.1.2 Blood Sample Labeling and Collection

Notification to APCF of Pending Collection	Tube Type	Labeling and Collection Details	Site of collection	Post-collection Instructions
Before a scheduled blood collection (**at least one day in advance)**: Notify Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) at the Analytical Pharmacology Core Facility (APCF) **to inform them of a pending collection.**	Cell free DNA BCT® tubes*	1. Label tubes with study number, subject ID (issued by DCC), institution, date and **actual** time point of collection, and if applicable patient initials. 2. Time points of collection are stated in Table 9.2.1.1. 3. If applicable, follow recommendations for order of draw outlined in Clinical and Laboratory Standards Institute (CLSI) H3-A6. a. BCT® tubes **must 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. 4. Blood samples will be collected from an indwelling venous catheter or by venipuncture. 5. The following 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 application. 6. Completely fill the tube. 7. Remove tube from adapter and immediately invert the tubes 8 to 10 times. 8. **DO NOT FREEZE** samples. Store samples at **18-25 °C** until shipment (see post-collection instructions on the right).	COH	Deliver the blood samples to the APCF, Shapiro room 1042.
			Non-COH	See Appendix F for shipping guidelines. *(Shipping **asap**, Mon-Wed only, via overnight courier. Samples need to reach APCF **asap** and within a **maximum of 5 days** from blood collection)**.* Include with shipment the blood collection form (Appendix E)

* Tubes are stable when stored at 2-30°C through expiration date. Do not use expired tubes. If there is any indication of cloudiness or visible precipitate please contact Streck.

** Please make every effort to ship the blood on the same day, especially for blood collected on Wednesdays.

Table 9.1.2.3 Blood Sample Processing (at APCF)

Processing of blood samples will **only** be performed **at COH Analytical Pharmacology Core Facility.**

Tube Type and Volume	Part of Blood	Processing Details (performed only at APCF)
Cell free DNA BCT® (~20 mL)	Plasma	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. Do not disturb the buffy coat while pipetting plasma; leave ~3-4mm of plasma behind to ensure the buffy coat is undisturbed. b. **Save** the remaining cells (PDWB) for additional processing (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. Take the remaining cellular layer from step 2b; this layer will be called plasma depleted whole blood (PDWB). PDWB should be mixed and aliquoted into 1-2mL aliquots 7. Freeze PDWB at -80°C. Do not fill tubes beyond 70% capacity.

10.0 STUDY CALENDARS

All assessments may increase in frequency as clinically indicated.

Table 10.1 Study enrollment, correlative blood collection, and QOL assessments through PET/CT-2

Protocol Activity	Screening	Standard of care ABVD			PET/CT-2[g]
		C1D1	C1D15	C2D1	
Informed Consent[a]	X				
Registration[b]	X				
Eligibility[c]	X				
Medical history[d]	X				
Correlative Tumor Tissue[e]	X				
Correlative Blood[e]		X	X	X	X
QOL Assessment[f]	X				X

a) Informed consent process to be fully documented (see Section 17.4). Informed consent must occur prior to any research-only (non-SOC) procedures.

b) See Section 4.0 and associated appendices. Registration can occur before or anytime after the start of standard of care ABVD therapy as long as protocol therapy can be started within timelines specified by the trial.

c) See Section 3.1. Please note that start of protocol therapy can only occur after criteria listed in Section 3.2 and requirements listed in Section 4.3 are met and after DCC sends out treatment confirmation and arm information.

d) Medical history to include a review of treatment history, any ongoing medical conditions, medical history pertaining to eligibility on study and involvement during study, and GHSG criteria.

e) See Section 9.0 and associated appendices. Correlative blood on C1D1, C1D15, and C2D1 can be collected up to 3 days before ABVD administration. Correlative blood at time of PET/CT-2 can be collected anytime after C2D15 of SOC ABVD and prior to start of protocol therapy. No correlative blood will be collected at SOC ABVD cycle 1, day 15 and SOC ABVD cycle 2, day 1 in patients who did not have a correlative blood collection performed at baseline (see Section 9.2.1).

f) See Section 11.3 and associated appendices. QOL assessment at time of screening can be done anytime after enrollment in the study but must be done prior to receiving C1D1 of standard of care ABVD. QOL assessment at time of PET/CT-2 can be done anytime after C2D15 of SOC ABVD and prior start of protocol therapy.

g) For patients who are already enrolled in the study at time of PET/CT-2, PET/CT-2 should be performed 6-15 days after administration of C2D15 of SOC ABVD. See response assessment in Section 11.1.

Table 10.2 -Brentuximab vedotin plus Nivolumab- Maintenance Arm A
(For PET/CT-2 Negative Patients Who Also Did Not Have a Bulky Mediastinal Mass at diagnosis)

- *Patients must meet criteria to start protocol therapy (Section 3.2).*
- *Treatment must start within 21-28 days post-C2D15 of standard of care ABVD.*
- *Each cycle of BV+Nivo maintenance (Mntc) is 21 days. Total is 3 cycles.*
- *Patients must have an **ANC ≥ 500/mm³ and platelets ≥ 75,000 cells/mm³** to be eligible for **day 1 of all cycles** on labs assessed within 3 days.*

Protocol Activity	Pre-treatment[a]	BV plus Nivo Mntc			End of Cycle 3*	Response Follow-Up[s] (+/- 30 days)
		C1D1 (+/- 3 days)	C2D1 (+/- 3 days)	C3D1 (+/- 3 days)		
AE Assessment		X	X	X	X	
Con-med review[b]	X	X	X	X	X	
ECOG Status[c]	X	X		X	X	
Vital Signs[d]	X	X	X	X	X	
Physical Exam[e]	X	X	X	X	X	
Labs[f] [CBC with diff Serum chemistry]	X	X	X	X	X	
Thyroid panel [f,g]		X	X	X	X	
Pregnancy Test[h]	X					
ECHO/MUGA[i]	(X)					
PFTs[i]	(X)					
BV		X	X	X		
Nivo		X	X	X		
PET/CT					X[m,w]	X[p,w]
CTs during FU						X[p,w]
Correlative Blood[k]	X[q]				X	
QOL Assessment[l]	X[q]				X	X

*** Protocol activities to occur 28 +/- 7 days from BV+nivolumab C3D1, unless otherwise specified.**

Table 10.3 ABVD followed by Nivolumab Maintenance Arm B1/B2 (Closed to accrual per protocol V8)
(For PET/CT-2 Negative Patients Including Those who had a Bulky Mediastinal Mass of ≥ 7.5 cm at diagnosis)

- *Patients must meet criteria to start protocol therapy (Section 3.2).*
- *Treatment must start within 14-28 days post-C2D15 of standard of care ABVD.*
- *Each ABVD (protocol therapy) cycle is 28 days (2 cycles of ABVD numbered C1 and C2).*
- *Each Nivolumab maintenance cycle is 14 days. Total is 6 cycles of Nivolumab alone.*

Protocol Activity	Pre-treatment[a]	Protocol ABVD				Nivo Mntc[v]	End of Cycle 6 of Nivo*	Response Follow-Up[s] (+/- 30 days)
		C1D1 (+/- 3 days)	C1D15 (+/- 3 days)	C2D1 (+/- 3 days)	C2D15 (+/- 3 days)	C1 to C6[j] (+/- 3 days)		
AE Assessment		X	X	X	X	X	X	
Con-med review[b]	X	X	X	X	X	X	X	
ECOG Status[c]	X	X		X		X	X	
Vital Signs[d]	X	X	X	X	X	X	X	
Physical Exam[e]	X	X	X	X	X	X	X	
Labs[f] [CBC with diff Serum chemistry]	X	X	X	X	X	X	X	
Thyroid panel [f,g]						X[t]	X	
Pregnancy Test[h]	X[h]					X[u]		
ECHO/MUGA[i]	(X)							
PFTs[i]	(X)							
ABVD		X	X	X	X			
Nivo						X		
PET/CT							X[n,w]	X[p,w]
CTs during FU								X[p,w]
Correlative Blood[k]	X[q]						X	
QOL Assessment[l]	X[q]				X		X	X

*** Protocol activities to occur 21 +/- 7 days from nivolumab C6D1, unless otherwise specified.**

Table 10.4 BV plus AVD <u>followed by</u> Nivolumab Maintenance Arm C
(For PET/CT-2 Positive patients)

- *Patients must meet criteria to start protocol therapy (Section 3.2).*
- *Treatment must start within 21-28 days post-C2D15 of standard of care ABVD.*
- *Each BV+AVD cycle is 28 days. Total is 4 cycles. Patients must have **platelets ≥ 75,000 cells/mm³** to be eligible for **day 1 of <u>all</u> cycles of BV+AVD** on labs assessed within 3 days.*
- *Each Nivolumab maintenance cycle is 14 days. Total is 6 cycles of Nivolumab alone.*

Protocol Activity	Pre-treatment[a]	BV plus AVD								End of Cycle 4 of BV plus AVD	Nivo Mntc[v] C1 to C6[j] (+/- 3 days)	End of Cycle 6 of Nivo*	Response FU[s] (+/- 30 days)
		Cycle 1		Cycle 2		Cycle 3		Cycle 4					
		D1 (+/- 3 days)	D15 (+/- 3 days)	D1 (+/- 3 days)	D15 (+/- 3 days)	D1 (+/- 3 days)	D15 (+/- 3 days)	D1 (+/- 3 days)	D15 (+/- 3 days)				
AE Assessment		X	X	X	X	X	X	X	X		X	X	
Con-med review[b]	X	X	X	X	X	X	X	X	X		X	X	
ECOG Status[c]	X	X		X		X		X			X	X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X		X	X	
Physical Exam[e]	X	X	X	X	X	X	X	X	X		X	X	
Labs[f] [CBC with diff Serum chemistry]	X	X	X	X	X	X	X	X	X		X	X	
Thyroid panel f,g											X[t]	X	
Pregnancy Test[h]	X[h]										X[u]		
ECHO/MUGA[i]	(X)												
PFTs[i]	(X)												
BV		X	X	X	X	X	X	X	X				
AVD		X	X	X	X	X	X	X	X				
Nivo											X		
PET/CT										X[o,w]		X[n,w]	X[p,w]
CTs during FU													X[p,w]
Correlative Blood[k]	X[q]			X						X[r]		X	X
QOL Assessment[l]	X[q]									X[r]		X	X

***Protocol activities to occur 21 +/- 7 days from nivolumab C6D1, unless otherwise specified.**

Start of protocol therapy can only occur after requirements listed in Section 4.3 are met and required information is submitted to the DCC.

Patients who discontinue protocol therapy before completion of planned protocol therapy (see Section 5.4) will proceed to "End of Cycle" visits (marked with * in the calendars) at similar timing to after last dose of therapy. If a previous scan was obtained within 8 weeks prior to the date of discontinuation, then repeating the scan at treatment discontinuation is not mandatory.

a) Pre-treatment activities will occur anytime after C2D15 of SOC ABVD and prior to Day 1 of protocol therapy, except as otherwise specified.
b) *Concomitant medications:* All concomitant medications and blood products administered or changed during protocol therapy until the end of treatment visit and the reason for administration must be recorded in the source documents and in eCRFs. See Section 5.7 and Section 5.8 for restrictions and guidelines.
c) See Appendix A.
d) Vital signs include heart rate, blood pressure, respiratory rate, oxygen saturation, and temperature.
e) Physical exam includes weight.
f) On treatment laboratory assessments can be performed within a window of -3 days. Serum chemistry panel to include glucose, BUN, creatinine, albumin, calcium, sodium, potassium, chloride, total CO_2, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, total protein, phosphate.
g) Thyroid panel includes TSH, free T4, and free T3.
h) For women of childbearing potential: serum or urine pregnancy test. Pregnancy test must be performed within 14 days prior to Day 1 of protocol therapy.
i) Results of MUGA/ECHO and PFTs performed within 120 days of start of protocol therapy will be used. Note: Typically, PFTs include spirometry, lung volume and diffusing capacity measurements, but for the purpose of this study only DLCO is required as criterion to start protocol therapy.
j) On Day 1 of each nivolumab cycle.
k) See Section 9.0 and associated appendices.
l) See Section 11.3 and associated appendices.
m) PET/CT should be performed 21 days +/-7 days after C3D1 of BV plus nivo. Any further treatment given for refractory and or relapsed disease should be recorded with outcomes if possible.
n) PET/CT should be performed 21 days +/-7 days after C6D1 of nivolumab maintenance. Any further treatment given for refractory and or relapsed disease should be recorded with outcomes if possible.
o) PET/CT should be performed within 15 days +/-7 days after C4D15 of BV plus AVD. Patients need to have a negative PET/CT defined as Deauville score of 1 to 3 to start nivolumab maintenance.
p) PET/CT or CT of neck, chest, abdomen/pelvis will be performed during the response follow-up period. If it is the institutional standard to defer CTs for long-term follow-up if patient had complete remission at time of end of treatment PET/CT, this is permitted as long as a careful neck exam is performed and documented at each point of response follow-up and documented in the medical record. Any further treatment given for relapsed disease should be recorded with outcomes if possible.
q) These time points are the **same** as those listed in the PET/CT-2 column in Table 10.1. Please refer to Table 10.1 (footnotes e and f), Section 9.0, Section 11.3, and associated appendices.
r) Anytime after C4D15 of BV+AVD and start of nivolumab.
s) Refer to Section 5.5 for details about the follow-up period. Imaging will be performed at 6, 12, and 18 months from end of treatment scan date. Response follow-up will be followed by survival follow-up.
t) Thyroid panel will be done every other cycle, i.e. on C1D1, C3D1 and C5D1 of nivolumab maintenance.
u) Pregnancy test to be done only on C1D1 of nivolumab maintenance.
v) Nivolumab maintenance should start within 14 to 28 days after C2D15 of protocol therapy ABVD for Arms B1/B2. Nivolumab maintenance should start within 14 to 45 days after C4D15 of BV plus AVD for Arm C.

w) If safe and feasible, it is recommended, but not mandatory, that patients with suspected refractory or relapsed disease undergo confirmatory biopsy.

11.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

11.1 Response

Lymphoma response will be evaluated using the 2014 Lugano Classification (see Appendix G). [83] Disease should be assessed by PET/CT preferably with IV contrast prior to start of standard of care ABVD and then for interim therapy imaging and end of treatment imaging. For follow-up, PET/CT or CT of neck, chest and abdomen/ pelvis preferably with IV contrast will be performed. Additional imaging studies such as MRI are permitted at the investigator's discretion. If patients on BV plus AVD have a repeat PET/CT prior to start of nivolumab maintenance that shows Deauville 4 or 5 it is strongly recommended, if safe and feasible, that patients undergo a confirmatory biopsy for active refractory disease.

11.2 Additional Clinical Endpoints

Progression-free survival (PFS) is defined as the time from start of standard of care ABVD C1D1 to the first observation of disease relapse/ progression or death due to any cause, whichever comes first. Patients with findings concerning for disease relapse/ progression are strongly recommended to undergo a confirmatory biopsy to document active cHL, if safe and feasible. 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-lymphoma treatment (with the exception of the 2 cycles of SOC ABVD) prior to disease progression, it is censored at the start of non-protocol anti-lymphoma treatment.

Overall survival (OS) is defined at the time from start of standard of care ABVD C1D1 to death from any cause. For patients alive at the last follow-up it is censored at the time of the last follow-up.

11.3 Quality of Life Assessments

As a component of the statistical analysis to assess arms of therapy subjects will undergo QOL assessments at specified time points utilizing the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire C30, version 3 (EORTC-C30) (see Appendix H).

This will be administered to patients at the following time points:

Table 11.3 Time points for QOL assessments

Time points	Arm A	Arms B1 and B2	Arm C
At baseline screening (prior to SOC ABVD cycle 1, day 1)*	X	X	X
At time of PET/CT-2**	X	X	X
At end of cycle 3 of BV+nivolumab	X	n/a	n/a
At C2D15 of protocol ABVD	n/a	X	n/a
At end of BV+AVD therapy***	n/a	n/a	X
At end of cycle 6 of nivolumab	n/a	X	X
At 6 months of follow-up	X	X	X
At 12 months of follow-up	X	X	X
At 18 months of follow-up	X	X	X

*For patients who started standard of care ABVD prior to study enrollment, it will not be possible to have the QOL assessment done at baseline, but the QOL assessment should still be performed at the subsequent time points.

** Anytime **after** C2D15 of SOC ABVD and **prior** to start of protocol therapy

***Anytime **after** C4D15 of BV+AVD and **prior** to start of nivolumab.

QOL assessment is strongly recommended, unless not feasible.

12.0 STATISTICAL PLAN

12.1 Statistical Considerations

This is a multi-arm phase II study for patients with newly diagnosed early stage (ES) cHL. After 2 cycles of standard of care ABVD, patients will be evaluated and classified by their PET scan results (PET/CT-2): negative if Deauville score is in the range of 1-3; positive if Deauville score is in the range of 4-5. Patients without PET/CT-2 results are not evaluable and will be replaced. Patients who are enrolled but do not proceed to receive protocol treatment will also be replaced.

The initial study design is as follows:
For PET/CT-2 negative patients without bulky disease (defined by mediastinal mass ≥ 7.5 cm at diagnosis), they will be randomized equally into the following two treatment arms, either

(A) 3 cycles of BV plus nivolumab, or
(B) 2 cycles of ABVD, then nivolumab maintenance q2w for 3 months.

All PET/CT-2 negative patients with bulky disease at diagnosis will be treated with Arm (B).
For PET/CT-2 positive patients, treatment will be:

(C) 4 cycles of BV plus AVD, then nivolumab maintenance q2w for 3 months.

Denotes Arms A, Arm B1, Arm B2, Arm C of patients who received treatment (A)-(C), respectively, where Arm B1 without bulky and Arm B2 with bulky disease. The objective of the study is to evaluate the efficacy and safety of the proposed combination treatments in Arms A, B1, B2, and C. The primary efficacy endpoint is progression free survival (PFS) rate. The primary analysis will be performed after all patients are followed for a minimum of 18 months.

Majority of the failures are expected to occur within the first 18 months (see below), thus 18-month PFS (PFS18) is chosen as the primary endpoint. It is difficult to ascertain the outcome of exactly comparable historical patients due to variations in definition of PET negativity, bulk disease, and therapy that patients received in the prior studies. Based on available historical data (see below), goals of the study treatment are to reach a PFS18 rate of 90% or more for PET/CT-2 negative non-bulky group, 80% or more for the PET/CT-2 negative bulky disease group, and 70% or more for the PET/CT-2 positive patients.

Oki et al. reported a 3-year PFS of 96% for early stage non-bulky patients with negative PET/CT-2 (n=114) treated with ABVD.[19] No events occurred after approximately 18 months. It was not clear how many cycles of ABVD in total patients received, and about half of the patients also received radiation; the definition of bulky disease was also somewhat different from the proposed study. Stratus et al. reported outcomes in early stage HL with non-bulky disease from CALGB/Alliance 50604.[46] In this study, patients with negative PET/CT-2 had 3-year PFS of 92% after a total of 4 cycles of ABVD (n=131). Only 1 of the 8 events occurred after 18 months; PFS18 appears around 94%. It was not clearly from the publication how bulky disease was defined in this study. Combining these data, we estimate that the historical PFS18 under the standard treatment for patients with negative PET/CT-2 without bulk disease is about 95%, and the goal of our study is to reach a PFS18 of 90% or more for PET/CT-2 non-bulky patients (Arm A/B1). To note, PET/CT-2 negative patients in our study will not be exposed to radiation therapy and thus potentially experience less long term toxicities.

In EORTC/LYSA/FIL H10, PET/CT-2 positive patients with early stage disease who received 3-4 cycles of ABVD plus radiation (n=192) had 3-year PFS of 77%.[44, 45] PFS18 appears around 83%. The 3-year PFS

was 77% for PET-2 positive non-bulky patients (n=13) and 20% for PET/CT-2 positive bulky stage II patients (n=5) after ABVD (some received with radiation) in the study by Oki et al.[19] All events occurred prior to 12 months. Stratus et al reported 66% 3-year PFS for PET/CT-2 positive patients (who received more intensive 2xBEACOPP plus radiation after ABVDx2) (n=13); all 4 events occurred within 18 months.[46] Little data can be found on outcome for PET/CT-2 negative patients with bulky disease who received ABVD. Oki et al. reported a 3-yr 83% PFS for Stage II bulky patients with negative PET/CT-2 (n=6); the only one event occurred prior to 18 months.[19] The goal of our study is to reach a PFS18 of 80% or more for PET/CT-2 negative bulky patients (Arm B2) and PFS18 of 70% of more for PET/CT-2 positive patients (Arm C).

12.1.2 Revised design per protocol version 08:

Given the slower rate of patient accrual and a lower proportion of patients with negative PET/CT-2 and initial non-bulky disease (i.e., those eligible for randomization), the study is being revised to close the randomization and Arm B. Arm B1/B2 will be closed for further patient enrollment and new patients will only be accrued to Arm A and Arm C. Starting with protocol version 08, patients who are PET/CT-2 negative (regardless of bulky disease status at diagnosis) will be assigned to Arm A (3 cycles of BV plus Nivolumab); patients who are PET/CT-2 positive will be assigned to Arm C (4 cycles of BV plus AVD, then nivolumab maintenance q2w for 3 months).

12.2 Sample Size Justification and Accrual Rate

The initial study sample size consideration is as follows:

We expect to enroll 264 patients in 22 months, with an accrual rate of 12 patients/month.

The sample size calculation is performed on the basis of the following assumption. Based on historical data, we first assume that overall PET/CT-2 positive rate is 12%, and there is a 5% drop-off over 18 months in each arm. Therefore, we expect to obtain binary PFS18 from 30 PET/CT-2 positive patients (Arm C) and 220 PET/CT-2 negative patients. Among 220 PET/CT-2 negative patients who will complete 18-month follow-up, we anticipate 25% (55 patients) will have bulky disease. Among the 165 PET/CT-2 negative patients without bulky disease, half of them (~82 patients) will be enrolled in Arm A and the other half (~82 patients) in Arm B1 with stratification by stage I vs II, and A vs B symptoms. If the goal of the targeted PFS18 is true (90% for Arms A and B1, 80% for Arm B2 and 70% for Arm C) and no arms are terminated early due to futility or toxicity, for PFS18, we expect 74 responses (patients failure-free for PFS18) in Arm A and in Arm B1, 44 responses in Arm B2 and 21 responses in Arm C, which will give an estimate of 90% credible interval for response rate with a width of 0.119, 0.174 and 0.266, respectively, using the prior distributions proposed in the following Bayesian continuous monitoring rules. Toxicity monitoring for Arm C will be based on any grade 3+ toxicity with a possible or higher attribution to any study agent during the first cycle of BV plus AVD.

12.2.2 Revised sample size consideration per protocol version 08:

As of 6/21/2022, the study enrolled 104 patients, with 102 who started protocol treatment and 2 terminated participation without receiving any protocol treatment: 24 on Arm A, 26 on Arm B1, 28 on Arm B2, and 24 on Arm C. The study is currently accruing about 50 patients per year. Per protocol version 08, the study will enroll up to 155 patients so that there are at least 150 patients who start protocol treatment.

With the revised protocol version 08, Arm B1 and B2 are closed, and patients will be assigned to Arm A or C only. Estimating a delay of up to 4 months for the revised protocol to be approved at the participating sites, the study will have enrolled approximately 5 more patients each on Arm A and B1, 6 more on Arm

B2, and 5 more on Arm C prior to the protocol version 08 approval. For the remaining ~31 patients enrolled per protocol version 08, the projected number is 24 Arm A and 7 Arm C patients. Therefore, the projected final numbers are: ~53 Arm A, ~65 Arm B (Arm B1/B2 combined), and ~36 Arm C.

The goal is to still reach a PFS18 rate of 90% for Arm A (which will now include ~7 patients with negative PET/CT-2 and initial bulky disease who would have been assigned to Arm B2 on the original design). With n=53, the 2-sided 95% confidence interval for PFS18 will have a width of approximately 16% at target PFS18 of 90%. The goal for Arm C is not changed as there is no change to this subgroup or its treatment. With 36 patients, the 95% confidence interval for PFS18 will have a width of approximately 30% at target PFS18 of 70%. With the revised design, patients enrolled to Arm B1/B2 will be analyzed as one group which will include approximately half patients with bulky disease and half without bulky disease; therefore, the target PFS18 is 85% which is the middle of Arm B1 and Arm B2 targets. With 65 patients, the 95% confidential interval for PFS18 will have a width of approximately 17%.

NOTE: per protocol version 09, dated 03/21/23, the maximum sample size is increased from 155 to up to 162 patients to allow a few more patients to be enrolled to ensure that at the end there will be at least 150 evaluable patients, due to the potential gap between enrollment and start of protocol treatment on this study.

12.3 Futility and Toxicity Monitoring

A Bayesian adaptive design method will be used for futility and toxicity monitoring.[84]A short term efficacy endpoint, 6-month progression free survival (PFS6) rate, will be examined for futility monitoring with the same target response rate of PFS18. Pre-specified toxicity monitoring rule will only be applied for Arm C within the first cycle treatment of BV plus AVD, while we are confident about low toxicity for Arms A and B based on abundant historical data.

Each arm will be monitored independently. The specific arms will be stopped early if

$$\Pr(\text{Arm A PFS6 rate} < 0.90 \mid \text{data}) > 0.975;$$

$$\Pr(\text{Arm B1 PFS6 rate} < 0.90 \mid \text{data}) > 0.975;$$

$$\Pr(\text{Arm B2 PFS6 rate} < 0.80 \mid \text{data}) > 0.975;$$

$$\Pr(\text{Arm C PFS6 rate} < 0.70 \mid \text{data}) > 0.95$$

or

$$\Pr(\text{Arm C toxicity rate in cycle 1 of BV + AVD} > 0.30 \mid \text{data}) > 0.95.$$

That is, Arm A or B1 will be stopped early if there is more than a 97.5% probability that the PFS6 rate is lower than 90%; Arm B2 will be stopped early if there is more than a 97.5% probability that the PFS6 rate is lower than 80%; Arm C will be stopped early if either there is more than a 95% probability that the PFS6 rate is lower than 70% or more than a 95% probability that the toxicity rate is higher than 30%. The smaller cutoff was chosen for Arm C because the maximum sample size in that arm is only around one half of the others. We assume that PFS6 rate in Arm A and B1 follows a prior distribution of beta (0.90, 0.10), PFS6 rate in Arm B2 follows a prior distribution of beta (0.80, 0.20), and PFS6 and toxicity rates in Arm C follow a prior distribution of beta (0.70, 0.30) and beta (0.30, 0.70), respectively. Each arm will be monitored in parallel. The early termination of an arm won't hinder the accrual for other arms.

The above futility and toxicity monitoring rules will be implemented by a cohort size of 12 for Arm A and B1, 11 for Arm B2 and 10 for Arm C, starting from the first 12th, 11th and 10th patients in each arm with PFS6/toxicity outcome available. The corresponding stopping boundaries are listed in Tables 12.3.1, 12.3.2, and 12.3.3. For example, if there are 4 or less patients achieving PFS6 among the first 10 patients,

stop Arm C early due to futility. Arm C also needs to be stopped early due to the agent is too toxic if there are 6 or more patients experience drug related grade 3 or higher toxicity at a possible or higher attribution during the first cycle of BV-AVD for any study drug among the first 10 patients. The patient enrollment won't be halted for interim looks. If any arm were stopped early for futility or toxicity, or has met target accrual for that arm, that treatment option would be dropped off from study and any future patients will receive the standard of care, but the recruitment for the other arms will continue.

Per protocol version 08, the study design is revised and Arm B1 & B2 are being closed. The monitoring boundaries for Arm B1 and B2 will be followed until the point these arms are closed. The monitoring boundary for Arm A will continue as below (even though per the revised design a few patients with initial bulk disease will now be included in Arm A rather than Arm B2 as the original design), as an informal assessment and outcome monitoring, until the entire study accrual is completed (Arm A projected final accrual is ~53 patients). Arm C design is not changed, but it will not be closed once 30 patients are enrolled. Arm C will close (with projected ~36 patients) when the entire study accrual is closed. Given that the projected final sample size for Arm C is only a few more than the initial design, we will not add an additional monitoring after 30 Arm C patients because: 1) there will be a 6-month delay in obtaining PFS6 data and by the time PFS6 data are available for 30 Arm C patients the study accrual will be (almost) finished; 2) there have not been any toxicity concern for Arm C so extending the monitoring to 30 patients is not considered necessary.

Table 12.3.1 Stopping boundaries for futility and toxicity monitoring

<table>
<tr><th rowspan="2">Interim

Look</th><th colspan="2">Arm A or Arm B1</th><th colspan="2">Arm B2</th><th colspan="3">Arm C</th></tr>
<tr><th>sample (n)</th><th>response (x)</th><th>sample (n)</th><th>response (x)</th><th>sample (n)</th><th>response (x)</th><th>toxicity (y)</th></tr>
<tr><td>1</td><td>12</td><td>≤8</td><td>11</td><td>≤5</td><td>10</td><td>≤4</td><td>≥6</td></tr>
<tr><td>2</td><td>24</td><td>≤18</td><td>22</td><td>≤13</td><td>20</td><td>≤10</td><td>≥10</td></tr>
<tr><td>3</td><td>36</td><td>≤28</td><td>33</td><td>≤21</td><td rowspan="5">30</td><td colspan="2" rowspan="5">Accrual target reached. Stop accrual to this arm.</td></tr>
<tr><td>4</td><td>48</td><td>≤38</td><td>44</td><td>≤29</td></tr>
<tr><td>5</td><td>60</td><td>≤48</td><td rowspan="3">55</td><td rowspan="3">Accrual target reached. Stop accrual to this arm.</td></tr>
<tr><td>6</td><td>72</td><td>≤59</td></tr>
<tr><td>7</td><td>~82</td><td>Accrual target reached. Stop accrual to this arm.</td></tr>
</table>

Given the first n patients, if actual response (i.e., the number of patients who are failure-free for PFS6) ≤ x, or number of patients with toxicity ≥ y during cycle 1 (Arm C only), we stop the arm early due to futility or toxicity.

The 2 tables below are the original design operating characteristics. However they are no longer relevant as the design is being changed in protocol version 08. None of the arms met any stopping criteria prior to this revision. There have been no safety concerns and starting with protocol version 08, all remaining arms will be closed at the same time at the end of the study, rather than potentially on an individual arm basis based on the individual arm outcome per the original design.

Table 12.3.2 Operating characteristics for Arms A, B1 and B2

(No Longer Applicable per Protocol Version 08)

True PFS6 Rate	Prob (stop Arm A or Arm B1 early)	Average number of patients treated*	Prob (stop Arm B2 early)	Average number of patients treated
0.70	0.995	22.2	0.403	44.0
0.75	0.953	30.9	0.171	50.3
0.80	0.764	46.1	0.045	53.7
0.85	0.373	65.4	0.007	54.8
0.90	0.070	78.4	0.000	55.0
0.95	0.003	81.8	0.000	55.0

Based on simulations from 10,000 trials.

*Number of patients whose data included in the interim monitoring. Because accrual is not suspended for interim monitoring and the delay in getting PFS6, if an arm is prematurely halted, the number of patients that have been treated at the time of suspension will be larger.

Table 12.3.3 Operating characteristics for Arm C (assuming independent PFS6 and toxicity)

(No Longer Applicable per Protocol Version 08)

True PFS6 Rate	True Toxicity Rate	Prob(stop the trial early)	Average number of patients treated*
0.50	0.10	0.630	19.9
	0.30	0.658	19.4
	0.50	0.863	15.2
0.70	0.10	0.076	28.8
	0.30	0.145	27.6
	0.50	0.658	19.4
0.90	0.10	0.000	30.0
	0.30	0.076	28.8
	0.50	0.630	19.9

Based on simulations from 10,000 trials.

*Number of patients whose data included in the interim monitoring. Because accrual is not suspended for interim monitoring and the delay in getting PFS6, if an arm is prematurely halted, the number of patients that have been treated at the time of suspension will be larger.

The above stopping boundaries and operating characteristics were calculated and adjusted using MultcLean (v.2.1.0) design software downloaded from http://biostatistics.mdanderson.org/SoftwareDownload.

12.4 Selection of Favorable Regimen for PET/CT -2 Negative Patients without Bulky Disease (Not Applicable per Protocol Version 08)

Below are the design considerations prior to protocol version 08. Given the design change in protocol version 08, the following considerations are being retired as they are no longer applicable/relevant.

In order for a regimen to be selected for PET/CT-2 negative non-bulky patients at the end of this trial for further investigation, the observed PFS18 on the corresponding arm (estimated based on Kaplan-Meier method) must be at least 90%. If neither arm meets the minimum PFS18 of 90%, then neither arm will be selected. If only one arm meets this minimum efficacy threshold, then this arm will be selected provided

that other factors such as toxicity appear reasonable. When both arms meet this minimum efficacy threshold, if one arm has a "favorable" PFS defined as an observed hazard ratio (HR) of 1.2 or higher, then this particular arm will be chosen provided that there are no significant concerns with this arm such as toxicity concerns. When both arms meet the minimum efficacy threshold and the observed HR is between 0.83 (1/1.2) – 1.2, meaning neither arm has a "favorable" PFS compared to the other arm, the selection decision will be deferred pending analysis examining other factors such as toxicity profile and cost of the therapy. The statistical decision rules outlined above are the general guidelines, not strict rules. Besides these guidelines, the study team will take into consideration all data collected on this study and any new knowledge about the disease and therapy that may become available later when making the final decision. Assuming exponential survival, 82 eligible patients per arm accrued within 2 years, with 1.5 years of additional follow-up, the probabilities of selecting Arm A, Arm B1, neither arm for further development based on PFS, or decision deferred to analysis on other factors are given in Table 12.4. Under the hypothesis of true 18-month PFS in both arms is 80%, the probability of moving forward incorrectly is 2%.

Table 12.4 Probabilities of selecting Arm A or Arm B1

True PFS18			Selection Probability based on PFS			
BV plus nivo (Arm A)	ABVD (Arm B1)	HR	BV plus nivo (Arm A)	ABVD (Arm B1)	Neither Arm	Decision Deferred
80%	80%	1.0	0.010	0.010	0.980	0.000
80%	90%	0.47	0.004	0.566	0.429	0.001
80%	95%	0.30	0.000	0.978	0.022	0.000
90%	80%	2.1	0.560	0.004	0.435	0.001
90%	90%	1.0	0.342	0.348	0.184	0.126
90%	95%	0.49	0.031	0.878	0.010	0.082
95%	80%	4.4	0.979	0.000	0.021	0.000
95%	90%	2.1	0.882	0.031	0.008	0.079
95%	95%	1.0	0.375	0.370	0.001	0.254

Based on simulations from 10,000 trials.

12.5 Statistical Analysis Plan

Data analysis will be performed using SAS or R, as appropriate. Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize toxicity profile and categorical variables. Response and its 95% confidence interval will be calculated. The distribution of time-to-event endpoints such as progression free survival will be estimated using the method of Kaplan and Meier. Log-rank test and Cox proportional hazards model will be applied to compare the treatment effects and clinical factors including bulky disease status. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. Longitudinal analysis will be applied to evaluate the quality of life over time by each arm using mixed-effects model. For the exploratory objects, descriptive statistics will be used to summarize the correlative study measures such as GEP and MRD assessments. Dynamic prediction modeling with time-dependent covariate in survival analysis will be explored based on ctDNA levels.

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 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 City of Hope's electronic capture system that is compliant with 21 CFR Part 11 (Medidata Rave).

13.3 Case Report Forms/Data Submission Schedule

Study personnel 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 Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated 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 AE assessment/notification
Response Assessment Forms	PET/CT-2 given the stratification of treatment must be entered within 3 business days of assessment with information in terms of the Deauville score of the PET/CT scan. Other response assessments can be entered within 10 calendar days of the assessment.
Other Assessment Forms (concomitant medications)	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 REPORTING OF ADVERSE EVENTS & UNANTICIPATED PROBLEMS

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

14.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy (available from the DCC). Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and 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 unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it 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 is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite –** The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

14.2 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 Lead Study PI and City of Hope DCC via an expedited report.

14.3 Pregnancies

14.3.1 Female subjects

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant, or in a male participant's partner, occurring after the participant receives the first dose of protocol therapy up to 6 months post-last dose of brentuximab vedotin or nivolumab are considered immediately reportable events. Protocol therapy is to be discontinued immediately. **The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Lead Study PI and City of Hope DCC immediately within 24 hours of awareness**; the lead Study PI or designee will subsequently inform Seattle Genetics and Bristol Myers Squibb along with information if female subject was exposed to brentuximab vedotin or nivolumab during pregnancy. The female subject may be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

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

Abnormal pregnancy outcomes and neonatal deaths that occur within 28 days of birth should be reported as an SAE per expedited reporting guidelines.

Any infant death after 28 days that the Investigator suspects is related to the in utero exposure to protocol therapy should also be reported as an SAE per expedited reporting guidelines; the Study PI or designee will subsequently inform Seattle Genetics and Bristol Meyers Squibb.

14.3.2 Male Participants

If a female partner of a male participant becomes pregnant within 90 days post-last dose of protocol therapy, the male participant should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

The Investigator should make every effort to follow the outcome of the pregnancy per institutional policies, and should notify the lead Study PI and the City of Hope DCC.

14.4 Routine AE Collection and Reporting Guidelines

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin at initiation of protocol therapy until ending study participation (No AE data will be collected during standard of care ABVD).

Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, etc.) must also be reported in routine study data submissions.

Note: The highest grade of any toxicity will be collected for each cycle during protocol therapy. For Arm C patients only, for the first cycle of BV + AVD, all grade 3 or higher toxicities (regardless of highest grade or not) will also need to be collected.

14.5 Expedited AE Reporting Guidelines

Each adverse event 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.

Table 14.5 indicates what events must be reported expeditiously.

Table 14.5 Expedited Reporting Guidelines

Time point	What to report expeditiously
From the signing of the consent to study completion	All unanticipated problems
From Screening until Day 1 of protocol therapy	All SAEs related to protocol procedures
From first dose of protocol therapy up to 30 days after the last dose of protocol 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 ▪ Secondary malignancy ▪ Pregnancy and lactation ▪ Discontinuation of protocol therapy due to unusual or unusually severe AE considered related to study agents.
After 30 days post-last dose of brentuximab vedotin or nivolumab (follow-up)	▪ All SAEs that are considered possibly, probably, or definitely related to therapy. ▪ Pregnancy and lactation (up to at least 6 months post-last dose)
Notes: Follow-up reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event. Reportable serious adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator; for ongoing reportable adverse events that are unrelated to protocol therapy, the follow-up period may end at the 30-days post last-dose assessment. The DCC should be consulted prior to ending the follow-up of events that have stabilized.	

14.5.1 Expedited reporting guidelines **(COH only)**

14.5.1.1 To the COH DSMC/IRB

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. This includes all SAEs and UPs that meet COH DSMC/IRB expedited reporting criteria that occurred at COH and non-COH sites.

14.5.1.2 To Participating Investigators

- Report all expedited reportable AEs 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 (if applicable), and, for non-COH sites, a statement that the report should be submitted to their local IRB for review if applicable per local IRB policy.

- Forward to participating sites all IND safety reports received from Seattle Genetics and BMS, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

14.5.2 Expedited reporting guidelines **(non-COH sites only)**

All events that meet the criteria specified in Table 14.5 will be reported to the DCC and Study PI within 24 hours of notification that the event met the expedited reporting criteria.

1. 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 COH DCC copies of the IRB submission and corresponding IRB response.
2. Document/describe the AE/UP on each of the following:
    a. MedWatch 3500A or local IRB submission document*
    MedWatch 3500A is downloadable form at https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
    *The local IRB submission document may be used if the document template is approved by the DCC
    b. Expedited Reporting Coversheet
    A modifiable Microsoft Word document is also available from the DCC. An electronic signature on the document will be accepted.
3. Scan and email above documents to the Study PI (aherrera@coh.org) and DCC@coh.org with the subject title as "Herrera NAHLC Early Stage Protocol SAE COH IRB # 18157".
    a. If available, sites may include the local IRB submission for this event in the submission.
4. If an email receipt from DCC personnel is not received within one working day, please email DCC@coh.org.

14.6 Reporting to Industry Partners

1. This study is **IND exempt** and therefore does **not** require reporting to the FDA. However, any SAE that meets the FDA's criteria for expedited reporting, regardless of the site of occurrence, should be reported to **Seattle Genetics and Bristol Myers Squibb**.

    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 to Seattle Genetics and Bristol Myers Squibb on a MedWatch 3500A form.

    The criteria that require expedited reporting to Seattle Genetics and BMS are:
    - Any unexpected fatal or life threatening adverse experience associated with use of the drug. Must be reported to Seattle Genetics and Bristol Myers Squibb no later than 7 calendar days after initial receipt of the information.

- Any adverse experience associated with use of the drug that is both serious and unexpected must be reported to Seattle Genetics and Bristol Myers Squibb no later than 15 calendar days after initial receipt of the information.
- Any follow-up information to a study report shall be reported to Seattle Genetics and Bristol Myers Squibb as soon as the relevant information becomes available.

Email: drug.safety@seagen.com (Fax: 425-527-4308 or 866-333-6627 [USA only toll free])

Email: Worldwide.Safety@BMS.com

2. Submit to Seattle Genetics and Bristol Myers Squibb all pregnancy related events within 48 hours of being aware of the event on the Seattle Genetics Pregnancy Report Form.

   Email: drug.safety@seagen.com (Fax: 425-527-4308 or 866-333-6627 [USA only toll free])

   Email: Worldwide.Safety@BMS.com

3. Additional communications to Seattle Genetics and Bristol Myers Squibb:
   a. Report to Seattle Genetics aggregate SAEs monthly via email :IST@seagen.com and to Bristol Myers Squibb at Worldwide.Safety@BMS.com
   b. For BMS: Aggregate SAEs and AEs every 3 months as per ISR safety reporting guidelines.
   c. Assist Seattle Genetics and Bristol Myers Squibb in investigating any SAE and will provide any follow-up information reasonably requested by them.

15.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the City of Hope Clinical Research Protocol Deviation policy.

Non-COH Sites:

Deviations meeting the criteria specified in the City of Hope Clinical Research Protocol Deviation policy (available from the DCC) will be reported to the DCC and Study PI within **24 hours** of notification that the event occurred.

Procedure for reporting deviations to the COH DCC:

1. Document the deviation on the Deviation Reporting Coversheet. This modifiable Microsoft Word document is available from the DCC. An electronic signature on this document will be accepted.
2. Scan and email the Deviation Reporting Coversheet to the Study PI (aherrera@coh.org) and DCC@coh.org **within 24 hours** of notification of the deviation with the email subject title of

"Herrera NAHLC Early Stage Protocol Deviation COH IRB # 18157". If an email receipt from the DCC is not received within one working day, please email DCC@coh.org.

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

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

16.1 All Investigator Responsibilities

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 subjects under the investigator's care; and for the control of drugs under investigation.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, site investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs 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.

16.4 Quality Assurance

Clinical site 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 Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

16.5 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because there is a high probability of an event that is serious and prolonged or permanent as a result of study participation (investigator-initiated/ industry sponsored, multi-center, randomized phase 2 trial that

includes interventions to prevent or treat a disease that leads to death or irreversible morbidity, and that have substantial risk or potential for severe toxicity).

16.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 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.

17.2 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 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

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Each participating non-COH 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). The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator, and, for external sites, the possession of the DCC, before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems 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.

All participating sites must follow the lead institution's IRB-approved protocol.

17.4 Informed Consent

Each participating non-COH 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 site's IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or participating institution or any relationship they have with City of Hope or participating institution. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant 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.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the site investigator and available for inspection by 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.

17.5 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. The COH DCC should be promptly notified of the change in participant status.

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

Participants who agreed to the collection of research specimens 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.

17.6 Special and Vulnerable Populations

17.6.1 Inclusion of Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. 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 the effects of brentuximab vedotin, nivolumab, and chemotherapy on embryogenesis, reproduction, and spermatogenesis in humans are unknown.

17.6.2 Inclusion of Pediatric Population

Pediatric participants age 16 to 18 are included in this trial. However, as the safety and effectiveness of the protocol therapy is not well described in younger patients those that are < 16 are excluded. Furthermore, Children's Oncology Group (COG) has pediatric cHL trials ongoing and/or planned per discussions with lead PI in COG.

17.6.3 Inclusion of HIV Positive Individuals

Participants with HIV are included based on specifications outlined in inclusion criteria.

17.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and 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 local IRB approval.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

17.7 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 subject authorization informing the subject 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, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects 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 subject 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 subjects 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, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient'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, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will be either: (a) discarded or (b) placed in a COH IRB approved biorepository with clinical information and potentially PHI attached. For patients who enrolled on the study but who end up not starting protocol therapy, any correlative blood sample collected will be destroyed.

With regard to which option will apply, each site IRB may choose to either: (a) leave the determination to the participant via a question in the informed consent document, which would be communicated to the study registrar (DCC) at the time of participant registration, OR b) may choose to make a single determination on behalf of their respective participants, and communicate that determination to their respective participants via the informed consent.

17.9 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. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Brentuximab vedotin and nivolumab will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope or at the non-COH site to the injured participant. 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.

17.11 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 between City of Hope and Seattle Genetics. 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 CRITERIA

ECOG Performance Scale [85]	
Grade	**Descriptions**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: DCC REGISTRATION COVERSHEET

COH Protocol # 18157: **A Phase 2 Front-Line PET/CT-2 Response Adapted Brentuximab Vedotin and Nivolumab Incorporated and Radiation Free Management of Early Stage Classical Hodgkin Lymphoma (cHL)**

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e-mail:

SECTION A

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution: Investigator/Treating Physician:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:

Race		Ethnicity	
☐	Black	☐	Hispanic
☐	Caucasian	☐	Non-Hispanic
☐	Asian	☐	Other _____
☐	American Indian		
☐	Native Hawaiian/Pacific Islander		
☐	Other_____ _____		

Method of Payment:_____

Codes:

01 Private	06 Military or Veterans Adm. sponsored
02 Medicare	07 Self-pay (no insurance)
03 Medicare & private ins.	08 No means of payment (no insurance)
04 Medicaid	09 Unknown
05 Medicaid & Medicare	

† For patients who have not yet started SOC ABVD therapy.

SECTION B - TO BE COMPLETED BY THE PI OR TREATING PHYSICIAN

Check one of the following boxes:

Note: Determination of bulky vs. non bulky disease is based on baseline PET/CT at diagnosis.

☐ PET/CT-2 POSITIVE ***or*** ☐ PET/CT-2 NEGATIVE, BULKY ***or*** ☐ PET/CT-2 NEGATIVE, NON-BULKY*

****If PET/CT-2 NEGATIVE, NON-BULKY, complete the following:***

☐ Stage I ***or*** ☐ Stage II
☐ B Symptoms ***or*** ☐ No B Symptoms

Date of SOC ABVD C2D15: _____

Projected start date of protocol therapy: _____

PI/Treating MD Signature: _____ Date: _____

APPENDIX C: CORRELATIVE TISSUE FORM (FOR ALL SITES)

A copy of this form should accompany the sample shipments to COH Pathology Core.

Non-COH sites: refer to Appendix D for shipping instructions to COH Pathology Core.

COH IRB number: 18157	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): _____/_____/_____	
Diagnosis:	
Tissue type (FFPE scrolls, slides):	
Number of scrolls:	Number of slides:

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

APPENDIX D: TISSUE SHIPPING GUIDELINES TO CITY OF HOPE PATHOLOGY CORE

*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.

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 C)** 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 E: CORRELATIVE BLOOD COLLECTION FORM

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

NOTES:

- For patients who enrolled on the study but who end up not starting protocol therapy, any correlative blood sample collected during SOC ABVD will be destroyed.
- For patients who started SOC ABVD prior to study enrollment, and who therefore did not have a correlative blood collection performed at baseline (prior to SOC ABVD cycle 1, day 1), their first correlative blood collection will occur at time of PET/CT-2.

Arms A, B1 and B2 only:

Sample #	Timepoint of Collection	Expected Volume	Tube Type Used (Select One)	Collected Volume	Time of Collection	Actual Date of Collection	Indicate which sample was collected
1.	Baseline	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
2.	SOC ABVD Cycle 1, Day 15	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
3.	SOC ABVD Cycle 2, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
4.	At time of PET/CT-2	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
5.	EOT	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐

Arm C only:

Sample #	Timepoint of Collection	Expected Volume	Tube Type Used (Select One)	Collected Volume	Time of Collection	Actual Date of Collection	Indicate which sample was collected
1.	Baseline	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
2.	SOC ABVD Cycle 1, Day 15	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
3.	SOC ABVD Cycle 2, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
4.	At time of PET/CT-2	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
5.	BV+AVD Cycle 2, Day 1	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
6.	End of BV+AVD therapy	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
7.	EOT	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
8.	12 months post-therapy	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
9.	18 months post-therapy	20 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐

EOT=End of treatment.

A copy of this form should accompany the sample shipments to APCF. Refer to Appendix F for **shipping instructions to APCF (City of Hope)**.

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

APPENDIX F: BLOOD SHIPPING GUIDELINES TO APCF (COH)

*Guidelines apply to **non-COH** sites.*

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

Laboratory receiving samples:	APCF
When to ship:	**As soon as possible**, and within **5 days** of collection*, should be shipped via **overnight courier**
Temperature conditions of shipment:	Ambient temperature
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

*Please make every effort to ship the blood on the same day, especially for blood collected on Wednesdays.

1. **On the day of shipment**, email Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org) or their representative the FedEx shipment #.
2. Ship samples with a copy of the **Blood Collection Form** (Appendix E) to:

Dr. Tim Synold
Analytical Pharmacology Core Facility
Shapiro 1042
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

APPENDIX G: LYMPHOMA RESPONSE CRITERIA [75]

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 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

Response	Site	CT-Based Response	PET-CT Based Response
	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
	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	New FDG-avid foci consistent with lymphoma at interim OR • End-of-treatment assessment

Response	Site	CT-Based Response	PET-CT Based Response
		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	
	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).

**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.

APPENDIX H: EORTC-QLQ-C30, VERSION 3 QUESTIONNAIRE [86]

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

Time point of collection (please check one)	*Arm A*	*Arms B1 and B2*	*Arm C*
At baseline	☐	☐	☐
At time of PET/CT-2	☐	☐	☐
At end of cycle 3 of BV+nivolumab	☐	n/a	n/a
At C2D15 of protocol ABVD	n/a	☐	n/a
At end of BV+AVD therapy	n/a	n/a	☐
At end of cycle 6 of nivolumab	n/a	☐	☐
At 6 months of follow-up	☐	☐	☐
At 12 months of follow-up	☐	☐	☐
At 18 months of follow-up	☐	☐	☐

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

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

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

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4

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

25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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