City of Hope National Medical Center
1500 E. Duarte Road
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TITLE: A Phase 2 Study of Brentuximab Vedotin Plus Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (CHEP-BV) Followed by BV Consolidation in Patients with CD30-Positive Peripheral T-cell Lymphomas

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DISEASE SITE: Non-Hodgkin Lymphoma
STAGE (if applicable): N/A
MODALITY: Drug-Antibody Conjugate and Chemotherapy
PHASE/TYPE: Phase 2 with Safety Lead-in

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Clinical Trial Protocol

A Phase 2 Study of Brentuximab Vedotin Plus Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (CHEP-BV) Followed by BV Consolidation in Patients with CD30-Positive Peripheral T-cell Lymphomas

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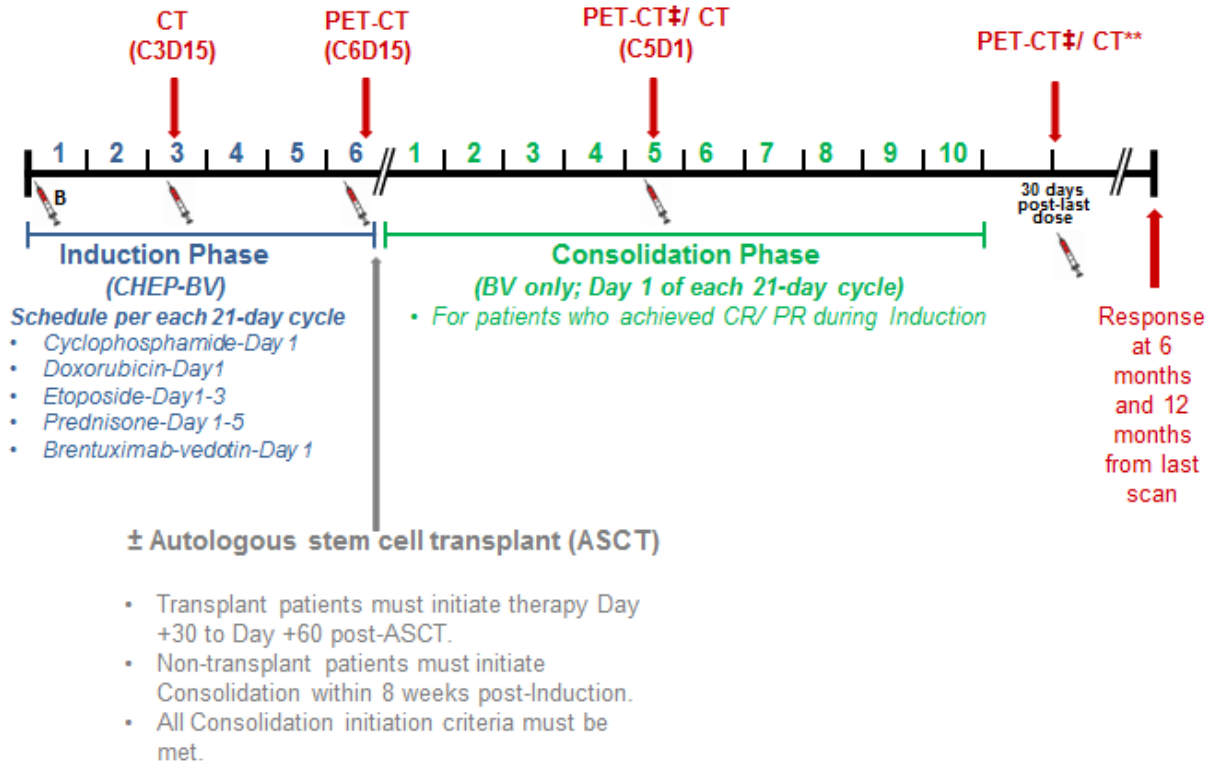
EXPERIMENTAL DESIGN SCHEMA



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

** CT/PET-CT to be performed if last imaging occurred >8-12 weeks ago.

Correlative blood (B) should be obtained at imaging timepoints.

PROTOCOL SYNOPSIS

Protocol Title

A Phase 2 Study of Brentuximab Vedotin Plus Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (CHEP-BV) Followed by BV Consolidation in Patients with CD30-Positive Peripheral T-cell Lymphomas

Study Detail

Population/Indication(s):	CD30-Positive Peripheral T-cell Lymphomas
Phase:	Safety Lead-in/ Phase 2
Sample Size:	**Safety Lead-in:** Evaluable 6-12 **Phase 2:** Evaluable 48 (includes evaluable participants from Safety Lead-in treated at the RP2D) Anticipated Maximum: 53
Estimated Accrual Duration:	36 months
Estimated Study Duration	~ 8 years
Participant Duration:	~ 5 years
Participating Sites:	• City of Hope Duarte, CA • MD Anderson • Hackensack University • BC Cancer Agency • Ohio State University
Study Agents:	Brentuximab vedotin, Cyclophosphamide, Doxorubicin, Etoposide, Prednisone
Sponsor:	City of Hope
Industry Partner:	Seattle Genetics
Industry Partner Protocol ID:	35-IST-039

Rationale for this Study

Peripheral T-cell lymphomas (PTCL) are an uncommon group of disorders, accounting for about 10% of all non-Hodgkin lymphomas (NHL). EBV-associated extranodal NK/T-cell lymphoma (NKTCL) is more common in parts of Asia and South America, while angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma, not otherwise specified (PTCL NOS) are more common in Western countries. PTCLs are generally associated with poor outcomes after standard therapy, with variation in prognosis according to disease subtype. With high relapse rates after standard therapy including ASCT and inadequate second line treatment options, novel strategies for decreasing relapse rates in patients with PTCL are urgently needed.

CD30 is a cell surface antigen expressed on several malignancies including Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL) and other peripheral T-cell lymphomas (PTCL). Brentuximab vedotin (BV), previously known as SGN-35, is an antibody drug conjugate (ADC) directed against the CD30 antigen that is being developed to treat patients with CD30-positive hematologic malignancies.

Brentuximab vedotin is an effective treatment for patients with PTCL. Brentuximab vedotin is FDA-approved for relapsed CD30 expressing systemic anaplastic large cell lymphoma [39]. In a single-arm Phase 2 study, 58 patients were treated with brentuximab vedotin 1.8mg/kg intravenously every 3 weeks, resulting in a 86% ORR, including 33 patients (57%) complete remissions, and 17 (29%) partial remissions. The median durations of overall response and CR were 12.6 and 13.2 months, respectively. More recently, in a Phase 2 study of brentuximab vedotin in 34 patients with relapsed or refractory PTCLs other than ALCL, brentuximab vedotin treatment resulted in an ORR of 41%, with a 54% ORR in patients with AITL. The median duration of response was 7.6 months, and the median follow-up time was 2.7 months. The overall disease control rate was 59%, with a 77% disease control rate in patients with AITL [1].

The ECHELON-2 trial is a randomized trial that is currently comparing the addition of brentuximab vedotin to cyclophosphamide, doxorubicin, and prednisone (CHP) with standard-of-care cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in the initial treatment of patients with CD30-positive PTCL. However, based on evidence that the addition to etoposide to standard CHOP (CHOEP) is beneficial, CHOEP is often administered as initial treatment of patients with PTCL. Therefore, while ECHELON-2 will address whether brentuximab vedotin added to CHP is superior to CHOP therapy, there are no data regarding the safety and efficacy of brentuximab vedotin added to etoposide-containing induction chemotherapy (cyclophosphamide, doxorubicin, etoposide, and prednisone - CHEP). Since November 16, 2018 and based on the ECHELON-2 trial, brentuximab vedotin is FDA-approved in combination with CHP chemotherapy for previously untreated, systemic ALCL or other CD30-expressing PTCL. We propose a Phase 2 study to assess the anti-lymphoma activity brentuximab vedotin when combined with CHEP (CHEP-BV) in patients with newly-diagnosed CD30-positive PTCL.

Objectives

Primary Objectives

Safety Lead-in

- Assess the safety and tolerability of CHEP-BV, as induction therapy in patients with CD30-positive peripheral T-cell lymphoma (PTCL)

Phase 2

- Assess the anti-lymphoma activity of CHEP-BV as induction treatment in patients with CD30-positive PTCL.

Secondary Objectives

- Describe outcomes of CD30-positive PTCL patients who go on to receive BV consolidation therapy post CHEP-BV induction with/without autologous hematopoietic cell transplantation/radiation.

Exploratory Objective

- Explore the rate of minimal residual disease (MRD) negativity (as assessed by next-generation sequencing) and MRD kinetics after CHEP-BV and BV consolidation therapy in CD30-positive PTCL.
- Explore the possible association between outcome after study treatment and CD30 expression, gene expression profiles (GEP), and genetic mutations as measured in PTCL tumor samples.

Study Design

This is an open-label multi-site Phase 2 study with a Safety Lead-in to test the safety and efficacy of CHEP-BV as Induction therapy followed by single-agent brentuximab vedotin consolidation therapy for the treatment of CD30-positive PTCL.

The safety lead-in segment with 2 dose levels (starting dose level and 1 de-escalation level) will follow standard 3+3 dose escalation/de escalation/expansion rules based on observed toxicity during Induction Cycle 1. The study will accrue 48 response evaluable patients for the Phase 2 response evaluation.

Newly diagnosed CD30-postitive PTCL patients will be treated with up to 6 cycles of CHEP-BV followed by up to 10 cycles of single-agent brentuximab vedotin for responding patients. Treatment cycles will be 21-days.

Following CHEP-BV Induction, responding patients in this trial may receive consolidation ASCT/ radiation prior to initiating Consolidation brentuximab vedotin.

Participants will continue with treatment until disease progression, unacceptable toxicity or completion of protocol therapy (induction and consolidation, ~ 12 months), whichever comes first. Participants who discontinue brentuximab vedotin during Induction may continue to receive CHEP therapy per standard of care.

Evaluation Criteria and Endpoints

Safety

- Toxicity will be recorded using the NCI CTCAE v 4.0. The highest grade of any toxicity will be collected for each cycle during protocol treatment and for the period of safety follow-up after end of treatment. For **Cycle 1 only**, all Grade ≥2 AEs (highest grade or not) will also be collected.

Unacceptable toxicity

Unacceptable toxicity will be defined as one of the following AEs that is **at least possibly** related to study treatment during **Cycle 1 of Induction**

Hematologic

- Delay in planned initiation of Cycle 2 Day 1 by more than 14 days due to Grade 4 neutropenia that does not resolve to Grade ≤ 2 or baseline despite growth factor support
- Grade 4 thrombocytopenia lasting ≥ 7 days
- Platelet nadir < 10,000/ mm^3
- Delay in planned initiation of Cycle 2 Day 1 by more than 7 days due to Failure to recover platelets to ≥ 50,000/ mm3 and/or ANC to ≥ 1000/ mm^3
- Any Grade 5 AE

Non-hematologic

- Any clinically relevant ≥ Grade 3 AE that does not resolve to Grade ≤ 2 within 7 days with the **exception** of:
  - Grade 3 asymptomatic laboratory abnormalities, including lipase or amylase, that are not clinically relevant, not requiring hospitalization or delay of treatment
  - Grade 3 nausea, vomiting, or fatigue controlled with supportive measures
  - Grade 3 inflammatory response attributed to local antitumor response
  - Vitiligo
- Delay in planned initiation of Cycle 2 Day 1 by more than 7 days due to Grade ≥2 peripheral motor neuropathy
- Any Grade 5 AE

Response

- Lymphoma response/progression will be evaluated using 2014 Lugano Classification.

Clinical Outcome Endpoints

Endpoint	Definition
*Progression-Free Survival (PFS)**	Defined as the time from enrollment to the first observation of disease relapse/progression or death from any cause, whichever occurs first. For patients who are alive and have not had disease relapse/progression at the last follow-up, it is censored at the time of last follow-up. If a patient recieves non-protocol anti-lymphoma treatment prior to disease progression, it is censored at the time of non-protocol anti-lymphoma treatment.
Overall Survival (OS)	Defined as the time from enrollment to death from any cause. For patients alive at the last follow-up, it is censored at the time of last follow-up.
Overall response (ORR) rate	Proportion of patients achieving CR or PR
Complete response (CR) rate	Proportion of patients achieving CR

Statistical Considerations

Safety Lead-in

The safety lead-in segment will follow standard 3+3 dose escalation/de-escalation/expansion rules based on observed toxicity during Induction Cycle 1. The starting dose level for brentuximib ventodin in CHEP-BV will be 1.8mg/kg (dose level 1). If ≥2/3 (after the initial 3) or ≥2/6 (after the total 6 in 2 cohorts) patients experience unacceptable toxicities during Cycle 1, 1.8 mg/kg will be considered not tolerable, and the study will then evaluate the safety and tolerability of the lower dose level of brentuximab vedotin at 1.2 mg/kg (dose level -1). If ≥2/3 (after the initial 3) or ≥2/6 (after the total 6 in 2 cohorts) patients experience unacceptable toxicities during Cycle 1, 1.2 mg/kg will be considered not tolerable, and the study accrual will be suspended.

Phase 2

The primary endpoint is CR rate after CHEP-BV induction. The Phase 2 sample size of 48 is based on the desire to discriminate a promising CR rate of 71% from a disappointing CR rate of 56%, using a type I error rate of 0.10 and power of 80% based on an exact binomial test. The design will require 32 or more CR among the 48 patients to consider the outcome encouraging. Patients enrolled during the Safety Lead-in segment who are treated at the final dose deemed tolerable will be included in the Phase 2 response evaluation provided that they are also evaluable for response.

CR rate after CHEP-BV induction therapy will be estimated by the proportion of evaluable patients achieving CR after CHEP-BV induction therapy, along with the 95% exact binomial confidence interval. ORR after CHEP-BV induction therapy and CR rate after BV consolidation will be similarly estimated. PFS and OS will be estimated using the product-limit method of Kaplan and Meier along with the Greenwood estimator of standard error. Observed toxicities of CHEP-BV induction therapy, those of BV consolidation after CHEP-BV induction and ASCT, and those of BV consolidation after CHEP-BV induction without ASCT will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v4.0 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.

Eligibility Criteria

Inclusion Criteria

- Documented informed consent of participant and/or Legally Authorized Representative.
- Agreement to allow the use of archival tissue from diagnostic tumor biopsies. If unavailable, exceptions may be granted with Study PI approval.
- Age: ≥ 18 years
- ECOG status ≤ 2
- Histologically confirmed mature peripheral T-cell or NK-cell lymphoma per WHO classification, including:
  - *****ALK-positive ALCL with IPI of 2 or higher (must have bulky [defined as mass ≥ 10 cm] Stage II, or Stage III-IV disease), *****ALK-negative ALCL, ***NOTE: per Amendment dated 05-10-19, ALCL will no longer be eligible except for Canada.** PTCL-NOS, AITL, ATLL, EATL, Hepatosplenic T-cell lymphoma
- CD30-positivity (e.g. at least 1%) by immunohistochemistry confirmed by hematopathology review at the participating institution.
- Measurable disease of at least 1.5cm on CT or PET-CT scan
- ANC ≥ 1,000/mm^3 (unless bone marrow involvement by lymphoma)
- Platelets ≥ 50,000/mm^3 (unless bone marrow involvement by lymphoma)
- Total serum bilirubin ≤ 1.5X upper limit of normal (ULN) (or ≤ 3X ULN for Gilbert's disease or documented hepatic involvement by lymphoma)
- AST and ALT ≤ 2 x ULN OR If hepatic involvement by lymphoma: AST and ALT ≤ 5 x ULN

- Creatinine clearance of ≥ 60 mL/min
- Left ventricular ejection fraction (LVEF) ≥ 45%
- Women of childbearing potential (WOCBP): negative urine or serum pregnancy test.
- Agreement by women of childbearing potential **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 protocol therapy.

Exclusion Criteria

- Prior treatment of PTCL with systemic anti-lymphoma therapies, investigational agents, radiation
  - **Exception:** May have received 1 cycle of CHOP-like therapy (e.g. CHOP, CHOEP, EPOCH) or 1 cycle of CHP-BV; these participants must initiate Day 1 Cycle 1 of study therapy (CHEP-BV) no less than 19 days from prior CHOP-like or CHP-BV therapy. Patients who received 1 cycle of CHOP-like or 1 cycle of CHP-BV therapy prior to initiating induction with CHEP-BV are allowed to receive only 5 cycles of CHEP-BV instead of 6 cycles, per investigator's discretion.
- History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years. *Exceptions:* Non-melanoma skin cancer and in situ cervical cancer.
- Symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), cerebrovascular event/stroke or myocardial infarction within the past 6 months.
- Central nervous system involvement by lymphoma, including leptomeningeal involvement.
- History of progressive multifocal leukoencephalopathy (PML).
- Active ≥ Grade 3 viral, bacterial, or fungal infection within 2 weeks prior to Day 1 of protocol therapy
- Any known human immunodeficiency virus (HIV) infection, hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection
- Baseline peripheral neuropathy ≥ Grade 2 or patients with the demyelinating form of Charcot-Marie-Tooth syndrome.
- Known severe hypersensitivity to any study related agent excipient(s)
- *Females only*: pregnant or breastfeeding
- 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.
- 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).

Investigational Product Dosage and Administration

	Agent	Dose	Route	Schedule (Days within each 21-day cycle)	Maximum # Cycles	
					Induction CHEP-BV^	Consolidation** BV
CHEP	Cyclophosphamide	750 mg/m^2	IV	Day 1	6	N/A
	Doxorubicin	50 mg/m^2	IV	Day 1	6	
	Etoposide***	100 mg/m^2	IV	Days 1-3	6	
	Prednisone	100 mg daily	Orally	Days 1-5	6	
	Brentuximab Vedotin (BV)	**Safety Lead-in** • **Dose Level 1*:** 1.8 mg/kg • **Dose Level -1:** 1.2 mg/kg **Starting dose* **Phase 2:** RP2D from Safety Lead-in	IV over 30 minutes (+10 minutes)	Day 1	6	10

^ G-CSF prophylaxis should be administered with each CHEP-BV Induction cycle. The schedule and G-CSF formulation are per investigator discretion.
**For participants with objective response (CR or PR)
*** Alternatively, etoposide may be given orally. In such case, the daily dose of oral etoposide will be 200 mg/m^2 [56] and the dose should be rounded to the nearest 50 mg.

Note: Patients who received 1 cycle of CHOP-like or 1 cycle of CHP-BV therapy prior to initiating induction with CHEP-BV are allowed to receive only 5 cycles of CHEP-BV instead of 6 cycles, per investigator's discretion.

Clinical Observations and Tests to be Performed

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

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ABBREVIATIONS

Abbrevation	Meaning
ASCT	Autologous Stem Cell Transplant
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BV	Brentuximab vedotin
C	Cycle
CFR	Code of Federal Regulations
CHEP	Cyclophosphamide-Doxorubicin-Etoposide-Prednisone
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
NHL	Non-Hodgkin Lymphoma
IB	Investigator Brochure
ICD	Informed Consent Document
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
PTCL	Peripheral T-cell Lymphoma
SAE	Serious Adverse Event
SD	Stable Disease
WHO	World Health Organization

1.0 OBJECTIVES

1.1 Primary Objectives

Safety Lead-in

- Assess the safety and tolerability of CHEP-BV, as induction therapy in patients with CD30-positive peripheral T-cell lymphoma (PTCL)

Phase 2

- Assess the anti-lymphoma activity of CHEP-BV as induction treatment in patients with CD30-positive PTCL.

1.2 Secondary Objectives

- Describe outcomes of CD30-positive PTCL patients who go on to receive BV consolidation therapy post CHEP-BV induction with/without autologous hematopoietic cell transplantation/radiation.

1.3 Exploratory Objective

- Explore the rate of minimal residual disease (MRD) negativity (as assessed by next-generation sequencing) and MRD kinetics after CHEP-BV and BV consolidation therapy in CD30-positive PTCL.
- Explore the possible association between outcome after study treatment and CD30 expression, gene expression profiles (GEP), and genetic mutations as measured in PTCL tumor samples.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

CD30 is a cell surface antigen expressed on several malignancies including Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL) and other peripheral T-cell lymphomas (PTCL), Kaposi's sarcoma (KS), cutaneous T-cell lymphomas (CTCL), a fraction of diffuse large B-cell lymphomas (DLBCL), some follicular lymphomas, and other lymphoproliferative diseases.[2-6] Brentuximab vedotin (BV), previously known as SGN-35, is an antibody drug conjugate (ADC) directed against the CD30 antigen that is being developed to treat patients with CD30-positive hematologic malignancies. Hodgkin lymphoma and ALCL are among the most common CD30-positive malignancies. BV is currently approved for the treatment of relapsed or refractory Hodgkin lymphoma and ALCL.

2.1.1 Peripheral T-cell Lymphoma

Peripheral T-cell lymphomas (PTCL) are an uncommon group of disorders, accounting for about 10% of all non-Hodgkin lymphomas (NHL). EBV-associated extranodal NK/T-cell lymphoma (NKTCL) is more common in parts of Asia and South America, while angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma, not otherwise specified (PTCL NOS) are more common in Western countries[7]. PTCLs are generally associated with poor outcomes after standard therapy, with variation in prognosis according to disease subtype [7]. ALK-expressing anaplastic large cell lymphomas (ALCL) have a favorable prognosis with 5-year survival exceeding 80%, though some studies suggest outcomes in ALCL are dependent on age rather than ALK status [7-9]. Anthracycline-based induction combination

chemotherapy is standard upfront treatment for patients with TCL; however, with the exception of ALK-positive ALCL, relapse rates are high [10-12]. The addition of etoposide to standard CHOP induction therapy (CHOEP) has been evaluated in patients with PTCL. In an analysis of multiple prospective clinical trials by the German High Grade Lymphoma Study Group, CHOEP, as compared to CHOP, resulted in improved 3-year event-free survival (75.4% [95% CI 62.1%-88.7%] vs 51.0% [95% CI 35.7%-66.3%], P = .003) However, the benefit of etoposide was only observed in patients < 60 years old. In a separate study, the addition of etoposide to CHOP was associated with improved PFS compared to CHOP alone in patients 60 years old or younger [13]. Based on the findings from these and other studies, CHOEP is a recommended regimen in the NCCN guidelines,[14] and is a commonly-used induction regimen for PTCL, particularly in younger patients.

Autologous hematopoietic stem cell transplantation (ASCT) is widely used as consolidation for PTCL patients in first remission to reduce the risk of relapse. Single-arm prospective and retrospective studies of consolidative ASCT for PTCL in 1st remission report improvements in survival compared to historical controls, but progression-free survival (PFS) remains low, ranging from 44-58% at 3-5 years [15-19]. Outcomes are poorer in patients who undergo ASCT with relapsed PTCL, with 3-5 year PFS ranging from 32-41% [19, 20].

Current approved therapies available for relapsed or refractory PTCLs include histone deacetylase inhibitors (romidepsin and belinostat), pralatrexate, and brentuximab vedotin (for ALCL). With the exception of brentuximab vedotin for ALCL, these agents are associated with poor single-agent response rates and short median progression free survival [21-23].

In the pivotal PROPEL trial, 115 heavily pre-treated PTCL patients (median 3 prior systemic therapies) received pralatrexate as a single agent. The overall response rate (ORR) in 109 evaluable patients was 29%, including 12 (11%) complete responses (CR) and 20 (18%) partial responses (PR), with a median remission duration of 10.1 months. Median PFS and OS were 3.5 and 14.5 months, respectively. The most common grade 3/4 adverse events were thrombocytopenia (32%), mucositis (22%), neutropenia (22%), and anemia (18%) [23].

Romidepsin is a histone deacetylase (HDAC) inhibitor that has been approved for the treatment of PTCL and cutaneous TCL (CTCL). Of the 131 patients enrolled in the pivotal phase II trial, 130 had histologically confirmed PTCL by central review. The objective response rate was 25% (33 of 130), including 15% (19 of 130) with CR/CRu. The median duration of response was 17 months, with the longest response ongoing at 34+ months. Of the 19 patients who achieved CR/CRu, 17 (89%) had not experienced disease progression at a median follow-up of 13.4 months. The most common grade ≥ 3 adverse events were thrombocytopenia (24%), neutropenia (20%), and infections (all types, 19%) [21].

Belinostat is a potent hydroxamic acid-derived pan-HDAC inhibitor. It was evaluated in an open-label phase II study. A total of 129 relapsed/refractory PTCL patients received 1000 mg/m^2 belinostat infusion on days 1–5 of every 3-week cycle. Among 120 evaluable patients, the ORR was 26%, including 10% CR, and median response duration was 8.3 months. The most common Grade 3–4 AEs were thrombocytopenia (13%), neutropenia (13%), and anemia (10%) [24].

With high relapse rates after standard therapy including ASCT and inadequate second line treatment options, novel strategies for decreasing relapse rates in patients with PTCL are urgently needed.

2.1.2 Autologous Stem Cell Transplantation for Peripheral T-cell Lymphoma

High dose therapy and ASCT is commonly used to treat patients with PTCL, both in the relapsed setting and as first-line consolidation. ASCT is widely used as consolidation for PTCL patients in first remission to

reduce the risk of relapse. The National Comprehensive Cancer Center Guidelines (NCCN) for NHL recommend consideration of ASCT for patients with T-cell NHL who achieve a CR or PR after primary therapy and are eligible based on age and co-morbidity [14]. Exceptions to this approach include ALK+ ALCL, CTCL, and very aggressive T-cell lymphomas (leukemic presentation). Over the past 20 years there have been several studies with more than 1400 T-NHL patients, assessing the role of ASCT for treatment at various disease stages. Most studies are heterogeneous in terms of patient populations, upfront treatment regimens, and conditioning regimens. Almost all studies exclude patients with leukemic variants of T-NHL and are limited to otherwise healthy patients with a median age under 60.

Single-arm prospective and retrospective studies of consolidative ASCT for PTCLs in 1st remission report improvements in survival compared to historical controls, but progression-free survival (PFS) remains low, ranging from 44-58% at 3-5 years.[15-19] Outcomes are poorer in patients who undergo ASCT with relapsed PTCL, with 3-5 year PFS ranging from 32-41%.[19, 20] Chemosensitive disease and ALCL histology seem to confer better outcomes in several studies. Other than transplantation in CR1, there is no consensus on prognostic factors that impact outcomes after ASCT in PTCL.

Prospective intent-to-transplant studies by various groups have shown that 41-73% of T-NHL patients enrolled on these trials are able to maintain eligibility for, and receive, ASCT [10, 25-29]. The remaining patients have progressive or unresponsive disease, are unable to mobilize sufficient stem cells, or have co-morbidities that prohibit ASCT. In the largest study by the Nordic Lymphoma Study Group [29], 160 patients were enrolled with a median follow-up of 60 months. Transplant-related mortality (TRM) was 4%, and 5-year OS and PFS were 51% and 44%, respectively. Outcomes were analyzed by histology: ALK- ALCL, 5-year OS of 70% and PFS of 61%; AITL, OS 52%, PFS 49%; PTCL-NOS, OS 47%, PFS 38%; EATL, OS 48%, DFS 38%. Female sex and ALCL histology conferred a favorable prognosis, and International Prognosis Index (IPI) had predictive value for OS in AITL, and for PFS in AITL and PTCL-NOS. Bone marrow involvement and increasing age were negative prognostic factors.

Most reports of ASCT for PTCL have reported the use of chemotherapy-based conditioning regimens, the most common being BEAM (BCNU/etoposide/ara-C/melphalan), BEAC (BCNU/etoposide/ara-C/cyclophosphamide), CBV (cyclophosphamide/BCNU/etoposide), and busulfan (Bu)/cyclophosphamide (Cy). Many patients have also received total body irradiation (TBI)-based regimens, usually in combination with cyclophosphamide or etoposide or both. City of Hope compared outcomes of 41 patients treated with TBI-based regimens to 26 patients with non-radiation-based regimens and reported no differences [30]. Conditioning regimen appears to be determined by physician choice and currently there are no specific recommendations regarding conditioning regimens for PTCL ASCT.

2.1.3 CD30 Expression in Peripheral T-cell Lymphoma

CD30 expression is universal in ALCL, but CD30 expression has also been demonstrated in other PTCL subtypes. In addition to 100% of ALCLs, some degree of CD30 expression has also been demonstrated in about 50% of patients with selected other PTCL subtypes, including: peripheral T-cell lymphoma, not otherwise specified (PTCL NOS): 32-58%[31-33]; angioimmunoblastic T-cell lymphoma (AITL): 43-63%[31, 33]; enteropathy-associated T-cell lymphoma (EATL): 38–100% (Type I)[31, 33, 34]; extranodal NK/T-cell lymphoma (NKTCL): 31-80%[31, 33, 35, 36]; and adult T-cell lymphoma/leukemia (ATLL): 50-56%[31, 37] The prognostic impact of CD30 expression in PTCLs has been evaluated in retrospective studies of heterogeneously treated patients, with the impact of CD30 expression varying by PTCL subtype. CD30 expression was associated with poorer survival in PTCL NOS, favorable outcome in NKTCL, a trend towards longer survival in ATLL, whereas it did not appear to impact prognosis in AITL or EATL.

2.1.4 Brentuximab Vedotin

Brentuximab vedotin, previously known as SGN-35, is an ADC consisting of the chimeric antibody SGN-30 (cAC10) chemically conjugated to a synthetic analog (monomethylauristatin E [MMAE]) of the naturally occurring anti-tubulin agent, dolastatin10. Brentuximab vedotin is proposed to have a multi-step mechanism of action that is initiated by binding to CD30 on the cell surface and internalization of the ADC. Upon trafficking to lysosomes, MMAE is released from the conjugate through proteolytic degradation of the drug linker.[38] Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis.[39]

Preclinical studies of brentuximab vedotin demonstrated antitumor activity in both *in vitro* and *in vivo* models. The toxicity of multiple doses of brentuximab vedotin has been assessed in rats and monkeys. In both species, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed. Histopathologic lesions were also observed in the spleen in monkeys and in the liver and testes in rats. In addition, decreases in peripheral blood counts were observed in both species, and elevations in liver enzymes were seen in rats only. The most significant clinical toxicity was neutropenia, observed in monkeys, which resulted in secondary bacterial infections leading to early deaths at the 6 mg/kg dose. Toxicity was dose-dependent, with a no-observable-adverse-effect level of 0.5 mg/kg in rats and 1 mg/kg in monkeys. See the brentuximab vedotin SGN-35 Investigator's Brochure for details of the nonclinical data.

2.2 Study Rationale

Brentuximab vedotin is an effective treatment for patients with PTCL. Brentuximab vedotin is FDA-approved for relapsed CD30 expressing systemic anaplastic large cell lymphoma [40]. In a single-arm Phase 2 study, 58 patients were treated with brentuximab vedotin 1.8mg/kg intravenously every 3 weeks, resulting in a 86% ORR, including 33 patients (57%) complete remissions, and 17 (29%) partial remissions. The median durations of overall response and CR were 12.6 and 13.2 months, respectively. Grade 3 or 4 adverse events in ≥10% of patients were neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (12%). More recently, in a Phase 2 study of brentuximab vedotin in 34 patients with relapsed or refractory PTCLs other than ALCL, brentuximab vedotin treatment resulted in an ORR of 41%, with a 54% ORR in patients with AITL. The median duration of response was 7.6 months, and the median follow-up time was 2.7 months. The overall disease control rate was 59%, with a 77% disease control rate in patients with AITL [1]. Response was not associated with the presence or degree of CD30 expression.

In addition, the clinical safety and activity of brentuximab vedotin administered sequentially and concurrently with multi-agent chemotherapy were evaluated in a phase 1 study in patients with newly diagnosed CD30-positive mature T- and NK-cell neoplasms, including sALCL (Study SGN35-011; NCT01309789). This Phase 1 study was implemented to determine the safety and activity of sequential and combination frontline treatment approaches of brentuximab vedotin with CHOP or CHP chemotherapy. In order to avoid excessive, overlapping toxicity from dual microtubule inhibition, vincristine was omitted from CHOP when BV was administered concurrently, so that BV-CHP were administered concurrently and CHOP and BV were administered sequentially. The maximum tolerated dose of brentuximab vedotin was 1.8 mg/kg given concomitantly with CHP. At an interim analysis in this study (data presented at the T-Cell Lymphoma Forum 2012), 20 patients in this study had been treated with brentuximab vedotin 1.2 or 1.8 mg/kg given concomitantly with CHP for 6 cycles, followed by continued brentuximab vedotin every 3 weeks for up to 10 additional cycles for responding patients. The most common adverse events were nausea, fatigue, and peripheral sensory neuropathy. Of the

patients who had a response assessment after 6 cycles of brentuximab vedotin plus CHP, 5 of 5 patients achieved a CR. In the final report of the study results, published in 2014 by Fanale et al., the ORR to sequential CHOP and brentuximab vedotin therapy was 85% with a CR rate of 62%, whereas the ORR to CHP-BV therapy was 100% with a CR rate of 88%. The most common Grade 3/4 AEs were febrile neutropenia (31%), neutropenia (23%), anemia (15%), and pulmonary embolism (12%). Based on the safety and efficacy observed in this Phase 1 study, a randomized Phase 3 study of CHP-BV compared to CHOP as upfront therapy is being conducted in patients with CD30+ PTCL.

The ECHELON-2 trial is a randomized trial that is currently comparing the addition of brentuximab vedotin to cyclophosphamide, doxorubicin, and prednisone (CHP) with standard-of-care cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in the initial treatment of patients with CD30-positive PTCL. However, based on evidence that the addition to etoposide to standard CHOP (CHOEP) is beneficial, CHOEP is often administered as initial treatment of patients with PTCL. Therefore, while ECHELON-2 will address whether brentuximab vedotin added to CHP is superior to CHOP therapy, there are no data regarding the safety and efficacy of brentuximab vedotin added to etoposide-containing induction chemotherapy (cyclophosphamide, doxorubicin, etoposide, and prednisone - CHEP). Since November 16, 2018 and based on the ECHELON-2 trial, brentuximab vedotin is FDA-approved in combination with CHP chemotherapy for previously untreated, systemic ALCL or other CD30-expressing PTCL. We propose a Phase 2 study to assess the anti-lymphoma activity brentuximab vedotin when combined with CHEP (CHEP-BV) in patients with newly-diagnosed CD30-positive PTCL.

With the exclusion of patients with favorable risk ALK+ ALCL, long term outcomes of patients with PTCL treated with standard anthracycline-based chemotherapy are dismal [10-13, 18], even when consolidative autologous stem cell transplantation is performed (progression-free survival of 41-58% at 3-5 years) [13, 15-19], and even among patients who achieve CR with induction therapy and/or consolidative transplantation are considered (4-year event-free survival 59% [10]). Improvement of upfront treatment of PTCL that can provide not only responses, but durable responses (the reason we are also evaluating BV consolidation with this study) is an urgent unmet need, and since evaluation of the safety of CHEP-BV induction is not feasible in patients with relapsed or refractory PTCL, the enrollment of newly diagnosed CD30+ PTCL patients in the safety lead-in is appropriate. In this study, enrollment will be limited to high risk subtypes of PTCL, whereas patients with early stage and low-risk ALK+ ALCL have been excluded to ensure that the use of an investigational induction regimen in newly diagnosed patients is appropriate. Furthermore, since BV has been combined with CHP previously and has been found to be safe [41], it is anticipated that the addition of etoposide will be safe and tolerable. An increased frequency of hematologic toxicity with the addition of etoposide is not anticipated, but is possible. Therefore, this study will mandate the use of G-CSF during induction CHEP-BV therapy. To ensure that we are adequately assessing the safety of the regimen, we have designed the safety lead-in similar to a Phase 1 study, with a starting dose-level and unacceptable toxicity (essentially DLT) criteria and a dose de-escalation level if a sufficiently high rate of unacceptable toxicity is observed. Since we are performing a Phase 2 study with a new regimen, stopping rules are also included to ensure that we are continuing to evaluate the safety of the regimen during the entire study.

2.3 Rationale for Brentuximab vedotin Maintenance in PTCL

Many patients with PTCL are treated with autologous hematopoietic stem cell transplantation (ASCT) in 1st remission to reduce the risk of relapse after upfront therapy. Single-arm prospective and retrospective studies of consolidative ASCT for PTCLs in 1st remission report improvements in survival compared to historical controls, but progression-free survival (PFS) remains low, ranging from 44-58% at

3-5 years [18, 19]. Based on these data, ASCT in 1st remission is supported by the NCCN guidelines for PTCL.

The AETHERA trial demonstrated that brentuximab vedotin consolidation treatment following ASCT prolongs PFS in patients with relapsed or refractory classical Hodgkin lymphoma compared to placebo [42]. In this randomized Phase 3 study, 329 patients received either placebo or brentuximab vedotin 1.8mg/kg IV every 3 weeks for 16 cycles starting 30-45 days after ASCT. Median PFS was 42.9 months for patients receiving brentuximab vedotin versus 24.1 months in patients receiving placebo (p=0.0013). A similar approach, using brentuximab vedotin consolidation therapy after ASCT, is an attractive strategy for PTCL. Outcomes after ASCT for patients with PTCL who undergo ASCT in CR1 are poor. With the encouraging response and disease control rates seen across PTCL subtypes, brentuximab vedotin treatment after ASCT could deepen and consolidate a patient's response to pre-ASCT therapy and provide continued disease control after ASCT.

Even if the paradigm of PTCL therapy shifts with the ongoing ECHELON-2 trial, which is currently evaluating the addition of brentuximab vedotin to upfront induction chemotherapy for CD30-positive PTCL, brentuximab vedotin consolidation after ASCT in patients with PTCL who relapse and require ASCT may be beneficial. The role of ASCT is not being evaluated in the ECHELON-2 trial, so patients with PTCL in 1st remission after brentuximab vedotin-containing induction therapy may still proceed to ASCT. Even in the setting of brentuximab vedotin-containing induction therapy, brentuximab vedotin consolidation after upfront ASCT may provide enhanced disease control in a disease with a high rate of relapse after initial response.

In the Phase 1 study of CHP-BV or CHOP followed by brentuximab vedotin, patients in response at the end of induction therapy were eligible to receive single-agent brentuximab vedotin consolidation for an additional 10 cycles. The 1-year PFS (71%) and OS (88%) rates observed to CHP-BV on this study was excellent, with a median PFS not reached in the CHP-BV group. Of note, all patients who were in CR after CHP-BV were in continued CR after 16 cycles of brentuximab vedotin therapy and one patient with a PR to CHP-BV converted to CR with maintenance therapy. These findings suggest that additional brentuximab vedotin treatment after induction therapy may prolong the remissions observed after brentuximab vedotin-containing induction therapy for CD30-positive PTCLs. In patients who are not treated with ASCT after induction therapy, brentuximab vedotin maintenance therapy could potentially deepen and consolidate responses to induction therapy and provide prolonged disease control similar to ASCT.

There is currently no standard of care treatment to prevent relapse after upfront treatment or ASCT for CD30-positive TCLs. An agent that could improve outcomes in this population would be a major contribution to the field, and is likely to be practice changing. Therefore, in addition to studying the anti-lymphoma activity of CHEP-BV as induction therapy, in patients who respond to induction CHEP-BV therapy, as a secondary objective we propose to add brentuximab vedotin consolidation after ASCT in patients treated with ASCT and to add brentuximab vedotin consolidation after CHEP-BV in patients who are not treated with upfront ASCT.

2.4 Rationale for Correlative Studies

Genomic signatures define distinct subsets of PTCL and are associated with outcome after standard therapy [43-45]. Molecularly distinct subgroups exist even within PTCL histologic subtypes that are biomarkers of outcome and enhance prognostication over simple morphologic classification. We will evaluate whether these genomic signatures as determined by mutational and gene expression profiles in pre-treatment tumor samples are associated with response and outcome after CHEP-BV therapy.

In addition, next-generation sequencing (NGS)-based minimal residual disease (MRD) detection using the immunoglobulin or T-cell receptor genes can identify circulating tumor DNA (ctDNA) in the peripheral blood mononuclear cells (PBMC) and plasma (cell-free) of patients with lymphoid malignancies. NGS-based ctDNA detection is at least as sensitive as existing MRD detection methods, and can detect MRD not identified by multi-parameter flow cytometry or allele-specific oligonucleotide polymerase chain reaction testing [46-48]. The NGS-based MRD detection method can identify ctDNA at diagnosis in a range of lymphomas, including classical Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL), subtypes in which MRD detection has previously been challenging [49-52]. In addition, ctDNA levels track with treatment response in DLBCL, and the persistence or recurrence of ctDNA during and after upfront therapy is associated with subsequent DLBCL relapse [51, 52]. We have previously shown that ctDNA assessment is feasible and that ctDNA can be detected in patients with PTCL [53]. In this study, we aim to further validate ctDNA detection in patients with PTCL, assess ctDNA kinetics in the setting of induction and consolidation therapy, and determine the rate of ctDNA-negativity after CHEP-BV induction and brentuximab vedotin consolidation.

2.5 Overview of Study

This is an open-label multi-site Phase 2 study with a Safety Lead-in to test the safety and efficacy of CHEP-BV as Induction therapy followed by single-agent brentuximab vedotin consolidation therapy for the treatment of CD30-positive PTCL.

Eligibility

Eligible patients will be adults with histologically confirmed CD30-positive PTCL or NK-cell lymphoma defined per WHO 2008 criteria [54]. **NOTE: per Amendment dated 05-10-19, ALCL will no longer be eligible except for Canada**. Eligible patients must be treatment naïve but may have received 1 cycle of CHOP-like therapy (e.g. CHOP, CHOEP, EPOCH) or 1 cycle of CHP-BV prior to initiating Induction with CHEP-BV. PTCL is an aggressive malignancy and patients are often started on therapy urgently, and BV is now FDA-approved in combination with CHP chemotherapy for previously untreated, systemic ALCL or other CD30-expressing PTCL. Allowing a prior cycle of chemotherapy or one cycle of CHP-BV before study entry will allow us to enroll a more representative population of PTCL patients with aggressive and non-aggressive disease and will facilitate accrual. Patients who received 1 cycle of CHOP-like or 1 cycle of CHP-BV therapy prior to initiating induction with CHEP-BV are allowed to receive only 5 cycles of CHEP-BV instead of 6 cycles, per investigator's discretion.

Treatment program

Newly diagnosed CD30-positive PTCL patients will be treated with up to 6 cycles of CHEP-BV followed by up to 10 cycles of single-agent brentuximab vedotin (IV once every 21-days) for responding patients. CHEP will be administered per institutional standards, and IV or oral etoposide is acceptable (see Section 5.3).

Since ASCT and/or radiation in 1st response is standard of care for some patients with PTCL, following CHEP-BV Induction, responding patients in this trial may receive consolidation ASCT/radiation prior to initiating Consolidation brentuximab vedotin.

Participants will continue with treatment until disease progression, unacceptable toxicity or completion of protocol therapy (induction and consolidation, ~ 12 months), whichever comes first. Participants who discontinue brentuximab vedotin during Induction may continue to receive CHEP therapy per standard of care.

Safety Lead-in

During the Safety Lead-in, up to 6-12 evaluable participants will be enrolled using a 3+3 design. The starting dose for brentuximab vedotin will be 1.8 mg/kg (Dose level 1) in combination with CHEP based on prior experience from study SGN35-011 (NCT01309789). Unacceptable toxicities will be evaluated during the first cycle of Induction therapy.

In the event the initial starting brentuximab vedotin dose is not tolerable (2+ patients with unacceptable toxicity in ≤6 evaluable participants), a brentuximab vedotin dose of 1.2 mg/kg (Dose level -1) will be explored in combination with CHEP in an additional 6 evaluable participants .

Phase 2

The Recommended Phase 2 Dose (RP2D) of brentuximab vedotin established during the Safety Lead-in will be used for the Phase 2 portion to test the Induction regimen. **Per Amendment dated 05-10-19**: Given the ECHELON-2 data results, the statistical design is being revised to consider a baseline rate of 56% instead of 40%, and to increase the total study accrual to 48 evaluable patients.

Response

Response assessments will occur during Induction (end of Cycles 3 and 6) and during Consolidation every 3-4 cycles. End of Cycle 6 response assessment will determine which participants may continue onto receive Consolidation therapy. Lymphoma response and progression will be assessed by investigators based on PET-CT/CT scans according to the 2014 Lugano Classification. [55] Patients who are receiving only 5 cycles of CHEP-BV per investigator's discretion (because they received 1 cycle of CHOP-like or 1 cycle of CHP-BV therapy prior to start of protocol therapy) will have their response assessment during Induction at end of Cycles 3 and 5.

Correlative studies

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

Planned correlative studies include:

- Gene expression and mutational profiling of PTCL tumor specimens to determine whether there are expression profiles and/or mutations associated with outcome after study therapy.
- Next-generation sequencing-based minimal residual disease (MRD) assessment. We will assess MRD at baseline, and at all pre-specified imaging time points. These sequential samples will allow us the track the temporal dynamics of MRD after CHEP plus BV, and to determine whether maintenance therapy can eradicate MRD in patients who are MRD+ after induction therapy.

3.0 ELIGIBILITY CRITERIA

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

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

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent of participant and/or Legally Authorized Representative.

__2. Agreement to allow the use of archival tissue from diagnostic tumor biopsies will be retrieved and submitted post-enrollment (See Section 9.2 for details)

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

Age Criteria and Performance Status

__3. Age: ≥ 18 years

__4. ECOG status ≤ 2

Nature of Illness and Transplant Related Criteria

__5. Histologically confirmed mature peripheral T-cell or NK-cell lymphoma per WHO classification, including:

- *ALK-positive ALCL with IPI of 2 or higher (must have bulky [defined as mass ≥ 10 cm] Stage II, or Stage III-IV disease)
- *ALK-negative ALCL

***NOTE: per Amendment dated 05-10-19, ALCL will no longer be eligible except for Canada.**

- PTCL-NOS
- AITL
- ATLL
- EATL
- Hepatosplenic T-cell lymphoma

__6. CD30-positivity (e.g. at least 1%) by immunohistochemistry confirmed by hematopathology review at the participating institution.

__7. Measurable disease of at least 1.5cm on CT or PET-CT scan

Clinical Laboratory and Organ Function Criteria

__8. ANC ≥ 1,000/mm^3 **Exception:** Unless documented bone marrow involvement by lymphoma.	ANC:	Date:
__9. Platelets ≥ 50,000/mm^3 **Exception:** Unless documented bone marrow involvement by lymphoma.	Plts:	Date:
__10. Total serum bilirubin ≤ 1.5X upper limit of normal (ULN) OR **If hepatic involvement by lymphoma**: ≤ 3X ULN for Gilbert's disease or documented hepatic involvement by lymphoma	ULN: Bil:	Date:
__11. AST ≤ 2 x ULN OR **If hepatic involvement by lymphoma:** AST ≤ 5 x ULN	ULN: AST:	Date:

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

__12. ALT ≤ 2 x ULN OR **If hepatic involvement by lymphoma**: ALT ≤ 5 x ULN	ULN: ALT:		Date:
__13. Creatinine clearance of ≥ 60 mL/min per the Cockcroft-Gault formula $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ (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)	Serum Cr: Cr Cl:		Date:
__14. Left ventricular ejection fraction (LVEF) ≥ 45%	LVEF:		Date:
__15. **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:

Contraception

__16. Agreement by WOCBP **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 protocol therapy.

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

3.2 Exclusion Criteria

Prior therapies

__1. Prior treatment of PTCL with systemic anti-lymphoma therapies, investigational agents, radiation

- **Exception:** May have received 1 cycle of CHOP-like therapy (e.g. CHOP, CHOEP, EPOCH) or 1 cycle of CHP-BV; these participants must initiate Day 1 Cycle 1 of study therapy (CHEP-BV) no less than 19 days from prior CHOP-like or CHP-BV therapy. Patients who received 1 cycle of CHOP-like or 1 cycle of CHP-BV therapy prior to initiating induction with CHEP-BV are allowed to receive only 5 cycles of CHEP-BV instead of 6 cycles, per investigator's discretion.

Other illnesses or conditions

__2. History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years.

- *Exceptions:* Non-melanoma skin cancer and in situ cervical cancer.

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

__3. Symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), cerebrovascular event/stroke or myocardial infarction within the past 6 months. See Appendix C.

__4. Central nervous system involvement by lymphoma, including leptomeningeal involvement.

__5. History of progressive multifocal leukoencephalopathy (PML).

__6. Active ≥ Grade 3 viral, bacterial, or fungal infection within 2 weeks prior to Day 1 of protocol therapy

__7. Any known human immunodeficiency virus (HIV) infection, hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection.

__8. Baseline peripheral neuropathy ≥ Grade 2 or patients with the demyelinating form of Charcot-Marie-Tooth syndrome.

__9. Known severe hypersensitivity to any study related agent excipient(s)

__10. *Females only*: pregnant or breastfeeding

__11. 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

__12. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

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

4.0 PARTICIPANT ENROLLMENT

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

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained.

The informed consent process is to be fully documented (see Section 16.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0.

4.2 Participant Enrollment

4.2.1 COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the DCC at City of Hope.

DCC staff are **available between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays).** DCC contact information is as follows:

- E-mail: DCC@coh.org

4.2.2 Slot verification and reservation

Designated study staff 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

Allow up to 24 hours for the DCC to review. To register a participant, the subsequent procedure must 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 should then e-mail a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:
    - Registration Cover Sheet (Appendix E)
    - Completed Eligibility Checklist (printed from Section 3.0 of the protocol) with required signature(s)
    - Signed informed consent
    - Signed HIPAA authorization form (if separate from the informed consent)
    - Signed subject's Bill of Rights (California only)

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 and cohort assignement:
    - 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 Form, COH study team will register the patient in OnCore. The DCC will register non-COH patients in OnCore.

4.3 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 (Appendix E) and submitted to the DCC.

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

4.4 Dose Level Assignment

During the Safety Lead-in stage, eligible participants will be assigned a dose level (Section 5.3). Once the recommended phase 2 dose (RP2D) is defined, participants will enroll at the RP2D dose (Section 5.4).

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a multi-center, open-label, Phase 2 clinical trial of brentuximab vedotin (BV) plus cyclophosphamide, doxorubicin, etoposide, and prednisone (CHEP-BV) followed by brentuximab vedotin consolidation for CD30-positive PTCL patients (Section 5.3).

The trial consists of a:

- **Safety Lead-in stage** to evaluate safety/tolerability of brentuximab vedotin with CHEP (Section 5.4) and
- **Phase 2 stage** to evaluate anti-tumor activity of the regimen in the study population (Section 5.5).

Each cycle will be 21 days (Section 5.2). Up to 16 cycles of protocol therapy is planned in the absence of unacceptable toxicity or disease progression (Section 5.10). If one agent is discontinued due to toxicity during CHEP-BV induction, then the participant may continue to receive the other protocol therapy agents.

Participants with objective response following Induction may undergo consolidative autologous stem cell therapy (ASCT)/ receive radiation prior to continuing with Consolidation brentuximab vedotin. See Section 5.7 for details.

Participants who end protocol therapy will undergo follow-up (Section 5.11). Windows for all assessments and treatments are detailed in Section 10.0.

5.2 Induction and Consolidation Treatment Cycle Definition

In the absence of a delay due to toxicity, each treatment cycle lasts 21 days with a ± 3 day window during Induction and Consolidation.

- **Induction CHEP-BV** (Section 5.6):
  - Day 1 of each cycle will be defined as the first day of administration of chemotherapy.
  - If chemotherapy is permanently discontinued and brentuximab vedotin is being continued, then Day 1 of each cycle will be defined as the day of administration of brentuximab vedotin.
- **Consolidation brentuximab vedotin** (Section 5.7): Day 1 of each treatment cycle is defined by the day of administration of brentuximab vedotin.

5.3 Treatment Plan

The treatment plan for the Safety Lead-in and Phase 2 cohorts is as follows (Table 5.3).

Table 5.3 Treatment Regimen and Schedule

	Agent	Dose	Route	Schedule (Days within each 21-day cycle)	Maximum # Cycles	
					Induction^ CHEP-BV (Section 5.6)	Consolidation-BV** (Section 5.7)
CHEP	Cyclophosphamide	750 mg/m^2	IV	Day 1	6	N/A
	Doxorubicin	50 mg/m^2	IV	Day 1	6	
	Etoposide***	100 mg/m^2	IV	Days 1-3	6	
	Prednisone	100 mg daily	Orally	Days 1-5	6	
	Brentuximab Vedotin (BV)	**Safety Lead-in** (Section 5.4) • Dose Level 1*: 1.8 mg/kg • Dose Level -1: 1.2 mg/kg **Starting dose* **Phase 2:** RP2D from Safety Lead-in (Section 5.5)	IV over 30 minutes (+10 minutes)	Day 1	6	10

^ G-CSF prophylaxis should be administered with each CHEP-BV Induction cycle. The schedule and G-CSF formulation are per investigator discretion.
**For participants with objective response (CR or PR)
*** Alternatively, etoposide may be given orally. In such case, the daily dose of oral etoposide will be 200 mg/m^2 [56] and the dose should be rounded to the nearest 50 mg.

Note: Patients who received 1 cycle of CHOP-like or 1 cycle of CHP-BV therapy prior to initiating induction with CHEP-BV are allowed to receive only 5 cycles of CHEP-BV instead of 6 cycles, per investigator's discretion.

5.4 Safety Lead-In Cohort

During the Safety Lead-in, up to 6-12 evaluable participants will be enrolled using a 3+3 design. The starting dose for brentuximab vedotin will be 1.8 mg/kg in combination with CHEP (Table 5.3). Unacceptable toxicities (defined in Section 11.2) will be evaluated during Cycle 1 of CHEP-BV Induction therapy.

In the event the initial starting brentuximab vedotin dose is not tolerable (2+ patients with unacceptable toxicity in ≤6 evaluable participants), a brentuximab vedotin dose of 1.2 mg/kg will be explored in an additional 6 evaluable participants.

5.5 Phase 2 Cohort

The Recommended Phase 2 Dose (RP2D) of brentuximab vedotin established during the Safety Lead-in will be used for the Phase 2 portion (Table 5.3). Participants treated at the tolerable dose during the Safety Lead-in participants will be included in the Phase 2 portion of the study if they are evaluable for

response. **Per Amendment dated 05-10-19**: Given the ECHELON-2 data results, the statistical design is being revised and the total study accrual is being increased to 48 evaluable patients.

See Section 12.0 for details.

5.6 Induction (CHEP-BV)

- See Section 5.13.2 regarding pegfilgrastim administration as supportive care.
- Up to 6 cycles of CHEP-BV
- If one agent is discontinued due to toxicity, then the participant may continue to receive the other protocol therapy agents.
- Participants with PR or CR on restaging prior to cycle 4 will continue to receive Cycles 4-6
- Participants with stable disease on restaging prior to cycle 4 may continue to Cycles 4-6 per investigator discretion

Timing and windows for imaging are detailed in Section 10.0.

5.7 Consolidation (Brentuximab Vedotin Single-Agent)

NOTE: Participants **must meet criteria** in Section 5.7.1 to initiate Consolidation.

- Maximum 10 cycles of brentuximab vedotin
- Initiate after
  - Post-consolidative autologous stem cell transplantation (ASCT); **OR**
  - Post-consolidative radiation therapy (with/without ASCT); **OR**
  - Post-Induction
- *If **NOT** receiving consolidation ASCT*
  - Initiate Consolidation within 8 weeks post-Induction.
- *If **receiving** consolidation ASCT*
  - Stem cell mobilization and collection and ASCT will be performed per institutional standards.
  - Initiate Consolidation between Day + 30 and Day + 60 post-ASCT. A delay of up to Day + 75 is permitted following consultation with the Study PI for certain criteria (see Section 5.7.1 below).
  - Screening may initiate 21 days after ASCT.

5.7.1 Criteria to Receive Consolidation Brentuximab Vedotin

Participants must meet the below criteria to receive Consolidation therapy with single-agent brentuximab vedotin after completing 6 cycles of CHEP-BV.

Note: Patients who qualify for receiving 5 cycles of CHEP-BV instead of 6 cycles can start consolidation therapy after completing Cycle 5 of CHEP-BV.

Criteria to be met in order to initiate Consolidation brentuximab vedotin	Action if criterion to the LEFT is NOT met
1. Achieved objective response per 2014 Lugano Classification on Cycle 6 Day 15 Induction assessment (or on Cycle 5 Day 15 for patients who qualify for receiving 5 cycles of CHEP-BV instead of 6 cycles)	Discontinue protocol therapy.
2. No ≥ Grade 3 peripheral motor neuropathy or Grade 4 peripheral sensory neuropathy	Follow dose modification guidelines in Section 6.2 if the participant is experiencing peripheral neuropathy.
3. Absence of unrelated toxicity not present at baseline that might adversely affect participation/ administration of brentuximab vedotin	Discontinue protocol therapy.
*Additionally, participants who **also received ASCT MUST meet** below criteria* ***Note: Screening can initiate 21 days post-ASCT***	
1. Recovered from ASCT toxicities Including: outpatient status, able to drink and eat normally, and do not need intravenous hydration prior to Cycle 1 Day 1 of Consolidation therapy	Following consultation with Study PI delay initiation of Consolidation up to Day +75 post-ASCT may be permitted.
2. Will initiate treatment between Day +30 and Day +60 post-ASCT	
3. ECOG ≤ 2 within the screening period	
4. ANC ≥ 1,000/mm^3 within 14 days prior to Day 1 of Consolidation *Exception*: Unless documented bone marrow involvement by lymphoma	
5. Platelets ≥ 50,000/mm^3 within 14 days prior to Day 1 of Consolidation *Exception*: Unless documented bone marrow involvement by lymphoma.	
6. Total serum bilirubin ≤ 1.5X upper limit of normal (ULN) **OR** if hepatic involvement by lymphoma ≤ 3X ULN for Gilbert's disease or documented hepatic involvement by lymphoma within 14 days prior to Day 1 of Consolidation	
7. AST ≤ 2 x ULN **OR** if hepatic involvement by lymphoma AST ≤ 5 x ULN within 14 days prior to Day 1 of Consolidation	
8. ALT ≤ 2 x ULN **OR** If hepatic involvement by lymphoma ALT ≤ 5 x ULN within 14 days prior to Day 1 of Consolidation	
9. Creatinine clearance of ≥ 60 mL/min within 14 days prior to Day 1 of Consolidation	

Criteria to be met in order to initiate Consolidation brentuximab vedotin	Action if criterion to the LEFT is NOT met
10. No active ≥ Grade 3 infection within 14 days prior to Day 1 of Consolidation	
11. No other primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome since last response assessment *Except:* Non-melanoma skin cancer and in situ cervical cancer	Discontinue protocol therapy.
12. No symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), cerebrovascular event/stroke or myocardial infarction within the last 6 months	Discontinue protocol therapy.
13. History of or current central nervous system involvement by lymphoma, including leptomeningeal involvement	Discontinue protocol therapy.
14. History of or current progressive multifocal leukoencephalopathy (PML)	Discontinue protocol therapy.

5.8 Agent Administration

NOTE: Infusion of study agents should occur at a site properly equipped and staffed to manage anaphylaxis should it occur.

5.8.1 Cyclophosphamide, doxorubicin, etoposide, and prednisone (CHEP)

Administer CHEP per institutional standards during Induction (Section 5.6) prior to brentuximab vedotin. Dosing should be based on the patient's pre-dose Cycle 1 baseline height and weight or per institutional standards.

IV or oral etoposide is acceptable (see Section 5.3). If etoposide is administered orally, the dose should be rounded to the nearest 50 mg.

There are no protocol-required pre- or post-medications for CHEP. See Section 5.13 for supportive care.

Dose modification guidelines for CHEP are described in Section 6.2.

5.8.2 Brentuximab vedotin

Brentuximab vedotin will be administered as an IV infusion over 30 minutes (+10 minutes) on Day 1 during Induction (Section 5.6) and Consolidation (Section 5.7). Refer to Section 8.1 for reconstitution, preparation and additional administration details.

Brentuximab vedotin will be administered within 1 hour of completing treatment with other agents during Induction.

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

There are no premedications recommended for the first dose of brentuximab vedotin. Consider observing the participant for 60 minutes following the first infusion with brentuximab vedotin. See Section 5.13 for supportive care.

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

5.9 Assessments and Special Monitoring

Refer to Section 10.0 summarizes the trial procedures to be performed. **Note:** Protocol therapy should be administered on Day 1 of each cycle after all procedures/safety assessments have been completed.

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

5.9.1 Infusion-related reactions

- Infusion or hypersensitivity reactions may occur to brentuximab vedotin or CHEP.
- If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions.
- Refer to Section 5.13.2 for infusion-related reaction/hypersensitivity guidelines.

5.10 Duration of Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy (Induction with CHEP-BV and Consolidation with brentuximab vedotin) until one of the below criteria are met:

- Confirmed disease progression per 2014 Lugano Classification
- Participant unable to proceed with Consolidation (Section 5.7.1)
- Completed protocol therapy (induction and consolidation) (~12 months)
- 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
- 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 (See Section 16.5)

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

5.11 Follow-Up

All participants who end protocol therapy will enter follow-up. Patients will be followed for 5 years (time from start of treatment). **NOTE:** Assessments may be combined if the windows for the two visits overlap.

Follow-up is comprised of:

- **Safety Follow-up**- 30 days post-last dose of protocol therapy.
  - **Note** the period for safety follow-up will be extended until stabilization or resolution for all reportable AEs (per the agreement of the Study PI) and accompanying follow-up safety report.
- **Active Follow-up**- for those who have yet to have disease progression.
- **Survival Follow-up**- for all participants who have progressed OR completed Active Response Follow-Up. This follow-up will be performed typically via medical record review. It will entail (a) Disease status (for those who have yet to progress) (b) Vital status (all participants).

Assessment time points and windows are detailed in Section 10.0.

5.12 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and follow-up after protocol treatment)
- Withdrawal of consent (See Section 16.5)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

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

5.13 Supportive Care, Prohibited Medications and Concomitant Therapy

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 the medical record.

Participants should be **cautioned** against excessive consumption of grapefruit, grapefruit juice or Seville orange juice while receiving Induction therapy. For a comprehensive list of CYP3A4 inhibitors and inducers refer to the Indiana University P450 Drug Interaction Table.

5.13.1 Prohibited medications/ therapies

- Prohibited from **Day 1 of protocol therapy until end of Induction**:
  - Strong CYP3A4 inhibitors/inducers: If there are no reasonable alternatives and these drugs are clinically necessary then participants must discontinue protocol therapy

- Prohibited from **Day 1 of protocol therapy until end of protocol therapy** (last day of study agent or decision to end study agent(s) whichever occurs later).
  - Herbal and natural remedies
  - Other investigational therapy

- Other concurrent systemic anti-cancer therapy: chemotherapy, biological response modifiers, hormone therapy, surgery, palliative radiation therapy, or immunotherapy.
  - **Exceptions post-Induction but prior to Consolidation with brentuximab vedotin: (a)** consolidation ASCT **(b)** consolidation radiation after ASCT, or **(c)** consolidation radiation without ASCT.

5.13.2 Supportive Care

With the exception of prohibited therapies (see Section 5.13.1), participants should receive prophylactic or supportive care as clinically indicated per institutional policies.

Routine anti-emetic prophylaxis should be administered per institution standard with induction chemotherapy.

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

Blood products and growth factors

- *Platelet and/or red blood cell supportive growth factors or transfusions*
  - Permitted when applicable
- *Colony stimulating factors (CSFs)*
  - **Induction:** - All patients should receive G-CSF with each CHEP-BV cycle. The schedule and G-CSF formulation are per investigator discretion.
  - **Consolidation**: Per investigator discretion and institutional practice use G-CSF for neutropenia.

Strong CYP3A4/5 inhibitors during Consolidation

- Closely monitor for AEs.

Routine infectious prophylaxis for Pneumocystis jiroveci pneumonia (PCP)

- Consider for all patients

Intrathecal prophylactic treatment for cerebral/meningeal disease

- Permitted at the discretion of the investigator

Infusion related reactions

- Supportive measures include:
  - infusion time extension and/or
  - premedication
- Premedicate if participant experienced infusion related reaction
  - Consider acetaminophen and a corticosteroid per institutional standards
  - For Grade 1 or Grade 2 infusion-related reaction to brentuximab vedotin premedicate 30–60 minutes prior to each brentuximab vedotin infusion.
  - The routine use of steroids as premedication is discouraged.
- If anaphylaxis occurs
  - Immediately stop infusion of study agent
  - Per investigator discretion permanently discontinue study agent/regimen

6.0 ANTICIPATED TOXICITIES & DOSE MODIFICATION/ DELAY

6.1 Anticipated Toxicities

6.1.1 Brentuximab vedotin

Per the IB V16 (Oct 2018) the expected toxicities for brentuximab vedotin are as follows:

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

System Organ Class	Adverse Reactions
General disorders and administration site conditions	
Very common	Fatigue, pyrexia, infusion-related reactions[a]
Common	Chills
Investigations	
Very common	Weight decreased

a Represents pooling of preferred terms

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

6.1.2 Cyclophosphamide

Per the package insert the expected toxicities for cyclophosphamide are as follows (no asterisk signifies>10%; * signifies 1-10%; †signifies < 1%):

Blood and Lymphatic System	Neutropenia, febrile neutropenia, myelosuppression*
Cardiac	Pericardial effusion†, arrythmias†, congestive heart failure†
Gastrointestinal	Nausea, vomiting, diarrhea
General Disorders and Administration Site	Pyrexia
Hepatobiliary	Veno-occlusive Liver Disease†
Infections and infestations	Infections*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Secondary malignancy†
Renal and urinary	Hematuria
Respiratory, Thoracic and Mediastinal	Pneumonitis†, pulmonary fibrosis†,respiratory failure†
Skin and Subcutaneous Tissue	Alopecia

6.1.3 Doxorubicin

Per the package insert the expected toxicities for doxorubicin are as follows (no asterisk signifies ≥ 10%; * signifies 1-10%, and † signifies < 1%):

Blood and lymphatic (including hematological labs)	Myelosuppression, leucopenia, haemorrhage, thrombocytopenia*, anaemia*, febrile neutropenia*
Cardiac	Cardiotoxicity, pericardial effusions*
Eye	Conjunctivitis*, lacrimation*
Gastrointestinal	Nausea, vomiting, mucositis, diarrhea, abdominal pain, ulceration*
General Disorders and Administration Site	Dehydration, facial flushing, chills and fever*
Immune system	Anaphylaxis*
Investigations (excluding hematological labs)	Transaminase changes*
Metabolism and Nutrition	Anorexia*
Nervous system	Drowsiness*
Renal and urinary	Renal damage*, hyperuricaemia*

Skin and Subcutaneous Tissue	Alopecia, rash*, palmar plantar erythrodysaesthesia*
Vascular	Thromboembolism*

6.1.4 Etoposide

Per the package insert the expected toxicities for etoposide are as follows (no asterisk signifies ≥ 10%; * signifies 2-10%, and † signifies < 2%):

Blood and lymphatic (including hematological labs)	Neutropenia, thrombocytopenia, anemia
Gastrointestinal	Nausea, vomiting, diarrhea*, stomatitis†, abdominal pain†
General Disorders and Administration Site	Fever*
Hepatobiliary	Hepatic toxicity†
Immune system	Hypersensitivity†
Metabolism and Nutrition	Anorexia
Nervous system	Peripheral neuropathy†
Skin and Subcutaneous Tissue	Alopecia
Vascular	Hypotension†

6.1.5 Prednisone

Per the package insert the expected toxicities for prednisone are as follows (no asterisk signifies ≥ 10%; * signifies 1-10%, and † signifies < 1%):

Cardiac	Bradycardia†, cardiac arrest†, cardiac arrhythmias†, congestive heart failure†, tachycardia†
Endocrine	Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome
Eye	Cataracts*, glaucoma*
Gastrointestinal	Gastrointestinal perforation*
General Disorders and Administration Site	Edema*
Immune system	Anaphylaxis†, angioedema†
Infections and infestations	Infections*
Investigations (excluding hematological labs)	Weight gain
Metabolism and Nutrition	Hyperglycemia, increased appetite, increased eletrolytes*, hypocalcemia*, hypokalemia*,
Musculoskeletal and Connective Tissue	Decreased bone density*, actue myopathy*
Psychiatric	Mood changes
Respiratory, Thoracic and Mediastinal	Pulmonary edema†
Vascular	Hypertension, thromboembolism†, thrombophlebitis†, vasculitis†

6.2 Dose Delay/ Modification Guidelines

- Toxicities will be graded using the NCI CTCAE v 4.0.
- Baseline values are from the last values obtained prior to treatment.

- If one agent is held due to toxicity for a given cycle, administration of the delayed agent should resume once the toxicity is resolved on the same schedule with the next cycle of combination therapy.
- If one agent is permanently discontinued, then the participant may continue with other agent(s).
- If all agents are held together due to toxicity and the toxicity lasts > 6 weeks, then protocol therapy will be discontinued.
- **Brentuximab vedotin**
  - Dose modification/ delay brentuximab vedotin-related toxicity are described in Table 6.2.1.
  - If toxicity does not resolve within 6 weeks, permanently discontinue brentuximab vedotin.
  - Doses reduced for brentuximab vedotin-related toxicity should not be re-escalated without discussion with the Study PI.
  - Dose reductions below 1.2 mg/kg are not permitted, and toxicities should be managed with dose delays or brentuximab vedotin should be permanently discontinued.
- **CHEP**
  - Dose modifications/ discontinuation of cyclophosphamide, doxorubicin, etoposide, or prednisone due to toxicity are permitted per investigator discretion/ institutional standards.

Table 6.2.1 Dose Modifications for Brentuximab Vedotin

Toxicity	Brentixumab Vedotin Dose Management Guidelines
Peripheral **Sensory** Neuropathy	
Grade 1 *Asymptomatic; loss of deep tendon reflexes or paresthesia*	Continue at same dose level
Grade 2 *Moderate symptoms; limiting instrumental ADL*	Reduce dose to 1.2 mg/kg and resume treatment
Grade 3 *Severe symptoms; limiting self care ADL*	Withhold until toxicity resolves to ≤ Grade 2 or baseline, then resume treatment at 1.2 mg/kg See above for guidance if the participant dose is already 1.2 mg/kg.
Grade 4 *Life-threatening consequences; urgent intervention indicated*	Discontinue brentuximab vedotin
Peripheral **Motor** Neuropathy	
Grade 1 *Asymptomatic; clinical or diagnostic observations only; intervention not indicated*	Continue at same dose level
Grade 2 *Moderate symptoms; limiting instrumental ADL*	Withhold until toxicity resolves to ≤ Grade 1 or baseline, then resume treatment at 1.2 mg/kg See above for guidance if the participant dose is already 1.2 mg/kg.
Grade 3/4 *G3: Severe symptoms; limiting self care ADL;*	Discontinue brentuximab vedotin

Toxicity	Brentixumab Vedotin Dose Management Guidelines
assistive device indicated *G4: Life-threatening consequences; urgent intervention indicated*	
Infusion Related Reaction	
Grade 1/2 *G1: Mild transient reaction; infusion interruption not indicated; intervention not indicated* *G2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs*	• During subsequent cycles – Prophylactic premedication is recommended (Section 5.13.2) – Maintain same dose level
Grade 3 *Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae*	• Stop infusion for that visit • Once toxicity resolves ≤ Grade 2 or baseline – Consult Study PI to continue to administer brentuximab vedotin during subsequent cycle(s) at the same dose level with prophylaxis premedication (Section 5.13.2) – Otherwise, permanently discontinue brentuximab vedotin.
Grade 4 *Life-threatening consequences; urgent intervention indicated*	• Discontinue brentuximab vedotin. • See Section 5.13.2 for supportive care.
Other unspecified non-hematologic	
Grade 1/2	Continue at same dose level
Grade 3	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume treatment at the same dose level. – **Note:** Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.
Grade 4	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the investigator [a,b] a. See above for guidance if the participant dose is already 1.2 mg/kg. b. Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.
Hematologic	
Grades 1-2	Continue at same dose level
Grade 3-4	• Withhold until toxicity resolves to ≤ Grade 2 or baseline – **NOTE:** Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption • Growth factor support (G-CSF or GMCSF) for neutropenia should be considered for subsequent cycles. • *First occurrence* resume at same dose level • *Second occurrence*

Toxicity	Brentixumab Vedotin Dose Management Guidelines
	- For any toxicity (including neutropenia despite the use of G-CSF), dose reduction to 1.2mg/kg should be considered - If the participant is already receiving 1.2 mg/kg, dose discontinuation should be considered.

7.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

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.

7.1 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 version 4.0. A copy of the scale can be found at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

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.

7.2 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.

7.3 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring while the participant receives the first dose of protocol therapy up to 6 months post-last dose of brentuximab vedotin 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 Study PI/ DCC immediately within 24 hours of awareness** (see Section 7.7.2); the Study PI or designee will subsequently inform Seattle Genetics using the Seattle Genetics Pregnancy Report Form (Section 7.6). 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 Study PI/ DCC.

Abnormal pregnancy outcomes and neonatal deaths that occur within 28 days of birth should be reported as an SAE per expedited reporting guidelines (see Section 7.6).

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 (see Section 7.6); the Study PI or designee will subsequently inform Seattle Genetics using the Pregnancy Report Form (Section 7.6).

7.3.1 Male participants

If a female partner of a male participant becomes pregnant within 90 days post-last dose, 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 Study PI/ DCC.

7.4 Routine AE Collection and Reporting Guidelines

Routine recording of adverse events (AEs) will occur via data entry into the study eCRF.

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

AEs will be collected from the signing of informed consent until ending study participation.

AEs will be monitored by the Protocol Management Team (PMT).

The highest grade of any toxicity will be collected for each cycle during protocol treatment and for the period of safety follow-up after end of treatment. For **Cycle 1 only**, all Grade ≥2 AEs (highest grade or not) will also be collected.

7.5 Expedited Reporting

Table 7.5 indicates what events must be reported expeditiously.

Table 7.5 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 • AEs associated with pregnancies (Section 7.3) • Discontinuation of protocol therapy due to unusual or unusually severe AE considered related to brentuximab vedotin.
After 30 days post-last dose of brentuximab vedotin (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)
NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or determined to be irreversible by the investigator. **The DCC should be consulted prior to ending the follow-up of events that have stabilized.**	

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

7.5.1.1 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. For non-COH sites, the DCC will be responsible for reporting (see Section 7.5.2).

7.5.1.2 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, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

7.5.2 Expedited reporting guidelines **(Non COH Sites only)**

7.5.2.1 To the DCC/Study PI

All events that meet the criteria specified in Table 7.5 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 http://www.fda.gov/medwatch/getforms.htm
    *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 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 CHEP-BV 17058 SAE".

    a. If available, sites may include the local IRB submission for this event in the submission.

    If an email receipt from DCC personnel is not received within one working day, please email DCC@coh.org.

7.6 Reporting to the FDA

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

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

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

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

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days of the anniversary of the date the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

7.7 Reporting to Industry Partner

a. Promptly forward to Seattle Genetics copies of all written IND safety reports submitted to the FDA.

    Email: drug.safety@seagen.com

b. Report to Seattle Genetics aggregate SAEs monthly via **email:** IST@seagen.com

or portal.

c. Assist Seattle Genetics in investigating any SAE and will provide any follow-up information reasonably requested by Seattle Genetics.

d. Submit to Seattle Genetics 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

e. Forward to Seattle Genetics (via COH OIDRA) copies of initial/annual/final FDA IND submissions**.**

   Email: IST@seagen.com

8.0 AGENT INFORMATION

8.1 Brentuximab Vedotin

Brentuximab vedotin has been FDA approved for the treatment of patients with classical HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT), after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, and treatment of patients with classical HL at high risk of relapse or progression as post-auto-HSCT consolidation. Brentuximab vedotin is FDA-approved for relapsed CD30 expressing systemic anaplastic large cell lymphoma [40]. Brentuximab vedotin is FDA-approved in combination with CHP chemotherapy for previously untreated, systemic ALCL or other CD30-expressing PTCL.

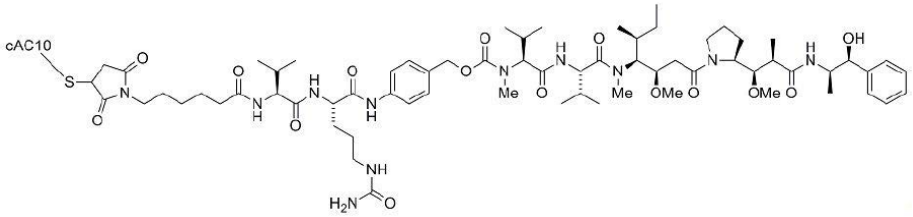
Please refer to the investigator brochure for a detailed description.

8.1.1 Other Names

ADCETRIS®, SGN-35

8.1.2 Description

Structural Formula:



Empirical Formula:	$C_{6476}H_{9930}N_{1690}O_{2030}S_{40}$ $(C_{68}H_{105}N_{11}O_{15})_{3–5}$
Type:	Antibody-drug conjugate (ADC). The chimeric monoclonal IgG1 antibody cAC10 is covalently linked to the monomethyl auristatin E (MMAE) via a protease-cleavable linker. About 4 molecules of MMAE are attached to each antibody molecule.
Source:	Mouse-human chimera
Target:	CD30
Molecular weight:	153 kDa

8.1.3 Mechanism of Action

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

8.1.4 Pharmacokinetics

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

ADC Elimination half-life:	4-6 days

8.1.5 Human Toxicity

See Section 6.1.1.

8.1.6 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.

8.1.7 Storage

Refrigeration should be set at 2–8°C for storage of vials and solutions containing brentuximab vedotin.

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.

8.1.8 Handling and Dispensing

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

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

If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact Seattle Genetics immediately using the investigational product complaint form. The DCC should be notified of any potential irregularities.

8.1.9 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. 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.
3. 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.

4. Refrigeration should be set at 2–8°C for storage of the reconstituted vials. The reconstituted vials must be administered within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

8.1.10 Preparation

1. Transfer the required volume of reconstituted product to a 100 mL to 250 mL infusion bag. (A glass, sterile bottle may be used instead of an infusion bag.)
    a. The infusion bag size should allow enough diluent to achieve a concentration of 0.4–1.8 mg/mL.
    b. The following bag types are compatible with brentuximab vedotin: polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, polypropylene, or polyethylene.
    c. 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 example calculations in Table 8.1.10 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 8.1.10 Examples of 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 or kits. Use vials from the same lot or kit number for a given dose.
6. Refrigeration should be set at 2–8°C for storage of the prepared dosing solution. The solution must be used within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

8.1.11 Dose and Administration

Administer brentuximab vedotin as an intravenous infusion only, over 30 minutes (+10 minutes).

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

See Section 5.8.2 for dosing and additional administration guidelines.

8.1.12 Supplier

- US sites:
  - For the induction phase: brentuximab vedotin will be supplied free of charge by Seattle Genetics until February 8, 2019 (included). Starting February 9, 2019 (BV is FDA-approved for previously untreated CD30-expressing PTCL in the US as of November 16, 2018), BV will be commercial supply. For patients who started the induction phase before February 8, 2019, Seattle Genetics will keep supplying BV free of charge for the remainder of the induction phase.
  - For the maintenance/consolidation phase: Seattle Genetics will supply BV free of charge.
- Non-US site:

Seattle Genetics will supply BV free of charge for all parts (induction and maintenance/consolidation) of the study.

8.1.13 Ordering

Sites will place orders for brentuximab vedotin via the Seattle Genetics Investigational Drug Request Form; **the Seattle Genetics Protocol ID 35-IST-039 must also be stated in the form.** 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.

8.1.14 Accountability

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

8.1.15 Destruction and Return

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.

8.2 Cyclophosphamide

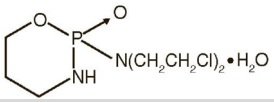
Cyclophosphamide is FDA approved for the treatment of a) malignant diseases, including Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma and b) biopsy proven minimal change nephrotic syndrome in pediatric patients who failed to adequately respond to or are unable to tolerate adrenocorticosteroid therapy.

Please refer to the package insert for a detailed description.

8.2.1 Other Names

Cytoxan®, Neosar®

8.2.2 Description

Structural formula:	
Empirical formula:	$C_7H_{15}Cl_2N_2O_2P \bullet H_2O$
Molecular weight:	279.1 g/mol
Chemical name:	2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate

8.2.3 Mechanism of Action

Cyclophosphamide is an alkylating agent that inhibits cell proliferation.

8.2.4 Pharmacokinetics

Elimination half-life:	3 to 12 hours
Total body clearance:	4 to 5.6 L/h
Distribution:	20% is protein bound. Some metabolites are protein bound to an extent greater than 60%.
Volume of distribution:	~ total body water 30 to 50 L
Metabolism:	~75% is activated by hepatic microsomal cytochrome P450s including CYP2A6, 2B6, 3A4, 3A5, 2C9, 2C18 and 2C19, with 2B6. Cyclophosphamide appears to induce its own metabolism. Auto-induction results in an increase in the total clearance, increased formation of 4-hydroxyl metabolites and shortened t values following repeated administration at 12- to 24-hour interval
Elimination:	10-20% via urine, 4 % via bile

8.2.5 Human Toxicity

See Section 6.1.2 for details.

8.2.6 Formulation

Formulation for infusion will be used for this study.

8.2.7 Storage, Handling, Preparation

Follow package insert instructions.

8.2.8 Dose and Administration

See Section 5.8.1 for dosing and additional administration guidelines.

8.2.9 Supplier

Cyclophosphamide is available commercially.

8.3 Doxorubicin

Indications:

- **Breast Cancer**: adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer.
- **Metastatic cancers or disseminated neoplastic conditions**: acute lymphoblastic leukemia, acute myeloid leukemia, Wilms tumor, neuroblastoma, soft tissue and bone sarcomas, breast cancer, ovarian cancer, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared with other cell types.

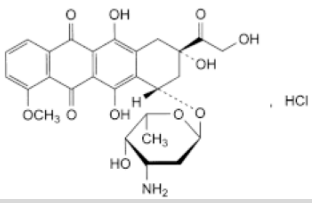
Please refer to the package insert for a detailed description.

8.3.1 Other Names

ADRIAMYCIN®, doxorubicin hydrochloride

8.3.2 Description

Structural formula:



Empirical formula:	$C_{27}H_{29}NO_{11}$,HCl
Molecular weight:	580 g/mol
Chemical name:	(8S,10S)-10-[(3-Amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]- 6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10- tetrahydrotetracene-5,12-dione hydrochloride

8.3.3 Mechanism of Action

Doxorubicin hydrochloride is an antineoplastic antibiotic. The precise mechanism of action is not fully understood. Cytotoxic effect of the drug may be related to a number of mechanisms including free radical formation secondary to metabolic activation of doxorubicin by electron reduction, intercalation of the drug into DNA, induction of DNA breaks and chromosomal aberrations, and alterations in cell membranes induced by the drug. In vitro studies suggests that apoptosis (programmed cell death) also may be involved in the drug's mechanism of action. These and other mechanisms (chelation of metal ions to produce drug-metal complexes) also may contribute to the cardiotoxic effects of the drug.

8.3.4 Pharmacokinetics

Half-life:	Multi-phasic; initial t½ is 5 minutes suggests rapid tissue uptake of doxorubicin. Slow elimination from tissues is reflected by a terminal t½ of 20-48 hours
Steady state distribution volume:	Exceeds 20-30 L/kg
Distribution:	75% protein bound
Metabolism:	Major matabolite is doxorubinol; metbolized via CYP3A4/ CYP2D6
Elimination:	40% of dose in bile in 5 days; 5-12% in urine in same period

8.3.5 Human Toxicity

See Section 6.1.3 for details.

8.3.6 Formulation

Formulation for infusion will be used for this study.

8.3.7 Storage, Handling, Preparation

Follow package insert instructions.

8.3.8 Dose and Administration

See Section 5.8.1 for dosing and additional administration guidelines.

8.3.9 Supplier

Doxorubicin is available commercially.

8.4 Etoposide

Indications:

- First-line small cell lung cancer
- Refractory testicular tumors

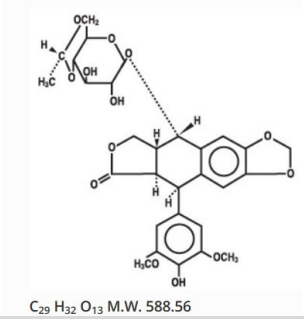
Please refer to the package insert for a detailed description.

8.4.1 Other Names

VePesid®, Etopophos®, VP-16

8.4.2 Description

Structural formula:



$C_{29}H_{32}O_{13}$ M.W. 588.56

Empirical formula:	$C_{29}H_{32}O_{13}$

Molecular weight:	589 g/mol
Chemical name:	(5S,5aR,8aR,9R)-5-[[(2R,4aR,6R,7R,8R,8aS)-7,8-dihydroxy-2-methyl-4,4a,6,7,8,8a-hexahydropyrano[3,2-d][1,3]dioxin-6-yl]oxy]-9-(4-hydroxy-3,5-dimethoxyphenyl)-5a,6,8a,9-tetrahydro-5H-[2]benzofuro[6,5-f][1,3]benzodioxol-8-one

8.4.3 Mechanism of Action

Etoposide, a semisynthetic derivative of podophyllotoxin, forms a complex with topoisomerase II and DNA resulting in DNA breaks.

8.4.4 Pharmacokinetics

Half-life:	Initial t½ is 1.5 hours. Mean terminal t½ is 4 to 11 hours
Distribution:	7-17 L/m^2
Protein binding:	94-98%
Metabolism:	Hepatic via CYP3A4/5
Elimination:	Urine (56%) within 120 hours; feces (44%) within 120 hours

8.4.5 Human Toxicity

See Section 6.1.4 for details.

8.4.6 Formulation

Formulation for infusion or oral formulation will be used for this study.

8.4.7 Storage, Handling, Preparation

Follow package insert instructions.

8.4.8 Dose and Administration

See Section 5.8.1 for dosing and additional administration guidelines.

8.4.9 Supplier

Etoposide is available commercially.

8.5 Prednisone

Indications:

- Anti-inflammatory or immunosuppressive agent
- Treatment of certain endocrine disorders
- Palliation of certain neoplastic conditions

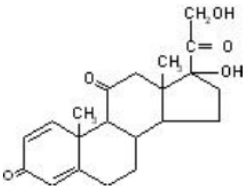
Please refer to the package insert for a detailed description.

8.5.1 Other Names

Orasone®, Pediapred®, Sterapred®, Deltasone, RAYOS

8.5.2 Description

Structural formula:



Empirical formula:	$C_{21}H_{26}O_5$
Molecular weight:	358.43 g/mol
Chemical name:	pregna-1,4-diene-3,11,20-trione monohydrate,17,21-dihydroxy-

8.5.3 Mechanism of Action

Prednisone suppresses the immune system. Anti-tumor effects may be related to inhibition of glucose transport, phosphorylating or induction of cell death in immature lymphocytes.

8.5.4 Pharmacokinetics

Elimination half-life:	2-3 hours
Protein binding:	< 50%
Metabolism:	Hepatic via CYP3A4 to active metabolite prednisolone
Elimination:	Urine

8.5.5 Human Toxicity

See Section 6.1.5 for details.

8.5.6 Formulation

Oral formulation will be used for this study.

8.5.7 Storage, Handling, Preparation

Follow package insert instructions.

8.5.8 Dose and Administration

See Section 5.8.1 for dosing and additional administration guidelines.

8.5.9 Supplier

Prednisone is available commercially.

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Correlative Study Plan

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

Table 9.1 Correlative Study Plan

Tissue type	Planned correlative analysis
Tumor tissue	• Gene expression and mutational profiling of PTCL tumor specimens to determine whether there are expression profiles and/or mutations associated with outcome after study therapy.
Blood	• Next-generation sequencing-based minimal residual disease (MRD) assessment. We will assess MRD at baseline, and at all pre-specified imaging time points –see Table 9.3. These sequential samples will allow us to track the temporal dynamics of MRD after CHEP plus BV, and to determine whether maintenance therapy can eradicate MRD in patients who are MRD+ after induction therapy

9.2 Tumor Tissue Studies

9.2.1 Timepoints 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 Study PI approval.
- *From participants who progress/ relapse during study (strongly encouraged, but not mandatory)*: If safe and feasible, submission of a tumor lesion core or excisional biopsy.

9.2.2 Guidelines for archival specimens

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

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

9.2.3 Guidelines for fresh tumor tissue processing (for patients with insufficient remaining tissue in diagnostic tissue block)

9.2.3.1 Non-COH sites

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

9.2.3.2 COH only

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

Core biopsies:

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

For excisional biopsies:

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

The diagnostic portion of the specimen:

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

9.2.4 Labeling of samples

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

9.2.5 Sample shipment and receiving lab

Tissue specimens collected at the above indicated timepoints will either be taken to (COH only) or batch-shipped (non-COH sites) to COH Pathology Core. For all sites, please include the **Correlative Tissue form (Appendix D-1)** 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-2 for shipping details.**

9.3 Blood samples

The table below provides an overview of correlative blood studies. Blood samples will be collected from an indwelling venous catheter or by venipuncture.

Table 9.3 Overview of correlative blood studies

Timepoint of collection	Total volume per timepoint	Tube Type	Processing/ Receiving Laboratory	Type of Laboratory Analysis
Induction ・ Cycle 1 Day 1 (baseline), ・ Cycle 3 Day 15 ・ Cycle 6 Day 15* **Consolidation** ・ Cycle 5 Day 1 Safety Follow-up (30-days post-last dose)	~20 mL	COH only Purple-top (K+EDTA) Non-COH Cell-free BCT® DNA tubes.	COH Analytical Pharmacology Core Facility (APCF)	Minimal residual disease (MRD) assessment using next-generation sequencing (NGS)
Note for Canada site: Efforts should be made collect correlative blood at the above stated timepoints. If blood is not collected, it will not be considered a protocol deviation. A note should be made to the study regulatory binder and the Study PI/ designee should also be notified promptly that blood was not collected for that timepoint. * Patients who qualify for receiving only 5 cycles of CHEP-BV will have their blood collection done on Cycle 5 Day 15.				

9.3.1 Blood sample collection and Labeling

Notification to COH APCF of Pending Collection	Site	Tube Type	Labeling and Collection Details	Post-collection Instructions
• Notify **at least one** day in advance) • **Send calendar invite via e-mail**: Leslie Smith-Powell (LSmith-Powell@coh.org) or Stephanie Lee (stlee@coh.org)	COH	Purple-top	1. Label tubes with COH protocol #, subject ID (issued by DCC), institution (for non-COH sites), date and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials. 2. Timepoints of collection are stated in Table 9.3. 3. Invert tubes eight times after collection. 4. **Immediately** place the tubes **on ice**.	**Promptly** deliver the blood samples on ice to the APCF, Shapiro room 1042 for processing **within 1-2 hours (± 15 minutes).**
	Non-COH	Cell free DNA BCT® tubes	1. Label tubes with COH protocol #, subject ID, institution (for non-COH sites), date and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials. 2. Timepoints of collection are stated in Table 9.3. 3. Fill in sample collection details in Appendix D-3. 4. If applicable, follow recommendations for order of draw outlined in Clinical and Laboratory Standards Institute (CLSI) H3-A6. a. BCT® tubes may not be drawn immediately following a heparin tube; if necessary collect a non-additive or EDTA tube as "waste tube" prior to collection in the BCT® tube. 5. Blood samples will be collected from an indwelling venous catheter or by venipuncture. 6. Below guidelines to **avoid possible backflow** from the tube should be followed since BCT® tubes contain a formaldehyde-free preservative: a. Keep patient's arm in the downward position during collection. b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection. c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of aapplication. 7. Completely fill the tube. 8. Remove tube from adapter and immediately invert the tubes 8 to 10 times. 9. **DO NOT FREEZE** samples. Store samples at **18-25 ºC** until shipment.	See Appendix D-4 for shipment details.

9.3.2 Sample Processing by APCF

Tube Type and Volume	Processing Details		Downstream assay
Purple-top (~20 mL) from COH only	Plasma	1. Centrifuge for 10 minutes at 1800 x g at 4 °C. 2. Remove the tubes from the centrifuge. Do not disturb the cellular layer. 3. Extract plasma carefully. a. **Do not disturb** the **buffy coat** while pipetting plasma; leave ~3-4mm of plasma behind to ensure the buffy coat is undisturbed. 4. Freeze plasma at -80°C in 1-2mL aliquots. Do not fill tubes beyond 70% capacity.	Sequencing-cell free circulating tumor DNA
	PBMC and Plasma depleted whole blood cells (PDWB)	5. The remaining content from the tube(s) used to extract the plasma will be split into 1/2 and processed as follows: a. Process ½ of the content for PDWB; 1-2mL PDWB aliquots will be frozen at -80°C b. Process ½ of the content for PBMC **per COH APCF procedures**; store per COH APCF procedures until use.	Sequencing
Cell free DNA BCT® (~20 mL) from Non-COH sites	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. **Save** the remaining cells 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.	Sequencing-cell free circulating tumor DNA
	PBMC and Plasma depleted whole blood cells (PDWB)	6. The remaining content from the tube(s) used to extract the plasma will be split into 1/2 and processed as follows: c. Process ½ of the content for PDWB; 1-2mL PDWB aliquots will be frozen at -80°C d. Process ½ of the content for PBMC **per COH APCF procedures**; store per COH APCF procedures until use.	Sequencing

10.0 STUDY CALENDAR

All procedures may increase in frequency if clinically indicated.

Table 10.0 Study Activity Calendar

		Protocol therapy [b,c]								Follow-up assessments may be combined if the windows for the two follow-up visits overlap.				
Protocol Activity	**Screening [a]**	**Induction CHEP-BV [kk]**							**End of Cycle 6 (If receiving ASCT/ RT) [g]**	**Consolidation BV**		**Follow-up (until ~5 years from start of treatment)**		
		C1	**C2**	**C3**		**C4-5**	**C6**			**C1**	**C2-10**			
		D1[d,e]	**D1[e]**	**D1[e]**	**D15[f]**	**D1[e]**	**D1[e]**	**D15[f]**		**D1[h]**	**D1[e]**	**Safety 30-days post [i]**	**Active 6 months & 12 months [j]**	**Survival [k]**
Informed Consent[l]	X													
Medical History [m]	X													
Eligibility [n]	X													
Registration [o]	X													
Height	X													
Physical Exam[p] & Vital signs [q]	X	X	X	X		X	X		X	X	X	X		
ECOG Status (Appx. A)	X	X	X	X		X	X		X	X	X	X		
Con-med review [r]	X	X	X	X		X	X		X	X	X	X		
AE Assessment [s]	X [s]	X [t]	X [t]	X [t]		X [t]	X [t]		X [t]	X [t]	X [t]	X [t]		
ECHO/MUGA	X [jj]													
Pregnancy [u]	X [v]													
CBC w/diff, plt & Serum chemistry [w]	X [v]	X	X	X		X	X		X	X	X	X		
Correlative MRD blood [x]		X			X			X [kk]			Cycle 5	X		
Correlative tumor tissue	X [y]	---------- X[z] ----------												
Bone marrow biopsy/ aspirate	X [bb]	---------- X[aa, cc] ----------												
CT	X [dd, jj]				X[ff]						X [ee,ff]	X [ee]	X [ee]	
PET-CT	X [dd, jj]							X [ff, kk]			X [ee, ff]	X [ee]	X [ee]	
Response [gg]					X [ff]			X [ff, kk]			X [ff]	X	X	
Cyclophosphamide IV [hh]		D1 of each cycle												
Doxorubicin IV [hh]		D1 of each cycle												
Etoposide IV [hh, ll]		D1-3 of each cycle												
Prednisone-Orally [hh]		D1-5 of each cycle												
Brentuximab vedotin IV-Induction[hh]		D1 of each cycle												
Criteria to initiate Consolidation [ii]										X				
Brentuximab vedotin IV Consolidation [hh, ii]										D1 of each cycle				
Survival status [k]														X

a. Screening activities to occur within 28 days prior to start of protocol therapy except for laboratory assessments and bone marrow biopsy. Refer to footnote jj for patients who received one cycle of CHOP-like or one cycle of CHP-BV therapy prior to starting study treatment.
b. Protocol therapy may last up to 16 cycles, until unacceptable toxicity or disease progression (see Section 5.10 for more comprehensive list).
c. In the absence of treatment delay, each treatment cycle lasts 21 ± 3 days.
d. Day 1 of Cycle 1 of Induction is defined as the day of chemotherapy (CHEP) administration.
e. Activities (except imaging and response assessment- footnote ff) and safety assessment review to be performed within 72 hours prior to initiation of the cycle.
f. Day 15 assessments have a ± 7 day window.
g. End of Cycle 6 safety visit (-7/ + 3 days) for those going on to receive consolidation ASCT/ radiation therapy (RT). Will occur at end of Cycle 5 (-7/ + 3 days) for patients who qualified for receiving only 5 cycles of CHEP-BV.
h. *For CR/ PR participants from Induction*: Day 1 of Cycle 1 of Consolidation is defined as the day of brentuximab vedotin administration. **NOTE:** Evaluations performed within 14 days prior to start of Consolidation Day 1 may serve as Day 1 evaluations. Refer to Section 5.7 for details.
i. The 30 days post-last dose assessments to occur 30 (±7) days post-last dose or, if > 30 days elapsed since last dose, within 7 days after decision to end treatment. Expedited reporting will occur during this period (See Section 7.6). Safety follow-up may be extended until resolution/ stabilization of reportable AEs.
j. For participants yet to progress, Active Follow-up will occur at 6 months (± 14 days) and 12 months (± 30 days) from the day of last response evaluation until progression or the initiation of a new therapy.
k. Participants who end Active Follow-up will enter Survival Follow-up. Survival assessment to occur bi-annually or as requested by the Study PI via medical record review, review of social security registry, or telephone call.
l. *Informed consent* process to be fully documented (see Section 16.4). Informed consent must occur prior to any research only (non-SOC) screening procedures.
m. *Medical history* to include a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
n. *Eligibility criteria* are detailed in Section 3.0.
o. *Registration* into a COH clinical trial management system (CTMS).
p. *Standard physical exam* includes weight and skin analysis.
q. *Vital signs*: heart rate, blood pressure, respiration rate, and temperature.
r. *Concurrent medications* and reason for administration to be documented from within 28 prior to protocol therapy up to 30-days-post last dose visit. See Section 5.13 for concomitant medication restrictions and guidelines.
s. *Adverse event (AE)* will be assessed using CTCAE v.4.0. SAEs related to study procedures will be recorded and reported from time of informed consent until Day 1 of protocol therapy.
t. AE recording and reporting will continue until the completion of Safety Follow-up period or until resolution or stabilization of any reportable AE occurring during Safety Follow-up.
u. *Women of child bearing potential*: Pregnancy serum or urine test.
v. *Screening laboratory assessments* to be performed within 14 days prior to start of protocol therapy.
w. *Serum chemistry* panel to include: glucose, Blood Urea Nitrogen (BUN), creatinine, uric acid, total protein, albumin, magnesium, bicarbonate, calcium, inorganic phosphorous, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT, AST, and LDH.
x. Correlative blood will be collected as follows. See Section 9.3 for timepoints and details for notifying APCF, processing and non-COH site shipment.
    - **COH only for MRD studies**: 20 mL into purple-top tubes per timepoint, and

- **Non-COH only for MRD studies**: 20 mL into cell free DNA BCT® tubes per timepoint

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

z. If safe and feasible, submission of left-over tissue from a standard of care tumor biopsy (fresh core or excisional biopsy) for participants who progress/relapse during study is encouraged. Refer to Section 9.2.1

aa. Following initial screening, and unless clinically indicated, bone marrow specimens will be collected only to confirm CR, and only on patients who had bone marrow involvement at screening.

bb. *Bone marrow biopsy/aspirate* performed within 120 days prior to Day 1 Induction may serve as Screening assessment.

cc. Perform bone marrow biopsies/ aspirate only: **(i)** to confirm CR, and **(ii)** as clinically indicated post-CR.

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

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

ff. *Imaging and response assessment to occur*:

- **Induction CHEP-BV:**
  Cycle 3 Day 15 (± 7 days) **and**
  Cycle 6 Day 15 (± 7 days), or Cycle 5 Day 15 (± 7 days) (if patient qualifies for receiving only 5 cycles of CHEP-BV)
- **Consolidation BV**: Cycle 5 Day 1 (-7 days)
- **30-days post-last dose (± 7 days)**: Only if last imaging assessment was performed > 8-12 weeks ago.
- **Active Follow-up:** at 6 months (± 14 days) and 12 months (± 30 days) from the day of last response evaluation

gg. *Response per 2014 Lugano Classification*: See Section 11.3 and Appendix B-2.

hh. Refer to Section 5.3 for the treatment plan and Section 5.8 for agent administration details. Refer to Section 6.2 for dose modification/ delay guidelines and Section 5.13 for supportive care guidelines.

ii. *Criteria to initiate BV Consolidation*: Section 5.7.1 criteria must be met.

jj. Patients who received one cycle of CHOP-like or 1 cycle of CHP-BV therapy prior to starting study treatment do not need to repeat echocardiogram/MUGA and pre-treatment (screening) imaging assessment if these tests were performed within 60 days of the cycle of CHOP-like or CHP-BV therapy, and providing that the results of these tests met the eligibility criteria for the current study.

kk. Patients who received 1 cycle of CHOP-like or 1 cycle of CHP-BV therapy prior to initiating induction with CHEP-BV are allowed to receive only 5 cycles of CHEP-BV instead of 6 cycles, per investigator's discretion. For these patients who qualify for receiving only 5 cycles of CHEP-BV, imaging, response assessment, and correlative blood collection scheduled on Cycle 6 will occur on Cycle 5.

ll. Alternatively, etoposide may be given orally (refer to Section 5.3).

11.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

11.1 Safety

Toxicity will be recorded using the NCI CTCAE v 4.0. The highest grade of any toxicity will be collected for each cycle during protocol treatment and for the period of safety follow-up after end of treatment. For **Cycle 1 only**, all Grade ≥2 AEs (highest grade or not) will also be collected.

11.2 Unacceptable Toxicity

Unacceptable toxicity will be defined as one of the following AEs that is **at least possibly** related to study treatment during **Cycle 1 of Induction**:

Hematologic

- Delay in planned initiation of Cycle 2 Day 1 by more than 14 days due to Grade 4 neutropenia that does not resolve to Grade ≤ 2 or baseline despite growth factor support
- Grade 4 thrombocytopenia lasting ≥ 7 days
- Platelet nadir < 10,000/ mm^3
- Delay in planned initiation of Cycle 2 Day 1 by more than 7 days due to failure to recover platelets to ≥ 50,000/ mm^3 and/or ANC to ≥ 1000/ mm^3
- Any Grade 5 AE

Non-hematologic

- Any clinically relevant ≥ Grade 3 AE that does not resolve to Grade ≤ 2 within 7 days with the **exception** of:
  - Grade 3 asymptomatic laboratory abnormalities, including lipase or amylase, that are not clinically relevant, not requiring hospitalization or delay of treatment
  - Grade 3 nausea, vomiting, or fatigue controlled with supportive measures
  - Grade 3 inflammatory response attributed to local antitumor response
  - Vitiligo
- Delay in planned initiation of Cycle 2 Day 1 by more than 7 days due to Grade ≥2 peripheral motor neuropathy
- Any Grade 5 AE

11.3 Response and Clinical Endpoints

11.3.1 Response/Progression

Lymphoma response/progression will be evaluated using 2014 Lugano Classification (see Appendix B-2) [55, 57].

Disease parameters and methods for assessing the disease are in Appendix B-1. Disease assessment will be performed either by PET-CT (FDG-avid histologies) or diagnostic quality CT of the neck, chest, abdomen and pelvis (N/C/A/P) with IV contrast. Although diagnostic quality CT is acceptable, at baseline and end of induction, PET-CT is the preferred assessment method. At the interim assessment on C3D15, diagnostic quality CT should be performed. PET and CT may be co-acquired or acquired separately. Patients with bone marrow involvement at baseline must have a bone marrow biopsy performed to

confirm CR (if applicable). After CR, additional bone marrow biopsy is only required if clinically indicated and, after CR, IV contrast-enhanced CT of the chest, abdomen, pelvis (and neck, if involved by lymphoma) can be performed rather than PET-CT. For patients not in CR who are receiving consolidation, although diagnostic quality CT is acceptable, PET-CT is preferred to assess for possible conversion to CR. Additional necessary restaging studies including dedicated CT scans or MRI, are permitted at the investigator's discretion. PET-CT and CT results will be read by a radiologist at each study site and investigator response assessment will be performed.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy be obtained whenever possible. Note that an FDG-negative PET scan will only be considered complete remission in patients whose tumor was FDG-avid at baseline. In patients who do not have FDG-avid disease at screening, diagnostic quality CT scans should be performed for treatment response assessment.

11.3.2 Clinical Outcome Endpoints

Evaluable patients are defined in Section 12.2.

Endpoint	Patients	Definition
*Progression-Free Survival (PFS)**	Evaluable patients	Defined as the time from enrollment to the first observation of disease relapse/progression or death from any cause, whichever occurs first. For patients who are alive and have not had disease relapse/progression at the last follow-up, it is censored at the time of last follow-up. If a patient recieves non-protocol anti-lymphoma treatment prior to disease progression, it is censored at the time of non-protocol anti-lymphoma treatment.
Overall Survival (OS)	Evaluable patients	Defined as the time from enrollment to death from any cause. For patients alive at the last follow-up, it is censored at the time of last follow-up.
Overall response (ORR) rate	Evaluable patients	Proportion of patients achieving CR or PR
Complete response (CR) rate	Evaluable patients	Proportion of patients achieving CR

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

12.1.1 Study Design Overview

This will be a multicenter, single-arm Phase 2 study evaluating the addition of brentuximab vedotin to cyclophosphamide, doxorubicin, etoposide, and prednisone (CHEP-BV) as induction therapy for CD30-positive peripheral T-cell lymphomas followed by BV consolidation. Patients will receive up to 6 cycles of CHEP-BV in 21-day cycle as induction therapy. Patients with objective response after induction therapy will be eligible to undergo consolidation therapy with an additional 10 cycles of single-agent BV, administered every 21 days, to be initiated either after a consolidative ASCT/radiation or after the completion of induction therapy.

The primary endpoint is complete response (CR) rate after CHEP-BV induction therapy. Secondary endpoints include toxicities of CHEP-BV induction therapy, toxicities of BV consolidation after CHEP-BV induction therapy and ASCT/radiation, toxicities of BV consolidation after CHEP-BV induction therapy without ASCT/radiation, ORR after induction therapy, CR rate after BV consolidation therapy, PFS and OS. The first 6-12 patients will be monitored as part of the Safety Lead-in segment as described below in Section 12.1.2. Patients enrolled during the safety lead-in segment who are treated at the final dose deemed tolerable will be included in the Phase 2 response evaluation provided that they are also evaluable for response.

The initial statistical design described below was based on CR rate of 60% vs. 40%.

The study adopts a Simon Two-Stage Minimax Design, with 16 patients at the first stage and a total of 28 patients at the second stage. The sample size is based on the desire to discriminate a promising CR rate of 60% after CHEP-BV induction from a disappointing CR rate of 40% after CHEP-BV induction, using a type I error rate of 0.10 and power of 80%. These rates were chosen based on prospective clinical trial data of anthracycline-based induction therapy for PTCL. The CR/CRu rate to CHOEP/CHOP (younger patients received CHOEP, patients 60 or older received CHOP) in a Phase 2 study of patients with PTCL is 52.6% (n=82/156)[18] while the CR/CRu rate to CHOP-based therapy in two prospective clinical trials is 33% (n=15/45, CHOP) and 49% (20/41, high-dose CHOP plus ESHAP) [10, 11]. Therefore, we would consider at least 60% a promising CR rate for this regimen to merit further study and a 40% CR rate (similar to CHOP) a discouraging rate.

In the Simon Two-Stage Minimax design, at the first stage, 16 patients will be entered on the study. If ≤ 6 complete responses are seen, the study will be terminated. If at least 7 patients achieve a complete response, the trial will continue to the second stage. At the second stage, 12 additional patients will be entered. At the end of stage 2, if 15 or more patients out of the total 28 experience a complete response, the combination will be considered worthy of further study. If ≤14 patients experience a complete response then no further investigation of the combination is warranted.

Per Amendment dated 05-10-19, the statistical design is being revised. The revisions are motivated by the recent published data from the randomized Phase III ECHELON-2 study (n=452)[58]. In the ECHELON-2 study, previously untreated CD30-positive PTCL patients were randomized to BV+CHP or CHOP for 6-8 cycles. The CR rate at end of treatment was 56% (95% CI 49%-62%) for CHOP arm and 68% (61%-74%) for BV+CHP arm (p=0.007). In our initial design described above, 40% CR rate was considered the baseline rate for CHOP-like induction thearpy. Given the ECHELON-2 data results, the study is being

revised to consider a baseline rate of 56% instead of 40%, and to increase the total study accrual to 48 evaluable patients. Patients enrolled during the Safety Lead-in segment who are treated at the final dose deemed tolerable will be included in the Phase 2 response evaluation provided that they are also evaluable for response. The sample size of 48 is based on the desire to discriminate a promising CR rate of 71% from a disappointing CR rate of 56%, using a type I error rate of 0.10 and power of 80% based on an exact binomial test. The design will require 32 or more CR among the 48 patients to consider the outcome encouraging.

At the time of this amendment, this study has already passed the initial/previous design Stage I efficacy rule and is at Stage 2 accrual. Among the 16 Stage I patients, there have been 9 end of induction CR, 1 end of induction PR, 2 interim CR and 2 interim PR pending end of induction response, and 2 pending any response evaluations. Given the efficacy of BV+CHP established by ECHELON-2 study and the preliminary efficacy data we observe with CHEP-BV on this study, this revised design is a single stage design without an interim monitoring rule.

12.1.2 Safety Lead-in

Prior to formally initiating the Phase 2 response evaluations, a patient safety lead-in segment will be conducted to ensure there are no unexpected toxicities. The safety lead-in segment will follow standard 3+3 dose escalation/de-escalation/expansion rules based on observed toxicity during Induction Cycle 1. The unacceptability toxicities are defined in Section 11.2. Patients evaluable for unacceptable toxicities during the Safety Lead-in are defined in Section 12.2.

Initially up to 3 patients can be enrolled and treated with CHEP-BV induction therapy at brentuximab vendotin dose level of 1.8 mg/kg (dose level 1). After 3 patients are treated and evaluated for unacceptable toxicities during Cycle 1, if ≤1 out of 3 patients experience unacceptable toxicities, up to 3 additional patients will be enrolled and treated at 1.8 mg/kg to bring the total number of patients treated to 6. If ≤1/6 patients experience unacceptable toxicities during Cycle 1, brentuximab vedotin at 1.8 mg/kg will be considered tolerable for the CHEP-BV therapy and the brentuximab vedotin consolidation therapy. If ≥2/3 (after the initial 3) or ≥2/6 (after the total 6 in 2 cohorts) patients experience unacceptable toxicities during Cycle 1, 1.8 mg/kg will be considered not tolerable, and the study will then evaluate the safety and tolerability of the lower dose level of brentuximab vedotin at 1.2 mg/kg (dose level -1).

A similar "3+3" design will be used to evaluate the dose level of 1.2 mg/kg if 1.8 mg/kg is not tolerable. Up to 6 patients will be enrolled in cohort of 3 patients. If ≤1/6 patients experience unacceptable toxicities during Cycle 1, 1.2 mg/kg will be considered tolerable. If ≥2/3 (after the initial 3) or ≥2/6 (after the total 6 in 2 cohorts) patients experience unacceptable toxicities during Cycle 1, 1.2 mg/kg will be considered not tolerable, and the study accrual will be suspended.

12.2 Evaluable Participants and Participant Replacement

- ***Evaluable toxicity***: Patients who receive at least one dose of protocol therapy are evaluable for toxicity.
- ***Evaluable for unacceptable toxicity during Safety Lead-in***: Patients evaluable for unacceptable toxicity (defined in Section 11.2) are:
    1) Those who receive the dose of brentuximab vedotin, the dose of cyclophosphamide, the dose of doxorubicin, all doses of Etoposide, and at least 80% doses of prednisone during Induction Cycle 1 OR

2) Those who experience any unacceptable toxicity during Cycle 1 regardless of actual dose received.

Patients who are not evaluable for unacceptable toxicities will be replaced.

- ***Evaluable for response:***
  - Evaluable patients are defined as eligible participants who have received at least one cycle of CHEP-BV Induction therapy, and have had at least one disease evaluation. Patients cannot proceed to BV consolidation without a response assessment after CHEP-BV induction. Patients will be evaluable and be considered non-CR in the primary response evaluation if they discontinued study therapy prior to having a response assessment because of progressive disease or unacceptable toxicity (rather than withdrawal of consent or investigator decision). If a patient discontinues study treatment prior to the first response assessment due to progressive disease, the treating physician is encouraged to obtain imaging to confirm progression.

    Eligible participants who are not evaluable for response will be replaced and excluded from efficacy analyses, but will be included in the general toxicity analyses if they received any protocol treatment.

12.3 Sample Size Accrual Rate

The Phase 2 response evaluation will require 48 response evaluable patients. The first 6-12 patients enrolled on the study will be part of the safety lead-in segment evaluating the two dose levels, as described in the Section 12.1.2. The patients enrolled during the safety lead-in segment who are treated at the final dose deemed tolerable will be included in the Phase II response evaluation provided that they are also evaluable for response. Accounting for up to 10% inevaluable patients and some of the patients treated at the safe dose during the safety lead-in segment not evaluable for response, the maximum accrual for the study is estimated to be 53 patients. In both 2012 and 2013, City of Hope saw ~160 PTCL patients per year, with ~30 new patients per year (mix of newly diagnosed and relapsed or refractory). We expect that about ~50% of patients will be CD30+, therefore, we expect to accrue 10 patients to this trial in 36 months at COH. Given that this is a multi-center study including 3 high-volume PTCL centers, we anticipate completing study accrual within 36 months.

12.4 Statistical Analysis Plan

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

CR rate after CHEP-BV induction therapy will be estimated by the proportion of evaluable patients achieving CR after CHEP-BV induction therapy, along with the 95% exact binomial confidence interval. ORR after CHEP-BV induction therapy and CR rate after BV consolidation will be similarly estimated. PFS and OS will be estimated using the product-limit method of Kaplan and Meier along with the Greenwood estimator of standard error. Observed toxicities of CHEP-BV induction therapy, those of BV consolidation after CHEP-BV induction and ASCT/radiation, and those of BV consolidation after CHEP-BV induction without ASCT/radiation will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v4.0 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.

For the exploratory objects, descriptive statistics will be used to summarize the correlative study measures such as GEP and MRD assessments. For continuous variables, number, mean, standard deviation, standard error, median (range) etc., will be provided. For categorical variables, patient counts and percentages will be provided. Changes in these measures before, during, and after treatment (when measured) will also be summarized by descriptive statistics and tables/plots. Various statistical analyses will be used to explore the association between these correlative measures (at different time points and the associated changes over time, when measured) with clinical outcomes. For the exploratory correlation of these endpoints with response, analyses comparing groups of participants defined by response may be conducted by various two sample tests such as two-sample t-test or Wilcoxon rank sum test for the continuous correlative endpoints, or Chi-square test/Fisher's exact test for the categorical correlative endpoints. For the exploratory correlation of these endpoints with survival outcomes, survival analysis techniques such as Log rank test will be considered. Appropriate regression models will also be considered, such as logistic regression for analyses on response and Cox proportional hazards models for survival outcomes. All these analyses are exploratory in nature and are intended to generate hypotheses that may be validated in larger studies; no multiple comparison adjustments will be made in these exploratory analyses.

12.5 Toxicity Monitoring after Safety Lead-in

Close and continuous monitoring for toxicity will occur throughout the study duration per institutional standards. The City of Hope Data Safety Monitoring Committee (DSMC) will review the toxicity data on this study quarterly. The expected rate of "unacceptable toxicity" as defined in Section 11.2 should not be ≥33%. The stopping rule for "unacceptable toxicity" will be assessed after at least 6 patients are treated at the final dose deemed tolerable for Phase 2 evaluation. If "unacceptable toxicity" events occur in ≥33% of patients treated at the final dose at the quarterly review, accrual will be halted and a full review of these events will be performed by the City of Hope DSMC. Patient accrual will not resume until approved by the DSMC to do so. These rules are in addition to the bi-annual review of all toxicities submitted to the City of Hope DSMC. Patients with ongoing toxicity will be followed until resolution or stability.

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 (EDC) that is compliant with 21 CFR Part 11.

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	**Safety Lead-in Induction Cycle 1**: Within 7 calendar days of the assessment/notification **Safety Lead-in remaining cycles and Phase 2**: Within 10 calendar days of the assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of completing treatment or being taken off study for any reason
Follow up/ Survival Forms	Within 14 calendar days of the protocol defined follow up visit date or call

13.4 Regulatory Records

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

14.0 ADHERENCE TO THE PROTOCOL

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 or submit your site-specific protocol deviation log if the log format has been approved for use by the DCC. 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 or protocol deviation log 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 CHEP-BV Deviation COH IRB #17058". If an email receipt from the DCC is not received within one working day, please email DCC@coh.org.

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).

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

15.1 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.

15.2 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.

15.3 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.

15.4 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.

15.5 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because this study involves a COH IND.

15.6 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.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Ethical Standard

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

16.2 Regulatory Compliance

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

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

16.3 Institutional Review Board

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.

16.4 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.

16.5 Participant Withdrawal

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

16.6 Special and Vulnerable Populations

16.6.1 Inclusion of Women and Minorities

The study is open 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 and chemotherapy on embryogenesis, reproduction, and spermatogenesis in humans are unknown.

16.6.2 Exclusion of Pediatric Population

Pediatric participants (< 18 years old of age) are excluded from this study since safety and effectiveness of protocol therapy has not been defined for PTCL. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult PTCL population.

The incidence of PTCL is rare in the pediatric population.

16.6.3 Inclusion of HIV Positive Individuals

Participants with HIV are excluded since safety and effectiveness of brentuximab vedotin therapy has not been defined for this population.

16.6.4 Vulnerable Populations

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

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

16.7 Participant Confidentiality

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

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed 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, ant 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 timepoint of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

16.8 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.

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.

16.9 Conflict of Interest

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

16.10 Financial Obligations, Compensation, and Reimbursement of Participants

Brentuximab vedotin 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.

16.11 Publication/ Data Sharing

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

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement 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: PERFORMANCE STATUS

ECOG Performance Scale [59]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: 2014 LUGANO RESPONSE CRITERIA

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

Response	Site	CT-Based Response	PET-CT Based Response
	Nonmeasured lesion	Absent/normal, regressed, but no increase	Not applicable
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No response or stable disease		Stable disease	No metabolic response
	Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasured lesion	No increase consistent with progression	Not applicable
	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	New FDG-avid foci consistent with lymphoma at interim OR • End-of-treatment assessment

Response	Site	CT-Based Response	PET-CT Based Response
		diameter (SDi) from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly	
	Nonmeasured lesion	New or clear progression of preexisting nonmeasured lesions	None
	New lesions	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
	Bone marrow	New or recurrent involvement	New or recurrent FDG-avid foci

Measured dominant lesions:

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

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

Nonmeasured lesions:

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

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

†PET 5-point scale:

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

Abbreviations:

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

APPENDIX C: NYHA CARDIAC GRADING CRITERIA

Modified from Dolgin et al., 1994 [60]

New York Heart Association Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

APPENDIX D-1: 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-2 for shipping instructions to COH Pathology Core.

COH IRB number: 17058	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

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

APPENDIX D-2: TISSUE SHIPPING GUIDELINES FOR EXTERNAL NON-COH SITES

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

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

Shipping guidelines can also be found on the FedEx website.

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

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

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

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

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

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

6. Ship samples with a **copy of the correlative tissue form** **(Appendix D-1)** and a **copy of the pathology report** to:

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

APPENDIX D-3: CORRELATIVE BLOOD COLLECTION FORM (NON-COH SITES)

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

Blood samples will be collected into Cell-free BCT® DNA tubes from an indwelling venous catheter or by venipuncture. Refer to Section 9.3 for details.

Sample #	Timepoint of Collection	Expected Volume	Tube Type	Collected Volume	Time of Collection	Date of Collection
Induction CHEP-BV						
1.	☐ Cycle 1 Day 1 (baseline)	~20 mL	BCT® tube	_____ mL	____:____ AM/ PM	____/____/____
2.	☐ Cycle 3 Day 15	~20 mL	BCT® tube	_____ mL	____:____ AM/ PM	____/____/____
3.	☐ Cycle 6 Day 15 **OR** ☐ Cycle 5 Day 15*	~20 mL	BCT® tube	_____ mL	____:____ AM/ PM	____/____/____
Consolidation BV						
4.	☐ Cycle 5 Day 1	~20 mL	BCT® tube	_____ mL	____:____ AM/ PM	____/____/____
5.	☐ 30-days post last-dose	~20 mL	BCT® tube	_____ mL	____:____ AM/ PM	____/____/____

* For patients who qualify for receiving only 5 cycles of CHEP-BV.

A copy of this form should accompany the sample shipments to COH APCF. **Refer to Appendix D-4 for shipping instructions COH APCF**.

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

APPENDIX D-4: BLOOD SHIPPING GUIDELINES FOR EXTERNAL NON-COH SITES

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

If applicable also follow International Air Transport Association (IATA) guidelines.

When to ship and temperature of shipment:	Promptly but no later than 3 days post-collection via overnight courier at **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.
Notification on the day of shipment	Email the FedEx shipment # with a copy of Appendix D-3. • Leslie Smith-Powell (LSmith-Powell@coh.org) or • Stephanie Lee (stlee@coh.org) or their representative
*What to include **with** the shipment*	• Copy of Appendix D-3 • Copy of the latest CBC results (with differential) and the date of the test
Shipment address	Dr. Tim Synold Analytical Pharmacology Core Facility Shapiro 1042 City of Hope National Medical Center 1500 E. Duarte Road Duarte, CA 91010

APPENDIX E: DCC REGISTRATION COVERSHEET

COH Protocol #17058: **A Phase 2 Study of Brentuximab Vedotin Plus Cyclophosphamide, Doxorubicin, Etoposide, and Prednisone (CHEP-BV) Followed by BV Consolidation in Patients with CD30-Positive Peripheral T-cell Lymphomas**

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

Site Principal Investigator
Name:
Address:

Phone:
Fax:
e-mail:

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

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