CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY AND HCT

TITLE: A MULTI-CENTER PHASE II TRIAL OF IBRUTINIB PLUS BRENTUXIMAB VEDOTIN IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 15334 **VERSION: 16**

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COH Amendment 15	Protocol Dated 11/07/2019	Version: 15
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SITE: Hodgkin Lymphoma
STAGE (If applicable): All
MODALITY: Intravenous and Oral
TYPE: Phase II Multi-center

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CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 15334 VERSION: 16

SPONSOR/IND NUMBER:	N/A
DISEASE SITE:	Hodgkin Lymphoma
DISEAS STAGE:	All
MODALITY:	Intravenous and Oral
PHASE/TYPE:	Phase II/Multi-center
PARTICIPATING SITES:	City of Hope Cornell Medical College University of California, San Diego Ohio State University
STUDY SPONSOR AND MONITOR:	City of Hope

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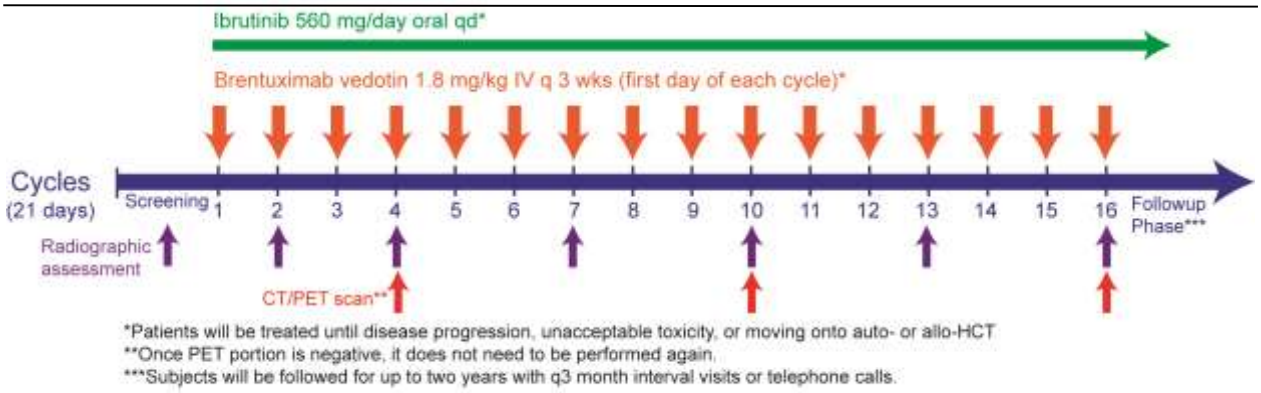
Experimental Design Schema



Note: There is a lead in portion using only 420 mg oral daily and 560 mg daily.

Protocol Synopsis

Protocol Title:
A multi-center phase II study of ibrutinib plus brentuximab vedotin in relapsed/refractory Hodgkin Lymphoma.
Brief Protocol Title (Lay Public):
A phase II study of ibrutinib plus brentuximab vedotin in high-risk Hodgkin Lymphoma
Study Phase:
Phase II with safety lead-in
Participating Sites:
▪ City of Hope ▪ Cornell ▪ UCSD ▪ OSU
Study Rationale:
Brentuximab vedotin (BV) is an antibody drug conjugate (ADC) consisting of the chimeric antibody SGN-30 (cAC10) chemically conjugated to the anti-tubulin agent monomethyl auristatin E (MMAE). BV binds to CD30 on the cell surface of Hodgkin-Reed-Sternberg cells and is internalized. Upon trafficking to lysosomes, MMAE is released from the conjugate and disrupts the microtubule network.[1] We previously participated in the multi-center phase II pivotal study investigating the use of single agent brentuximab vedotin (BV) in patients with relapsed/refractory Hodgkin lymphoma (HL) post autologous hematopoietic stem cell transplantation (AHCT). This trial showed that BV has an overall response rate of 75%, with a 34% complete response rate and tolerable toxicity.[2] Because of the high response rate, BV was granted accelerated FDA approval for the treatment of relapsed/refractory HL following failed AHCT. Although this drug has high response rates in HL, the complete response rate and the duration of response can be improved. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor, which inhibits activation of the B cell receptor signaling cascade. It has demonstrated activity in patients with relapsed/refractory B cell lymphomas[3] and has already received FDA approval for the treatment of CLL and MCL.[4,5] Ibrutinib is also an ITK inhibitor, which can be active against activated T cells. It is possible that ibrutinib can inhibit B cells and T cells in the microenvironment of HL. We performed a synergy assay testing the combination of ibrutinib and brentuximab vedotin (the latter previously known as SGN-35) in L428 (HL cell line) and found a synergistic effect. Since there is evidence of synergy in preclinical studies and the toxicity profiles do not appear to be the similar, it is reasonable to combine the two agents in relapsed/refractory Hodgkin lymphoma.
Objectives:
In patients with relapsed/refractory Hodgkin Lymphoma: **Primary:** ▪ Evaluate the anti-tumor activity of the two agent combination ibrutinib and brentuximab vedotin, as assessed by complete response (CR) rate. **Secondary:** ▪ Assess the safety and tolerability of the two agent combination through evaluation of toxicities, including type, frequency, severity, attribution, time course and duration.

- Obtain estimates of overall response rate (ORR), response duration and survival (overall and progression-free).
- Describe outcomes of patients who ultimately undergo autologous or allogeneic hematopoietic cell transplantation following treatment with ibrutinib/brentuximab vedotin.

Exploratory:

- Collect DNA/RNA from lymphoma specimens and serial plasma samples for future biomarker evaluation.

Study Design:

This study will be conducted as a multi-center phase II trial; a Simon Two-Stage (Minimax) Design will be employed. Prior to formally initiating the phase II trial, a *patient safety lead-in* segment will be conducted to ensure there are no unexpected toxicities during cycle 1. Ultimately a total of 39 patients will be treated and evaluated for response at the ibrutinib/brentuximab vedotin doses considered safe -as determined during the *safety lead-in* segment of this study.

The first nine to twelve patients enrolled will be part of the *patient safety lead-in*. Initially, a group of up to 3 patients can be enrolled. Because both brentuximab vedotin and ibrutinib have been extensively studied as single agents with tolerable toxicity profiles, it is assumed that the standard FDA-approved dosing would be tolerable (dose level 2: Ibrutinib 560mg/brentuximab vedotin 1.8mg/kg). However, during the safety lead in patients will initially be treated with 420 mg of Ibrutinib (dose level 1).

Following the *safety lead-in*, the phase II trial will formally be initiated. In the first stage, 19 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 stage 2, 20 additional patients will be entered. At the end of stage 2, if 17 or more patients experience a complete response, the combination will be considered worthy of further study. If ≤ 16 patients experience a complete response then no further investigation of the combination is warranted.

In addition to response assessment, using the Cheson Criteria (Cheson et al. 2014)[24], survival, toxicity information, and lymphoma specimens/plasma samples will be collected for exploratory biomarker evaluation.

Endpoints:

The primary study endpoint is complete response (CR) rate and is based on the Cheson Criteria (Cheson et al. 2014)[24].

The primary endpoint for the patient *saftey lead-in* segment of the study is toxicity. Toxicity will be scored using the NCI CTCAE v4.0 Scale. Unacceptable toxicity in a given patient is defined as any non-hematologic grade 3|4 toxicity or, for hematologic toxicities, any grade 3|4 that does not resolve to a grade 1|2 within 7 days per NCI CTCAE v4.03 toxicity criteria and is considered at least possibly related to ibrutinib and/or brentuximab vedotin, or any other regimen-related cause of death.

Sample Size:

Assuming 1) the ibrutinib 560mg and brentuximab vedotin 1.8mg/kg doses are well tolerated and 2) the study does not close for futility, 39 evaluable (received at least one cycle of treatment) patients will be enrolled on the phase II portion of the study. Note: Expected accrual for safety lead-in segment: n=9.

Estimated Duration of the Study

In the event that the study does not close for futility, accrual is expected to be completed in 45 months; with approximately 1-2 patients enrolled each month. Patients will be treated in 21-day treatment cycles until disease relapse, progression, unacceptable toxicity, or withdrawal of consent. Patients who discontinue study treatment for reasons other than disease relapse/progression will continue to have disease assessments per Cheson criteria[24] until relapse or progression, initiation of new anticancer treatment, or death whichever occurs first. Patients will be followed to collect further anticancer treatment (including HCT) and survival information until death, loss to follow-up, withdrawal of consent, study termination or up to 24 months post completion/ discontinuation of treatment.

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

1) Relapsed/refractory biopsy-proven CD30+ Hodgkin Lymphoma
2) Age ≥ 15 years old and > 40kg
3) ECOG Performance status 0-2
4) Prior exposure to brentuximab vedotin (relapsed disease after 3 month, not refractory disease) is allowed
5) Prior autologous hematopoietic cell transplant is allowed
6) Prior allogeneic hematopoietic cell transplant (allo-HCT) is allowed, provided there is no active GVHD and the patient is not taking immunosuppressive agents. Patient has to be at least 3 months out of allo-HCT.
7) Prior radiation therapy is allowed.
8) Patients may be on steroids before initiation of treatment, provided that use was tapered down to ≤20 mg prednisone or equivalent by cycle 1 day 1.

Exclusion Criteria:

1) Patients may not have developed progressive disease with prior treatment with brentuximab vedotin and may not have hypersensitivity to the drug. Prior ibrutinib for HL is not allowed.
2) Age < 15 years old or ≤40kg
3) Patients may not be taking other investigational products or concurrent biological therapy, chemotherapy, or radiation therapy.
4) Platelet count < 50,000, ANC < 1,000, hemoglobin < 8.5. (Growth factor support or transfusions to achieve targets are allowed provided that they have not received growth factor support for at least 14 days prior to entering trial)
5) Patients should not have any uncontrolled illness or active infection, including detectable HIV, HCV, and HBV. Patients with recent infection requiring systemic treatment that was completed ≤ 14 days before the first dose of study drugs are ineligible.
6) Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03) grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of stable neuropathy, vitiligo, alopecia, or other irreversible toxicity not reasonably expected to be exacerbated by study treatment (e.g., hearing loss)
7) Patients must not be vaccinated with live, attenuated vaccines with 4 weeks of the first dose of the study drugs.
8) Patients with active CNS disease or history of brain metastases are ineligible.

9) Patients must not have another malignancy within 3 years of enrollment. Exceptions: complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
10) Pregnant women are excluded from the study.
11) Patients with a myocardial infarction within 6 months, or those with severe or poorly controlled cardiovascular illness are ineligible.
12) Patients must not have baseline grade II peripheral neuropathy.
13) Patients must not have known bleeding disorders, or history of stroke or intracranial hemorrhage within 6 months before enrollment.
14) Concomitant use of warfarin or other vitamin K antagonists is not allowed. Patients requiring treatment with a strong cytochrome P450 (CYP) 3A4 inhibitor are ineligible. (see Appendix 1)
15) Unable to swallow capsules or malabsorption syndrome, disease or condition significantly affecting gastrointestinal function, or resection of the stomach or small bowel, or partial or complete bowel obstruction
16) Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification

Investigational Product Dosage and Administration:

- Ibrutinib 560mg orally daily (expected dose, phase II)
- Ibrutinib 420mg and 560mg orally daily (planned doses, safety lead-in)
- Brentuximab vedotin (commercial supply) 1.8mg/kg intravenously every 3 weeks
- 1 cycle = 21 days

Clinical Observations and Tests to be Performed:

Physical exams, tumor measurements by radiographic imaging, blood tests to examine toxicities, and analysis on lymphoma specimens. See section 9.0 for details.

Statistical Considerations:

The primary hypothesis is that, in patients with relapsed/refractory Hodgkin Lymphoma (HL), the two agent combination ibrutinib and brentuximab vedotin (BV) can increase the complete response (CR) rate.

In a multi-center phase II trial investigating the use of single agent BV in relapsed/refractory HL patients post-AHCT, the overall response rate was 75%, the CR rate was 34%.[2] Although single agent BV therapy is associated with a high overall response rate and tolerable toxicity, the CR rate and the duration of response can be improved.

The primary objective is to evaluate the antitumor activity of the two agent combination ibrutinib and brentuximab vedotin, as assessed by complete response (CR) rate, in patients with relapsed/refractory HL. The primary endpoint is a confirmed tumor response of CR and is based on the Cheson Criteria[24]. A single cycle of treatment will be given in a 21 day cycle. Each patient's disease status will be evaluated at baseline; response will be assessed as outlined in the study schema.

Statistics/Sample Size and Accrual: This study will implement a Simon Two-Stage (Minimax) Design[30,31] to evaluate the activity of the two agent combination ibrutinib and brentuximab vedotin. The null hypothesis that the true CR rate is 30% will be tested against a one-sided alternative. The phase II portion of the study is expected to enroll a minimum of 19 and a maximum of 39 patients.

The sample size is based on the desire to discriminate a promising CR rate of 50% from a disappointing response rate of 30% using a type I error rate of 0.05 and power of 80%. During the first stage, 19 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, 20 additional patients will be entered. At the end of stage 2, if 17 or more patients experience a complete response, the combination will be considered worthy of further study. If ≤16 patients experience a complete response then no further investigation of the combination is warranted. A total of 39 patients will be included in the phase II portion of trial. The study will also have a lead in phase where a minimum of three patients will be enrolled with 420 mg oral daily dosing of ibrutinib. **Analysis:** All patients who met the eligibility criteria (with the exception of those who received no study medication) will be included in the main analysis of response and survival endpoints and all of the secondary or correlative analysis described below.
Sponsor/Licensee:
This is a COH investigator initiated trial with COH holding the IND and Pharmacyclics providing funding support and drug supply.
Case Report Forms
Medidata Rave EDC®

Table of Contents

Abbreviations

Abbreviation	Meaning
AE	Adverse Event
BV	Brentuximab Vedotin
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease

1.0 Goals and Objectives

In relapsed/refractory Hodgkin Lymphoma patients:

Primary Objective:

- Evaluate the anti-tumor activity of the two agent combination ibrutinib and brentuximab vedotin, as assessed by complete response (CR) rate.

Secondary Objectives:

- Assess the safety and tolerability of the two agent combination through evaluation of toxicities, including type, frequency, severity, attribution, time course and duration.
- Obtain estimates of overall response rate (ORR), response duration and survival (overall and progression-free).
- Describe outcomes of patients who ultimately undergo autologous or allogeneic hematopoietic cell transplantation following treatment with ibrutinib/brentuximab vedotin.

Exploratory Objective:

- Collect DNA/RNA from lymphoma specimens and serial plasma samples for future biomarker evaluation.

2.0 Background

2.1 Introduction/Rationale for Development

Hodgkin Lymphoma:

Hodgkin lymphoma (HL) is a neoplasm of lymphoid tissue that is histopathologically defined by the presence of malignant Hodgkin-Reed-Sternberg (HRS) cells in a background of inflammatory cells.[6] The characteristic surface antigen expressed on HRS cells is CD30. In 2008, it was estimated that approximately 8,220 new cases of HL would be diagnosed in the United States and 1,350 patients would die of their disease.[7] It was also estimated that approximately 7,882 new cases of HL would be diagnosed in 2008 in 5 major EU countries (UK, France, Germany, Italy, and Spain; Mattson Jack's Cancer Impact Epidemiology Database).[8] Similarly, it was estimated that approximately 890 new cases of HL would be diagnosed in 2008 in Canada and 110 would die of their disease.[9]

Advances in the use of combined chemotherapy and radiotherapy in HL over the past half-century have resulted in a durable remission rate of approximately 70%.[6] However, these multi-agent regimens are associated with significant morbidity, including secondary malignancies, cardiac disease, pulmonary disease, and infertility.[10-12] Furthermore, approximately 30-40% of patients presenting with HL will become refractory to initial therapy or will relapse. The therapeutic options for patients with refractory or relapsed disease are very limited and carry a high morbidity rate.[13,14]

Brentuximab vedotin:

Brentuximab vedotin (BV), previously known as SGN-35, is an antibody-drug conjugate (ADC) consisting of the chimeric antibody SGN-30 (cAC10) chemically conjugated to a synthetic analog (monomethyl auristatin E [MMAE]) of the naturally occurring antitubulin agent, dolastatin 10.[15] 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.[1] Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis.[15]

Preclinical studies of brentuximab vedotin demonstrated antitumor activity in both in vitro and in vivo models. In a Phase 1 dose-escalation study of brentuximab vedotin administered IV every 21 days (SGN35-0001), 45 patients were treated. The dose-limiting toxicity (DLT) experienced in the first cycle of therapy was more common at the 2.7 mg/kg dose level than at the 1.8 mg/kg dose level. DLTs observed in 3 of 12

patients treated at the 2.7 mg/kg dose level included Grade 4 neutropenic fever, Grade 3 prostatitis, Grade 3 hyperglycemia, and 1 case of unrelated acute renal failure. One occurrence of Grade 4 thrombocytopenia qualified as a DLT at the 1.8 mg/kg dose level. The maximum tolerated dose (MTD) was defined as 1.8 mg/kg IV administered every 3 weeks.[16]

Phase II experience: 102 patients were treated in a multicenter pivotal phase II study of brentuximab vedotin. The dosing level and schedule was brentuximab vedotin 1.8 mg/kg intravenously every 3 weeks. The overall response rate was 75%, with a 34% complete response rate and tolerable toxicity.[2] The toxicity profile is similar to the phase I experience published by Younes et al.[16] Because of the high response rate and tolerability, BV was granted accelerated FDA approval for the treatment of relapsed/refractory HL following failed AHCT.

Although this drug has high response rates in HL, the complete response rate and the duration of response can both be improved. Among patients who only achieve a best response of partial remission, almost all eventually develop progressive disease.[2] We have performed tumor biopsies on patients with recurrent and progressive HL (status post-treatment) with brentuximab vedotin; interestingly, surface CD30 expression still exists.[17] It appears that CD30 targeting can still be utilized in this group of patients, but we must add other agents to increase the activity of brentuximab vedotin in this setting. Thus, it is important that we find a logical combination treatment strategy.

Ibrutinib:

Ibrutinib is a first-in-class, potent, orally administered covalently binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B cell receptor (BCR) signaling pathways and thus prevents B cell proliferation.[18] In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family, with 10-fold specificity over non-BTK kinases. Ibrutinib (IMBRUVICA®) is approved by the FDA for the treatment of 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate, 2) chronic lymphocytic leukemia (CLL), and 3) CLL in patients with 17p deletion and 4) Waldenström's Macroglobulinemia. Ibrutinib is currently under investigation for various indications.

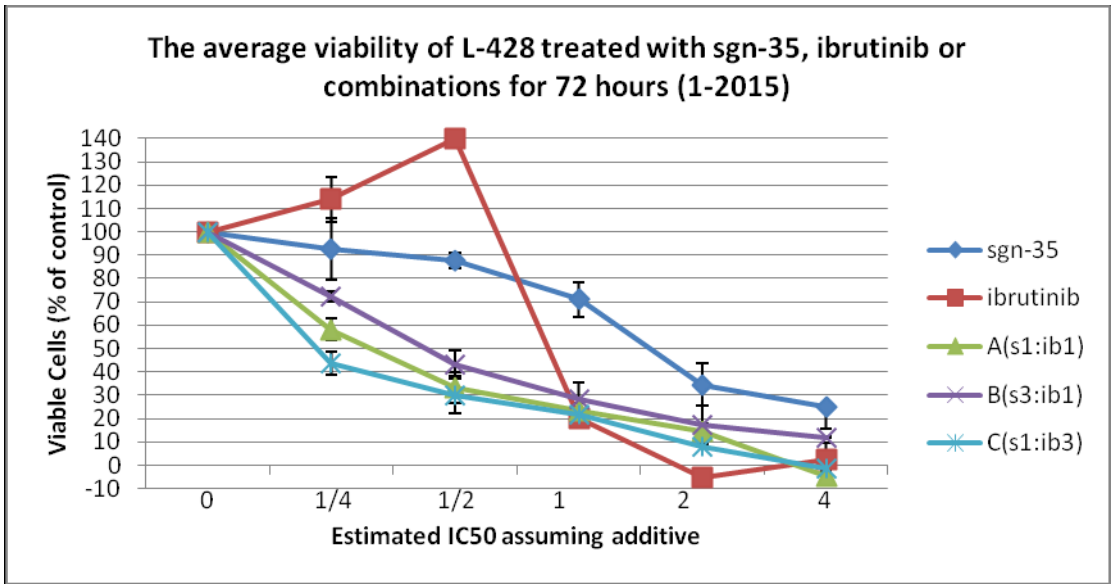
B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B cells express cell surface immunoglobulins comprising the B cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways.[19] The process of B cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B cell lymphomas and CLL result from mutations and translocations acquired during normal B cell development. Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B cells. The BTK protein is expressed in most hematopoietic cells with the exception of T cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B cells.[20]

Data from Study PCYC-04753 demonstrate that, although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post dose at dose levels ≥2.5 mg/kg. In this study, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort were all above 90% at either 4 or 24 hours after drug administration.

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology, refer to the latest version of the ibrutinib Investigator's Brochure.[21]

We performed a synergy assay testing the combination of ibrutinib and brentuximab vedotin (SGN-35) in L428 (HL cell line) and found a synergistic effect. The CI was 0.253 for brentuximab vedotin 1: ibrutinib 1, which is highly synergistic. Ibrutinib is also an ITK inhibitor, which can be active against activated T cells.[22,23] It is possible that ibrutinib can inhibit B cells and T cells in the microenvironment of HL. Because of our in vitro synergy data, and because the two agents have a tolerable toxicity profile with little overlap, we propose a phase II study of ibrutinib plus brentuximab vedotin in patients with relapsed/refractory HL.



2.2 Overview of Proposed Study

This is an open label, multi-center phase II study of ibrutinib and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma. Ibrutinib will be given 560mg orally daily; brentuximab vedotin will be administered intravenously at 1.8mg/kg once on the first day of each cycle. Each cycle is 21 days. The primary efficacy endpoint of this study is complete response rate. Response will be assessed according to modified criteria for malignant lymphoma, based on (Cheson et al. 2014) and (Cheson et al. 2007).[24,25] Response assessment will be performed after cycles 2, 4, 7, 10, 13, and 16. Patients who achieve complete response (CR) can stop treatment after they have received 2 cycles of therapy post CR and at least 4 cycles of treatment. For patients who develop progressive disease while off treatment, they can return to treatment again provided that they have not received other investigational agents during the period of the protocol. (Autologous stem cell transplantation or allogeneic stem cell transplantation are allowed).

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

2.3 Preclinical Studies

2.3.1 Brentuximab vedotin

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.[26]

2.3.2 Ibrutinib

Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of BTK.[27] In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B cell receptor and blocks primary B cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression.[28]

For more detailed and comprehensive information regarding nonclinical pharmacology, refer to the current Investigator's Brochure.

Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

On the basis of data from rats and dogs, including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat), and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study, ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the daily dose of 420 and 560 mg, respectively.

2.3.2.1 *Carcinogenesis, Mutagenesis, Impairment of Fertility*

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

2.4 Human Studies

2.4.1 Brentuximab vedotin

In the Phase 1 dose-escalation study of brentuximab vedotin administered IV every 21 days (SGN35-0001), 45 patients were treated. The dose-limiting toxicity (DLT) experienced in the first cycle of therapy was more common at the 2.7 mg/kg dose level than at the 1.8 mg/kg dose level. DLTs observed in 3 of 12 patients treated at the 2.7 mg/kg dose level included Grade 4 neutropenic fever, Grade 3 prostatitis, Grade 3 hyperglycemia, and 1 case of unrelated acute renal failure. One occurrence of Grade 4 thrombocytopenia qualified as a DLT at the 1.8 mg/kg dose level. The maximum tolerated dose (MTD) was defined as 1.8 mg/kg IV administered every 3 weeks.

Phase II experience: 102 patients were treated in a multicenter pivotal phase II study of brentuximab vedotin. The dosing level and schedule was 102 patients relapsed post ASCT, using brentuximab vedotin 1.8 mg/kg intravenously every 3 weeks. The overall response rate was 75%, with 34% complete response rate and tolerable toxicity.[2] The toxicity profile is similar to the phase I experience published by Younes et al. (2010).[16] Treatment-emergent AEs (TEAEs) occurring in ≥20% of patients in the phase 2 studies were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infections (28%), neutropenia (21%), and vomiting (20%). These events were primarily mild to moderate and reversible. Approximately half of patients had treatment-emergent peripheral neuropathy, predominantly sensory neuropathy, with an onset and severity pattern consistent with a cumulative effect. Dose delay and subsequent reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively; these events were typically of short duration and well managed by brief dose delays with growth factor support in some cases. Infusion-related reactions occurred in approximately 10% of patients and were typically managed by dose interruption. Infusion-related reaction prophylaxis in subsequent treatment cycles was instituted at the discretion of the investigator. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), and leukocytes (5%); and high glucose levels (6%). Only 1 patient in the phase 2 studies had Grade 3 alanine aminotransferase (ALT) and Grade 3 aspartate aminotransferase (AST) levels. In the phase 2 studies, 31% of patients had an SAE, 28% had a Grade 3 or higher SAE, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAE preferred terms (2%) were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. A higher proportion of patients with sALCL experienced SAEs, including deaths within 30 days of last dose, relative to patients with HL, likely due to the older age and the more aggressive nature of the malignancy in this patient population. Because of the high response rate and tolerability, BV was granted accelerated FDA approval for the treatment of relapsed/refractory HL following failed AHCT.

Pediatric experience: Fanale et al (2011) conducted a retrospective analysis of two phase 1 and two phase 2, multicenter brentuximab vedotin drug development studies which included the enrollment of pediatric patients age 12-17 years old.[29] Nine patients (median age=16 years, male=5) were included in this analysis. Patients received brentuximab vedotin, as a 30 minute outpatient infusion, at a dose of either 0.8 mg/kg or 1.2 mg/kg weekly for 3 out of 4 weeks or doses of 1.2 mg/kg or 1.8 mg/kg every 3 weeks (median of 15 cycles). The majority (n=6) of patients received 1.8 mg/kg every 3 weeks. Complete response was observed in 6/9 pediatric patients who had treatment-refractory lymphoma. Grade ≥3 treatment-emergent adverse events included neutropenia (n=3), decreased white blood cell count (n=1), thrombocytopenia (n=1), catheter site infection (n=1), and hyperesthesia (n=1). No patient discontinued treatment because of an adverse event.

Although this drug has high response rates in HL, the complete response rate and the duration of response can both be improved. Among patients who only achieve a best response of partial remission, almost all eventually develop progressive disease.[2] We have performed tumor biopsies on patients with recurrent and

progressive HL (status post treatment) with brentuximab vedotin; interestingly, surface CD30 expression still exists.[17] It appears that CD30 targeting can still be utilized in this group of patients, but we must add other agents to increase the activity of brentuximab vedotin in this setting. Thus, it is important that we find a logical combination treatment strategy.

This study will include patients eligible for both autologous and allogeneic stem cell transplantation. We have already shown that brentuximab vedotin as a single agent can successfully enables patients to undergo either allogeneic stem cell transplantation or autologous stem cell transplantation (32,33). Brentuximab vedotin is already included in the NCCN guideline as second line therapy in 2015 based on two publications (33,34). We also know that patients who have chemosensitive disease at the time of transplantation have improved outcomes post transplantation (32,34). We are allowing patients who achieved PR or CR to the combination of brentuximab vedotin and ibrutinib be able to go onto autologous or allogeneic stem cell transplantation.

2.4.2 Ibrutinib

Ibrutinib is under late-stage development as a single orally administered anticancer agent with lead indications in the relapsed/refractory setting and for treatment-naïve patients with B cell malignancies. Combination studies with chemoimmunotherapy and immunotherapy have been initiated. There are 20 ongoing and 4 company-sponsored trials as of the 6 April 2014 data cutoff date; 26 ongoing and 9 completed company-sponsored clinical trials have investigated the safety, efficacy, and pharmacokinetics (PK) of ibrutinib in humans as a single agent and in combination with chemotherapy and immunotherapy. Across all studies, malignancies under investigation include CLL, small lymphocytic lymphoma (SLL), MCL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), multiple myeloma (MM),. As of the data cut-off of 6 April 2013, safety data are available for 736 subjects administered ibrutinib: 506 subjects receiving ibrutinib monotherapy, 100 healthy subjects summarized in the PK/clinical pharmacology studies, and 130 subjects receiving ibrutinib in combination with 1 or more marketed chemo/immunotherapeutic agents. In addition, approximately 537 subjects have been treated with ibrutinib or placebo in 5 randomized, controlled trials. In Study PCYC-1103-CA, the current version of the rollover extension study, 196 subjects continue to be treated with ibrutinib.

Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased, with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of BTK, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of a human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance > 30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater

than 30 mL/min creatinine clearance). There are no data in patients with severe renal impairment or patients on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

Summary of Clinical Safety

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies, which included1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR, FCR, ofatumumab, and R-CHOP. The median duration of treatment for this pool was 14.0 months (range: 0.2 to 27.1 months). Refer to the ibrutinib IB, edition 9.0, dated 30 June 2015 for additional details concerning these studies

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs > 10%	Most frequently reported Grade 3 or 4 TEAEs > 2%	Most frequently reported Serious TEAEs > 1%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	

For more detailed information refer to the current version of the Investigator's Brochure.

Risks

Bleeding-Related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and some major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied.

Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. In particular, subjects with a history of cardiac arrhythmias should be monitored closely. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

Diarrhea

Diarrhea is the most frequently reported nonhematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged, ibrutinib treatment should follow the protocol dose modification guidelines.

Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE v4.03). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

Liver Failure

Rare cases of liver failure have been reported in patients treated with ibrutinib.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity.

Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

Lymphocytosis and Leukostasis

Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/SLL treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, >400000/mcL) has been observed in some subjects. Lymphocytosis was not observed in subjects with WM treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

Interstitial lung disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Randomized, controlled Phase 3 studies did not show an increased incidence rate of ILD in subjects treated with ibrutinib as compared to subjects treated with active control. Subjects should be monitored and evaluated for symptoms (eg, dyspnea, cough or pyrexia) and treated symptomatically, including interruption of the suspected agent as appropriate.

3.0 Patient Eligibility

The eligibility criteria listed below are interpreted literally and cannot be waived. An abnormal test (such as a WBC) may be repeated, or a low hemoglobin or platelet count may be corrected with transfusion to make the patient eligible for study. Tests should be performed within 10 days of study entry. (For patients who re-enter the study after receiving autologous or allogeneic transplantation, they will be re-screened for eligibility per the inclusion and exclusion criteria).

3.1 Inclusion Criteria

- Patients must have histologically documented or cytologically confirmed Hodgkin lymphoma with CD30 expression.
- Patients must have ANC ≥1000/μL, Plt ≥ 50,000/μL, and hemoglobin ≥ 8.5 g/dl. Neupogen can be given before and during treatment to achieve target ANC ≥ 1000/uL. Platelet transfusion and packed red blood cell transfusion can also be given prior to the start of treatment and during treatment to achieve a target plt ≥ 50,000/uL and hemoglobin of ≥ 8.5/ul provided that patients have not received growth factors for at least 14 days prior to entering trial.
- Patients must have measurable disease > 1.5 cm evidenced by CT scan of the neck/chest/abd/pelvis or CT/PET scans.
- Patients must be either refractory to or relapsed after 1 line of therapy.
- Prior radiation therapy is allowed.
- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
- Female subject is either post-menopausal, surgically sterilized, or willing to use an acceptable method of birth control (i.e. a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.
- Male subject agrees to use an acceptable method of contraception for the duration of the study.
- Age ≥ 15years old and over 40 kg. Life expectancy of greater than 3 months.
- ECOG of 0-2.
- Patients must have normal organ and marrow function as defined below:
    - Total bilirubin within 1.5x the upper limit of normal institutional limits. Patients with elevation of unconjugated bilirubin alone, as in Gilbert's disease, are eligible.
    - AST/ALT ≤ 3.0x institutional upper limit of normal (unless demonstrated Hodgkin lymphoma involvement of the liver). Estimated creatinine clearance ≥30 ml/min (Cockcroft-Gault) and/or 24 urine analysis as needed
    - PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN.

3.1.1 Child Bearing Potential

The effects of brentuximab vedotin and ibrutinib on the developing fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for six months following duration of study participation. Should a woman become pregnant or suspect that she is pregnant while participating on the trial, she should inform her treating physician immediately.

3.1.2 Informed Consent/Assent

All subjects must have the ability to understand and the willingness to sign a written informed consent. They are to give voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

3.1.3 Prior Therapy

- Patient must be either refractory to or relapsed after 1 line of therapy.
- Prior radiation therapy is allowed.
- Prior hematopoietic transplantation is allowed (autologous and/or allogeneic)
- Prior brentuximab vedotin is allowed provided that patients were not refractory (defined as developing progressive disease while on treatment or progressed within 3 months of finished last dose of brentuximab vedotin)
- Prior ibrutinib for Hodgkin lymphoma is not allowed.

3.2 Exclusion Criteria

- Age < 15 and less than or equal to 40 kg
- Prior ibrutinib for Hodgkin lymphoma is not allowed.
- Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
- Unwilling or unable to participate in all required study evaluations and procedures.
- Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
- Patients should not have any uncontrolled illness including ongoing or active infection.
- Patients may not be receiving any other investigational agents, or concurrent biological therapy, chemotherapy, or radiation therapy.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib and BV.
- Patients must not have received prior chemotherapy or radiation for $\leq$ 3 weeks before study enrollment, or those who have not recovered from the adverse events due to agents administered more than 3 weeks earlier are excluded.
- Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the Investigator as not medically relevant.
- Significant screening electrocardiogram (ECG) abnormalities including, but not limited to, left bundle branch block, 2nd degree atrioventricular (AV) block type II, 3rd degree block, or corrected QT interval

(QTc) ≥470 msec. Subjects with a cardiac pacemaker who have a QTc interval of ≥470 msec may be eligible if these findings are considered not clinically significant as documented via a cardiology evaluation.

- Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
- Patients with active CNS disease or history of brain metastases are excluded from study.
- Patients may be on steroids prior to initiation of treatment, provided that, by cycle 1 day 1, steroids use was tapered down to less than or equal to 20 mg of prednisone.
- Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued.
- Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
- Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.
- Known active infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). Testing to be done only in patients suspected of having infections or exposures. *Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. Subjects who have an undetectable HIV viral load with CD4 ≥ 200 and are on HAART medication are allowed.*
- Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification

3.2.1 Study-Specific Exclusions

- Patient has hypersensitivity to brentuximab vedotin
- Refractory to prior brentuximab vedotin (defined as developing progressive disease while on treatment or progressed within 3 month of finished last dose of brentuximab vedotin)
- Prior ibrutinib for Hodgkin lymphoma is not allowed.
- No active GVHD or on immunosuppressive medication for GVHD
- Recent infection requiring intravenous anti-infective treatment that was completed ≤14 days before the first dose of study drug
- Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), Grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria, with the exception of alopecia
- Baseline Grade II peripheral neuropathy
- Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.
- History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- Major surgery within 4 weeks of first dose of study drug.
- Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.

- Concomitant use of warfarin or other Vitamin K antagonists.
- Requires treatment with a strong cytochrome P450 (CYP) 3A4/5 inhibitor. (see Appendix 1)

3.2.2 Non-Compliance

Subjects, who in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

3.3 Inclusion of Women and Minorities

The study is open to anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 39 subjects, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. 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.

4.0 Participant Enrollment

4.1 Screening , Informed Consent and Enrollment

4.1.1 Pre-Enrollment Informed Consent and Screening Procedures

The investigational nature and objectives of the trial, the procedures and treatments involved, and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject, and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

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 ins Section 9.0.

4.1.2 Enrollment

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

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

4.1.3 Slot verification and reservation

Issues that would cause treatment delays should be discussed with the Study PI. Designated study staff should call or email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials). Slots can only be held for a limited time.

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

4.1.4 Registration Process

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

1. The study team should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The protocol nurse or CRC should then e-mail a copy of the following documents to DCC@coh.org:
    - Registration Cover Sheet (non-COH sites only, see Appendix 7)
    - Completed Eligibility Criteria List (printed from Section 3.0 of the protocol)
    - Source documentation to support eligibility criteria**
    - Signed informed consent document
    - Signed HIPAA authorization form
    - Signed subject's Bill of Rights

    It is **NOT acceptable to submit emails as source documentation.
3. After having received all documentation, the DCC will complete the review the documents to verify eligibility, working with the study team as needed to resolve any missing required source elements. A participant failing to meet all protocol eligibility requirements will not be registered.
4. Once eligibility is confirmed DCC staff will send a Confirmation of Registration Form, and signed Eligibility Checklist within 24 hours, including the participant study number and dose level assigned to:
    - the study team: site PI, treating physician, biostatistician, protocol nurse, CRC, and pharmacy.
    - the COH sponsor team designees.
5. Upon receipt of the Confirmation of Registration email from the DCC, COH study team will register the patient in OnCore. DCC will register non-COH patients in OnCore.

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

Notify the DCC if the participant screen fails after registration or if the participant does not start treatment.

4.2 Dose Level Assignment

The Data Coordinating Center will be responsible for centrally registering all subjects for this trial and therefore will provide the participating site's the specific information pertaining to the dose level for each patient.

5.0 Treatment Program

5.1 Treatment Overview

Treatment will be given on an outpatient basis unless patients are already hospitalized for symptoms of Hodgkin lymphoma.

5.1.1 Brentuximab vedotin Dose and Administration

Brentuximab vedotin (BV): BV is an antibody-drug conjugate consisting of the anti-CD30 antibody cAC10 conjugated to MMAE, an anti-tubulin agent. BV is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. BV is supplied commercially in single-use, Type

1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains BV, trehalose, sodium citrate, and polysorbate 80.

BV will be administered on Day 1 of each 21-day cycle. The dose of BV is 1.8 mg/kg and is administered by outpatient IV infusion given over approximately 30 minutes until PD or unacceptable toxicity. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute infusion period. BV must not be administered as an IV push or bolus. BV should be administered through a dedicated IV line. BV cannot be mixed with other medications.

Dosing should be based on baseline weight; doses will be adjusted for patients who experience a ≥10% change in weight during the study. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. BV dose should be rounded per institutional policy.

5.1.2 BV Required Premedication and Postmedication

Routine premedication should be administered prior to the first dose of BV. Please see Section 5.1.3 below. Patients who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with BV at the discretion of the Investigator.

5.1.3 BV Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of BV. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for 60 minutes following the first infusion of BV.

During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institution standards. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

Premedications consist of acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 25–50 mg IV),IV or oral pepcid 20-40 mg and hydrocortisone (maximum of 100 mg) administered 30–60 minutes prior to each 30-minute BV infusion. Premedication is required prior to each cycle of BV + IB. These medications may be given again as treatment of infusion related reactions. The infusion of BV can also be slowed down to 60-90 minutes if patients has developed previous infusion reaction of any grade.

5.1.4 Ibrutinib (to be given prior to infusion with BV)

5.1.4.1 *Formulation/Packaging/Storage*

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drugs will be dispensed in child-resistant packaging.

Refer to the site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.1.5 Dose and Administration

In the lead in phase, an initial dose of ibrutinib 420 mg is given orally once daily. Once that is proven to be safe, we will give 560 mg of ibrutinib orally daily. In the phase II portion, Ibrutinib 560 mg (4 x 140-

mg capsules) is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact, and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (See Appendix 1).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. A subject diary will be used to aid with as well as document study drug administration compliance. At any given visit, enough ibrutinib capsules to carry the subject to the next visit should be dispensed. Unused ibrutinib capsules dispensed during previous visits must be returned, and drug accountability records should be updated. Returned capsules must not be redispensed to anyone. Subjects should return all empty bottles to the site. Empty bottles should be destroyed at the site or returned to the Sponsor after the site monitor has completed a review of drug accountability

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit.

5.1.6 Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in patients. No MTD was reached in the phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

5.1.7 Schedule

For a tabular view of the treatment, monitoring, and follow-up schedule, see study calendar in Section 9

Each cycle is 21 days	**Ibrutinib**	**Brentuximab Vedotin**
Dose level 1	420 mg orally daily	1.8 mg/kg IV every 3 weeks
Dose level 2	560 mg orally daily	1.8 mg/kg IV every 3 weeks

Brentuximab vedotin dosing can be given during a window of ± 3 days due to scheduling issues.

Prior to formally initiating the phase II trial, a *patient safety lead-in* segment will be conducted to ensure there are no unexpected toxicities during cycle 1. Ultimately a total of 39 patients will be treated at phase II and evaluated for response at the ibrutinib/brentuximab vedotin doses considered safe -as determined during the *safety lead-in* segment of this study.

The first nine to twelve patients enrolled will be part of the *patient safety lead-in*. Initially, a group of up to 3 patients can be enrolled on dose level 1; given the potential for overlapping toxicity, the initial dose of ibrutinib tested will be 420 mg daily. During the *safety lead-in*, no more than 3 patients can be under active cycle 1 toxicity evaluation. Note: Unacceptable toxicity in a given patient is defined as any non-hematologic grade 3|4 toxicity or, for hematologic toxicities, any grade 3|4 that does not resolve to a grade 1|2 within 7 days per NCI CTCAE v4.03 toxicity criteria and is considered at least possibly related to ibrutinib and/or brentuximab vedotin, or any other regimen-related cause of death.

The *safety lead-in* segment will follow standard 3+3 dose escalation/de-escalation/expansion rules based on observed toxicity during cycle 1: (Note: Dose de-escalation, escalation or cohort expansion will only take place after 3 patients are fully assessed using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.03 following the completion of cycle 1.)

- If 0 out of 3 evaluable patients experience unacceptable toxicity during cycle 1, then the next dose level of combination therapy will be tested.
- If 1 out of 3 evaluable patients experience unacceptable toxicity during cycle 1, three additional patients will be assessed at the same dose level of combination therapy.
- If 2 out of 3 evaluable patients experience unacceptable toxicity during cycle 1, dose escalation will cease and the next lower dose level of combination therapy will be expanded. Note: If 2 out of 3 experience unacceptable toxicity on dose level 1, the trial will be stopped. Doses below 420mg (ibrutinib)/1.8mg/kg (brentuximab vedotin) will not be considered.
- If 1 out of 6 evaluable patients experience unacceptable toxicity during cycle 1, then dose escalation to the next dose level of combination therapy will continue.
- If 2 or more out of 6 evaluable patients experience unacceptable toxicity during cycle 1, dose escalation will cease and the next lower dose level of combination therapy will be expanded. Note: If 2 or more out of 6 experience unacceptable toxicity on dose level 1, the trial will be stopped. Doses below 420mg (ibrutinib)/1.8mg/kg (brentuximab vedotin) will not be considered.

The highest dose level that produces ≤1/6 evaluable patients with unacceptable toxicity during cycle 1 will be the declared safe dose and brought forward for phase II evaluation.

5.2 Planned Duration of Therapy

BV will be given intravenously once every 3 weeks, ibrutinib will be given daily. Each cycle is 21 days. Patients will be treated until disease progression, unacceptable toxicity, or moving onto autologous or allogeneic-HCT. The minimum number of cycles required prior to discontinuation should be 4, unless the patient developed progressive disease or intolerable AEs. For patients who achieve CR/PR and then relapse while off treatment (for toxicities, auto-HCT, or allo-HCT), they can receive additional cycles of treatment. There will be no maximum cycles of treatment for patients at retreatment. There is no limit on the number of times patients can be retreated. For patients who ultimately undergo autologous or allogeneic-HCT and then relapse post transplant, these patients will be allowed to re-enter the study.

5.3 Criteria for Removal from Treatment

Disease progression, intolerable AEs, non-compliance, or patient withdraws consent.

5.4 Subject Follow-Up

Patients will be followed for the duration of active treatment per treatment visit. After treatment, subjects will be followed for up to two years with q3 month interval visits or telephone calls. For patients who undergo autologous or allogeneic HCT, patients will be followed for up to two years with q3 months interval visits or phone calls post HCT.

5.5 Supportive Care, Other Concomitant Therapy, Prohibited Medications

Use of neutrophil growth factors or biosimilars is permitted per institutional policy and the American Society of Clinical Oncology (ASCO) guidelines. Transfusions may be given in accordance with institutional policy.

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For subjects requiring the initiation of therapeutic anticoagulation therapy (e.g. atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

Chemotherapy, anticancer immunotherapy, corticosteroids for cancer-related reasons (at doses equivalent to prednisone >20 mg/day for >14 days), experimental anticancer therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib and brentuximab vedotin. Corticosteroids for the treatment of non-cancer-related reasons for longer than 14 days and/or at doses >100 mg/day of prednisone or its equivalent are also prohibited.

Ibrutinib may increase the risk of bleeding with invasive procedures or surgery. The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed and for at least 7 days after the urgent surgical procedure.
Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If a strong CYP3A inhibitor must be used, either reduce ibrutinib dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Appendix 1).

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix 1. A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

Ibrutinib may be associated with opportunistic infections, therefore it is recommended but not required that patients be placed on antibiotic prophylaxis per institutional standards such as (acyclovir for VZV reactivation or bactrim for PCP prophylaxis)

6.0 Dose Modification for Adverse Events

6.1 Anticipated Toxicities

6.1.1 Ibrutininb

Per the package insert (January 2019) the expected toxicities for ibrutinib are as follows:

System Organ Class	Adverse Reactions
Gastrointestinal disorders	
Very common	Nausea, diarrhea, vomiting, constipation, abdominal pain, stomatitis, dyspepsia
Frequency not known	Gastrointestinal esophageal reflux disease
Infections and infestations	
Very common	Infection[a], upper respiratory tract infection, sinusitis, pneumonia, urinary tract infection, skin infection
Frequency not known	Hepatitis B reactivation
Blood and lymphatic system disorders	
Very common	Neutropenia, thrombocytopenia
Common	anemia
Cardiac disorders	
Very Common	Ventricular tachyarrythmias[a]
Common	Atrial fibrillation
Immune system disorders	
Frequency not known	Anaphylactic reaction, angioedema, urticaria
Metabolism and nutrition disorders	
Common	Decreased appetite, dehydration, hypoalbuminemia, hypokalemia, hyperuricemia
Frequency not known	Tumor lysis syndrome
Nervous system disorders	
Very common	Dizziness, headache
Frequency not known	Peripheral neuropathy
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnea, epistaxis, oropharyngeal pain
Frequency not known	Interstitial lung disease[a]
Hepatobiliary disorders	
Frequency not known	Acute hepatic failure, hepatic cirrhosis
Eye disorders	

System Organ Class	Adverse Reactions
Very common	Blurred vision
Skin and subcutaneous tissue disorders	
Very common	Rash[a], pruritus, bruising, petechiae
Frequency not known	Stevens-Johnson syndrome, panniculitis, onychoclasis
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal pain[a], myalgia, muscle spasms
Neoplasms, benign malignant and unspecified	
Very common	Secondary malignancy
General disorders and administration site conditions	
Very common	Fatigue, pyrexia, peripheral edema, asthenia, chills
Vascular disorders	
Very common	Hypertension, hemorrhage[a]
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).

Refer also to Section 2.4.2.

6.1.2 Brentuximab Vedotin

Per the IB (version 16, October 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	Anemia, 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

System Organ Class	Adverse Reactions
Common	Dizziness
Uncommon	Demyelinating polyneuropathy
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnea
Gastro-intestinal disorders	
Very common	Nausea, diarrhea, vomiting, constipation, abdominal pain
Uncommon	Pancreatitis acute
Hepatobiliary disorders	
Common	Alanine aminotransferase/aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	
Very common	Rash[a], pruritus
Common	Alopecia
Uncommon	Stevens-Johnson syndrome/toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, myalgia
Common	Back pain
General disorders and administration site conditions	
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).

6.2 Dose Modifications

Given that brentuximab vedotin has demonstrated activity in this disease setting, ibrutinib should be preferentially dose reduced in the event of toxicity. The only exception is in the event of peripheral motor or sensory neuropathy, in that case, brentuximab vedotin dose will be reduced 1st given its direct correlation to brentuximab vedotin.

Ibrutinib (supplied by Pharmacyclics):

Interrupt or discontinue therapy

- Interrupt therapy for any non-hematological toxicity ≥Grade 3, neutropenia with infection or fever ≥Grade 3, or Grade 4 hematological toxicities
- Reinitiate ibrutinib at the starting dose (indicated specific) once toxicities have resolved to Grade 1 or baseline (recovery)
- If the toxicity reoccurs, reduce dose by 1 capsule (140 mg/day)
- A second reduction of dose by 140 mg may be considered as needed
- Discontinue if these toxicities persist or recur following 2 dose reductions

Hepatic impairment

- Mild (Child Pugh class A): 140 mg PO qDay
- Moderate-to-severe (Child Pugh Classes B and C): Avoid use

Brentuximab vedotin and Ibrutinib:

If either agent were held for toxicities, the next cycle of treatment will be delayed until toxicities become acceptable for both drugs before treatment continues. Both drugs will be given at the start of each cycle. For example, if brentuximab vedotin was dose delayed for peripheral neuropathy for 4 weeks, Ibrutinib dosing will stop after 3 weeks and held. Ibrutinib will be given again when it is deemed acceptable to start brentuximab vedotin. If Ibrutinib was held for thrombocytopenia at D15 and can be resumed at D18, brentuximab vedotin can be given at the original scheduled infusion day. However, if ibrutinib was held at D15 and cannot resume for 2 weeks later, then brentuximab vedotin will only be given at the same time Ibrutinib is restarted.

Brentuximab vedotin (commercial supply):

Peripheral Neuropathy: Peripheral neuropathy should be managed using a combination of dose delay and reduction to 1.2 mg/kg. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 peripheral neuropathy, BV should be discontinued.

Neutropenia: Neutropenia should be managed by dose delays and reductions. For grade 1 or 2, continue at same dose. The dose of BV should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. In patients with recurrent Grade 4 neutropenia despite the use of growth factors, and despite dose reduction specified for ibrutinb, discontinuation or dose reduction of BV to 1.2 mg/kg may be considered.

Anemia and thrombocytopenia: For Grade 1 or 2, continue at same dose. For Grade 3 and 4, withhold dose until toxicity is $\leq$ Grade 2 or has returned to baseline, then resume treatment at the same dose level. For second occurrence of Grade 4, withhold until toxicity $\leq$ Grade 1 or has returned to baseline, then resume treatment at 1.8 mg/kg but reduce ibrutinib dose from 560 mg to 420 mg. For third occurrence, withhold until toxicity $\leq$ grade 1 or has returned to basleine, then resume BV at 1.8 mg/kg but reduce ibrutinib dose from 420 mg to 280 mg. In patients with recurrent grade 4 anemia and thrombocytopenia despite dose reduction specified for ibrutinib, then resume treatment of BV at 1.2 mg/kg. If patient was already at 1.2 mg/kg of BV, then discontinue treatment of BV and ibrutinib.

Other non-hematological toxicities: For Grade 1 or 2, continue at same dose. For Grade 3, withhold dose until toxicity is $\leq$ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For Grade 4, withhold until toxicity $\leq$ Grade 1 or has returned to baseline, then resume treatment at same dose level but reduce ibrutinib dose from 560 mg to 420 mg. For second occurrence of Grade 3, withhold dose until toxicity $\leq$ Grade 1 or has returned to baseline, then resume BV at same dose level, but reduce ibrutinib from 560 mg to 420 mg. For second occurrence of Grade 4, withhold until toxicity < Grade 1 or has returned to baseline, then resume BV at same dose level but reduce ibrutinib from 420 mg to 280 mg. For third occurrence of Grade 3, withhold dose until toxicity < Grade 1 or has returned to baseline, then resume BV at same dose level but reduce ibrutinib from 420 mg to 280 mg. For third occurrence of grade 4 toxicity, discontinue ibrutinib. In patients with recurrent grade 3 and 4 non hematological toxicities despite dose reduction specified for ibrutinib, then reduce treatment of BV to 1.2 mg/kg. If patient was already at 1.2 mg/kg of BV, then discontinue treatment of BV and ibrutinib.

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

Doses reduced for drug-related toxicity should generally not be re-escalated. However, intra-patient re-escalation to the previous dose level may be permitted at the discretion of the PI.

7.0 Agent Information and Risks

7.1 7.1 Brentuximab vedotin

7.1.1 Description

Brentuximab vedotin (BV), is also named SGN-35, or Adcetris. BV is an antibody-drug conjugate consisting of the anti-CD30 antibody cAC10 conjugated to MMAE, an anti-tubulin agent. BV is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. It is supplied by Seattle Genetics in single-use, Type 1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains BV, trehalose, sodium citrate, and polysorbate 80.

7.1.2 Toxicology

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 toxicology data.

7.1.3 Pharmacology – Handling, Storage, Dispensing and Disposal

BV will be from a commercial supply. Please see package insert for dose preparation and storage information.

7.2 Ibrutinib

7.2.1 Description

Ibutinib is also named Imbruvica. It is an inhibitor of Bruton's tyrosine kinase. It is a small molecule with the molecular formula $C_{25}H_{24}N_6O_2$ and a molecular weight of 440.5. Ibrutinib capsules for oral administration are supplied as gray opaque capsules that contain 140 mg ibrutinib as the active ingredient. The inactive ingredients are croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

Figure 1. Ibrutinib

7.2.2 Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

On the basis of data from rats and dogs, including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat), and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study, ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the daily doses of 420 and 560 mg, respectively.

7.2.3 Pharmacology-Handling, Storage, Dispensing, and Disposal:

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All of the study drug will be dispensed in child-resistant packaging.

Refer to product label for additional guidance on study drug storage, preparation dispensing, handling and disposal.

8.0 Correlative/Special Studies

Each subject will have either a fresh core or excisional biopsy of a tumor lesion prior to starting study therapy or will have available archival tissue from a biopsy that was performed after the most recent therapy and within 3 months of the screening date. If feasible, all subjects will also undergo biopsy of a tumor lesion at the time of disease progression.

Guidelines for tumor sampling are as follows:

- For fresh biopsies:
    a. For core biopsies, 2 core biopsy tumor samples will be immediately frozen and processed
    b. For excisional biopsies, an approximately 5mm x 5mm tumor sample will be immediately frozen and processed
    c. The remainder of the specimen will be processed in a routine fashion by hematopathology. Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:
        i. 10 x 5 micron paraffin slices
        ii. 10 x 5 micron unstained slides
- Fresh or frozen tissue from excisional biopsies or 2-3 needle cores will be minced into smaller fragments. Using a lysis buffer, the nuclei will be released and isolated using a gradient solution. The pelleted nuclei will then be stained with DAPI and sorted by flow cytometry by DNA content/ploidy at the City of Hope Cytometry Core. The supernatant from the gradient, which

contains the cytoplasmic contents of the Hodgkin cells and inflammatory background cells, will be saved for RNA extraction. DNA will be extracted from the Hodgkin nuclei as well as normal/diploid, and the paired samples will be evaluated by whole exome sequencing.

- FFPE tissue blocks will be examined for CD30 expression, drug exporter expression, and CD68 tumor macrophages. We will also isolate DNA/RNA from inflammatory cells in the microenvironment and perform gene expression profiling signatures.
- We will also obtain tumor biopsies from patients who develop progressive disease while on treatment. We will test for CD30 and drug exporter expression by immunohistocytochemistry and will compare with the pre-treatment sample. We will also perform gene expression profiling on post-treatment relapse samples and compare with pre-treatment samples.
- For archival specimens:
    a. Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:
        i. 10 x 5 micron paraffin slices
        ii. 10 x 5 micron unstained slides

For non COH sites refer to Appendix 3 for tissue shipping guidelines.

- For peripheral blood collections:
    a. 36 ml of peripheral blood will be drawn on day 1 prior to dosing, day 8 during cycle 1, and on day 1 cycle 2 prior to dosing. They will be analyzed for:
        i. T/B/NK cell subsets. 20 ml of blood will be drawn in sodium heparin tube. They will be sent to Dr. Peter Lee's lab at COH. 8-color flow cytometric analysis will be performed to phenotype immune cell subsets and functional readouts. A prototype BD microfluidic FACS instrument that can analyze small cell numbers will be used. Markers to be assessed: TIGIT, PD-1, CD45, CD4, CD8, CD103, CD69, and CCR7. BTK and ITK occupancy will also be evaluated Leftover blood to be processed into viable cryopreserved PBMCs and stored for future analysis. For non COH sites, refer to Appendix 5 for blood shipping guidelines.
        ii. ITK and BTK occupancy will be assessed by Pharmacyclics. See Appendix 2 for instructions. 2 x 8 ml CPT citrate tube whole blood (PBMC and plasma) to support BTK/ITK occupancy and optional retrospective cytokine/chemokine testing at PCYC.

9.0 Study Calendar

	Pre-Study (within 28 days)	Cycle 1			Cycle 2 and beyond (Each cycle 3 weeks)			Off Study Visit
		Wk 1	Wk 2 +/- 1 day	Wk3 +/- 1 day	Wk1	Wk2	Wk3	
BV		X			x			
Ibrutinib		X	X	X	x	x	x	
Informed consent	X							
Demographics	X							
Medical history	X							X
Concurrent meds	X				x			X
Physical exam	X	X			x			X
Vital signs	X	X			x			X
Height	X							
Weight	X	X			x			X
Performance Status	X	X			x			X
CBC w/diff, plts	X	X	X	X	x			X
Serum chemistry[a]	X	X	X	X	x			X
PT/PTT/INR	X				x			
EKG (as indicated)	X							
Adverse event evaluation		X	X	X	X			X
Tumor measurements	X				X[b]			
Radiologic evaluation	X				X[c]			
B-HCG	X							
Tissue for correlative studies[d]	X							X
Peripheral blood for correlative studies[e]		X	X		X			

a. Serum chemistry includes (comprehensive metabolic profile: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, AST, ALT, Alkaline phosphate, total bilirubin, calcium, albumin, total protein, magnesium, phosphate).
b. Tumor measurements to be done at end of C2 (+/- 7 days), C4 (+/- 7 days),, C7 (+/- 7 days),, and every 3 cycles until patients achieves CR. Once CR documented twice by CT scan, intervals can be increased to q6 cycles while patient is still on study drug. If patient comes off study, CT scan will only be performed q6 month for 2 years and no protocol scans will be done 2 years post treatment.
c. CT/PET to be done at C4 (+/- 7 days),, C10 (+/- 7 days),, and q 6 cycles until patient achieves CR. However, once CT/PET is negative, only CT scan need to be done after that, PET can be avoided.
d. Each subject will have either a fresh core or excisional biopsy of a tumor lesion prior to starting study therapy or will have available archival tissue from a biopsy that was performed after the most recent therapy and within 3 months of the screening date. ***If feasible***, all subjects will also undergo biopsy of a tumor lesion at the time of disease progression. Refer to Section 8 for details.
e. Peripheral blood for correlative studies to be collected prior to cycle 1, day 8 of cycle 1, and day 1 of cycle 2 prior to treatment. Refer to Section 8 for details.

10.0 Endpoint Evaluation Criteria/Measurement of Effect

10.1 Definitions

Evaluable for toxicity: All participants will be evaluable for toxicity from the time of their first treatment with ibrutinib plus brentuximab vedotin.

Evaluable for objective response: Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below.

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR, per Cheson criteria[24], (whichever is first recorded) until the first date that relapsed or progressive disease is objectively documented.

Duration of overall CR: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, per Cheson criteria[24], taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Overall Survival (OS): OS is defined as the duration of time from start of treatment to time of death (due to any cause).

Progression-Free Survival (PFS): PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10.2 Transplant Endpoint Definitions

Overall Survival (OS): OS is defined as the duration of time from start of HCT treatment to time of death (due to any cause). Evaluated and recorded at day 30, day 100, 6 months, 1-year and 2-years post HCT.

Progression-Free Survival (PFS): PFS is defined as the duration of time from start of HCT treatment to time of progression or death, whichever occurs first. Evaluated and recorded at day 30, day 100, 6 months, 1-year and 2-years post HCT.

Relapse/Progression (CIR): The event is relapse/progression. The time to this event is measured from start of HCT treatment. Deaths without relapse/progression are considered a competing risk. Surviving patients with no history of relapse/progression are censored at time of last follow-up. Evaluated and recorded at day 30, day 100, 6 months, 1-year and 2-years post HCT.

Non-relapse mortality (NRM): NRM is defined as death occurring in a patient from causes other than relapse or progression. NRM is measured from start of treatment until non-disease related death, or last follow-up, whichever comes first. Deaths from relapse/progression are considered a competing risk. Evaluated and recorded at day 30, day 100, 6 months, 1-year and 2-years post HCT.

Stem cell mobilization: mobilization regimen used, median number of cells collected, median number of days to reach minimum collection.

Engraftment (Recovery of Granulopoiesis and Megakaryopoiesis): Engraftment will be assessed using three distinct milestones: 1) (Autologous and Allogeneic) ANC (neutrophils) $\geq 0.5 \times 10^3/\mu L$ achieved and sustained for 3 consecutive lab values on different days with no subsequent decline; 2) (Autologous) Platelets (PLT) $\geq$ 20 K/μL independent of platelet transfusion support; and 3) (Allogeneic) PLT $\geq$ 25 K/μL

independent of platelet transfusion support. For platelet recovery, date should reflect no transfusions in previous 3 days and the first of 3 consecutive lab values on different days.

10.3 Response Criteria and Methods for Evaluation of Measurable Disease

Diagnostic quality CT of the neck, chest, abdomen, and pelvis (N/C/A/P) will be performed at the end of Cycles 2, 7, 10, 13, and 16, and every 3 months after. PET-CT scans will be performed at end of Cycles 4, 10, and 16. Once PET-CT is negative, it does not need to be performed again. If CT/PET remains positive at the end of Cycle 4 and CT/PET scan to be performed at cycle 10 and 16, dedicated CT does not need to be performed at end of cycle 10 or 16. MRI may be performed at the Investigator's discretion for lesions not well-visualized by CT.

The determination of anti-tumor efficacy will be based on objective response assessments made according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2014)[24] and treatment decisions by the investigator will be based on these assessments. Clinical response of progressive disease (PD), stable disease (SD), partial remission (PR), or complete remission (CR) will be determined at each assessment. Selection of up to 6 of the largest dominant nodes or nodal masses to follow for response assessment must be PET FDG-avid at baseline. Investigator evaluation of baseline radiographic assessment will enable study enrollment per Inclusion Criteria based on the presence of measurable disease > 1.5 cm evidenced by CT scan of the neck/chest/abdomen/pelvis or CT/PET scans. In addition, per the Revised Response Criteria for Malignant Lymphoma, these nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

If the bone marrow was positive at baseline, a follow-up bone marrow aspirate and biopsy is required and must be negative for assessment of a CR. If the follow-up morphology is indeterminate, the biopsy tissue must be negative by immunohistochemistry or the patient will be assessed as a PR.

11.0 Statistical Considerations

11.1 Study Design

11.1.1 Phase II

The primary hypothesis: in patients with relapsed/refractory Hodgkin Lymphoma (HL), the two agent regimen combination of ibrutinib and brentuximab vedotin (BV) can increase the complete response (CR) rate.

In a multi-center phase II trial investigating the use of single agent BV in relapsed/refractory HL patients post-AHCT, the overall response rate was 75%, the CR rate was 34%.[2] Although single agent BV therapy is associated with a high overall response rate and tolerable toxicity, the CR rate and the duration of response can be improved.

This multi-center, single arm phase II trial will implement a Simon Two-Stage Minimax Design (Simon 1989; Jung 2004) to evaluate the antitumor activity of the two agent combination ibrutinib and brentuximab vedotin, as assessed by complete response (CR) rate, in patients with relapsed/refractory Hodgkin lymphoma. The study is expected to enroll a minimum of 19 and a maximum of 39 patients. The sample size is based on the desire to discriminate a promising CR rate of 50% from a disappointing response rate of 30% using a type I error rate of 0.05 and power of 80%.

At stage 1, 19 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 stage 2, 20 additional patients will be entered. At the end of stage 2, if 17 or more patients experience a complete response, the combination will be considered worthy of further study. If ≤ 16 patients experience a complete response then no further investigation of the combination is warranted.

11.1.2 Safety Lead-In

Prior to formally initiating the phase II trial, a *patient safety lead-in* segment will be conducted to ensure there are no unexpected toxicities during cycle 1. Ultimately a total of 39 patients will be treated and evaluated for response at the ibrutinib/brentuximab vedotin doses considered safe -as determined during the *safety lead-in* segment of this study.

The first nine to twelve patients enrolled will be part of the *patient safety lead-in*. Initially, a group of up to 3 patients can be enrolled on dose level 1; given the potential for overlapping toxicity, the initial dose of ibrutinib tested will be 420 mg daily. During the *safety lead-in*, no more than 3 patients can be under active cycle 1 toxicity evaluation. . Note: Unacceptable toxicity in a given patient is defined as any non-hematologic grade 3|4 toxicity or, for hematologic toxicities, any grade 3|4 that does not resolve to a grade 1|2 within 7 days per NCI CTCAE v4.03 toxicity criteria and is considered at least possibly related to ibrutinib and/or brentuximab vedotin, or any other regimen-related cause of death.

The *safety lead-in* segment will follow standard 3+3 dose escalation/de-escalation/expansion rules based on observed toxicity during cycle 1: (Note: Dose de-escalation, escalation or cohort expansion will only take place after 3 patients are fully assessed using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.03 following the completion of cycle 1.)

- If 0 out of 3 evaluable patients experience unacceptable toxicity during cycle 1, then the next dose level of combination therapy will be tested.
- If 1 out of 3 evaluable patients experience unacceptable toxicity during cycle 1, three additional patients will be assessed at the same dose level of combination therapy.
- If 2 out of 3 evaluable patients experience unacceptable toxicity during cycle 1, dose escalation will cease and the next lower dose level of combination therapy will be expanded. Note: If 2 out of 3 experience unacceptable toxicity on dose level 1, the trial will be stopped. Doses below 420mg (ibrutinib)/1.8mg/kg (brentuximab vedotin) will not be considered.
- If 1 out of 6 evaluable patients experience unacceptable toxicity during cycle 1, then dose escalation to the next dose level of combination therapy will continue.
- If 2 or more out of 6 evaluable patients experience unacceptable toxicity during cycle 1, dose escalation will cease and the next lower dose level of combination therapy will be expanded. Note: If 2 or more out of 6 experience unacceptable toxicity on dose level 1, the trial will be stopped. Doses below 420 mg (ibrutinib)/1.8mg/kg (brentuximab vedotin) will not be considered.

The highest dose level that produces ≤1/6 evaluable patients with unacceptable toxicity during cycle 1 will be the declared safe dose and brought forward for phase II evaluation.

11.2 Sample Size Accrual Rate

Assuming 1) the ibrutinib 560 mg and brentuximab vedotin 1.8mg/kg doses are well tolerated and 2) the study does not close for futility, 39 evaluable participants (received at least 1 cycle of treatment) will be enrolled on the phase II portion of the study. Study enrollment will be complete within 24 months from activation (accrual of 1-2 participants per month). Note: Expected accrual for the safety lead-in segment: n=9.

11.3 Safety Analysis and Stopping Rules for Excessive Toxicity

Following the *patient safety lead-in segment*, the early stopping rule for safety/toxicity will continue to be assessed for each patient after cycle 1. The expected rate of unacceptable toxicity should not be ≥33%. See section 5.1.7 for unacceptable toxicity definition. This rule is in addition to the quarterly review of all toxicities submitted to the COH DSMC. Given the number of patients treated, if the unacceptable toxicity rate is ≥33%, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee (DSMC) will be mandated.

11.4 Statistical Analysis Plan

In general, data will be summarized by using counts and percents for discrete parameters, and by descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum) for continuous parameters. The complete response rate will be calculated as the percent of evaluable patients that have confirmed CR; exact 95% confidence intervals will be calculated for this estimate. Observed toxicities will be summarized in terms of type (organ affected or laboratory determination), severity, time of onset, duration, probable association with the study regimen and reversibility or outcome. Baseline information (e.g. the extent of prior therapy) and demographic information will be presented as well to describe the patients treated in this study. Time to response and survival endpoints will be estimated using the product-limit method of Kaplan and Meier. The cumulative incidence of relapse/progression and non-relapse mortality will be calculated as competing risks.

11.5 Analysis of Correlative Endpoints:

Because of the limited sample size inherent to phase II studies, the analysis of correlative endpoints is primarily exploratory. Standard descriptive methods will be used to summarize: 1) the role of CD30, CD68, and drug exporters on lymphoma specimens and 2) the role of T/B/NK cell subsets and BTK and ITK occupancy in the peripheral blood. If the combination is not found to have sufficient activity, these patterns may help explain the lack of activity. If sufficient activity is found, then participants who experience an objective response will be compared to those who did not in terms of correlates. Estimates of variation will also prove useful for future clinical research on this regimen. Formal testing of these comparisons is not planned. All analysis will clearly document the exploratory nature of these studies, although no attempt will be made to adjust for multiple comparisons inherent in correlative studies.

12.0 Data Handling, Data Management, Record Keeping

12.1 Source Documents

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

12.2 Data Capture Methods and Management

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

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF). A system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked,

and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

The Data Coordinating Center will run monthly data expectation reports that will list any outstanding and overdue data. The Data Coordinating Center will send via email to the participating site a report monthly on any missing and/or overdue data forms. The participating site will be required to complete the missing and/or overdue data forms within 1 week of receipt of the report.

Query reports will be generated on a monthly basis by the Data Coordinating Center. The Data Coordinating Center will send via email to the participating site a report monthly on any outstanding queries.

The participating site staff (whether Principal Investigator or the staff collecting data at site) are required to take an eLearning Module within Medidata RAVE in order to obtain full access. The participating site staff will receive training via teleconference by COH DCC staff to review eCRFs that are specific to this protocol. Continuous training will be offered to participating sites if any amendments affect changes to the eCRFs during the course of the trial. The eCRFs within Medidata RAVE for this trial will have detailed instructions in the form of Help Text that provide instructions for completing each required field on each form.

12.3 Case Report Forms/Data Submission Schedule

Study personnel at each site will enter data from source documents corresponding to a subject'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 subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

All data will be collected using electronic data collection system described in Section 12.2, and will be submitted according to the timelines indicated in Table 12.3.1.

All data will be collected within 1-2 weeks using standard Medidata Electronic Data Capture (EDC) case report forms. Data will be collected and stored on secure computers as indicated in 12.2. After 2 years, we will access the COH CIBMTR data repository to retrieve data regarding post-HCT long-term outcomes through study termination.

Table 12.3.1 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 10 business days of registration
Baseline Assessment Forms	Within 10 business days of registration
Treatment Forms	Within 10 business days of treatment administration
Adverse Event Report Forms	Within 5 business days For transplant patients: within 10 business days of the end of evaluation period.
Response Assessment Forms	Within 10 business days of response assessment

Other assessment forms (e.g. concomitant meds, transplant data including mobilization, etc.)	Within 10 business days of the assessment
Transplant Core Intake Form	Within 10 business days of stem cell infusion
Post Transplant Disease Assessment Form	Within 14 days of the end of evaluation period
Off Treatment/Off Study Forms	Within 10 business days of completing treatment or being taken off study for any reason
Follow up/Survival Forms	Within 10 business days of the protocol defined follow up visit date or call

12.4 Regulatory Records

The Investigator will maintain records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations. Additional information regarding required documents is provided in the DCC Operations Manual, a supplement to this protocol.

13.0 Adverse Events and Unanticipated Problems

13.1 Definitions

13.1.1 Adverse Event (AE)

An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

13.1.2 Serious Adverse Event (SAE)

A serious adverse event is defined as *any expected* or *unexpected adverse event*s that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy*
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*Modified from the definition of unexpected adverse drug experience in 21 CFR 312.32

13.1.3 Unanticipated Problems Involving Risks to Subjects or Others

An unanticipated problem is any incident, experience, or outcome that **meets all three** of the following criteria:

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

13.1.4 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to Pharmacyclics Drug Safety per SAE reporting timelines.

13.1.4.1*Major Hemorrhage*

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*. Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 13.1.4 above.

13.2 Assessment of Adverse Events

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

13.2.1 Assessment of Adverse Event Name and Grade

Adverse events will be characterized using the descriptions and grading scales found in the most recent version of CTCAE v4.03. A copy of the scale can be found at https://evs.nci.nih.gov/ftp1/CTCAE/About.html . The determination of severity for all other events not listed in the CTCAE v4.03 should be made by the investigator based on medical judgment and the severity categories of Grade 1 to 5 as defined below:

• Grade 1 (mild) – An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

• Grade 2 (moderate) – An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

• Grade 3 (severe) – An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

• Grade 4 (life threatening) – An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).

- Grade 5 (fatal) – Death (loss of life) as a result of an event.

13.2.2 Assessment of Attribution

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 related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.

Unlikely -The event is doubtfully related to the investigational agent. The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

Possible –The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

Probable - The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.

Definite - The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs, AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

13.2.3 Assessment of Expectedness

The following definitions will be used to determine the expectedness of the event:

- **Unexpected** - An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event. *Modified from 21 CFR 312.32 (a).
- **Expected** – An adverse event is expected if it does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

13.3 Reporting of Adverse Events

13.3.1 Routine reporting of Non-Serious Adverse Events by Site Investigators

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. AEs will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

AEs recorded in the eCRF include:

- Highest Grade for all toxicities
- All SAEs

13.3.2 Expediting Reporting Requirements of SAEs and UPs by Site Investigators

13.3.2.1 *Criteria for Reporting SAEs/Ups to the Coordinating Center*

Serious Adverse Events meeting the criteria specified below will be reported to the Coordinating Center within **24 hours** of notification that the event occurred.

Adverse events that require expedited reporting include:

- AEs or SAEs that meet the definition of an unanticipated problem
- All deaths that occur within 30 days of active treatment
- All deaths that occur after 30 days of active treatment that are unexpected and possibly, probably, or definitely related to the study agent or procedure
- All serious adverse events, regardless of relationship to study agent or study procedure, that occur within 30 days of the last day of treatment
- All serious adverse events that occurred after 30 days of active treatment/therapy that are considered possibly, probably, or definitely related to the study agent or procedure

Note: Follow-up reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

Reportable serious adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the participating investigator; for ongoing reportable adverse events that are unrelated to study agent, the follow-up period may end at the 30-days post study-drug assessment. The Coordinating Center should be consulted prior to ending the follow-up of events that have stabilized.

13.3.3 SAE Reporting to Local IRB

13.3.3.1*Non COH Sites: Procedure for Reporting SAEs/UPs to the COH Data Coordinating Center*

1. Sites are to report to their local IRB per their sites' specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH Data Coordinating Center copies of the IRB submission and corresponding IRB response.
2. Document/describe the SAE/UP on each of the following:
   a. MedWatch 3500A
      i. Downloadable form at http://www.fda.gov/medwatch/getforms.htm
   b. UP/SAE Coversheet
      i. SAE Coversheet is found in Appendix 6. A modifiable Microsoft Word document is also available from the Data Coordinating Center. An electronic signature on the document will be accepted.
3. Scan and email above documents to DCC@coh.org with the subject title as "15334 SAE".
   a. All SAE reports received at this account are forwarded immediately to study Principal Investigator, and to Coordinating Center personnel.
   b. While not required, if available and applicable, please also include the local IRB submission for this event in the submission.

4. If an email receipt from Coordinating Center personnel is not received within one working day, please call 626-218-7904 and/or email DCC@COH.org.

13.3.3.2 *COH Investigative Sites: Procedure for Reporting SAEs/Ups to the Coordinating Center*

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

13.3.4 Additional Reporting Requirements of the Study Principal Investigator

13.3.4.1 *Reporting to COH IRB and DSMC*

The study PI (or designee) will report to COH IRB and DSMC via iRIS all reportable serious adverse events that occur at COH and non-COH sites and meet COH IRB and DSMC expedited reporting criteria and occur at non-COH sites according to City of Hope's Institutional policy. The study PI will also submit a Protocol Management Team (PMT) report to the COH DSMC at the frequency outlined in Section 15.6. this report will include a review of aggregate adverse event data.

13.3.4.2*Reporting to the FDA*

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's Institutional policy.

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

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

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

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

13.3.4.3*Reporting to Participating Investigators*

The study PI (or designee) will report all reportable serious adverse events to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the

protocol title, the IND#, whether the FDA was informed, and, for non-COH sites, a statement that the report should be submitted to their local IRB for review as an IND safety report if applicable per local IRB policy.

The study PI will also forward to participating sites all IND safety reports received from Pharmacyclics, indicating whether a consent form or protocol change is required within 30 days of notification to study PI.

13.3.4.4*Reporting to Pharmacyclics*

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA MedWatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakePM@pcyc.com) or fax (408-215-3500) by the Study PI to Pharmacyclics Drug Safety, or designee, within 15 days of the event.

The Study PI will report to Pharmacyclics summary safety information every three months.

14.0 Protocol Deviations and Single Subject Exceptions

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Brief interruptions and delays may occasionally be required because of travel delays, airport closures, inclement weather, family responsibilities, security alerts, government holidays, and so forth. Delays can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such a deviation does not threaten patient safety or protocol scientific integrity. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

14.1 Definitions

14.1.1 Deviation

A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval. Investigators may deviate from the protocol to eliminate immediate hazard(s) for the protection, safety, and well-being of the study subjects without prior IRB approval.

Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in treatment schedule due to non-availability of the research participant for treatment; and c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety.

14.1.2 Single Subject Exceptions (SSE)

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

14.2 Reporting of Deviations and SSEs

14.2.1 Reporting Deviations

For any deviation, the Study PI will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy.

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

For non-COH sites:

- The local IRB and/or DSMC must be notified according to local institutional policies.

- The study Principal Investigator must be notified as soon as practical (within 24 hours of notification of the event) via email to aherrera@coh.org and dcc@coh.org. This email should provide input on the following:
    - Description of the event
    - Impact on participant safety or the safety to others
    - Impact on the study design
    - A corrective and preventative action plan

14.2.2 Reporting Single Subject Exceptions

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

All non-emergency planned deviations from the protocol must have **prior** approval by the Study Principal Investigator, the Site Principal Investigator, COH IRB, and when applicable, the local IRB. In addition, if contractually obligated, the sponsor must also approve the deviation. Any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB.

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.

All Investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor (see Section 14) approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

15.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312. Subpart D are executed in accordance with federal regulations.

15.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT) minimally consisting of the study PI, site investigators, collaborating 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) at least monthly to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed. It is recommended that minutes of these discussions will be taken to document the date of these meetings, attendees and the issues that were discussed (in a general format).

15.4 Monitoring

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 Auditing and Monitoring (OCTAM), whose SOP is provided as a supplement to this document.

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

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

15.5 Quality Assurance

The City of Hope Clinical Research Information Support will provide support for this multi-center trial as detailed in the COH DCC Operations Plan provided as a supplement to this document.

15.6 City of Hope Data and Safety Monitoring Committee

This is a Risk Level 4 study as defined in the City of Hope Institutional Data and Safety Monitoring Plan (Appendix 8), as COH is the IND holder.

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

The Study Principal Investigator is required to submit periodic status reports (i.e., the PMT Report) according to the frequency prescribed in the City of Hope Institutional Data and Safety Monitoring Plan (Appendix 7). Data and safety will be reported to the COH DSMC using the PMT report and submitted quarterly from the date of activation.

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team. The COH DSMC Charter is a supplement to this protocol. The PMT report and DSMC recommendations will be circulated to all participating sites for submission to their IRBs, in accordance with NIH guidance.

16.0 Ethical and Regulatory Considerations

16.1 Ethical Standard

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

16.2 Regulatory Compliance

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

- US Code of Federal Regulations (CFR) governing clinical study conduct
    - Title 21 Part 11 – Electronic Records; Electronic Signatures
    - Title 21 Part 50 – Protection of Human Subjects
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    - Title 21 Part 56 – Institutional Review Boards
    - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
    - Title 21 Part 312 – Investigational New Drug Application
    - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
    - Health Insurance Portability and Accountability Act of 1996
    - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17

- Applicable institutional research policies and procedures

16.3 Institutional Review Board

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

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

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

16.4 Informed Consent

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

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

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

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

16.5 Recruitment of Subjects

Patients of both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in Section 3.0. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made

to accrue a representative sample. If differences in outcome appear to be associated with gender or ethnic identity, then a follow-up study will be designed to investigate those differences more fully.

16.6 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, lay summary to be posted on City of Hope's public Clinical Trials On-Line[SM] website, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

16.7 Study Location and Performance Sites

This study will be performed at COH, Cornell Medical College, UCSD and Ohio State Medical Center.

16.8 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 the coordinating center for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and 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.

16.9 Financial Obligations and Compensation

The investigational drug, Ibrutinib, will be provided free of charge by Pharmacyclics. The insurance carrier will be asked to pay for the cost of brentuximab vedotin since this drug is commercially available

The standard of care drugs and procedures provided will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study. However, neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope to the injured research participant; however, financial compensation will not be available.

The research participant will not be paid for taking part in this study.

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