PROTOCOL

A phase I/II trial of Brentuximab vedotin (BV), Ifosfamide (I), Carboplatin (C), and Etoposide (E) for patients with relapsed or refractory Hodgkin lymphoma (BV-ICE).

Trial of the Fred Hutchinson Cancer Research Center (FHCRC), the University of Washington (UW), and the Seattle Cancer Care Alliance (SCCA)
Supported in part by Seattle Genetics

Current Version Date: 12 November 2019

Previous Version Date: 13 November 2018

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This trial is supported in part from the Lymphoma Research Foundation.

PROTOCOL ACTIVITY

Accrual Activated:

Protocol Revision Record:

Original Version:	08/01/2014
Amendment #1:	02/06/2015
Amendment #2:	05/11/2015
Amendment #3:	02/17/2017
Amendment #3.1:	12/01/2017
Amendment #4.0:	08/29/2018
Amendment #5.0:	11/13/2018
Amendment #5.1:	07/25/2019

SCHEMA

Registration

Brentuximab Vedotin, Ifosfamide, Carboplatin, and Etoposide (BV-ICE)
Given Approximately Every 21 Days for 2 Cycles

Dosing Schema

Treatment	Dosing Days 1-3 and 8 of each Cycle			
	1	**2**	**3**	**8**
Brentuximab Vedotin IV *Dose per escalation schema*	X*			X*
Ifosfamide 5 g/m^2		X		
Mesna 5 g/m^2		X		
Carboplatin AUC 5 IV (**Cap carboplatin dose at 800 mg**)		X		
Etoposide 100 mg/m^2 IV	X	X	X	

G-CSF ≥ 5 μg/kg SQ daily starting on day 4 or 5 and to be continued until absolute neutrophil count > 1,000/μL after nadir (pegylated G-CSF may be used when stem cell mobilization is not being attempted).

G-CSF is considered standard of care and may be administered at a local clinic upon approval of the Sponsor-Investigator or Lead Sub-Investigator.

* Brentuximab vedotin administration will be allowed +/- 1 day of these relative dates.

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1.0 OBJECTIVES

1.1 Primary objectives

1. To determine maximally tolerated dose of brentuximab vedotin that can be combined with ifosfamide, carboplatin and etoposide chemotherapy in patients with relapsed or refractory Hodgkin lymphoma.
2. To gain a preliminary assessment of the efficacy of the above regimen.

1.2 Secondary objectives

1. To determine the safety and toxicity of the above regimen.
2. To determine the ability to proceed to peripheral blood stem cell collection following the above regimen (the impact of above regimen on stem cell reserve).
3. To assess the impact of this regimen on biomarkers from the microenvironment in Hodgkin lymphoma tumors.

2.0 BACKGROUND

Hodgkin lymphoma (HL) was newly diagnosed in about 9,000 people in the United States in 2012 [1]. Fortunately, the majority of these patients will be cured with standard treatment approaches [2-5]. However, when relapsed or refractory HL is encountered, it can be particularly challenging to treat. To salvage these relapses, several aggressive multi-agent regimens have been investigated. However, the complete response (CR) rates to these regimens range from approximately 10 to 50% [6]. Furthermore, for patients who are deemed eligible for such an approach, high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) improves long-term remission rates over conventional chemotherapy [7]. The success of this intervention can be predicted by the presence of persistent disease at the time of transplant, measured most frequently in the modern era by functional imaging with fluorodeoxyglucose-positron emission tomography (FDG-PET) [8-11]. Thus, it would be a substantial improvement to develop a salvage regimen that has a higher CR rate without leading to prohibitive toxicity.

At the time of relapse, most oncologists employ aggressive cytoreductive chemotherapy regimens to determine chemo-responsiveness as well as to optimally debulk patients prior to stem cell collection. Historically, many recent cytoreduction regimens have included platinum-based agents because of their considerable activity in lymphoid malignancies. One of the first such combination regimens employed Dexamethasone, high dose Cytarabine, and Cisplatin (DHAP). This regimen was found to be relatively well tolerated with overall response rates (ORR) in the 50-90% range with CRs in the 20-30% range [12, 13]. In addition, these investigators were able to demonstrate the ability to harvest bone marrow or peripheral blood stem cells following treatment. Despite the encouraging efficacy of the DHAP regimen, toxicities including emetogenicity of cisplatin, nephrotoxicity of cisplatin, and limited ability to treat older adults with high-dose Ara-C prompted other investigators to develop novel platinum-containing combination regimens for salvage of lymphoid malignancies.

In order to reduce the nephrotoxicity and emetogenicity, a second platinum-based combination chemotherapy regimen for lymphoid malignancies was developed containing Ifosfamide, Carboplatin and Etopside (ICE). This regimen demonstrated promising response rates with ORR of 70-90% and CR in up to 60% [11, 13, 14]. Furthermore, successful peripheral blood stem cell collection was accomplished in a majority of patients. Finally, as was the goal of this combination regimen, significant nephrotoxicity was not observed. This regimen has become the national standard for use prior to transplantation.

Despite the activity of this regimen, the majority of patients do not attain complete remissions and nearly 30% of patients do not respond [13, 14]. As noted above, the inability to achieve CR prior to transplantation portends a poor outcome after transplant. In B-cell non-Hodgkin lymphoma (B-NHL), investigators have successfully added rituximab to ICE (RICE) with promising results based on its single agent activity, potential synergy with chemotherapy, and lack of overlapping toxicity [15]. This strategy increased the CR rate to 53% in transplant-eligible patients that had only received 1 prior regimen and who had never received rituximab. Unfortunately, further escalation with more traditional cytotoxic agents is not possible due to the considerable hematologic toxicity and non-hematologic toxicity of the RICE regimen [15]. Thus, the addition of a monoclonal antibody to an established cytotoxic chemotherapy regimen can be effective for relapsed/refractory B-NHL. To date, however, this approach has not been fully realized for relapsed/refractory HL.

We propose to address this need by adding brentuximab vedotin (BV) to the standard salvage regimen, ICE. BV is an anti-CD30 antibody conjugated to the anti-microtubule agent monomethyl auristatin E (MMAE). It was shown in a phase II study to yield a single-agent objective response rate of 75% with CR observed in 34%, comparable as monotherapy to the multiagent chemotherapy regimens noted above [6, 16]. On this basis, it was approved by the United States Food and Drug Administration (FDA) for the treatment of relapsed or refractory HL following ASCT or at least 2 prior multi-agent systemic therapies. In terms of toxicity, this phase II study noted NCI Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or worse toxicity in 55 patients (56% of the total cohort) when administered at 1.8 mg/kg every 3 weeks to a median of 9 cycles (range: 1-16). Most of these events were either peripheral neuropathy (PN) or hematologic/laboratory abnormalities, with no deaths attributed to study drug. More recently, a phase I study investigated the safety of more frequent administration (i.e., weekly for 3 out of 4 weeks) of BV [17]. Using this dosing schedule, the maximum tolerated dose (MTD) was established at 1.2 mg/kg. The toxicity profile was similar to that seen with the every 3 week schedule, with the median number of cycles administered across all dose levels of 4 (range: 1-12). Again, no treatment-related deaths were observed.

Given the encouraging results with BV and the need to improve the therapeutic options for patients with relapsed/refractory HL, broader application of this agent is needed. Preliminary data from a prospective study of PET-adapted sequential BV followed by augmented ICE as first salvage of HL suggest excellent efficacy without prohibitive toxicity [18]. In a more straightforward approach, we will investigate the safety and efficacy of BV given concurrently with ICE (BV-ICE) for first salvage of HL. As the patients in both of the above-cited studies with single-agent BV were (in general) more

heavily pretreated than the patients that would be enrolled in this study, and since they received significantly more of this agent over the course of these studies than what is proposed here, we hypothesize that patients will be able to tolerate higher doses of BV when given over fewer cycles. We are thus including a dose-escalation portion of the study to increase the delivery of this agent with the hope of achieving a higher CR rate in a shorter interval. Details of this study are described below.

As treatment regimens have improved, efforts are also underway to identify biomarkers associated with risk of relapse following established treatments. Such features may allow us to individualize treatment based on specific biological features of the lymphoma. One potential avenue for these efforts is with factors identified within the tumor microenvironment of HL, which vastly over-represents the malignant Hodgkin Reed Sternberg (HRS) cells [19]. In particular, the degree of MΦ infiltration into HL tumors is associated with outcome from both primary and secondary treatment [20, 21]. What makes this biomarker particularly desirable is that it is relatively easy to assess with immunohistochemistry (IHC) for surface markers such as CD68 and CD163 [22]. Other biomarkers associated with the inflammatory microenvironment in HL include gene expression profiling of tumors as well as levels of pre-treatment serum cytokines [23, 24], which potentially represent a particularly innovative approach to the risk-stratification of relapsed/refractory HL.

The primary objectives of this study are to determine the MTD of brentuximab vedotin that can be combined with ifosfamide, carboplatin, and etoposide, and to preliminarily assess the efficacy of this combination. We will also be evaluating the safety of this regimen in this particular patient population as well as the ability to collect peripheral blood stem cells following cytoreduction with this approach. Lastly, we also will explore how factors in the inflammatory microenvironment may impact the results from this regimen.

3.0 DRUG INFORMATION

3.1 Ifosfamide, carboplatin, etoposide, and G-CSF must be obtained from commercial sources. Please refer to the current FDA-approved package inserts or the *Physician Desk Reference* for information about possible side effects and instructions for preparation, handling, dosing and storage of these drugs.

3.2 Brentuximab vedotin

3.21 General Information

BV is a CD30-directed antibody-drug conjugate (ADC) that has been approved by the FDA for use in patients with HL after failure of ASCT or failure of at least two prior treatment regimens in patients who are not candidates for ASCT. BV is marketed in the United States under the name ADCETRIS™ by Seattle Genetics, Inc.

3.22 Description

BV is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. BV will be 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. The drug product vial is reconstituted with the appropriate amount of Sterile Water for Injection.

3.23 Toxicity

For the most up-to-date information, refer to the Investigator's Brochure for BV (most recent version at this amendment = version 16). The following list of side effects corresponds to adverse events which have occurred in patients in pivotal phase 2 studies and are considered to have a possible association with BV by the Sponsor.

Side Effect	**Incidence**
Abnormal nerve function in arms or legs (peripheral neuropathy)	67%
Alopecia	13%
Back Pain	12%
Chills	13%
Constipation	18%
Cough	21%
Diarrhea	34%
Dizziness	13%
Fever	31%
High blood sugar	6%
Infection risk	10%
Infusion-related reactions	15%
Itching	17%
Low platelets	10%
Low red blood cells	9%
Low white blood cells	35%
Joint pain	18%
Muscle pain	16%
Nausea	41%
Rash	18%
Shortness of breath	15%
Tiredness	43%
Upper respiratory tract infection	31%
Vomiting	20%

This table presents additional serious or potentially life-threatening events that could have possible association to BV. Events in this section have occurred infrequently in patients treated with BV in clinical trials or in the commercial setting.

Side Effect	**Incidence**

Stevens-Johnson syndrome and toxic epidermal necrolysis	≤ 0.1%
Tumor lysis syndrome	≤ 0.1%
Progressive multifocal leukoencephalopathy	≤ 0.1%
Acute pancreatitis	≤ 0.5%
Hepatotoxicity	< 2%

Drug interactions:
In humans, BV did not affect the PK of midazolam, a sensitive CYP3A4 substrate, suggesting that BV and MMAE are neither inhibitors nor inducers of CYP3A4. In humans, data from co-administration of BV with rifampin, a CYP3A4 and P-gp inducer, or ketoconazole, a strong CYP3A4 and P-gp inhibitor, indicate that MMAE is a substrate of CYP3A4. This is consistent with results from in vitro studies, which show that the metabolites of MMAE are produced primarily through the action of CYP3A4. No dose adjustment should be necessary based on co-administration of a CYP3A4 inducer. Patients receiving strong CYP3A4 inhibitors concomitantly with BV should be closely monitored for adverse events.

Pregnancy:
The effects of BV on embryogenesis, reproduction, and spermatogenesis in humans are unknown. In addition, data about the effects of BV in pregnant women are unavailable. Therefore, women of childbearing potential and fertile men should be advised to use adequate and effective contraception during and after treatment with BV.

3.24 Storage and Stability
Vials containing BV must be stored under refrigeration at 2-8°C. Chemical and physical stability of the reconstituted brentuximab vedotin drug product has been demonstrated for 24 hours at 2-8°C and 25°C. However, BV does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours under refrigeration at 2–8°C. It is recommended that BV vials and solutions be protected from direct sunlight until the time of use.

3.25 Supplier
BV used under this study will be provided by Seattle Genetics and will be identical to the commercially marketed product.

3.26 Drug Accountability
The sponsor-investigator, or a responsible party designated by the sponsor-investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received for this study using the study specific Investigational Agent Accountability Record form or NCI Drug Accountability form.

Transfer of Brentuximab Vedotin
Brentuximab vedotin may not be used outside the scope of this protocol, nor can brentuximab vedotin be transferred or licensed to any party not participating in this clinical study.

Return of unused Brentuximab Vedotin
Only un-dispensed drug supplies should be returned to the UW IDS. Drug returns should be noted on the drug accountability log. Please send a drug return form along with the study drug to:

Investigational Drug Services
University of Washington medical Center
1959 NE Pacific St., Rm EA-128 Box 356015
Seattle, WA 98195-6015

4.0 STAGING CRITERIA

4.1 The Ann Arbor staging criteria will be utilized; staging should be the highest stage established, either at diagnosis or relapse of disease.

4.2 For patients from whom data are available, international prognostic score from the time of diagnosis will be documented (per Hasenclever, et al. [25]) as detailed below:

1. Serum albumin, < 4 g/dl
2. Hemoglobin, < 10.5 g/dl
3. Male sex
4. Stage IV disease
5. Age ≥ 45 years
6. White-cell count ≥ 15,000/μL
7. Lymphocyte count < 600/μL or < 8% of white-cell count

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.11 Patients must have primary refractory or first relapse of CD30+ Hodgkin lymphoma.

5.12 Patients must have measurable disease defined as lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), plain x-ray, or other conventional technique and a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters ≥ 2 cm. Further, at least 1 of these lesions must be positive by PET scan (i.e., Deauville score of 4 or more). Note: CT scans remain the standard for evaluation of nodal disease.

5.13 Patients must have a CT of chest, abdomen, and pelvis with PET within 28 days of enrollment. Patients with evidence of lymphadenopathy in the neck must have a dedicated CT of neck.

5.14 Patients must have an ECOG performance status of 0 or 1. (Performance status of 2 will be allowed if poor performance status is thought to be directly secondary to patient's HL.)

5.15 Patients must be 18 years of age or older.

5.16 Patients must have adequate bone marrow, renal, and hepatic function as defined below. All tests must be performed within 28 days prior to registration:

Bone Marrow Function: ANC $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL (without transfusion or growth factor support).

Renal Function: serum creatinine < 1.5 mg/dl or creatinine clearance (CrCl) > 60 mL/min by the following formula

$$\text{CrCl} = \frac{(140\text{-age}) \text{ (Wt in Kg)}}{72 \times \text{serum Cr}} \times 0.85 \text{ (female) OR } 1.0 \text{ (male)}$$

Hepatic function: total bilirubin < 2 times upper limit of normal (unless due to Gilbert's syndrome), AST < 2.5 times upper limit of normal.

5.17 All patients must be informed of the investigational nature of this study and have given written consent in accordance with institutional and federal guidelines.

5.18 Patients must be anticipated to complete 2 cycles of chemotherapy.

5.2 Exclusion Criteria

5.21 Patients known to be positive for HIV.

5.22 Pregnant or nursing women. Men or women of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

5.23 Patients with other prior malignancies except for adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, breast or cervical cancer *in situ*, or other cancer from which the patient has been disease-free for 5 years or greater, unless approved by the protocol Chair or Co-Chair.

5.24 Patients with known allergy, intolerance, or resistance (i.e., remission duration less than 6 months or lack of response) to ifosfamide, carboplatin, or etoposide.

5.25 Patients with evidence of active central nervous system lymphoma.

5.26 Patients with prior receipt of brentuximab vedotin.

5.27 Patients with peripheral neuropathy of > Grade 1.

5.28 Patients who have other medical conditions that would contraindicate treatment with aggressive chemotherapy (including active infection, uncontrolled hypertension, congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, or uncontrolled arrhythmia). If the patient's cardiac history is questionable, a measurement of left ventricular ejection fraction should be obtained within 42 days prior to registration. Patients with left ventricular ejection fraction < 50% are not eligible.

5.29 Prior failed (< $5x10^6$ CD34/kg) peripheral blood stem cell (PBSC) collection.

5.210 Patients who had pelvic radiation within 12 months.

5.211 Previous chemotherapy/immunotherapy within 3 weeks before study entry.

5.212 Concurrent use of other anti-cancer agents or experimental treatments.

6.0 REGISTRATION

6.1 Patients must be registered prior to the start of protocol therapy. A completed eligibility checklist with source documentation, a copy of the signed consent form and a signed HIPAA authorization are required for registration. All of the eligibility requirements according to Section 5.0 must have been met.

7.0 TREATMENT PLAN

7.1 For treatment or dose-modification related questions, please contact Dr. Lynch at (206) 606-1739 or Dr. Gopal at (206) 606-2037. (MedCon may also be used to contact MDs at 206-543-5300.)

7.2 Administration of Brentuximab Vedotin added to Ifosfamide, Carboplatin, and Etoposide (BV-ICE). Each cycle of therapy is given every 21 days +/- 3 days. Two cycles of chemotherapy should be administered. The days noted in the table below are to be considered a general timeframe: variations +/- 1 day will be permitted for administrative/scheduling flexibility.

Dosing should be based on actual weight except for patients weighing greater than 100kg; dose will be calculated based on 100 kg for these individuals. BV dose should be rounded to the nearest whole number of milligrams.

Drug	**Dose**	**Route**	**Days**	**Duration**
Brentuximab vedotin	Per assigned dose-escalation schema (cap weight for dose calculation at 100kg)	IV	1 and 8	~30 minutes
Ifosfamide	5 g/m^2	IV	2	Infused over ~24 hrs
Mesna	5 g/m^2	IV	2	Infused over ~24 hrs
Carboplatin	AUC 5 (cap carboplatin dose at 800 mg)	IV	2	~1 hr
Etoposide	100 mg/m^2	IV	Days 1, 2, and 3	~1 hr
Filgrastim OR Pegfilgrastim	≥ 5 mcg/kg/day 6 mg	SQ SQ	Day 4 or 5 Day 4, 5, or 6 x 1	Daily until ANC > 1,000 Once

Post Protocol Treatment
Following the 2 cycles of treatment patients may go on to receive other therapy at the discretion of their physician. It is anticipated that most patients will proceed to HDT and ASCT. Brentuximab vedotin will no longer be supplied.

7.21 Brentuximab Vedotin

Dose level will be assigned at enrollment. BV is administered intravenously on days 1 and 8 (+/- 1 day at each timepoint). Advice on BV reconstitution and administration:

- Reconstitute lyophilized BV by adding 10.5 mL Sterile Water for Injection, USP to the 50 mg vial, directing the stream to the side of the vial.
- Dilute reconstituted product in either 0.9% Sodium Chloride Injection, USP, Lactated Ringer's solution, USP, or dextrose 5% in water (D5W), USP. Gently invert the infusion bag. DO NOT SHAKE.
- The final concentration of BV in infusion bag should be in the range of 0.4–1.8 mg/mL.
- Refrigeration should be set at 2–8°C for storage of the prepared dosing solution. The solution must be used within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.
- BV should be administered over approximately 30 minutes and cannot be mixed with other medications. In-line filters should not be used during the IV administration.

7.22 Carboplatin Dose Calculation and Administration

Carboplatin dose will be calculated for an AUC of 5 using the Calvert Formula as described below. **Carboplatin dose should be capped at 800 mg.**

Carboplatin dose = 5 x (GFR* + 25)

* Calculated creatinine clearance (CrCl) is substituted for GFR based on the formula below. Dose is in mg NOT mg/m^2.

$$\text{CrCl} = \frac{(140\text{-age})\ (\text{Wt in Kg})}{72 \times \text{serum Cr}^{**}} \times 0.85\ (\text{female})\ \text{OR}\ 1.0\ (\text{male})$$

**Serum creatinine must be obtained within 3 days of receiving chemotherapy for each cycle.

7.3 Peripheral Blood Stem Cell Mobilization and Collection

For patients that plan to go on to consolidative HDT and ASCT, PBSC can be mobilized following the 2nd cycle of study therapy at the discretion of the treating

physician. The following includes general guidelines regarding PBSC mobilization and collection. Deviations from this plan to accommodate particular clinical scenarios, logistical issues, etc. will be permitted.

In general, G-CSF is given at a dose of 10 μg/kg/day at least 24 hours after the last dose of ICE chemotherapy (adjusted weight may be used at the clinical discretion of the treating physician). Apheresis will proceed as per standard practice and at the discretion of the treating physician (large volume apheresis is preferred for all collections). In general, apheresis will commence on the day after the post nadir WBC ≥ 1,000/μL and will continue daily for a minimum of 3 days or until the target of ≥ 5 x 10^6 CD34+/kg has been met. A CD34 count of ≥ 5/μL or preferably ≥ 10/μL can also be used as a guide as to when to initiate apheresis, in general, CD34 counts are obtained starting 24 hours after recovery from nadir. Additional apheresis will be at the discretion of the treating physician with no more than 7 days of apheresis. G-CSF will continue until PBSC collection is completed (unless WBC is > 100,000/μL in which case G-CSF will be discontinued). The use of adjunctive mobilization agents (e.g., plerixafor) will be left to the discretion of the treating physician.

For the secondary endpoint related to PBSC collection, adequate stem cell collection will be defined as ≥ 5 x 10^6 CD34+/kg obtained within 7 days of apheresis.

G-CSF is considered standard of care and may be administered at a local clinic upon approval of the Sponsor-Investigator or Lead Sub-Investigator.

7.4 Prophylaxis

7.41 Nausea/vomiting prophylaxis: Ondansetron 8 mg IV is recommended to be given daily before chemotherapy on Days 1-3. Dexamethasone 10 mg by mouth daily is highly recommended before chemotherapy on Days 1-3. Other anti-emetics (e.g., lorazepam, promethazine, etc.) should be prescribed according to the discretion of the prescribing physician.

7.42 Infection prophylaxis: Levofloxacin 500 mg by mouth daily (or equivalent) is highly recommended to be used once a patient's ANC is less than or equal to 1,000 cells/μL.

7.5 Patients will be assessed for response as specified in section 10.0, at least 3 weeks following the second cycle of chemotherapy. Criteria for removal from protocol treatment:

7.51 Documented progression of disease.

7.52 Development of any related grade 4 non-hematologic toxicity (excluding asymptomatic grade 4 laboratory abnormalities) or other dose limiting toxicity as defined in Section 11.

7.53 Development of any other unacceptable toxicities unless prophylactic measures can be taken for subsequent cycles.

7.54 Delay of treatment for more than 3 weeks due to adverse events.

7.55 Completion of protocol treatment (maximum of 2 cycles).

7.56 The patient may withdraw from the treatment at any time for any reason.

8.0 DOSAGE MODIFICATIONS

The dose of brentuximab vedotin will be adjusted according to the dose modification plan described in Statistical Considerations (Section 11). Standard dose adjustments for ifosfamide, carboplatin, and/or etoposide during treatment may be made based on changes in hepatic and renal function. Parameters for retreatment and treatment modifications are as follows:

8.1 Modifications for Hematologic Toxicity

8.11 Subsequent cycles of therapy will not begin until the ANC is ≥ 1,000/μL and the platelet count is ≥ 50,000/μL. Therapy will be delayed a maximum of 3 weeks until these values are achieved. Patients who fail to recover adequate counts within 3 weeks will be removed from study treatment.

8.2 Modifications for Impaired Renal Function

8.21 Serum creatinine must be < 1.5 mg/dl or an *estimated* or measured creatinine clearance must be > 60 ml/minute on Day 1 of each cycle (lab may be drawn up to 3 days prior to day 1). If these values are not met, treatment may be delayed for up to 3 weeks. If these values do not recover within 3 weeks, the patient will be removed from protocol treatment.

8.3 Modifications for Impaired Liver Function

8.31 Total bilirubin must be < 2 times upper limit of normal, and ALT and AST < 2.5 times upper limit of normal on Day 1 of each cycle (lab may be drawn up to 3 days prior to day 1). If these values are not met, treatment may be delayed for up to 3 weeks. If these values do not recover within 3 weeks, the patient will be removed from protocol treatment. Please notify the Study Chair of any Grade 3 or 4 elevated liver function tests that occur on Day 1, prior to starting the next cycle.

8.5 Modifications for Other Adverse Events

8.51 Any related grade 4 non-hematologic toxicity (excluding asymptomatic grade 4 laboratory abnormalities) or other dose-limiting toxicity as defined

in Section 11 will result in the patient being removed from protocol treatment.

8.52 Patients should receive appropriate medical management for adverse events. Treatment may be delayed for clinically significant grade 2 or 3 adverse events and unrelated grade 4 adverse events at the discretion of the treating physician. If treatment is delayed for 3 weeks, the patient will be removed from protocol treatment.

8.6 Concomitant Therapy

Medications used during the course of the study should be documented.

8.61 *Prohibited Concomitant Therapy*:
The administration of concurrent medications intended to treat the primary cancer is not allowed during protocol therapy. This includes any chemotherapy, investigational agent, biologic agent or other anti-tumor agents. Radiation therapy is also prohibited.

8.62 Patients should be strongly discouraged from taking any "alternative" or "naturopathic" medications since these agents may interact with study treatment. Any use of these medications should be at the judgment of the treating physician and should be documented in the patient's medical record.

9.0 STUDY CALENDAR

Required Studies	Pre-Entry (within 4 weeks unless indicated otherwise)	Within 3 days prior to each cycle	Post Therapy[6, 11]	Follow-up
Physical				
History and Physical	X	X[9]	X[6,11]	X[7]
Performance Status	X	X[9]	X[6,11]	
Clinical Disease Assessment	X	X[9]	X[6,11]	
Adverse Event Assessment	X	X[9]	X[6,11]	
EKG	X			
CBC, Diff, platelets	X	X[9]	X[6]	
Serum creatinine, total bilirubin, SGOT (AST), electrolytes, glucose	X	X[9]	X[6]	
Albumin	X[1]			
LDH	X		X[6]	
Bone Marrow Studies	X[2]		X[2,6]	
Pregnancy test	X[8]			
Laboratory Correlative Studies	X[3]	X[3]	X[3,6]	X[10]
Radiology				
CT Chest, abdomen and pelvis; CT neck if cervical adenopathy present	X		X[6]	
Left Ventricular Ejection Fraction (LVEF)	X[4]			
PET/CT	X[5]		X[5,6]	

[1] Albumin is used for documenting prognostic criteria

[2] Bone Marrow Studies include aspirate and unilateral or bilateral biopsy. If all bone marrow studies are negative at enrollment, these do not need to be repeated at completion of the study. Patients who do not have a bone marrow study at enrollment with PI's approval will need to have bone marrow study at completion of treatment to confirm CR if needed.

[3] Laboratory correlative studies: In patients from whom a biopsy specimen is available from the time of initial diagnosis and/or relapse/progression, tissue blocks and/or slides maybe obtained to perform prognostic/predictive correlative studies. Pre-treatment biopsy to confirm relapsed/refractory disease is recommended, but not required, for study enrollment. Peripheral blood samples may also be obtained prior to Cycle 1 and after study treatment for similar correlative analyses (including a satellite vial of patients' stem cells that will be collected at time of apheresis for such analyses).

[4] Measurement of LVEF should be done if medically indicated. LVEF must be $\geq$50%

[5] PET scans should have a Deauville score assigned [26].

[6] Post therapy studies should be done at least 3 weeks post cycle 2 or after the patient's last cycle, whichever comes first, unless otherwise specified.

[7] Follow-up should be performed as clinically indicated. A typical follow-up schedule would be that follow-up assessments are done every 3 months for 1 year then every 6 months for 4 years (total follow-up time 5 years).

[8] Pregnancy test is only required in women of childbearing potential.

[9] For Cycle 1 Day 1, pre-entry H&P, performance status, disease assessment and adverse event assessment may be used (these do not need to be repeated within 3 days) and labs done within 14 days are acceptable.

[10] For patients that proceed on to ASCT, an optional blood draw may be performed on or around day 30 post-transplant for additional correlative studies.

[11] Patients who move on to receive care from the SCCA Transplant Team will be followed via detailed medical records rather than having a Post Therapy clinic visit directly with the Sponsor-Investigator or Lead Sub-Investigator.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Definitions of Disease, Criteria for Evaluation and Endpoint Definitions – response will be defined by standard NCI criteria (Cheson, *et al.*) for lymphoid malignancies [27].

10.1 Measurability of Lesions:

10.11 Measurable Disease: Lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), plain x-ray, or other conventional technique and a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters ≥ 2 cm. Note: CT scans remain the standard for evaluation of nodal disease.

10.12 Non-measurable Disease: All other lesions including uni-dimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques, or disease documented by indirect evidence only (e.g., lab values).

10.2 Objective Disease Status: Objective status is to be recorded at each evaluation. The three largest measurable lesions at baseline should be identified as target lesions and be measured at initial and follow-up imaging. All remaining lesions may remain unmeasured; these lesions should be noted as to site and presence or absence on follow-up imaging. 'Absence', in general, will be defined as not pathologically enlarged.

10.21 Complete Response (CR): Complete disappearance of all evidence of disease with the exception of nodes for which the following must be true: all measurable nodal lesion and nodal masses >1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤1.5 cm in GTD; nodal masses that were 1.1 to 1.5 cm in their longest axis and more than 1.0 in their short axis before treatment must have decreased to ≤1.0 cm in their shortest axis after treatment. A post treatment residual mass of any size is permitted as long as it is PET negative (i.e., Deauville score of 3 or less [26]). If patients have an isolated site on post-therapy imaging that appears to represent persistent disease, but a subsequent biopsy fails to identify evidence of Hodgkin lymphoma, such patients shall be defined as CR. PET scans should not be performed for at least 3 weeks, and preferably 6 to 8 weeks after completion of therapy. No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable. If bone marrow was positive at baseline, it must be negative based on biopsy and aspirate at the same site. If a sample that is considered negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes (<2%) by flow cytometry will be considered a CR. Normalization of markers (e.g., LDH definitely assignable to HL). All disease must be assessed using the same technique as baseline.

10.22 Partial Response (PR): At least a 50% decrease in sum of the product of the diameters (SPD) for up to six identified dominant lesions. No new lesions and no increase in the size of liver or spleen or other nodes. Splenic and hepatic nodules must have regressed in size by at least 50% in SPD. Sites that were PET positive (i.e., Deauville score of 4 or more) pre-treatment should still be positive in at least 1 site post-treatment. Bone marrow assessment is irrelevant if the sample is positive before treatment. All disease must be assessed using the same technique as baseline.

10.23 Stable disease (SD): Does not qualify for CR, PR, or Relapsed/Progressive Disease. All disease must be assessed using the same technique as baseline.

10.24 Relapsed Disease: If a CR was achieved at a previous assessment, a 50% increase in the SPD of target measurable lesions over the smallest sum observed (over baseline if no decrease during therapy) or 50% increase in the GTD of any node greater than 1 cm in shortest axis using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of a new lesion/site. Death due to disease without prior documentation of progression.

10.25 Progressive Disease (PD): If a CR was not achieved at a previous assessment, a 50% increase in the SPD of target measurable lesions over the smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Appearance of a new lesion site. Lesions should be PET positive unless the lesion is too small to be detected with current PET systems (1.5 cm in its long axis by CT). Unequivocal progression of non-measurable disease in the option of the treating physician (an explanation must be provided).

10.26 Assessment inadequate, objective status unknown: Progression has not been documented and one or more target lesions or other sites of disease have not been assessed or inconsistent methods of assessment were used.

10.3 Bone Marrow Status: Bone marrow status is evaluated as follows:

Positive: Unequivocal cytological or architectural evidence of malignancy.

Negative: No aggregates or only a few well-circumscribed lymphoid aggregates.

Indeterminate: Does not qualify for either Positive or Negative Status. *Note this typically consists of increased number or size of aggregates without cytological or architectural atypia.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Objectives: This study has two primary objectives. The first is to define the maximally tolerated dose (MTD) of BV that can be combined with ICE chemotherapy. The MTD will be defined as below, based on the proportion of patients that experience a dose-limiting toxicity (DLT). For the purposes of this study, a DLT is defined as:

- Any non-hematologic grade 4 or 5 NCI CTCAE adverse event (excluding asymptomatic grade 4 laboratory abnormalities) that is possibly, probably or definitely related to the drug combination within 28 days of the last dose of the study drug, with the following exception: Any treatment-emergent grade 3 or higher peripheral neuropathy will also be considered a DLT.
- The patient did not complete one full cycle of therapy due to toxicity from the treatment. Patients choosing to stop study medication for adverse events that are not considered medically significant by the Investigators, will not be scored as a DLT.
- Treatment delay of > 3 weeks following cycle 1 due to prolonged recovery from observed toxicity (see Section 8 for details)

The second primary objective is to gain a preliminary assessment of the efficacy of this regimen. This will be defined as the percentage of patients that achieve a complete remission (CR) following study treatment, as defined above in Section 10.2. Further, we will describe the progression-free and overall survival from the time of initiation of study therapy and from ASCT (for those who go on to receive this treatment).

11.2 Phase I (Dose Escalation) Design: Dose escalation/de-escalation will be conducted by a "3+3" approach. The starting dose level will be Dose Level 1 (see table below). Toxicities occurring in the first or second cycle will be evaluated for DLT. If a patient receives only one cycle of therapy, they will still be considered evaluable for DLT. Dose escalation will not occur until sufficient time has elapsed to evaluate for DLTs in all patients treated at that dose level. We anticipate treating 9-12 patients in this phase of this study.

Three patients will be entered at Dose Level 1. The following rules will dictate the dose escalation/de-escalation schema:

- If 0 of 3 patients treated at Dose Level 1 experience a DLT, then the next 3 patients will be enrolled at Dose Level 2. If $\leq$ 1 of these patients experiences a DLT, then another 3 patients will be enrolled at Dose Level 2. If $\leq$ 1 of these 6 patients experience a DLT, then Dose Level 2 will be declared the MTD and the dose escalation phase will stop.
- If 1 of 3 patients treated at Dose Level 1 experience a DLT, then another 3 patients will be enrolled at Dose Level 1. If $\leq$ 1 of these 6 patients experience a DLT, then Dose Level 1 will be declared the MTD and the dose escalation phase will stop.
- If $\geq$ 2 of 3 patients treated at Dose Level 1 experience a DLT, then up to 6 patients will be enrolled at Dose Level -1. If $\leq$ 1 of 6 patients treated at Dose Level -1 experience a DLT, then Dose Level -1 will be declared the MTD and the dose escalation phase will stop.

- If ≥ 2 patients in any group of 6 patients experience a DLT, then the dose will be de-escalated by one dose level, 3 patients will be treated at that lower dose level, and so forth as above.

If de-escalation is indicated at Dose Level -1, the investigators may submit a modification to the IRB to request further dose de-escalation. There will be no intra-patient dose escalation. Based on the above rules, we anticipate treating 9-12 patients in this phase of the study.

Dose Level	Brentuximab vedotin dose (mg/kg, each cycle)	
	Day 1	Day 8
-1	1.8	none
1 (starting dose)	1.2	1.2
2	1.5	1.5

11.3 Phase II (Expansion Cohort) Design: Once the MTD of BV has been determined, enrollment will continue with all patients receiving this dose of BV. The primary endpoint of this section will be the CR rate. We recognize that a precise estimate of CR rate will require a larger sample size than possible within the context of this trial. Thus, we will consider the phase II portion a pilot study/MTD expansion with a minimum of 36 additional patients treated beyond the 9-12 patients treated in the phase I portion. This means that a total of 42 patients will be treated at the MTD (6 patients in the phase I portion plus 36 patients in the phase II portion). If the true CR rate using BV-ICE is 78% and we treat 42 patients at the MTD, this would provide 80% power to detect a statistically-significant increase in CR rate from a historical rate of 60% [11], based on a one-sample chi-square test with one-sided significance level of 5%. Analyses of secondary endpoints (e.g., PBSC yield, PFS, and OS) will be primarily descriptive.

Stopping Rules: The dose escalation schema will act as stopping rules unless a dose lower than the lowest dose-level is considered the MTD, at which point the protocol will be closed.

11.4 Anticipated accrual: We anticipate that accrual will take 3-4 years.

11.5 Estimated* distribution of study population by gender and race and ethnicity:

Ethnic Category	Females	Males
American Indian/Alaska Native		
Asian	2	3
Native Hawaiian or Other Pacific Islander		
Black or African American	1	2
White	12	25
More than one race		
Unknown or not reported		
Racial Categories: Total of all subjects	15	30

The exact sample size is not known since it is dependent on the number of evaluable patients, but we estimate the total enrollment will be 30.

12.0 STUDY MONITORING AND REPORTING PROCEDURES

12.1 Adverse Event Reporting

AEs of Grade 3 and above, and Serious Adverse Events (SAEs) occurring at any grade will be monitored and recorded in study-specific case report forms (CRFs) from the time of study enrollment through 30 days following the end of study treatment, or until the patient receives an alternative anti-cancer therapy, whichever date comes first. AEs related to biopsies that are done solely for research study screening purposes will be monitored, recorded, and reported according to the same standards, with the exception that assessment of study drug attribution will be excluded from reporting criteria.

The NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) will be used to classify and grade toxicities.

The CTC can be found on the Cancer Therapy Evaluation Program (CTEP) homepage at:
http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev4.pdf.

12.2 Definitions and descriptions of terms used in adverse event reporting.

Adverse Event (AE)
An AE is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Serious Adverse Event (SAE) or Adverse Drug Reaction (ADR)
A *Serious Adverse Event* or *Adverse Drug Reaction* means any AE/ADR occurring at any dose that results in:

- Death;
- A life-threatening AE/ADR (i.e, the patient/subject was, in the view of the initial reporter/investigators, at immediate risk of death from the AE as it occurred. It does not refer to an AE that hypothetically might have caused death if more severe);

- Inpatient hospitalization or prolongation of existing hospitalization(i.e, hospitalization was required to treat or diagnose the AE/ADR: excludes hospitalization for unrelated reasons);

- A persistent or significant disability or incapacity (disability here means that there is a substantial disruption of a person's ability to conduct normal life functions;

- A congenital anomaly/birth defect;

- An important medical event (i.e., AEs/ADRs that might not be immediately life-threatening, or result in death or hospitalization might be considered serious when, based upon appropriate medical and scientific judgment, they might jeopardize the patient/subject or might require medical or surgical intervention to prevent one of the other serious outcomes listed above);

- Any suspected transmission via a medicinal product of an infectious agent.

Sponsor-Investigator shall use his/her judgment to determine the relationship between the Serious Adverse Drug Experience and the Study Drug.

Grade

Grade is defined as the severity of the adverse event. The CTCAE Version 4.0 must be used to determine the grade of the adverse event. If toxicity is not listed in the CTCAE use the following general criteria for grading.

0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

Attribution

Attribution is defined as the determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories are as follows:

- *Unrelated* The adverse event is *clearly NOT related* to therapy
- *Unlikely* The adverse event is *doubtfully related* to therapy
- *Possible* The adverse event *may be related* to therapy
- *Probable* The adverse event is *likely related* to therapy
- *Definite* The adverse event is *clearly related* to therapy

Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Unexpected Adverse Event
An *unexpected adverse event* is any adverse event for which the specificity or severity is not listed in the current Investigator's Brochure or the package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

12.3 Routine Reporting

Routine reporting will be conducted in accordance with FHCRC/Cancer Consortium IRB policies, applicable FDA regulations, and agreements with Seattle Genetics Inc.

Reports may include data after each cycle of therapy and 30 days after the last dose of study drugs, or until the patient receives an alternative anti-cancer therapy, whichever date comes first.

12.4 Expedited Reporting

Expedited reporting will be conducted in accordance with FHCRC/Cancer Consortium IRB policies, applicable FDA regulations, and agreements with Seattle Genetics Inc.

12.5 Reporting to Seattle Genetics, Inc.

The study coordinating office will notify the IRB and Seattle Genetics within two business days, by facsimile or e-mail, upon learning of the occurrence during the Study of:

- All Serious AE/ADRs, regardless of causality;
- Any exposure of a pregnant Study participant to the Study Drug within thirty (30) days of exposure;
- A female partner of a male Study participant becoming pregnant within thirty (30) days of exposure;
- Any medical event which may reasonably be believed to impair the integrity, validity or ongoing viability of the Study.

All such occurrences listed in this section shall be reported to Seattle Genetics using an approved local regulatory form. An aggregate listing of all SAEs will also be sent monthly to Seattle Genetics electronically.

In the event the IRB requests additional safety information from the Sponsor-Investigator, the Sponsor-Investigator shall notify Seattle Genetics of such request within one (1) business day.

12.6 Reporting to the IRB

Institutions should follow the guidelines of their local IRB for reporting serious adverse events in a timely manner.

12.7 Data Safety and Monitoring Plan

All serious adverse events are communicated to the study Sponsor-Investigator and regulatory agencies as described above. A status report including accrual, adverse events, and death information will be reviewed by the Sponsor-Investigator and the Fred Hutchinson Cancer Research Center (FHCRC) Data Safety Monitoring Committee (DSMC) annually. In addition, the study will be monitored by the Research Trials Office according to the Fred Hutchinson Cancer Research Center monitoring plan.

12.8 Required Records and Materials

Under the supervision of the investigators, research staff will maintain case report forms and secured databases on the relevant clinical and laboratory data. Records maintained in investigators' offices will be secured with access limited to study personnel. Authorization for access to medical records will be obtained from all patients in accordance with provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Original signed informed consent forms will be kept within the secured study team office, access is limited to study personnel. A copy of the signed informed consent form is given to the participant. Data will be collected on patient characteristics, disease characteristics, protocol therapy, response to treatment, adverse events and follow-up for relapse and survival. Copies of the patient's medical record including history and physical exams, documentation of protocol therapy, labs, scans, x-rays, hospitalizations, operative reports, pathology reports etc. are required.

13.0 ELEMENTS OF INFORMED CONSENT

All Institutional, NCI, State and Federal regulations concerning informed consent and peer judgment will be fulfilled. Written consent will be obtained from all patients entering the study.

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