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UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
FRED HUTCHINSON CANCER CENTER

A Pilot Study of Weekly Brentuximab Vedotin or Brentuximab Vedotin Plus Nivolumab Every 3 Weeks in Patients with CD30+ Malignancies Refractory to Every ≥ 3 Week Brentuximab Vedotin

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This trial is supported by Seattle Genetics, Inc.

SCHEMA

ARM A (Closed to Accrual)
Registration

↓

Brentuximab vedotin 1.2 mg/kg IV

Given Weekly 3 of 4 Weeks in a 28 day Cycle for Up to 4 Cycles

ARM A DOSING SCHEMA (Closed to Accrual)

EACH CYCLE (UP TO 4 CYCLES TOTAL)				
Chemotherapy	**Treatment Day** (Actual treatment dates may vary up to +/- 2 days)			
	1	**8**	**15**	**22**
Brentuximab vedotin 1.2 mg/kg (maximum 120 mg) IV over approximately 30 minutes	X	X	X	(Rest)

↓

Follow-up will be performed 3 - 5 weeks following final cycle; then per standard of care.

ARM B (Open to Accrual)

Registration

Brentuximab vedotin 1.8 mg/kg IV

Given every 3 weeks (21 day cycle) for Up to 4 Cycles

ARM B DOSING SCHEMA (21-day cycle) (Open to Accrual)

EACH CYCLE (UP TO 4 CYCLES TOTAL)				
Chemotherapy	**Treatment Day** (Actual treatment dates may vary up to +/- 2 days)			
	Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
	Day 1	**Day 1**	**Day 1**	**Day 1**
Brentuximab vedotin 1.8mg/kg IV	X	X	X	X
Nivolumab 3mg/kg IV	X	X	X	X

Follow-up will be performed 3 - 5 weeks following final cycle; then per standard of care.

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1.0 OBJECTIVES

1.1 Primary objectives

1.1.1. ARM A:
To estimate the response rate following weekly brentuximab vedotin (1.2mg/kg 3 of 4 weeks for up to four 28-day cycles) in patients with lack of response (<PR) or progression following brentuximab vedotin and demonstrating persistent expression of CD30.
1.1.2 ARM B:
To evaluate the response rate of combination brentuximab vedotin and nivolumab in patients with lack of response (<PR) or progression within 6 months following brentuximab vedotin

1.2 Exploratory objectives (will be completed as feasible, based on availability of data collected in the course of standard clinical assessments/follow-up)

1.2.1. To monitor clinical outcome following the study treatment regimen.

1.2.2. To estimate the frequency of CD30 loss in patients following resistance to brentuximab vedotin.

1.2.3. To describe the pattern of CD30 expression (membranous, cytoplasmic, golgi) in comparison to the pre-brentuximab vedotin expression.

1.2.4. To semi-quantitatively estimate and compare the surface density of CD30 pre and post brentuximab vedotin as measured by flow cytometry.

1.2.5. To correlate response with CD30 density as measured by flow cytometry

1.2.6. To evaluate the tolerability of the weekly regimen in patients previously exposed to brentuximab vedotin. To explore the tolerability of brentuximab vedotin and nivolumab in patients previously exposed to brentuximab vedotin in a 21-day cycle.

2.0 BACKGROUND

2.1 Rationale for development of new lymphoma therapies

Lymphoma is the seventh most common cancer in the United States. There are approximately 75,000 new diagnoses of lymphoma each year in the United States and approximately 30% of these patients may be cured with anthracycline-based chemotherapy regimens. Unfortunately, most of these patients will fail their initial therapy and will require a more aggressive treatment in an attempt to induce a remission [1-7]. For patients with aggressive lymphoid malignancies such as diffuse large B-cell lymphoma and Hodgkin's lymphoma, high dose therapies (HDT) followed by autologous stem cell transplantation (ASCT) have been shown to improve both progression-free and overall survival [8-10]. A number of factors have been shown to be predictive of improved outcome following HDT and ASCT. Among these factors, some of the most important predictors include sensitivity of the disease to cytoreductive chemotherapy, disease bulk at the time of transplant, and patients' overall performance status [11-16].

However, many patients are either not candidates for HDT and ASCT or will relapse following this procedure, indicating a need for novel therapies for this group of patients.

2.2 CD30 as a target for lymphoma therapy

CD30, a cell surface antigen and member of the TNF superfamily group of receptors, is expressed on several malignancies including Hodgkin's lymphoma (HL), anaplastic large cell lymphoma (ALCL), Kaposi's sarcoma (KS), cutaneous T cell lymphomas (CTCL), diffuse large B-cell lymphoma (DLBCL), some follicular lymphomas, and other lymphoproliferative diseases [17, 18]. Importantly, the expression of CD30 is thought to be very limited on normal tissues primarily limited to a subset to T-cells. These features make CD30 an attractive target for anti-lymphoma therapy in the subset of diseases where its expression is documented.

2.3 Every 3 week dosing of brentuximab vedotin in HL and ALCL

Based on the potential limited expression of CD30 on normal tissues, preclinical data, and the high-level expression on HL and ALCL, the antibody drug conjugate (ADC), brentuximab vedotin (BV) was evaluated in these patient populations [19]. BV is comprised of a chimeric mouse-human anti-CD30 monoclonal antibody with the addition of a dipeptide linker that enables the attachment of Monomethyl auristatin E (MMAE), a potent anti-microtubule agent. Specifically, BV is thought to bind CD30, followed by internalization and intracellular release of MMAE after lysosomal degradation. MMAE then binds to tubulin within the cell and induces cell cycle arrest and apoptosis [19]. In a large, multi-center phase II trial presented by Chen et al, the safety and efficacy of brentuximab vedotin were evaluated in patients with HL recurring after ASCT. A total of 102 patients were enrolled and given 1.8 mg/kg IV brentuximab vedotin every 21 days as outpatient 30-minute infusions for up to 16 cycles [20]. Patients had a median of 3.5 (1-13) prior systemic chemotherapy treatments (excluding ASCT). The objective response rate (ORR) was 75% (76 of 102 patients), with CR in 34% (35 of 102). For patients with CR, the median duration of response (DOR) had not been reached (0.3 + to 61.4+ weeks). A similar study was presented by Shustov et al evaluating BV in relapsed/refractory ALCL [21]. In this series of 58 ALCL patients who had received a median of 2 prior regimens, an ORR of 86% was observed with a CR rate of 57%.

The most common Grade 3-4 adverse events (AEs) occurring in patients from the above studies were neutropenia (21%); peripheral sensory neuropathy (8-10%); anemia (2-10%); and thrombocytopenia (9-10%) with 21% of patients discontinuing therapy due to an AE [20].

2.4 Weekly dosing of brentuximab vedotin

As part of the development of this agent, a weekly regimen given on Days 1, 8, and 15 of a 28-day cycle was evaluated [22]. The MTD of this regimen was found to be 1.2 mg/kg (capped at 120 mg). In this study of 44 patients (38 HL, 5 ALCL, 1 peripheral T cell lymphoma), tumor regressions were observed in 85% of patients with ORR and CR rates of 59% and 34%, respectively. Importantly, the toxicity profile of this regimen from this small study was comparable to the every 3 week regimen.

2.5 Resistance mechanisms to brentuximab vedotin

Despite the high-response rates to BV, between 14-27% of patients failed to respond to the initial exposure of this agent and many more eventually progressed despite ongoing BV therapy

[20, 21]. Potential mechanisms of resistance could include specific resistance to intracellular MMAE, impaired CD30 internalization mechanisms, or modulation or loss of the target CD30. Data to date suggest that CD30 loss following progression or lack of response to BV does not routinely occur, though this has not been evaluated in a prospective fashion, nor quantified by flow cytometric methods [23 (and Gopal et al unpublished data)]. Nevertheless, the presence of persistent CD30 after post-BV disease progression suggests that it may remain a viable antigen for tumor targeting.

Anecdotal data supports the potential to overcome resistance by increasing dose density. A 50 year old female who had received multiple lines of prior therapy (ABVD; GVD; ASCT with TBI, VP-16, and cyclophosphamide conditioning, and ICE) was enrolled on a clinical trial using BV, 1.8 mg/kg every 21 days. Following her second dose of BV, the patient achieved a complete remission which was confirmed through the 7th dose of this agent. In order to accommodate the patient's schedule, BV infusions were adjusted to every 5 weeks through the 15th dose at which time imaging indicated progressive disease. Biopsy of the tumor site revealed classical HL, with CD30 expression documented by immunohistochemistry and flow cytometry. The patient resumed BV at 1.8mg/kg every 3 weeks and achieved a second response (partial response) which lasted an additional 4 months. We evaluated this approach in Arm A of this study and treated 8 patients. Though 4 of 8 patients achieved at least some reduction in target lesions (ranging from 16.5-50.2%) only one patient achieved a short-lived PR. This arm was, thus, closed due to limited efficacy and an alternative strategy was proposed to evaluate the potential use of brentuximab vedotin in patients with prior brentuximab exposure.

2.6 Nivolumab in HL:

Nivolumab is a human IgG4 anti-PD-1 antibody which blocks this T cell inhibition, thereby enhancing anti-tumor T cell activity[16]. Nivolumab is now FDA approved for treatment of relapsed/refractory cHL patients based on two studies[17]. Nivolumab showed an objective response rate of 65% in the pooled analysis of 95 patients treated on the phase I CheckMate-039 trial and phase II CheckMate-205 trial[17]. The patients in these studies were heavily pre-treated with chemotherapy, autologous stem cell transplant and novel antibody drug conjugate, Brentuximab-Vedotin. Nivolumab was overall well tolerated, no grade 4-5 drug related toxicities, and mostly mild grade 1-2 rash, pruritis and diarrhea were reported. Five patients had reversible Grade 3 drug related toxicities.

2.7 Combination therapies of brentuximab and checkpoint inhibitors

Preclinical data indicate that through disruption of the microtubule network, brentuximab vedotin induces apoptotic cell death, and can initiate a localized antitumor immune response (i.e., immunogenic cell death) through the induction of endoplasmic reticulum (ER) stress.[25] Based on these data investigators have hypothesized that brentuximab vedotin could synergize with immune checkpoint inhibitors. To test this hypothesis a phase I/II trial was carried out and the data were recently presented showing that 3mg/kg of nivolumab and 1.8mg/kg brentuximab could be safely administered together every 21 days.[26] This study showed that these agents could be safely delivered together, though an increase in infusion reactions mandated use of premedications prior to BV. Importantly, these investigators observed an overall response rate

of 90% and complete response rate of 62% suggesting at least additivity in anti-tumor response noting that none of the patients on this trial were known to have disease that was refractory to either agent. Arm B of this trial will build on these data by evaluating patients with BV-refractory disease and will allow nivolumab refractory patients to be enrolled to truly test the potential synergy of these agents.

2.8 Summary

Data to date indicate that BV can induce remissions in the majority of patients in a 21 day, single dose cycle, but the majority will either not respond or relapse. This protocol is designed to evaluate BV in the setting of BV-refractory disease. The first cohort (Arm A) using BV was evaluated and showed only modest activity and was closed. The second cohort (Arm B) will test the combination of BV with nivolumab in a 21-day cycle. We thus hypothesize that through this iterative multi-arm study we will be able to identify a BV dosing scheme or combination that may show acceptable safely and efficacy in patients with prior BV exposure and importantly BV-resistant disease.

3.0 DRUG INFORMATION

3.1 General Information

Brentuximab vedotin (BV) is a CD30-directed antibody-drug conjugate (ADC) that has been approved by the U.S. Food and Drug Administration (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, and for use in patients with systemic ALCL after failure of at least one prior regimen. BV is marketed in the United States under the name ADCETRIS™ by Seattle Genetics, Inc.

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

Nivolumab will be obtained from commercial sources and administered as standard of care.

3.2 Description

Brentuximab vedotin (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.

Vials containing brentuximab vedotin must be stored under refrigeration at 2-8°C.

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

Nivolumab will be from commercial supplies and all relevant information is available from the package insert.

4.0 STAGING CRITERIA

4.1 The Ann Arbor staging criteria will be utilized. Staging should be the highest stage established from the time of diagnosis.

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.1.1. Relapsed or refractory CD30+ lymphoma that has either achieved <PR to brentuximab vedotin (minimum of 2 cycles), progressed while receiving brentuximab vedotin, or progressed within 6 months of the last dose of brentuximab vedotin.

5.1.2. Documented expression of CD30 on tumor cells

5.1.3. ANC >1,000/µL.

5.1.4. Platelets >50,000/µL.

5.1.5. Serum creatinine <1.5 mg/dL OR creatinine clearance >60 mL/min.

5.1.6. Bilirubin <1.5 x ULN.

5.1.7. AST and ALT <2.5 x ULN.

5.1.8. Measurable disease by CT or similar (e.g. MRI) criteria (>1.5 cm). (Patients with cutaneous lymphoma only require measurable disease by Olsen Criteria[27].)

5.1.9. Resolution of all non-hematologic brentuximab vedotin-related and nivolumab-related AEs to <Grade 2.

5.1.10. Age ≥18 yrs at the time of the first dose of study drug.

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

5.1.12. Patients must be anticipated to complete at least 2 cycles of chemotherapy on study.

5.1.13. Expected survival if untreated of >90 days.

5.2 Exclusion Criteria

5.2.1. Prior transplant within 100 days.

5.2.2. Radioimmunotherapy within 12 weeks.

5.2.3. Known HIV or hepatitis B positivity or prior PML.

5.2.4. Active infection or other medical condition which would preclude treatment in the opinion of the principal investigator. This would include a corrected DLCO of <60% predicted or symptomatic interstitial lung disease.

5.2.5. ECOG performance status >2.

5.2.6. Known active CNS involvement.

5.2.7. Peripheral neuropathy >Grade 1 if due to brentuximab vedotin or any peripheral neuropathy >Grade 2.

5.2.8. Intolerance to brentuximab vedotin.

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

5.2.10. No current or prior autoimmune disease with the exception of vitiligo and autoimmune alopecia (Arm B only).

5.2.11. Pregnancy or breastfeeding. (Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 7 days prior to the first dose of brentuximab vedotin. Females with false positive results and documented verification that the patient is not pregnant are eligible for participation. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraceptive methods during the study and for 6 months following the last dose of brentuximab vedotin or 6 months following the last dose of nivolumab, whichever is later.)

6.0 REGISTRATION

6.1 Patients will be registered by research staff prior to the start of protocol therapy.

7.0 TREATMENT PLAN

7.1 For treatment or dose modification related questions, please contact Dr. Gopal at (206) 606-2037. Dose adjustment of nivolumab may follow the US package insert (opdivo.com)

7.2 Each cycle of therapy is given every 21 days. Up to 4 cycles of chemotherapy will be administered on protocol. Following protocol therapy, patients may go on to receive other therapy at the discretion of their physician. Brentuximab vedotin will no longer be supplied by the study.

ARM B (Open to Accrual) EACH CYCLE (UP TO 4 CYCLES TOTAL)				
Chemotherapy	**Treatment Day** (Actual treatment dates may vary up to +/- 2 days)			
	Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
	Day 1	**Day 1**	**Day 1**	**Day 1**
Brentuximab vedotin 1.8mg/kg (maximum 180 mg) over approximately 30 minutes	X	X	X	X
Nivolumab 3 mg/kg	X	X	X	X

7.3 Dose and Administration

Arm B: BV will be administered on Day 1, of each21 day cycle. The dose of BV is 1.8 mg/kg and is administered by outpatient IV infusion given over approximately 30 minutes. In the absence of infusion toxicities, the infusion rate for all patients should be calculated in order to achieve an infusion period of approximately 30 minutes. 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 actual weight except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg (i.e., maximum dose of 180 mg) for these individuals. BV dose should be rounded to the nearest whole number of milligrams.

BV should be given prior to nivo whenever possible if both are given on the same dosing day; a recommend ≥30 minute window should be planned between completion of BV and initiation of nivo infusion.

Dose modification in response to toxicity is described under section 8.0 below.

Nivolumab is administered over 30-60 min as standard of care for relapsed HL and will be obtained from commercial sources. Other drugs should not be co-administered through the same IV line (e.g., brentuximab vedotin).

7.4 Required Premedication and Postmedication

Routine premedication is required prior to the first dose of BV and nivolumab as described below. However, patients who still experience a Grade 1 or Grade 2

infusion-related reaction may receive subsequent BV infusions with additional premedication per institutional standard, as described below.

7.4.1 Nausea/vomiting prophylaxis: Nausea vomiting prophylaxis is not required by this protocol or for this agent; however it may be used per institutional practice.

7.4.2 Infusion reaction prophylaxis: Infusion reaction prophylaxis should include 100mg of hydrocortisone (or equivalent) and 25mg of diphenhydramine (or institutional equivalent) prior to dosing.

7.4.3 Infection prophylaxis: Infection prophylaxis is not required by this protocol or for this agent; however it may be used per institutional practice and could be considered for those with extensive pretreatment (e.g. transplantation, multiple prior therapies), cytopenia (lymphopenia, neutropenia), and/or recurrent infections. In these situations prophylaxis or monitoring for agents such as PCP, HSV, VZV, GNR, and/or CMV could be considered.

7.5 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of BV or nivolumab. All infusions are administered at a site properly equipped and staffed to manage potential infusion-related reactions, including anaphylaxis. Supportive measures will be given as appropriate throughout the treatment according to institutional standards.

A patient who experiences a Grade 1 or Grade 2 infusion-related reaction may receive subsequent BV infusions with additional premedication according to institutional standards.

Criteria for removal from protocol treatment:

7.5.1 Documented progression of disease.

7.5.2 Development of any related Grade 4 non-hematologic toxicity or other dose limiting toxicity as defined under section 8.0.

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

7.5.4 Delay of a treatment cycle for more than 4 weeks due to adverse events.

7.5.5 Completion of protocol treatment (maximum of 4 cycles).

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

8.0 DOSE LIMITING TOXICITIES AND DOSAGE MODIFICATIONS

Parameters for retreatment and treatment modifications are as follows:

8.1 Modifications for Hematologic Toxicity

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 4 weeks until these values are achieved for Day 1 of each cycle. Mid-cycle doses will not require delay due to

hematologic toxicity. Hematopoietic growth factors and blood product support is allowed.

8.2 Modifications for Impaired Renal Function

Serum creatinine must be <1.5mg/dL or an *estimated* or measured creatinine clearance >60 mL/min on Day 1 of each cycle (labs may be drawn up to 3 days prior to Day 1). If these values are not met, treatment may be delayed for up to 4 weeks. If these values do not recover within 4 weeks, the patient will be removed from protocol treatment.

8.3 Modifications for Impaired Liver Function

Total bilirubin must be <1.5 times the upper limit of normal, and ALT and AST <2.5 times the upper limit of normal on Day 1 of each cycle (labs 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 4 weeks, the patient will be removed from protocol treatment.

8.4 Modifications for study treatment-related peripheral neuropathy

Note: these rules apply to **EVERY** dose of study drug and are relevant for treatment-emergent AEs only.

Table 1. Dose Modification Guidelines for Treatment-Related Peripheral Neuropathy

Toxicity	Grade 1	Grade 2	Grade 3 or Grade 4
Neuropathy: Motor	Continue at the same dose and schedule	Withhold dose until toxicity is Grade ≤1 or has returned to baseline. First occurrence: Reduce dose to 1.2mg/kg. Second occurrence: Omit Day 8 dosing from subsequent cycles. Third occurrence: patient will be removed from study.	Discontinue treatment at the discretion of the Sponsor-Investigator.
Neuropathy: Sensory	Continue at the same dose and schedule.	Withhold dose until toxicity is Grade ≤1 or has returned to baseline. First occurrence: Reduce dose to 1.2mg/kg. Second occurrence: Omit Day 8 dosing from subsequent cycles. Third occurrence: patient will be removed from study.	Discontinue treatment at the discretion of the Sponsor-Investigator.

8.5 Modifications for Other Adverse Events

The patient will be removed from protocol treatment for any related Grade 4 non-hematologic toxicity or other dose-limiting toxicity as described.

8.5.1 Patients should receive appropriate medical management for adverse events. Treatments 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 cycles are delayed for more than 4 weeks due to adverse events, the patient will be removed from protocol treatment.

8.5.2 Management of nivolumab-related adverse events should be per standard of care.

9.0 CONCOMITANT THERAPY

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

9.1 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, however, patients who have not achieved a PR by the mid-course imaging AND have > 1 site of measurable disease may receive low dose (up to 4Gy) radiation to a solitary site at the discretion of the treating investigator. Responding radiated sites will not be included in response assessments.
- Topical and inhaled corticosteroids to treat other medical conditions are allowed. Systemic corticosteroids up to the equivalent of 20 mg prednisone per day are allowed. Intermittent corticosteroid usage to treat infusion reactions is allowed.

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

10.0 CORRELATIVE STUDIES

10.1 Correlative studies will include a peripheral blood at baseline and Day 1 (+/- 2 days) of each cycle and up to 10 unstained slides of diagnostic tumor tissue, if available. These assays can include assessment for PD1/PDL1 expression, T-cell subsets, and cytokines and will be correlated with clinical endpoints in an exploratory, hypothesis-generating fashion.

11.0 STUDY CALENDAR

Required Studies	**Pre-Entry (Within 4 weeks of enrollment unless indicated otherwise)**	**Within 3 Days Prior to Each Cycle**	**Post Cycle 2**	**Post Therapy[7]**	**Follow-Up**
Physical					
Medical history	X				
Physical exam	X	X[10]		X[7]	X[8]

Performance status	X	X[10]		X[7]	
Clinical disease assessment	X	X[10]		X[7]	
Adverse event assessment	X	X[10]		X[7]	
Cardiology					
EKG	X				
Lab					
CBC with differential, platelets	X	X[10]		X[7]	
Serum creatinine, total bilirubin, SGOT (AST), electrolytes, glucose	X	X[10]		X[7]	
TSH	X			X	
Albumin *(Hodgkin's lymphoma)*	X[1]				
LDH	X[2]			X[7]	
Bone marrow studies	X[3]			X[3,7]	
Pregnancy test	X[9]				
Molecular studies	X[4]			X[4,7]	
Correlative Studies	X[14]	X[14]			
Lymph node (tumor) biopsy to assess CD30 expression	X[11]				
PFT with DLCO	X[12]				
Pregnancy test	X[13]				
Radiology					
CT chest, abdomen and pelvis; CT neck if cervical adenopathy present	X		X[5]	X[5,7]	
PET/CT	X[6]			X[6,7]	

[1] Albumin is *recommended* in patients with Hodgkin's lymphoma for documenting staging/prognostic criteria
[2] LDH must be done within 14 days prior to study entry.
[3] Bone Marrow Studies include aspirate and unilateral or bilateral biopsy, flow cytometry if clinically indicated. If all bone marrow studies are negative at enrollment, these do not need to be repeated at completion of the study. Baseline bone marrow may be waived with PI or Sub-Investigator's approval. Patients who do not have bone marrow studies done at baseline will need to have bone marrow studies at completion of treatment to confirm CR if needed.
[4] Molecular Studies: May be done on blood or bone marrow at enrollment and at completion of the study at the discretion of the treating physician and availability of such testing. If these studies are negative at enrollment, they do not need to be repeated.
[5]CT scans are required post cycle 2 and post therapy.
[6] PET scans are strongly recommended pre-therapy and are required post therapy to confirm CR.
[7] Post therapy studies should be done 3 - 5 weeks post cycle 4 or after the patient's last cycle, whichever comes first, unless clinically indicated.
[8] Follow-up should be done as per the clinical standard of care. A typical schedule includes every 3 months for 1 year then every 6 months for 4 years (total follow-up time 5 years)
[9] Pregnancy test in women of childbearing potential.
[10] For Cycle 1 Day 1, pre-entry physical exam, 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.
[11] This requirement will be waived for patients who have had a previous lymph node biopsy (documenting CD30 expression or with tissue available for CD30 testing) performed at any time. Additional CD30 expression data from earlier or follow-up clinical records will be used as appropriate for comparison with study entry data.
[12] PFT with DLCO can be within 90 days.
[13]Pregnany test should be within 7 days of the first dose of study drug.

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[14]See Section 10 Correlative Studies for additional information

12.0 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 [24].

The initial response assessment will occur after Cycle 2. After Cycle 2, patients with a complete response (CR), partial response (PR), or stable disease (SD) will be allowed to receive additional cycles of BV using the same schedule and dose adjustments as noted above. Patients who achieve clinical benefit at the discretion of the treating physician and have not experienced unacceptable toxicities may receive up to 4 cycles total on study. Disease assessments should be performed per standard of care, but in general every 2 - 3 cycles and at the conclusion of therapy. PET should be used to evaluate residual masses that were previously FDG-avid whenever possible.

13.0 STATISTICAL CONSIDERATIONS

13.1 The primary objective of the trial is to determine the overall response rate as measured by the Cheson 2007 criteria. Since this a pilot study exploring both the feasibility and potential efficacy of this strategy likely in a range of histologies and clinical scenarios (e.g. primary refractory vs PD after prior response to brentuximab vedotin) no formal statistical measures will be pre-specified. However, we will deem this protocol a "success" if the absolute response rate in this group of patients is ≥20% in Arm A or ≥40% in Arm B. We expect to treat up to 20 patients on each arm in this study.

13.2 Anticipated accrual per Arm: We anticipate accrual of 20 patients over 18 - 24 months. As arm A is closed, we anticipate accruing 20 patients to Arm B.

13.3 Estimated distribution of study population by gender, ethnicity and race.

MAXIMUM ANTICIPATED ENROLLMENT in Arm B			
Ethnic Category	**Sex / Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	8	11	19
Ethnic Category Total of All Subjects*	8	12	20
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	8	11	19
Racial Categories: Total of All Subjects*	8	12	20

14.0 GUIDELINES FOR ADVERSE EVENT MONITORING AND REPORTING

14.1 Definitions

Adverse Event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure.

Serious Adverse Event (SAE) is defined as an AE that results in any of the following outcomes:

- Death;
- A life-threatening AE (i.e,, the patient/subject was, in the view of the initial reporter/investigator, 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: 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 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.

Grade is defined as the severity of the AE. The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version – 4.0 will be used for grading. The following general criteria are used 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 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 is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event (21 CFR 312.23).

Unexpected Adverse Event is defined as an AE that is not consistent in nature or severity with the product information documented in the current Investigator's Brochure or package insert, or in the protocol, consent form, and/or prior reports.

Note: The following events are ***not*** identified as AEs in this study:

- Disease progression or relapse. However, clinical events associated with progression/relapse may be reportable as AEs.
- Medical or surgical procedures in and of themselves, including those that require hospitalization (e.g., surgery, endoscopy, biopsy procedures) are not considered AEs. However, an event or condition requiring such procedures may be an AE.
- Abnormal laboratory values will be identified and recorded as AEs only if clinical intervention is required as a result.

14.2 Adverse Event Monitoring

AEs of Grade 3 and above, and 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 100 days after the last dose of nivolumab whichever is later or until the patient receives an alternative anti-cancer therapy.. AEs related to lymph node (tumor) 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 Sponsor-Investigator will assess AE grading, attribution, and expectedness.

14.3 Expedited Reporting Requirements

Expedited reporting will be conducted in accordance with FHCC/Cancer Consortium IRB policies, FDA regulations, and agreements with Seattle Genetics. Reportable events and required time frames include:

Individual expedited SAE reports required by competent health authority (i.e. FDA, Health Canada)	At time of submission to competent authority: Seattle Genetics Drug Safety by: Facsimile (425) 527-4308 or (866) 333-6627 (USA only toll free) Email: drug.safety@seagen.com
Cumulative aggregate listing of all SAEs	Monthly: IST@seagen.com or portal

Reporting Timeframe: The Sponsor-Investigator will report all Serious Adverse Event (SAE)s that occur in a study subject within the following timeframe:

- SAEs/Suspected Adverse Reactions that are *fatal or life-threatening*, will be reported to the FDA as an IND Safety Report (via narrative report or MedWatch form 3500A) within 7 calendar days of the Sponsor-Investigator's awareness of the event including assessment of causality to the Product. Notification to the FDA will be submitted concurrently to Seattle Genetics.
- SAEs/Suspected Adverse Reactions that are *unexpected,* will be reported to the FDA as an IND Safety Report (via narrative report or MedWatch form 3500A) within 15 calendar days of the Sponsor-Investigator's awareness of the event including assessment of causality to the Product. Notification to the FDA will be submitted concurrently to Seattle Genetics.
- AEs that are *unexpected*, *possibly, probably or definitely related to the study drug*, and *serious or suggest a risk of greater harm from the research than previously known* will be reported to the IRB within 10 calendar days of the Sponsor-Investigator's awareness of the event.
- **Reporting Period:** The reportable events that are subject to this provision are those that occur from the start of administration of the first dose of the

Product through thirty (30) days after discontinuation of the Product. SAEs occurring more than thirty (30) days after discontinuation of the Product that are assessed by the Sponsor-Investigator as related to the Product should also be reported.

- **Pregnancy Reporting Requirements:** Based on the estimated date of conception, all pregnancies that occur from time of informed consent to within 30 days of last study drug dose, including any pregnancies that occur in the partner of a male study patient, are required to be reported to SGI within 7 days of becoming aware of such pregnancy. At the time of reporting SGI will provide the Sponsor-Investigator a Pregnancy Reporting form for collecting information. All pregnancies that occur during this time period will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Initial reporting will occur in the time frames noted above. The Sponsor-Investigator will assist Seattle Genetics in investigating any SAE and will provide any follow-up information reasonably requested by Seattle Genetics.

14.4 Routine Reporting Requirements

Routine reporting of adverse events will be conducted in accordance with FHCC/Cancer Consortium IRB policies, FDA regulations, and agreements with Seattle Genetics. This will include annual summary reporting of AEs to the IRB as per the requirements of the Continuation Review Report structure, and annual reporting of the most frequent and most serious AEs to the FDA as part of annual reporting to the IND under the provisions of 21 CFR 312.33. Annual reports to the FDA will be submitted concurrently to Seattle Genetics.

15.0 DATA AND SAFETY MONITORING PLAN

Ongoing trial oversight is carried out by the Principal Investigator and the study coordinator. These individuals will meet on a regular basis to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

Institutional support of trial monitoring is provided in accordance with the FHCC Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, the FHCC Clinical Research Support office coordinates monitoring for data accuracy and compliance by consultants, contract research organizations, or FHCC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits. In addition, protocols are reviewed at least annually by the Data and Safety Monitoring Committee (DSMC) and the Institutional Review Board (IRB). The DSMC reviews accrual, adverse events, stopping rules, and adherence to the data and safety monitoring plan for studies actively enrolling or treating patients. The

FHCC/Cancer Consortium IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of both committees as applicable is necessary to continue the study.

This protocol does not require a separate data safety monitoring board. The trial will comply with the standard guidelines set forth by the regulatory committees of the FHCC (Scientific Review Committee, IRB, DSMC) and other state and federal guidelines.

16.0 RECORDS

Research staff under the supervision of the investigators 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).

17.0 REGULATORY RESPONSIBILITIES OF SPONSOR-INVESTIGATOR

The Sponsor-Investigator of the IND and protocol will ensure that the study is conducted in accordance with all applicable institutional, state, and federal regulatory requirements, including, but not limited to: compliance with requirements for IRB and other regulatory approvals, monitoring responsibilities, reporting obligations, and compliance with standards for written informed consent from all patients entering the study.

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