Masonic Cancer Center
University of Minnesota

Phase II Study of Brentuximab Vedotin and Bevacizumab in Men with Refractory CD-30 Positive Germ Cell Tumors

CPRC #2015LS190
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Revision History

Revision #	Version Date	Summary of Changes	Consent Revision
	07/08/2016	Original to CPRC	n/a
	10/10/2016	In response to CPRC stipulations	n/a
	11/02/2016	Replace BV with full name at study sponsor's request Original to IRB and FDA	n/a
1	05/10/2017	Added clarification to follow-up activities, as follows: • AEs that are probably or definitely related to study treatment will be followed until resolution or until initiation of new anti-cancer therapy, whichever is sooner. • Follow-up data includes survival and initiation of new cancer therapy Clarified the proteinuria eligibility criteria and dose hold requirements. Page 4 - Listed the participating institutions and key personnel. Added signature line for IND-sponsor to review eligibility checklists from affiliate sites. Clarified Study Calendar to state that the pre-screening activity does not fall into the 28 day screening window Minor clarifications throughout.	No

Table of Contents

Key Study Personnel Contact Information

Site	Contact Information	Role
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Refer to the Procedures Manual for Affiliate Sites for a complete list of study personnel and contact information.

List of Key Abbreviations

AE	adverse event
AFP	alpha-fetoprotein
ANC	absolute neutrophil count
bHCG	beta human chorionic gonadotropin
CD-30	antigen-30
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTCs	circulating tumor cells
CTO	Clinical Trials Office
CYP3A4	cytochrome P450 3A4
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food And Drug Administration
GCT	germ cell tumors
GFR	glomerular filtration rate
IHC	immunohistochemistry
IND	Investigational New Drug
IV	intravenous
Kg	kilogram
LDH	lactate dehydrogenase
MCC	Masonic Cancer Center
MMAE	Monomethyl auristatin E
MTD	maximum tolerated dose
OS	overall survival
PD	progressive disease
PFS	progression free survival
P-gp	P-glycoprotein
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAEs	serious adverse event
SD	stable disease
VDGF	vascular endothelial growth factor

Protocol Synopsis

Title:	Phase II Study of Brentuximab Vedotin and Bevacizumab in Men with Refractory CD-30 Positive Germ Cell Tumors
Study Phase:	II
Study Design:	Multi-center phase II study of brentuximab vedotin in combination with bevacizumab for the treatment of refractory CD-30+ germ cell tumors (GCT) in men, after prior treatment with 2 or more lines of platinum-based chemotherapy, or at least 1 line of platinum-based chemotherapy if patient is ineligible for further platinum based chemotherapy or refuses 2nd line platinum based chemotherapy. For primary mediastinal germ cell tumors, failure of first-line platinum based chemotherapy will be accepted. Brentuximab vedotin and bevacizumab will be administered every 21 days until disease progression or unacceptable toxicity.
Primary Objective:	Objective response rate
Secondary Objectives:	1. Safety and tolerability of brentuximab vedotin and bevacizumab in CD-30+ refractory GCT 2. To evaluate progression free survival 3. To determine overall survival
Exploratory Objectives:	1. To study the expression of CD-30 in tumor and blood and VEGF in blood and correlate with clinical outcomes 2. To assess for circulating tumor cells (CTCs) and correlate with clinical outcomes.
Enrollment:	21 patients over 3 years

1 Objectives

1.1 Primary Objective

To determine the efficacy of brentuximab vedotin and bevacizumab when given in combination for the treatment of refractory CD-30+ germ cell tumors (GCT) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

1.2 Secondary Objectives

- To evaluate safety and tolerability of brentuximab vedotin and bevacizumab in CD-30+ refractory GCT
- To evaluate progression free survival
- To determine overall survival

1.3 Exploratory Objective

- To study the expression of CD-30 in tumor and blood and VEGF in blood and correlate with clinical outcomes
- To assess for circulating tumor cells (CTCs) and correlate with clinical outcomes.

2 Background and Rationale

2.1 Refractory Germ Cell Tumors

There is no standard for salvage therapy for refractory germ cell tumors (GCT) after failure of 2nd line chemotherapy. Typical second-line chemotherapy regimens include vinblastine, ifosfamide, and cisplatin (VeIP) and paclitaxel, ifosfamide, and cisplatin (TIP), with gemcitabine, paclitaxel, and oxaliplatin usually reserved for subsequent administration and there is no standard for subsequent therapies. (1-16) Complete responses with third-line or later salvage chemotherapy for GTCs are seen in only less than 10 % patients and are short-lived. Patients progressing after several lines of chemotherapy, including high dose chemotherapy have a dismal prognosis and die from disease. Novel targeted therapies and combination strategies are urgently needed for this patient population with a goal of improving outcomes where currently no curative treatment exists.

2.2 CD-30 and VEGF and Germ Cell Tumors

Cluster of Differentiation antigen-30 (CD-30) is expressed in untreated embryonal carcinoma, implicating that CD-30 is a rational target in this disease. In addition, CD-30 staining was retained in over 70% cases of embryonal carcinoma even after various lines of chemotherapy and high dose chemotherapy, making this a suitable target for refractory CD-30 expressing GCT (embryonal carcinoma or GCT with embryonal component) (17)

Angiogenesis is essential for tumor growth and metastasis and vascular endothelial growth factor (VEGF) expression is involved in tumor development, angiogenesis, and metastasis in GCT.(18)

In an ongoing phase 2 study of monotherapy in patients with CD-30+ heavily pretreated GCT (embryonal carcinoma) who were refractory to treatment, there is evidence of clinical benefit and was well tolerated. (19)

Targeting VEGF with bevacizumab, a monoclonal antibody to VEGF has shown promising activity in GCT. (20, 21)

Moreover, inhibition of VEGF can reduce tumor vessel permeability, remodeling the tumor vasculature, and restoring tumor interstitial pressure. This may potentially help improve drug delivery of other agents. (21) Based on these preclinical and clinical findings, combination of brentuximab vedotin and bevacizumab may be synergistic in refractory CD-30+ GCT and do not have any potential overlapping toxicities. This combination would also help spare heavily pretreated patients with toxicity from conventional cytotoxic chemotherapies.

2.3 Brentuximab Vedotin

Brentuximab Vedotin (formerly SGN-35) is a novel antibody drug conjugate that combines the agent mono-methyl auristatin E (MMAE) to a CD-30 specific monoclonal antibody by a protease-cleavable linker. After binding to CD-30, brentuximab vedotin in internalized and processed into lysosomal vesicles leading to the release of MMAE from the antibody by reduction or acid hydrolysis within the lysosomes. Subsequently, MMAE is released into cytoplasm and inhibits microtubule polymerization leading to cell cycle arrest followed by cell death (Figure 1). As HRS cells die, a small amount of MMAE is released into the tumor microenvironment which can kill neighboring cells by a CD-30-independent manner. It is approved by the FDA for treatment of relapsed Hodgkin lymphoma and anaplastic large cell lymphoma. Efficacy data for brentuximab vedotin are available from two noncomparative multicentre, phase II trials; one in patients with Hodgkin lymphoma who had relapsed after HDCT/ASCT (22) and one in patients with relapsed systemic ALCL after at least one prior treatment.(23) In both trials, patients received intravenous brentuximab vedotin 1.8 mg/kg every 3 weeks, based on results from a phase I, dose-escalation trial in 45 patients with relapsed or refractory CD-30-positive haematologic cancers showing this to be the maximum tolerated dose (MTD). (24)The most commonly reported treatment-related adverse events of any grade were peripheral sensory neuropathy, nausea, fatigue, pyrexia, and diarrhea. Treatment-emergent grade 3 adverse events occurring included neutropenia (14 %) and peripheral sensory neuropathy (8 %). The only treatment-emergent grade 4 adverse event that was reported was neutropenia (6 %). No cases of febrile neutropenia were reported. No deaths were attributed to brentuximab vedotin treatment. (22, 23)

2.4 Bevacizumab

Bevacizumab is a humanized monoclonal neutralizing antibody binding all 5 isoforms of human VEGF. It has been shown to bind to VEGF-A with high affinity and neutralize its activity. Inhibition of angiogenesis resulted in reduced tumor growth in many ex vivo models of pediatric and adult malignancies. Bevacizumab is an effective therapeutic agent in multiple types of human cancer in which VEGF-dependent angiogenesis plays an important role in tumor cell survival. (25, 26) Bevacizumab is currently approved for a variety of cancers. (27)

2.5 Study Rationale

The preclinical and clinical data of brentuximab vedotin and bevacizumab in GCT support the concept that combination of brentuximab vedotin and bevacizumab may be synergistic in refractory GCT without potential overlapping toxicities.

3 Study Design

This is a multi-center phase II study of brentuximab vedotin in combination with bevacizumab for the treatment of refractory CD-30+ GCT after disease progression on imaging and/or tumor marker progression documented by serially rising AFP or bHCG measured on at least 2 consecutive visits and determined by treating physician to be clinically significant. Patients unable to receive 2nd line of platinum-based chemotherapy due to toxicity or refusal would also be eligible.

This study will enroll patients with CD-30 expressing GCTs; any level of expression of CD-30 (≥ 1%) will be allowed, as there has been no correlation between higher expression of CD-30 and clinical responses with brentuximab vedotin. The genitourinary pathologists at local sites will assess for CD-30 expression as per their standard procedure and report presence of CD 30 and scoring if applicable.

Patients must have received 2 or more lines of platinum-based chemotherapy, or at least 1 line of platinum-based chemotherapy if patient is ineligible for further platinum based chemotherapy or refuses 2nd line platinum based chemotherapy.

For primary mediastinal germ cell tumors, failure of first-line chemotherapy will be accepted.

Brentuximab vedotin and bevacizumab will be given once every 21 days until disease progression, unacceptable toxicity or patient refusal. A disease reassessment will be done every 2 treatment cycles.

4 Patient Selection

4.1 Inclusion Criteria

4.1.1 Male, ≥ 18 years of age

4.1.2 Diagnosis of CD-30 positive GCT. CD-30 expression will be tested by immunohistochemistry (IHC) in archival or fresh tumor tissue as is routinely done for diagnosis.

4.1.3 Disease progression on imaging or tumor marker progression (clinical significance of tumor marker progression to be decided per the discretion of treating physician) after at least 2 lines of platinum-based chemotherapies unless patient is ineligible for further platinum based chemotherapy or refuses 2nd line platinum based chemotherapy due to toxicity. For primary mediastinal germ cell tumors, failure of first-line chemotherapy will be accepted. Prior high dose chemotherapy with hematopoietic stem cell rescue is allowed. Prior treatment with bevacizumab is allowed.

4.1.4 At least 3 weeks should have elapsed since the last treatment (e.g. chemotherapy, targeted small molecule therapy, immunotherapy or radiation) and must have recovered to grade 1 or better from the acute effects of prior therapy.

4.1.5 Presence of measurable disease according to RECIST 1.1 (Section 9)

4.1.6 ECOG performance status 0 or 1

4.1.7 Adequate marrow and organ function within 28 days prior to study registration as defined below:

- Leukocytes ≥ 3,000/μL
- ANC ≥ 1500/μL
- Hemoglobin ≥ 9 g/dL
  Note: Blood transfusion will be allowed for patients with hemoglobin < 9 g/dl and G-CSF is allowed for neutropenic patients at time of enrollment.
- Platelets > 100,000/mm^3
- Creatinine: ≤3mg/dl OR if serum creatinine > 3 mg/dl, estimated GFR >30 mL/min/1.73m^2
- INR: <1.5 x institutional upper limit of normal OR < 3 if on warfarin or other anticoagulants. There should be no evidence of active bleeding while on anticoagulants.
- Total bilirubin: ≤ 2 x institutional upper limit of normal (ULN)
- SGOT (AST) or SGPT (ALT): < 3 x institutional upper limit of normal (< 5 x ULN if liver metastases present)
- If patient has proteinuria, it should be <2+ (< 100 mg/dl or per institutional guidelines). If proteinuria is 2+ or greater (≥ 100 mg/dl per

institutional guidelines), patients should undergo a 24- hour urine collection and 24 hour urinary protein should be less than < 2 grams.

4.1.8 Sexually active men with partners of women of childbearing potential must agree to practice effective methods of contraception during the study and for 6 months after the last treatment

4.1.9 Provide voluntary written consent and HIPAA authorization for release of personal health information, approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC)

4.2 Exclusion Criteria

4.2.1 Prior treatment with BV.

4.2.2 Known active brain metastases and or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided brain metastases are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study registration. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

4.2.3 History of blood clots, pulmonary embolism, or deep vein thrombosis in previous 6 months unless controlled by anticoagulant treatment

4.2.4 Known history of HIV

4.2.5 Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)

4.2.6 Received a live vaccine within 1 week prior to the first dose of study treatment

4.2.7 Has active autoimmune disease that required systemic treatment with use of disease modifying agents, corticosteroids or immunosuppressive drugs

4.2.8 Any clinically significant active infection that requires systemic treatment at the time of enrollment.

4.2.9 Known allergy to bevacizumab or brentuximab vedotin or any of its excipients

4.2.10 Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction (MI) within 6 months of study registration

4.2.11 History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess in previous 6 months

4.2.12 Prior major surgery within the previous 28 days of study registration and/or presence of any non-healing wound, fracture, or ulcer.

4.2.13 Use of an investigational agent within the previous 28 days of study registration.

4.2.14 Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥150 mmHg and/or diastolic blood pressure (DBP) of ≥ 90mmHg]. Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study registration

4.2.15 Arterial thromboembolic events, including transient ischemic attack (TIA), cerebrovascular accident (CVA), unstable angina, or MI within 6 months of study registration

4.2.16 History of posterior reversible encephalopathy syndrome

4.2.17 Other malignancies unless the patient is considered to be disease-free and has completed therapy for the malignancy > than 6 months prior to study entry

4.2.18 Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures

4.2.19 Concurrent use of rifampin or ketoconazole

5 Patient Registration

To be eligible for registration to this study, the patient must meet the criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record.

5.1 Registration with the University of Minnesota Clinical Trials Office

Upon completion of the screening evaluation, eligibility checklist (appendix I) and obtaining consent, the Site Study Coordinator or designee will enroll the patient in OnCore.

Complete registration information is found in the study's Procedures Manual for Affiliate Sites.

Affiliate sites only: At the time of registration, the signed consent will be uploaded into OnCore as an attachment under the patient's record within the study.

Affiliates are responsible for fulfilling any local registration requirements.

5.2 Patients Who Are Registered and Do Not Receive Study Treatment

If a patient is registered to the study and is later found not able to begin study treatment, the patient will be removed from study and treated at the physician's discretion. The reason for removal from study prior to starting study treatment will be clearly indicated in OnCore. The patient will be replaced to complete enrollment.

6 Study Drug Administration

Drug	Administration Sequence	Dose And Frequency
bevacizumab	1st	15 mg/kg every 21 days
brentuximab vedotin	2nd	Dose level 1: 1.8 mg/kg every 21 days (up to 180 mg)
		Dose level -1 :1.2 mg/kg every 21 days (up to 120 mg)

Infusions may be given +/- 3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc.

6.1 Bevacizumab

Bevacizumab will be administered at a dose of 15 mg/kg IV every 21 days; over 90 minutes during 1st infusion, over 60 minutes as 2nd infusion and over 30 minutes for subsequent infusions if prior infusions well tolerated.

If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well-tolerated. Patients may receive premedication with diphenhydramine 25 to 50 mg intravenously 30 minutes prior to bevacizumab if they have previously experienced allergic reactions. Stop infusion if a grade 3, or 4 infusion reaction occurs and administer appropriate medical therapy per institutional standards.

6.2 Brentuximab Vedotin

Brentuximab vedotin will be administered first at 1.8 mg/kg (maximum dose of 180 mg) IV over 30 minutes every 21 days.

Dosing is based on patient's weight according to the institutional standard and actual weight will be used except for patients weighing greater than 100 kg. The dose for patients with weight greater than 100 kg will be calculated based on 100 kg (180 mg).

Patients will be monitored for infusion related reactions. If anaphylaxis occurs, brentuximab vedotin will be immediately and permanently discontinued and appropriate medical therapy will be administered with 100 mg methylprednisolone IV, diphenhydramine 25 mg IV, or 0.3cc epinephrine (1:1000) IV.

If any other infusion related reaction occurs, infusion should be stopped and appropriate medical management initiated and then infusion may be resumed. Patients who experience infusion-related reactions should receive premedication which may include acetaminophen, antihistamine and corticosteroid for subsequent infusions.

6.3 Dose Modifications and Delays

Bevacizumab: No intra-patient dose reduction will be allowed for bevacizumab; the dose will be 15 mg/kg.

Brentuximab Vedotin: One intra-patient dose reduction will be allowed. The brentuximab vedotin dose may be reduced to 1.2 mg/kg if patients are unable to tolerate 1.8 mg/kg dose. If a further dose reduction is needed, treatment will be permanently discontinued.

If one of the study drugs cannot be administered due to reversible toxicity, the patient can receive only the other drug per schedule for up to 3 consecutive cycles. Any patient who cannot resume one of the study drugs after 3 consecutive cycles, will be taken off study. Treatment delays of any particular cycle will be allowed for up to 4 weeks for toxicity or adverse events related or unrelated to study drugs.

6.3.1 Bevacizumab Related Toxicity

Complete list of adverse event can be found in the package insert. (27)

No intra-patient dose reduction will be allowed for bevacizumab; the dose will be 15 mg/kg.
Discontinue bevacizumab permanently per package insert guidelines for:

- gastrointestinal perforations
- wound dehiscence and wound healing complications requiring medical interventions.
- serious hemorrhage (i.e., requiring medical intervention*)*
- life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism
- posterior reversible encephalopathy syndrome (pres)
- nephrotic syndrome
- arterial thromboembolism

Hold bevacizumab temporarily for:

- 4 weeks prior to elective surgery
- severe hypertension not controlled with medical management
- proteinuria:

- If result is 2+ on dipstick urinalysis (≥ 100 mg/dL but ≤ 200 mg/dl or as reported per Institutional guidelines) can give dose per treating physician's discretion. Proceed with a 24 hour urine collection prior to next dose.
- If result is 3+ on dipstick urinalysis (> 200 mg/dl or as reported per Institutional guidelines), withhold dose and recheck 24 hour urine within 3 days prior to next scheduled dose. Resume when proteinuria is < 2 gm/24 hours.

- venous thrombosis: If superficial, continue bevacizumab. If grades 3 or 4 DVT, hold for 2 weeks; restart bevacizumab after 2 weeks if therapeutic dose anticoagulation is stabilized, if no grade 3 or 4 hemorrhage has occurred, and if the tumor does not appear to abut on any major vessel.

6.3.2 Brentuximab Vedotin Related Toxicity

Complete list of adverse events can be found in the pharmacy instructions (version 9, dated October 2015) provided by Seattle Genetics. Refer to it and the Investigator Brochure (version 13, dated October 12, 2015).

The most common adverse reactions (≥20%) are neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting.

Peripheral Neuropathy*:* For new or worsening Grade 2 or 3 neuropathy, brentuximab vedotin should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 peripheral neuropathy, brentuximab vedotin should be discontinued.

Neutropenia: Brentuximab vedotin should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Consider G-CSF prophylaxis for subsequent cycles in patients who experience Grade 3 or 4 neutropenia in the previous cycle. In patients with recurrent Grade 4 neutropenia despite the use of G-CSF prophylaxis, consider dose reduction to 1.2 mg/kg.

Renal Insufficiency: Hold brentuximab vedotin if creatinine clearance is < 30 ml/min. Restart once creatinine clearance is > 30 ml/min

Hepatic Impairment: For Child Pugh A hepatic impairment, decrease brentuximab vedotin dose to 1.2 mg/kg, hold brentuximab vedotin for Child Pugh- B and C hepatic impairment.

6.4 Supportive Care

Supportive care will be provided per institutional guidelines and investigator's discretion.

G-CSF is permitted and is recommended for patients experiencing grade 3 and 4 neutropenia.

Appropriate antibiotics, blood products, fluids, electrolytes and general supportive care may be used as medically appropriate.

No other anti-cancer therapy is permitted during the study period (through the end of treatment visit).

6.5 Duration of Treatment

Treatment may continue until one of the following criteria applies:

- Disease progression, as defined in Section 9
- Prolonged intercurrent illness that prevents further administration of treatment
- Unacceptable AEs
- Treatment delays necessitating taking patient off study, as specified in Section 6.3
- Patient decides to withdraw from the study
- Any changes in patient's condition that render him unacceptable for further treatment in the judgement of the investigator.

6.6 Duration of Study Participation

A final end of treatment visit will occur 28 days (+ /-7 days) after the last dose of BV. However, Adverse Events that are determined to be probably or definitely related to study treatment will be followed until resolution to baseline or until initiation of new anti-cancer therapy, whichever is sooner.

All patients, regardless of disease status at the end of treatment, will be followed for survival and for initiation of new cancer therapy every 3 months for 2 years. Follow-up may be done by record review or patient contact.

7 Study Drug Information

7.1 Bevacizumab (Avastin)

7.1.1 Description

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

Bevacizumab is classified as a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor.

7.1.2 Availability

Commercial supplies of bevacizumab will be used in this study and billed to third party payers. Based on available data of efficacy of bevacizumab in GCT, this is usually approved by third-party payers.

7.1.3 How Supplied

Bevacizumab is supplied in sterile single-use vials individually packaged in a carton (one vial to a carton) containing either 100 mg per 4 mL vial (NDC: 50242-060) or 400 mg per 16 mL vial (NDC: 50242-061).

7.1.4 Storage, Handling, and Accountability

Unopened vials of bevacizumab are stable until the expiration date indicated on the package when stored at 2° to 8ºC (36° to 46ºF). Bevacizumab vials should be protected from light. Do not freeze or shake. Diluted bevacizumab solutions may be stored at 2° to 8ºC (36° to 46ºF) for up to 8 hours. Store in the original carton until time of use. No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed.

7.1.5 Description

Bevacizumab is supplied in a sterile form for intravenous use only. Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. Bevacizumab is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of bevacizumab (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

7.1.6 Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Withdraw necessary amount of bevacizumab and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives. Do not administer as an intravenous push or bolus. Administer only as an IV infusion, as specified in Section 6.1

7.2 Brentuximab Vedotin

7.2.1 Description

Brentuximab vedotin (formerly SGN-35) is a CD-30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD-30; 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.

Each antibody molecule has, on average, two of its interchain disulfides reduced and the resulting cysteine residues alkylated with SGD-1006 Intermediate (enzyme-cleavable linker + MMAE), leading to a molar ratio of four drugs per antibody. Brentuximab vedotin is a heterogeneous mixture of a range of drug-load variants and isoforms. The overall average drug-to-antibody mole ratio (MRD) is approximately 4. The calculated molecular mass for the nominal form of brentuximab vedotin is approximately 153 kDa.

The anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD-30-expressing cells, followed by internalization of the ADC-CD-30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell.

7.2.2 Availability

Brentuximab vedotin will be supplied by Seattle Genetic for the purposes of this study.

7.2.3 Product Description

Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder, supplied in single-use vials. Brentuximab vedotin drug product is reconstituted with water for injection (WFI), USP, or equivalent. The reconstituted brentuximab vedotin drug product is a clear to slightly opalescent, colorless solution with no visible particulate matter.

The reconstituted solution is subsequently diluted in sterile 0.9% Sodium Chloride for Injection, 5% Dextrose Injection, or Lactated Ringer's Injection for intravenous (IV) administration. The diluents should be USP grade or equivalent.

Brentuximab vedotin is the United States Adopted Name (USAN) and the International Nonproprietary Name (INN) assigned to SGN-35. Drug product vials may be labeled as SGN-35 or as brentuximab vedotin; the 2 names can be used interchangeably.

7.2.4 Formulation

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

7.2.5 Vial Storage and Handling

Refrigeration should be set at 2–8°C for storage of vials and solutions containing brentuximab vedotin. Chemical and physical stability of the reconstituted brentuximab vedotin drug product has been demonstrated for 24 hours at 2–8°C and 25°C. However, brentuximab vedotin does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use. Recommended safety measures for the handling and preparation of brentuximab vedotin for Injection include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

7.2.6 Reconstitution

Reconstitute lyophilized brentuximab vedotin by adding 10.5 mL Sterile Water for Injection, USP, or equivalent to the 50 mg vial, directing the stream to the side of the vial. The concentration of reconstituted brentuximab vedotin is 5 mg/mL with a total volume of 11 mL. Gently swirl the vial until contents are completely dissolved. The vial must not be shaken. Slight “bubbling” of the solution upon reconstitution may be observed. Allow the reconstituted vial to settle for a minute to allow bubbles to dissipate. The reconstituted product should be a colorless, clear to slightly opalescent solution with no visible particulates. Refrigeration should be set at 2–8°C for storage of the reconstituted vials. The reconstituted vials must be administered within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

7.2.7 Dose Preparation

1. Transfer the required volume of reconstituted product to a 100 mL to 250 mL infusion bag. (A glass, sterile bottle may be used instead of an infusion bag.) It is recommended that the infusion bag be labeled with the patient number or name, and the drug name and lot number (or kit number in the case of a blinded study). The infusion bag size should allow enough diluent to achieve a concentration of 0.4–1.8 mg/mL. The following bag types are compatible with brentuximab vedotin: polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, polypropylene, or polyethylene. Discard any remaining reconstituted product.

2. Dilute reconstituted product in either 0.9% Sodium Chloride Injection, Lactated Ringer's solution, or dextrose 5% in water (D5W). The diluents should be USP grade or equivalent. The final concentration of brentuximab vedotin in infusion bag should be in the range of 0.4–1.8 mg/mL.
   - Total dose = patient weight x dose level. Note that for patients weighing more than 100 kg, total dose will be calculated using 100 kg.
   - Volume of reconstituted product required = total dose/5 mg per mL
   - Final concentration = total dose/total volume of infusion.

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

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

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

6. Refrigeration should be set at 2–8°C for storage of the prepared dosing solution. The solution must be used within 24 hours.

7.2.8 Disposal

Any partially used vials or prepared dosing solutions may be discarded according to institutional drug disposal procedures. Partially used vials may not be used to provide treatment for a different patient. See the Pharmacy Binder for instructions for disposing of unused vials.

7.2.9 Drug Interactions

CYP3A4 Inhibitors/Inducers: Monomethyl auristatin E (MMAE) is primarily metabolized by CYP3A. Co-administration of brentuximab vedotin with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions. Co-administration of brentuximab vedotin with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

P-gp Inhibitors: Co-administration of brentuximab vedotin with P-gp inhibitors may increase exposure to Monomethyl auristatin E (MMAE). Patients who are receiving P-gp inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions.

Effect of Brentuximab Vedotin on Other Drugs: Co-administration of brentuximab vedotin did not affect exposure to midazolam, a CYP3A4 substrate. MMAE does not inhibit other CYP enzymes at relevant clinical concentrations. Brentuximab vedotin is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

8 Study Calendar/Procedures

8.1 Study Calendar

	Screening 28 days prior to starting C1	Cycle 1 Day 1	Cycles 2-6 Day 1 (+/- 3 days)	Cycle 7 and beyond Day 1 (+/- 3 days)	End of Treatment visit within 28 days (+/- 7 days) of last treatment	Follow-up for 2 years
pre-screening consent [1]	X					
Consent	X					
screening assessment	X					
demographics	X					
medical history	X	X			X	
concurrent medications	X	X	X	X	X	
physical exam	X	X	X	X	X	
vital signs	X	X	X	X	X	
weight	X	X	**X**	X	X	
ECOG PS	X	X	**X**	X	X	
CBC with diff	X	X	X	X	X	
AFP, bHCG, LDH	X	X	X	X	X	
CMP [6], uric acid, magnesium, phos	X	X	X	X	X	
coagulation studies including PT, PTT,INR	X	X	X	X	X	
Urinary protein	X	X	X	X	X	
Adverse event evaluation		X	X	X	X	**X**[7]
Radiologic evaluation [2, 3]	X		X	X	X	
Brentuximab Vedotin		X	X	X		
Bevacizumab		X	**X**	X		
Follow-up						X[8] (every 3 months by record review or phone)
Archival tissue	X[1, 4]					
Tumor Biopsy	X[1, 4]				R[5]	
Serum CD-30		R (on day of cycle 1 prior to treatment	R (on day of cycle 3 prior to treatment)		R	
Plasma VEGF		R (on day of cycle 1 prior to treatment)	R (on day of cycle 3 prior to treatment)		R	
Circulating tumor cell (CTC) Biocept CTC send out kits		R(on day of cycle 1 prior to treatment)	R (on day of cycle 3 prior to treatment)			

All schedules procedures/visits can be performed +/- 3 days unless specifically mentioned.

[1] Not applicable if the subject's pathology report provides documentation of CD-30 positive expression. The 28 day screening window does not apply to the pre-screening consent.
[2] CT scan of Thorax, Abdomen and Pelvis will be performed after cycle 2, prior to starting cycle 3 and every 2 cycles subsequently.
[3] Scans will be done at end of treatment visit unless they were done 3 weeks prior to end of treatment visit. Bone scans will be done in patients with known bone metastases along with CT thorax, abdomen, and pelvis.
[4] CD-30 expression in archival or fresh tissue (if archival tissue not available) is a requirement for enrollment in the study. The 28 day screening window does not apply to the pre-screening test for CD-30 expression.
[5] Tumor biopsy for patients is strongly encouraged at treatment discontinuation to evaluate for changes in CD-30 expression from baseline.
[6] CMP (comprehensive metabolic panel) consists of albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, glucose, lytes (CO2, Cl, Na, K), total bilirubin, and total protein
[7] Adverse Events that are determined to be probably or definitely related to study treatment will be followed until resolution to baseline or until initiation of new anti-cancer therapy, whichever is sooner.
[8] Follow-up is for survival and for initiation of new cancer therapy

R denotes research related procedures

8.2 Correlatives/Special Studies

8.2.1 CD-30 Expression

CD-30 is expressed in untreated and refractory GCT (embryonal carcinoma or GCT with embryonal features), making it a potential rational therapeutic target. (17) CD-30+ tumors have a poorer prognosis compared to CD-30- tumors. (17) From Angiogenesis is essential for tumor growth and metastasis and VEGF expression is involved in tumor development, angiogenesis, and metastasis in GCT.(18)

This study would aim to correlate CD-30 expression in tumor tissue with clinical response to brentuximab vedotin and bevacizumab. Archival tissue from formalin-fixed, paraffin-embedded, tumor specimen from orchiectomy or any other surgical site will be used for CD-30 evaluation by IHC. If these archival tissues are unavailable or insufficient, a fresh core needle or incisional biopsy from a metastatic lesion would be used for CD-30 evaluation.

Any level of expression (1% or more) will be considered positive for determining eligibility. If pathology report states tumor is CD-30+, that would be sufficient for deeming eligibility.

For correlating responses with expression of CD-30, a scale of 0-3 will be used to score the CD-30 staining (**0**: no staining; **1+**: 1–10% of staining, **2+:** 11–50% of staining; **3+:** >50% of staining). The pathologists at local sites can evaluate the level of expression. Levels of CD-30 expression in tumor tissue will be tested at baseline and end of study tissue biopsy (if applicable) to correlate with clinical outcomes as well as evaluate changes in CD-30 expression after treatment with brentuximab vedotin and bevacizumab.

8.2.2 Serum CD-30 Levels

Serum CD-30 levels on day of cycle 1, cycle 3 and at end of treatment will be measured and correlated with clinical outcomes.

8.2.3 Plasma VEGF Levels

Plasma VEGF level on day of cycle 1, cycle 3 and at end of treatment will be measured and correlated with clinical outcomes.

8.2.4 Circulating Tumor Cells (CTCs)

We propose to assess for CTCs in using a novel CTC and CTDNA detection platform (Biocept) with capability to capture even CTCs with low levels of epithelial markers. (28) CTCs will be assessed on day of cycle1 and cycle 3 prior to treatment with study drugs and will be correlated with clinical outcomes.

9 Measurement of Effect

Patients will be evaluated for response at the end of every 2 cycles (6 weeks).

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

In addition to CT scan to assess for disease evaluation, whole body bone scans will be done for patients with known or suspected bone metastases to assess for bone lesions.

Serologic tumor markers, including AFP, b-HCG and LDH will be measured at baseline and at every cycle. AFP and b-HCG will be used for determining tumor markers trend. Patients with a PR on imaging and normalized or decreasing tumor markers will be classified as PR. PD will be defined as serially rising AFP or bHCG measured on at least 2 consecutive visits (as long as checked at least 3 weeks or later after cycle 1 to avoid false positives form flare-up) or disease progression per RECIST on radiologic imaging, except when there is pathologic evidence of a growing teratoma syndrome. If after an initial response in tumor markers and PR on imaging, there is serial rise in AFP or bHCG, measured on at least 2 consecutive visits, (not explained by any other reasons for a spurious rise in tumor markers), it would constitute as PD.

The decision to continue on study would be based on treating physician's discretion and in case where patients are deriving clinical benefit, they would be allowed to continue on study.

9.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with brentuximab vedotin and bevacizumab.

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

9.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, MRI or calipers by clinical exam.

Note: Tumor lesions that are situated in a previously irradiated area would be considered measurable if lesion has grown in size since radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required,

but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT Scans: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

9.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Serologic tumor markers, including AFP, b-HCG and LDH will be measured at baseline and at every cycle. AFP and b-HCG will be used for determining tumor markers trend. Patients with a PR on imaging and normalized or decreasing tumor markers will be classified as PR. PD will be defined as serially rising AFP or bHCG measured on at least 2 consecutive visits (as long as checked at least 3 weeks or later after cycle 1 to avoid false positives form flare-up) or disease progression per RECIST on radiologic imaging, except when there is pathologic evidence of a growing teratoma syndrome. If after an initial response in tumor markers and PR on imaging, there is serial rise in AFP or bHCG, measured on at least 2 consecutive visits, (not explained by any other reasons for a spurious rise in tumor markers), it would constitute as PD. Treatment continuation decision would be based on treating physician's discretion, what constitutes a clinically significant progression and the decision to continue on

study if patient is deriving clinical benefit. Treatment beyond progression would be allowed if patient deriving clinical benefit.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.**Evaluation of Non-Target Lesions**
Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Treatment continuation decision would be based on treating physician's discretion, what constitutes a clinically significant progression and the decision to continue on study if patient is deriving clinical benefit. Treatment beyond progression would be allowed if patient deriving clinical benefit.

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD

Any	PD	Yes or No	PD
Any	Any	Yes	PD
It would be up to treating physician's discretion to determine overall response after integrating tumor markers as discussed above.			

9.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Overall Survival

Overall survival is the duration of time from enrollment until death from any cause.

10 Adverse Event Monitoring, Documentation and Reporting

Toxicity and adverse events will be classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

The following definitions of adverse events (AEs) and serious adverse events (SAEs) will determine whether the event requires expedited reporting via the OnCore SAE Report Form in addition to routine documentation in the OnCore AE case report form (CRF).

The reporting timeframes for SAEs and other reportable events are located in Section 10.6

10.1 Adverse Event Terminology

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Event: An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization for more than 24 hours or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Event: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Thus, adverse events that occur as part of the disease process (including relapse and death from such) or underlying medical conditions are considered unexpected; and will be reportable per Section 10.3.

Critical and Major Clinical (Protocol/Patient) Deviations as defined by the Masonic Cancer Center:

Critical Deviations:

- Causes subject harm, puts subject at immediate risk of harm or requires medical intervention to prevent harm
- Done to eliminate apparent immediate harm caused by the protocol
- Affects subject's rights or welfare
- Significantly increases risk to subject
- Non-adherence to significant protocol requirements, regulations or GCP guidelines

Major Deviations:

- Changes risk or benefit to one or more subjects
- Leads to a change in the protocol, consent form or study process
- Deviation which is not trivial but does put a subject at immediate risk of harm, or requires medical intervention to prevent harm (pertains to non-adherence to protocol requirements, regulations or GCP guidelines)

10.2 Adverse Event Monitoring and Documentation

The monitoring for adverse events will begin with the 1st dose of study drug through the end of treatment visit.

Since a key outcome parameter of this study is to characterize the toxicities of brentuximab vedotin and bevacizumab when used in combination, adverse event documentation requirements will be determined based on grade, expectedness and relationship to each study drug. In addition, unexpected events and expected events that are not listed in protocol or the consent form must be documented.

All adverse events are to be recorded in the AE Log case report form found in OnCore beginning with the 1st dose of study drug through the end of treatment visit. Adverse Events that are determined to be probably or definitely related to study treatment will be followed until resolution to baseline or until initiation of new anti-cancer therapy, whichever is sooner.

10.3 SAE Documentation and Reporting Requirements

All SAEs are documented using the MCC OnCore SAE Report Form and reported within the timeframes indicated in Section 13.7.

Expedited SAE Reporting Requirements:

Report Within 24 Hours: A subset of SAE's must be reported expeditiously to the Masonic Cancer Center Affiliate Sites Manager within 24 hours of knowledge.

Any event that is both serious and unexpected and at least possibly related to the study treatment requires expedited reporting

10.4 Early Stopping Rule Events Documentation and Reporting Requirements

The following event count toward an early study stopping rule and must be reported to the MCC Affiliate Sites Manager using the Event Form found OnCore under the reports tab:

- Any grade 4 or 5 event with the exception of grade 4 hypertension that is related to study drugs

An event that counts toward an early stopping rule does not necessarily constitute a SAE and should be reported as such only if they meet the criteria for reporting as defined in Section 10.3.

10.5 Other Event Documentation and Reporting Requirements

Deaths, including due to disease, will be recorded as an SAE and reported per Section 10.6. Deaths due to disease should be recorded as a Grade 5 Neoplasm. In addition, the death date and cause must be reported in the patient follow-up tab in OnCore using the comment field in the survival status section to record the cause.

10.6 Institutional Event Reporting Table

Individual institutional sites will be responsible for reporting any event meeting local reporting requirements to their institutional IRB and/or other research oversight committees.

Event Type	Reporting Timeframe	OnCore Form to Use	Report to
SAEs Requiring Expedited Reporting	Within 24 hours of knowledge	SAE Report Form	Masonic Cancer Center (MCC) Affiliate Sites Manager eorchols@umn.edu Local institutional IRB or other entities per institutional policies and guidelines
All other SAEs	Not required	n/a	
Stopping Rule Events	Within 24 hours of knowledge	Event Form	
Major and Critical Clinical Deviations	Within 5 working days of knowledge	Deviation Report Form	

Safety events of interest that may require expedited reporting and/or safety evaluation include, but are not limited to overdose, medication error with or without subject/patient exposure to brentuximab vedotin or bevacizumab.

10.7 MMC Reporting Requirements

As the study sponsor, the Masonic Cancer Center has the following expedited reporting responsibilities for events reported in Section 10.6:

Agency	**Criteria for reporting**	**Timefra me**	**Form to Use**	**Submission address/**	**Copy to:**

				fax numbers	
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	MCC SAE	Submit to FDA as an amendment to IND	Seattle Genetics Drug Safety by: Facsimile (425) 527-4308 or (866) 333-6627 (USA only toll free) Email: drug.safety@seagen.com
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar -Days			
Masonic Cancer Center SAE Coordinator	Events that count toward the early study stopping rule.	At time of reporting	Event Form	SAE Coordinator mcc-saes@umn.edu	Not applicable
Seattle Genetics	**Aggregate listing of all SAEs -** SAE log must include SAEs reported expeditiously to FDA and Seattle Genetics, in addition al all other SAEs. Subject identifier, event term, start date and attribution to treatment must match the expedited report information to allow Drug Safety staff at Seattle Genetics to match reports	monthly	Summary format	IST@seagen.com or portal	with a copy to each participating institution

The SAE Coordinator will provide the Masonic Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

11 Study Data Collection and Monitoring

11.1 Data Management

This study will report clinical data using The Online Enterprise Research Management Environment (OnCore™), a web based Oracle® database utilizing study specific electronic case report forms. Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore. Patient demographics, patient specific study treatment calendars, adverse events and other information required for IND annual reporting will be placed in OnCore and other databases maintained by the Cancer Center.

11.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Institutional Study Coordinator or designee will be responsible

for registering the patient into OnCore at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

11.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP)

For the purposes of data and safety monitoring, this study is classified as high risk (under a locally held IND – Dr. Gupta as the Sponsor/Investigator (S/I)). Therefore the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the study's progress at least quarterly.
- The S/I will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The S/I will oversee the submission of all reportable adverse events per the definition of reportable in Section 10.7 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, Seattle Genetics, and the FDA.
- The S/I with assistance with the MCC Clinical Trials Office will oversee affiliate site monitoring who will, at a minimum, adhere to the University of Minnesota Masonic Cancer Center's DSMP.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

11.4 Affiliate Site Monitoring

The PI (Dr. Gupta) with the CTO has oversight responsibility for trial monitoring at affiliate sites. Affiliate sites must self-monitor following the University of Minnesota Masonic Cancer Center Data and Safety Monitoring Plan (DSMP - http://z.umn.edu/dmsp) and the CTO Affiliate Site Monitoring SOPs.

The investigator will permit study-related monitoring, audits, and inspections by the study's Principal Investigator and/or IND sponsor and/or any designees, the local IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.5 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at 6 years after the study file is closed with the IRB and FDA.

Please contact the CTO before destroying any study related records.

12 Statistical Considerations

12.1 Study Endpoints

12.1.1 Primary Endpoint

Disease response rate, as defined by the RECIST 1.1 criteria (as defined in Section 9), integrated with tumor marker response.

12.1.2 Secondary Endpoints

- Progression-free survival (as defined in Section 9)
- Overall survival (as defined in Section 9)
- Adverse Events

12.1.3 Correlative Endpoints

- Expression of CD-30 in tumor tissue
- Plasma CD-30 levels
- Serum VEGF levels
- CTCs

12.2 Study Design and Sample Size Considerations

This trial will use Simon's two-stage Minimax design. [30] For the purposes of the design, we specify a null response rate of 0.05 and an alternative hypothesis of 0.20. A total of 21 subjects will be enrolled. In stage 1, we will enroll 12 subjects and the study will stop for futility if 0 out of 12 subjects have a tumor response. In stage 2, we will enroll an additional 9 subjects (for a total of 21 subjects) and reject the null hypothesis if at least 2 of 21 subjects have a tumor response. This design will provide 80% power to reject the null hypothesis of a response rate of 0.05, assuming an alternative hypothesis of a response rate of 0.20 and a type-I error rate of 0.1.

12.3 Analysis

12.3.1 General Considerations

All statistical analyses will be completed using SAS 9.1 (Cary, NC, USA) or the R statistical programming language. [31] P-values less than 0.05 will be considered statistically significant unless otherwise noted.

12.3.2 Description of the Study Population

The study population will be described by summarizing demographic and baseline clinical covariates. Categorical variables will be summarized by counts and percentages, while continuous variables will be summarized by the mean and standard deviation or median and interquartile range, as appropriate.

12.3.3 Analysis of Primary Endpoint

Tumor response will be summarized by the tumor response rate as estimated by the sample proportion with exact 95% confidence intervals. Hypothesis testing of the tumor response rate will be as dictated by Simon's two-stage design (as described in Section 12.2). Secondary analyses of the tumor response rate will involve univariate tests of the association between demographic and baseline clinical and correlative covariates and the tumor response rate using Fisher's exact test or the two-sample t-test, as appropriate. Multivariate analyses will not be completed given the small sample size of the trial.

12.3.4 Analysis of Secondary Endpoints

The primary analysis of secondary endpoints will be primarily descriptive. Survival endpoints (progression-free and overall survival) will be summarized by the Kaplan-Meier curve. In addition, we will also complete a secondary analysis to evaluate the univariate association between demographic and baseline clinical covariates and survival endpoints using Cox proportional hazards regression. Adverse events will be tabulated and the adverse event rate will be summarized by the sample proportion with exact 95% confidence intervals.

12.3.5 Analysis of Correlative Endpoints

We will evaluate the association between expression of CD-30 and VEGF and the primary and secondary outcomes. The association between CD-30 and VEGF expression and tumor response will be analyzed using logistic regression and the association between CD-30 and VEGF expression and survival endpoints (progression-free and overall survival) will be analyzed using Cox proportional hazards regression.

12.4 Safety Monitoring

Pocock-type sequential stopping boundaries will be used to monitor the adverse event rate and accrual will be halted if excessive number of grade 4 or 5 AEs are observed.[29] That is, accrual will be halted if 2 grade 4 or 5 AEs are observed in the first 2 patients, 3 in the first 6 patients, 4 in the first 11 patients, 5 in the first 17 patients or 6 at any point in the trial. This boundary was chosen such that the probability of crossing the stopping boundary is at most 0.05 when the true rate of AEs is equal to the acceptable rate of 0.1. The acceptable rate of adverse events reflects the expected adverse event rates based on the adverse event rate for each agent, individually, and assuming no synergistic AEs. The probability of crossing the stopping boundary is 0.74, assuming

a true Grade 4 or 5 AE rate of 0.30 (related to study drugs), with the exception of grade 4 hypertension from bevacizumab.

13 Conduct of the Study

13.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

13.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

13.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

14 Publications

The study of these patients and results of all laboratory studies are considered private and confidential. The progress and results of this study will not be presented without approval by the Principal Investigator.

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Appendix I – Eligibility Checklist

Phase II Study of Brentuximab Vedotin and Bevacizumab in Men with Refractory CD-30 Positive Germ Cell Tumors (CPRC 2015LS190)
Patient Eligibility Checklist – page 1 of 3

Patient initials: _____ Patient Sequence ID# _____

INCLUSION CRITERIA

A "NO" response to any of the following disqualifies the patient from study entry.

		Yes	No
1.	Male, ≥ 18 years of age	☐	☐
2.	Diagnosis of CD-30 positive GCT. CD-30 expression will be tested by immunohistochemistry (IHC) in archival or fresh tumor tissue as is routinely done for diagnosis	☐	☐
3.	Disease progression on imaging or tumor marker progression (clinical significance of tumor marker progression to be decided per the discretion of treating physician) after at least 2 lines of platinum-based chemotherapies unless patient is ineligible for further platinum based chemotherapy or refuses 2nd line platinum based chemotherapy due to toxicity. For primary mediastinal germ cell tumors, failure of first-line chemotherapy will be accepted. Prior high dose chemotherapy with hematopoietic stem cell rescue is allowed. Prior treatment with bevacizumab is allowed.	☐	☐
4.	At least 3 weeks should have elapsed since the last treatment (e.g. chemotherapy, targeted small molecule therapy, immunotherapy or radiation) and must have recovered to grade 1 or better from the acute effects of prior therapy	☐	☐
5.	Presence of measurable disease according to RECIST 1.1	☐	☐
6.	ECOG performance status 0 or 1	☐	☐
7.	Adequate marrow and organ function within 28 days prior to study registration as defined below: • Leukocytes ≥ 3,000/μL • ANC ≥ 1500/μL • Hemoglobin ≥ 9 g/dL Note: Blood transfusion will be allowed for patients with hemoglobin < 9 g/dl and G-CSF is allowed for neutropenic patients at time of enrollment. • Platelets > 100,000/mm^3 • Creatinine: ≤3mg/dl OR if serum creatinine > 3 mg/dl, estimated GFR >30 mL/min/1.73m^2 • INR: <1.5 x institutional upper limit of normal OR < 3 if on warfarin or other anticoagulants. There should be no evidence of active bleeding while on anticoagulants. • Total bilirubin: ≤ 2 x institutional upper limit of normal (ULN) • SGOT (AST) or SGPT (ALT): < 3 x institutional upper limit of normal (< 5 x ULN if liver metastases present) • If patient has proteinuria, it should be <2+ (< 100 mg/dl or per institutional guidelines). If proteinuria is 2+ or greater (≥ 100 mg/dl per institutional guidelines), patients should undergo a 24- hour urine collection and 24 hour urinary protein should be less than < 2 grams.	☐	☐
8.	Sexually active men with partners of women of childbearing potential must agree to practice effective methods of contraception during the study and for 6 months after the last treatment	☐	☐
9.	Provide voluntary written consent and HIPAA authorization	☐	☐

Phase II Study of Brentuximab Vedotin and Bevacizumab in Men with Refractory CD-30 Positive Germ Cell Tumors (CPRC 2015LS190)

Patient Eligibility Checklist – page 2 of 3

Patient initials: _____ Patient Sequence ID# _____

EXCLUSION CRITERIA

A "YES" response to any of the following disqualifies the patient from study entry.

		Yes	No
10.	Prior treatment with BV	☐	☐
11.	Known active brain metastases and or carcinomatous meningitis.	☐	☐
12.	History of blood clots, pulmonary embolism, or deep vein thrombosis in previous 6 months unless controlled by anticoagulant treatment	☐	☐
13.	Known history of HIV	☐	☐
14.	Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)	☐	☐
15.	Received a live vaccine within 1 week prior to the first dose of study treatment	☐	☐
16.	Has active autoimmune disease that required systemic treatment with use of disease modifying agents, corticosteroids or immunosuppressive drugs	☐	☐
17.	Any clinically significant active infection that requires systemic treatment at the time of enrollment	☐	☐
18.	Known allergy to bevacizumab or brentuximab vedotin or any of its excipients	☐	☐
19.	Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction (MI) within 6 months of study registration.	☐	☐
20.	History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess in previous 6 months	☐	☐
21.	Prior major surgery within the previous 28 days of study registration and/or presence of any non-healing wound, fracture, or ulcer	☐	☐
22.	Use of an investigational agent within the previous 28 days of study registration	☐	☐
23.	Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥150 mmHg and/or diastolic blood pressure (DBP) of ≥ 90mmHg]	☐	☐
24.	Arterial thromboembolic events, including transient ischemic attack (TIA), cerebrovascular accident (CVA), unstable angina, or MI within 6 months of study registration	☐	☐
25.	History of posterior reversible encephalopathy syndrome	☐	☐
26.	Other malignancies unless the patient is considered to be disease-free and has completed therapy for the malignancy > than 6 months prior to study entry	☐	☐
27.	Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures	☐	☐
28.	Concurrent use of rifampin or ketoconazole	☐	☐

Phase II Study of Brentuximab Vedotin and Bevacizumab in Men with Refractory CD-30 Positive Germ Cell Tumors (CPRC 2015LS190)

Patient Eligibility Checklist – page 3 of 3

Patient initials: _____ Patient Sequence ID# _____

Statement of Eligibility

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this patient is eligible.

_____
Printed name of enrolling investigator

_____ _____
Signature of enrolling investigator Date

For Affiliate Sites Only: University of Minnesota Review of Patient Eligibility Checklist

Patient is deemed: ☐ Eligible ☐ Ineligible – reason for ineligibility: _____

_____
Printed name of IND Sponsor-Investigator or Representative

_____ _____
Signature of IND Sponsor-Investigator or Representative Date