



**MELVIN AND BREN SIMON
CANCER CENTER**

INDIANA UNIVERSITY

**A Multicenter Phase II Study of Brentuximab Vedotin in Relapsed/Refractory
Germ Cell Tumors**

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Indiana University Simon Cancer Center and keep a record for your files.

 Signature of Site Investigator

 Date

 Site Investigator Name (printed)

 Site Investigator Title

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CANCER CENTER CLINICAL TRIALS OFFICE**

SYNOPSIS

TITLE	Phase II Study of Brentuximab Vedotin in Relapsed/Refractory Germ Cell Tumors
SHORT TITLE	ADCETRIS in refractory testicular cancer
PHASE	II
OBJECTIVES	<p><u>Primary Objective:</u> To determine the anti-tumor efficacy of brentuximab vedotin in relapsed/refractory NSGCT.</p> <p><u>Secondary Objectives:</u></p> <ol style="list-style-type: none"> 1) To determine the progression free survival in patients with relapsed/refractory NSGCT treated with brentuximab vedotin. 2) To determine the overall survival of patients with relapsed/refractory NSGCT treated with brentuximab vedotin. 3) To determine the safety and tolerability of brentuximab vedotin in this patient population. <p><u>Exploratory Objectives:</u></p> <ol style="list-style-type: none"> 1) To characterize the intensity and localization (cell wall vs. cytoplasmic) of CD30 staining among tumors from patients with relapsed or refractory NSGCT enrolling on the study. 2) To correlate the intensity and localization of tumor staining for CD30 with objective response and progression-free survival for patients enrolling on the study.
STUDY DESIGN	Phase II study with 2 cohorts in parallel using a Simon two-stage design
ELIGIBILITY CRITERIA	<p>Main Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Age \geq 18 years at the time of screening. 2. Patients with histologically or serologically confirmed relapsed/refractory non-seminoma germ cell tumor, (i.e. embryonal carcinoma, choriocarcinoma, or yolk sac tumors) including female GCT and primary mediastinal NSGCT. 3. Patients must have progressed after prior high dose chemotherapy (HDCT) treatment, been deemed not to be a candidate for high dose chemotherapy or refused high-dose chemotherapy, and be considered incurable by other standard therapies including further chemotherapy or surgery. There is no maximum allowable number of previous therapies.

	<ol style="list-style-type: none"> 4. Patients with measurable disease according to RECIST v1.1, or with rising AFP or BHCG above the upper limit of normal on two consecutive determinations if no measurable radiologic disease. 5. Patients with brain metastases are allowed onto the study as long as patients have completed their treatment for brain metastasis, no longer require corticosteroids, and are asymptomatic. Subjects with neurological symptoms should undergo a head CT scan or brain MRI to exclude brain metastasis, at the discretion of the treating physician. 6. Patients with ECOG performance status of 0-2. 7. Adequate organ and marrow function as detailed in the protocol. 8. Patients who are willing and able to comply with the protocol and study procedures including willingness to undergo tumor biopsy for tumor cells before therapy to assess for CD30 status (unless archival tumor tissue from orchiectomy or other previous sample is not obtainable despite efforts to do so and a fresh tumor biopsy is not feasible). <p>Main Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Patients with pure seminoma. 2. Patients with pure teratoma. 3. Chemotherapy within 2 weeks of initiating study treatment. 4. Major surgery within 3 weeks of starting study treatment. There is no minimum time requirement for minor procedures such as biopsy or vascular access placement. 5. Radiation within 2 weeks of starting study treatment. 6. \geq Grade 3 neuropathy at the time of enrollment. 7. Pregnancy or breast-feeding. 8. Previous treatment with any anti-CD30 directed therapy.
<p>STATISTICAL CONSIDERATIONS</p>	<p>a) Definition of primary outcome/endpoint:</p> <p>Objective response rate is the proportion of patients who achieve either a partial or complete response.</p> <p>Complete response is defined as disappearance of all target lesions and normalization of serum tumor markers (AFP and beta-hCG) for at least 4 weeks. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Complete Response must be confirmed four or more weeks after initial CR is observed.</p> <p>In patients whose only evidence of disease is elevated serum tumor markers (AFP or beta-hCG), then values must fall below the upper limit of normal for the assay employed and remain at that level for at least 4 weeks.</p> <p>Partial response is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. This should be present on at least 2 measurements 1 month</p>

apart. The serum tumor markers (AFP and beta-hCG) should be stable or decreasing. Partial Response must be confirmed four or more weeks after initial PR is observed.

In patients whose only evidence of disease is elevated serum tumor markers (AFP or beta-hCG), then values must fall $\geq 90\%$ below baseline pretreatment levels for beta-hCG or 50% decrease below baseline pretreatment levels for AFP and persist for 6 weeks. If both tumor markers are elevated and one falls below 90% the other should fall at least below 50% of baseline pretreatment levels.

b) Definition of secondary outcomes/endpoints:

Progression-free survival (PFS) time is the time measured from the date of initiation of therapy until disease progression or death, whichever comes first. Patients alive and progression-free will be censored at their last follow-up.

Overall survival (OS) is the time measured from the date of initiation of therapy until death, regardless of cause. Patients alive at the time of data analysis will be censored at their last date of contact.

c) Analytic plan for primary objective:

The ORR and its 95% exact CI will be summarized for the total population and by cohort using the F distribution method (Collett 1991).

d) Analytic plan for secondary objectives:

- Both PFS and OS will be estimates using the methods of Kaplan and Meier for each cohort separately.
- Toxicities will be assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The maximum grade of each toxicity will be recorded for each patient over the course of treatment (all cycles). Toxicities will be recorded up until 30 days after the last day of treatment. The incidence of treatment delays, dose reductions, and early discontinuations of treatment due to toxicity or patient choice, will also be recorded as a means of assessing the tolerability of treatment for each cohort.
- CD30 staining will be characterized by intensity (0 to 3+) and by localization (cell wall vs. cytoplasmic) and correlated with response using logistic regression and with PFS using proportional hazards regression.

e) Sample size justification:

An optimal Simon two-stage design will be used for each cohort of patients to differentiate between the null hypothesis that the response rate P is $\leq 5\%$ ($P \leq 0.05$) and the alternative hypothesis that the response rate is $\geq 20\%$ ($P \geq 0.20$). Under this design, the probability of

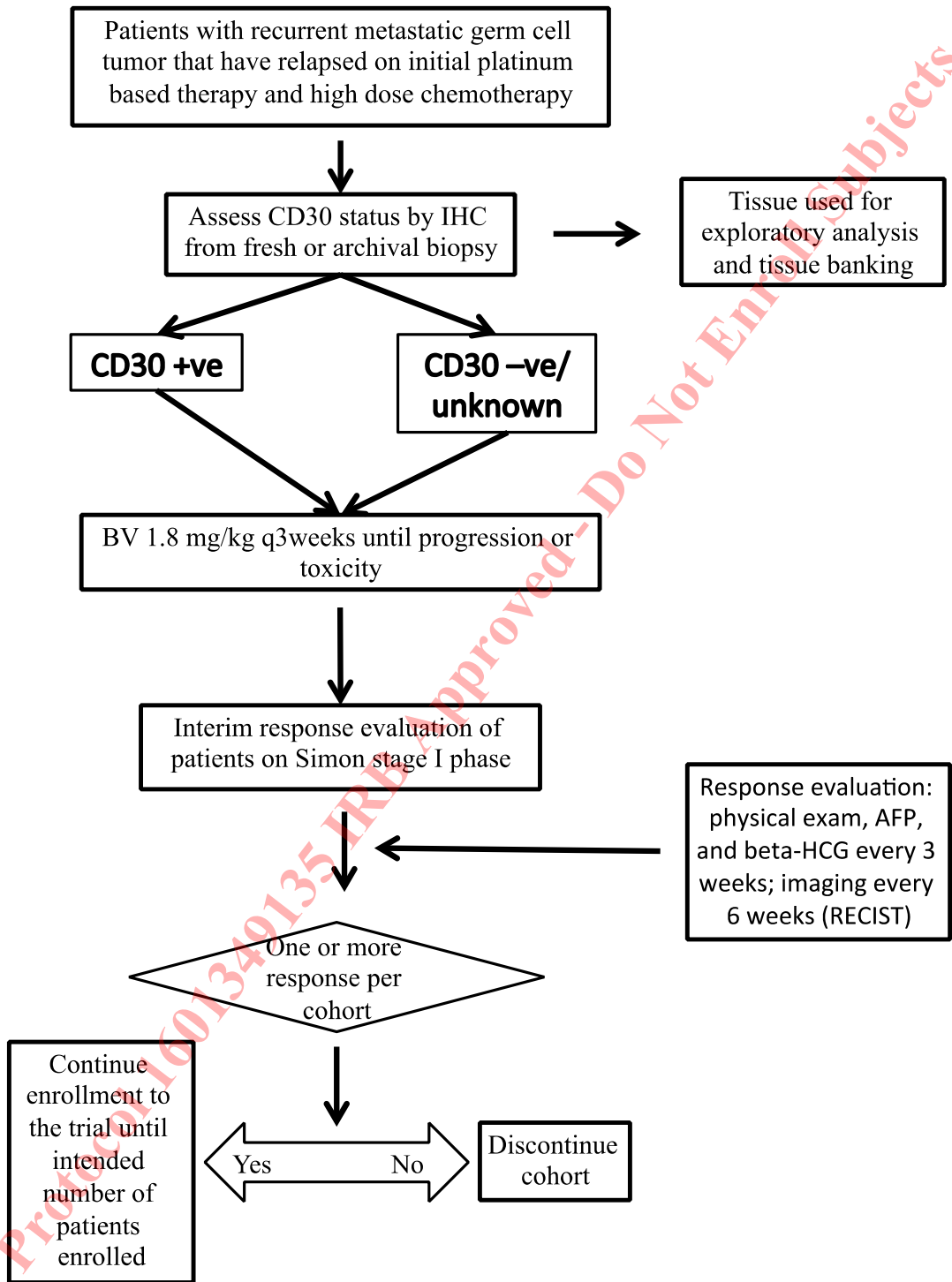
	<p>early termination under the null hypothesis is 0.599. This design yields a type I error rate, α (probability of concluding that the drug is not effective when it is actually effective) of 0.047 and a power of 0.801 (type II error rate 0.199) when the true response rate is $\geq 20\%$. In the first stage in each cohort, 10 patients will be enrolled. If there are no objective responses, then that cohort will terminate. If ≥ 1 response is observed, then an additional 19 patients will be enrolled in the second stage for a total sample size of 29 patients per cohort. If 3 or fewer responses are observed out of the 29 patients, then brentuximab vedotin will be declared as not worthy of further study. If ≥ 4 objective responses are achieved, then brentuximab vedotin will be deemed active in refractory/relapsed NSGCT and worthy of further study.</p> <p>f) Accrual estimation: We estimate enrolling 2 patients/month for the CD30 negative cohort and 1 patient/month for the CD30 positive patients.</p>
TOTAL NUMBER OF SUBJECTS	N = 58 (10 patients in the first stage + 19 patients in the second stage= 29 per cohort x 2 cohorts)
ESTIMATED ENROLLMENT PERIOD	Estimated 24 months
ESTIMATED STUDY DURATION	Estimated 36 months

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SCHEMA



1. BACKGROUND AND RATIONALE

1.1 Relapsed and Refractory Germ Cell Tumors

Germ cell tumors (GCT) are the most common malignancies among men between ages 15 and 35. In 2013, 7,920 cases and 370 deaths were estimated to occur in the United States.(1) Cisplatin-based chemotherapy has transformed this disease from the most common cause of cancer death among young men to a model of curative malignancy.(2) Patients who are not cured with initial platinum-based chemotherapy are usually treated with salvage chemotherapy. Approximately 50% of these testicular cancer patients will subsequently be cured with salvage chemotherapy with tandem transplant of high-dose chemotherapy with peripheral stem cell rescue. Today, with modern chemotherapy and surgery techniques, 80-90% of patients will survive their disease. For the unfortunate 10-20% who are not cured by these measures, there is a desperate need for novel therapeutic agents.

Germ cell tumors of the ovary are very rare. Relapsed ovarian GCT after chemotherapy carries a poor prognosis and there are very few trials that looked at novel therapies for this disease.(3)

1.2 Current Standard of Care

Seven phase 2 clinical trials evaluated single-agents activity in 90 refractory GCT patients at MSKCC showed median progression free survival (PFS) of 4 weeks and median overall survival (OS) of 4 months.(4) Similar experience at Indiana University (IU) showed that chemotherapy post-HDCT result in a response rate of less than 20%, with a median survival time of 8 months. All deaths occurred within 12 months of HDCT.(5) An average of more than 35 years of life is lost when a patient dies from GCT, well over a decade longer than any other adult malignancy. Therefore, there is currently no standard of care for patients who relapse after high-dose chemotherapy and have no surgically resectable disease. The development of novel treatment options for this patient population is needed.

1.3 Brentuximab Vedotin

Brentuximab vedotin (SGN-35 or ADCETRIS) is an antibody-drug conjugate (ADC) consisting of 3 components: 1) the antibody cAC10, specific for human CD30; 2) the potent antimicrotubule agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell. Contributions to the mechanism of action by other antibody-associated functions have not been excluded.(6)

1.3.1 Experience with Brentuximab Vedotin

To date, more than 700 patients have received brentuximab vedotin in 10 completed

clinical studies.

Two phase 2 studies evaluating the efficacy and safety of brentuximab vedotin as a single agent have been performed in patients with relapsed or refractory Hodgkin lymphoma (HL; Study SG035-0003) and systemic anaplastic large cell lymphoma (ALCL; Study SG035-0004). The objective response rate (ORR) for HL patients was 75%, with approximately one-third of patients achieving a complete response/remission (CR) (Seattle Genetics, Clinical Study Report No. SG035-0003, 2010). ALCL patients had an ORR of 86%, with over 50% of patients achieving a CR (Seattle Genetics, Clinical Study Report No. SG035-0004, 2010). In both studies, brentuximab vedotin was generally well tolerated with manageable side effects.

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the Investigator's Brochure.

Brentuximab vedotin is currently FDA-approved in relapsed or refractory Hodgkin's lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma.

1.4 Rationale

CD30 is expressed in the vast majority of testicular embryonal carcinomas.(7-11) Estimates range as high as 93%-98% of cases, with staining in >50% of tumor cells. There have been reports of weak expression of CD30 in yolk sac tumors and primary mediastinal germ cell tumors,(12, 13) though the percentage of cells in primary mediastinal ECs staining positive for CD30 was seen to vary widely, from 5% to >90%. A recent retrospective study found that CD30 expression was retained in patients with non-seminoma germ cell tumors (NSGCT) even after multiple lines of therapy, confirming that it is a reliable treatment target.(14)

Five patients with refractory GCT were recently enrolled on protocol SGN00-001. This study treated CD30-positive nonlymphomatous malignancies with brentuximab vedotin. A clinical benefit was observed in 3 of these patients (1 complete response, 1 partial response and 1 with stable disease). One of these patients achieved a complete response after 4 cycles of treatment and ultimately completed 14 cycles of therapy. He remains disease free at this point, despite being off brentuximab vedotin for more than 16 months (J Clin Oncol 31, 2013 (suppl 6; abstr 327)). A second study is currently evaluating brentuximab vedotin as salvage therapy in refractory GCT but it mandates tumor cells to be CD30-positive (NCT01851200).

We propose a phase 2 study to evaluate activity of brentuximab vedotin in relapsed/refractory NSGCT. For this study we propose treating patients regardless of the tumor's CD30 status. The rationale for this study in CD30-negative patients is that it is unknown whether tumor positivity for CD30 by immunohistochemistry (IHC) is truly predictive of benefit with this agent. In a recent study looking at the activity of brentuximab vedotin in B cell non-Hodgkin lymphoma(15, 16), there was no statistical correlation between response and CD30 expression by central visual IHC or by computer-assisted review. Specifically, in 48 DLBCL patients, the median percent of CD30-positive cells by

visual central review was 25% in the responders vs. 25% in the nonresponders. Twenty-one percent of the responders had <10% CD30 expression. Two patients with DLBCL with ≤1% detectable CD30 expression by central pathologist review achieved CR. Although the precise mechanisms underlying this phenomenon remain unknown, some evidence indicates a 'bystander effect', whereby free MMAE is released from dying cells in concentrations sufficient to kill neighboring tumor cells(17) either directly or indirectly by altering the tumor microenvironment.(18)

Patients will be enrolled into two cohorts, one for CD30 positive patients and one for CD30 negative (or CD30 unknown). CD30 status may be unknown in the unlikely case of tumor-marker-only relapse or when a fresh tumor biopsy is not feasible, and archival tumor tissue is not obtainable despite efforts to do so. We would like to enroll such patients if they are otherwise eligible for the study and would include them in the CD30 negative cohort for analysis purposes, since statistically NSGCT are more likely to be CD30 negative. **The number of such patients with unknown CD30 status should not exceed 5 patients.**

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To determine the anti-tumor efficacy of brentuximab vedotin in relapsed/refractory NSGCT.

2.1.2 Secondary Objectives

- 1) To determine the progression free survival in patients with relapsed/refractory NSGCT treated with brentuximab vedotin.
- 2) To determine the overall survival of patients with relapsed/refractory NSGCT treated with brentuximab vedotin.
- 3) To determine the safety and tolerability of brentuximab vedotin in this patient population.

2.1.3 Correlative/Exploratory Objectives

- 1) To characterize the intensity and localization (cell wall vs. cytoplasmic) of CD30 staining among tumors from patients with relapsed or refractory NSGCT enrolling on the study.
- 2) To correlate the intensity and localization of tumor staining for CD30 with objective response and progression-free survival for patients enrolling on the study.

2.2 Endpoints

2.2.1 Primary Endpoint

Objective response (CR + PR) measured by RECIST Criteria v1.1 if there is measurable disease. In case of no measurable disease (marker-only patients), response can be assessed by either a reduction of BHCG by >90% (with no rise in AFP on two

consecutive measures) or a reduction of AFP by >50% (with no rise in BHCG on two consecutive measures).

2.2.2 Secondary Endpoints

1. Progression-free survival time defined from the start of the treatment until death, criteria for disease progression are met, or last follow-up visit. Overall survival time defined from the start of the treatment until death or last follow-up visit.
2. Toxicity measured by Common Toxicity Criteria 4.0 and need for treatment delay, dose reduction, or early discontinuation.
3. Correlation between tumor CD30 staining intensity/localization and objective response and progression-free survival.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Age \geq 18 years at the time of informed consent.
2. Patients with histologically or serologically confirmed relapsed/refractory non-seminoma germ cell tumor, (i.e., embryonal carcinoma, choriocarcinoma, or yolk sac tumors) including female GCT and primary mediastinal NSGCT.
3. Patients must have progressed after prior high dose chemotherapy (HDCT) treatment, been deemed not to be a candidate for high dose chemotherapy or refused high-dose chemotherapy, and be considered incurable by other standard therapies including further chemotherapy or surgery. There is no maximum allowable number of previous therapies.

“Failure” of prior therapy is defined as:

- a. A >25% increase in the products of perpendicular diameters of measurable tumor masses during prior therapy which are not amenable to surgical resection.
- b. The presence of new tumors which are not amenable to surgical resection.
- c. An increase in AFP or beta-hCG (two separate determinations at least one week apart are required if rising tumor markers are the only evidence of failure).

NOTE: Patients with clinically growing “teratoma” (normal declining tumor markers and radiographic or clinical progression) should be considered for surgery.

4. Patients must have evidence of recurrent or metastatic carcinoma by one or more of the following:
 - i) The appearance of metastatic disease by standard imaging techniques
 - ii) The appearance of rising serum tumor marker, AFP or beta-hCG

- NOTE:** If a rising tumor marker is the only evidence of progressive disease, at least 2 consecutive rising values at least one week apart are needed. Patients with only evidence of disease is rising tumor marker AFP and beta-hCG will be provided alternate causes of increased serum levels of these markers are not present, such as cross reaction with luteinizing Hormone (LH) (that can be tested if needed by testosterone suppression of LH), hepatitis, use of marijuana or second primary tumor, etc.
5. Patients with primary medistinal non seminomatous germ cell tumor are eligible if they have received first line platinum based chemotherapy and their recurrence is not amenable to surgical resection based on the treating physician expert opinion.
 6. Patients with late relapse (>2 years) of non seminomatous germ cell tumors are eligible if they have received first line platinum based chemotherapy and their recurrence is not amenable to surgical resection based on the treating physician expert opinion.
 7. Patients with brain metastases are allowed onto the study as long as patients have completed their treatment for brain metastasis, no longer require corticosteroids, and are asymptomatic. Subjects with neurological symptoms should undergo a head CT scan or brain MRI to exclude brain metastasis, at the discretion of the treating physician.
 8. Patients with ECOG performance status of 0-2.
 9. Adequate organ and marrow function as defined below:
 - a. Hemoglobin ≥ 8 g/dL
 - b. Absolute neutrophil count $\geq 1,000/\text{mm}^3$
 - c. Platelet count $\geq 75,000/\text{mm}^3$
 - d. Total bilirubin $\leq 1.5 \times \text{ULN}$ except patients with documented Gilbert's syndrome ($\leq 3 \times \text{ULN}$)
 - e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times \text{ULN}$; for patients with hepatic metastases, ALT and AST $\leq 5 \times \text{ULN}$
 - f. Calculated creatinine clearance ≥ 30 mL/min as determined by the Cockcroft-Gault equation.
 10. Patients who are willing and able to comply with the protocol and study procedures including willingness to undergo tumor biopsy for tumor cells before therapy to assess for CD30 status (unless archival tumor tissue from orchiectomy or other previous sample is not obtainable despite efforts to do so and a fresh tumor biopsy is not feasible).
 11. Females of childbearing potential must not be pregnant or breast-feeding. Male and female patients of reproductive potential must agree to use *two forms* of highly effective contraception from the screening visit through 28 days after the

last dose of study drug unless patient is practicing true abstinence. Acceptable forms of effective contraception include:

- Oral, injected or implanted hormonal methods of contraception.
- Tubal ligation
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
- Male sterilization (defined as complete retrograde ejaculation or the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.]

Pregnancy tests for females of childbearing potential are required; must be serum at screening and the post treatment safety assessment visit. A positive urine pregnancy test must be confirmed by a serum pregnancy test and a pelvic US since some NSGCT may secrete beta-hCG and cause a false positive pregnancy. A pelvic US does not need to be repeated with each cycle unless the treating physician thinks it is necessary to do so.

12. Potential subject must have the ability to understand (as judged by the treating physician) and willingness to provide written informed consent and HIPAA authorization for release of personal health information.

NOTE: HIPAA authorization may be included in the informed consent or obtained separately. Written informed consent must be obtained from a potential subject prior to the conduct of any study-specific procedures.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Patients with pure seminoma.
2. Patients with pure teratoma.
3. Chemotherapy within 2 weeks of initiating study treatment. There is no maximum allowable number of previous therapies.
4. Major surgery within 3 weeks of starting study treatment. There is no minimum time requirement for minor procedures such as biopsy or vascular access placement.
5. Radiation within 2 weeks of starting study treatment.
6. \geq Grade 3 neuropathy at the time of enrollment.
7. Pregnancy or breast-feeding.
8. Previous treatment with any anti-CD30 directed therapy.

4. SUBJECT REGISTRATION

All patients will be registered with the Indiana University Cancer Center Clinical Trials Office. Regulatory files will be maintained by the Clinical Trials Office. Applicable regulatory documents must be completed and on file prior to registration of any patients. Potential patients will be identified in the Oncology outpatient clinics or by referrals from outside physicians. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the Eligibility Criteria. The original signed IRB approved Informed Consent Document and completed eligibility checklist will be forwarded to the Clinical Trials Office designee for eligibility verification and registration in the OnCore[®] database. Notification will be sent to the principal investigator, treating physician and research nurse when registration is complete to confirm registration and inform them of patient ID number.

Study data will be collected and stored in OnCore[®], developed by Forte Research Systems, Inc. (www.forteresearch.com). OnCore[®] Enterprise Research is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. It has been licensed by Indiana University (IU) to support the operations and data capture of clinical research trials.

The system has been installed and configured within a HIPAA-aligned, Information Technology (IT), operations center supported by IU's IT organization, University Information Technology Services (UITS). OnCore[®] provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

The system is comprised of three specific applications—Clinical Research Management (CRM), Biospecimen Management (BSM), and Unified Registries Management (URM). Indiana University leverages OnCore[®] to support clinical research operations specifically as it relates to the following functions/processes: electronic Scientific Review Committee (SRC), regulatory management, protocol and subject life cycle management, coverage analysis, study financials management, subject registration and visit management, subject safety monitoring, protocol deviation monitoring, study auditing and monitoring, electronic data management, correlative study sample management, specimen banking and management, registries management, effort tracking, and reporting.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within **7 business days** of registration.

5. TREATMENT PLAN

- Eligible patients will be divided into two cohorts, those who are CD30 positive and those who are CD30 negative/unknown. Both groups will be treated similarly and in parallel but analyzed separately.
- CD30 status may be unknown in the unlikely case of tumor-marker-only relapse or when a fresh tumor biopsy is not feasible, and archival tumor tissue is not obtainable

despite efforts to do so. These patients will be included in the CD30 negative cohort for analysis purposes, since statistically NSGCT are more likely to be CD30 negative.

The number of such patients with unknown CD30 status should not exceed 5 patients.

- Enrollment to the study does not have to wait for determination of CD30 status prior to treatment, unless in the situation where one arm is closed for enrollment or an interim assessment of response for the Simon stage I phase is needed. For example:
 - The first 10 patients can enroll on the study and start on therapy without waiting for CD30 status assessment. Prior to enrolling patient number 11, CD30 status need to be determined for all patients to make sure an interim assessment of response for the Simon stage I phase is not needed (i.e. one arm is at 10 patients).
 - If an arm has closed for lack of efficacy, CD30 status need to be assessed prior to starting therapy to make sure that patients belong to the open arm.
 - If both arms advance to the second stage of the Simon design then enrollment can again be pursued without waiting for CD30 status until one arm is closed to accrual.
- Eligible patients will be treated with brentuximab vedotin at 1.8 mg/kg IV every 3 weeks (maximum dose of 180 mg) indefinitely until disease progression, unacceptable toxicity, or study closure.
- Eligible patients with grade 2 peripheral neuropathy at enrollment will be treated with brentuximab vedotin at 1.2 mg/kg IV every 3 weeks (maximum dose of 180 mg) indefinitely until disease progression, unacceptable toxicity, or study closure.
- Response to treatment will be assessed clinically with history, physical exam and tumor markers measurement (BHCG and AFP) on day 1 of each cycle and with CT scans after cycle 2, 4, and every 4 cycles thereafter while receiving treatment.

5.1 Treatments Administered

Brentuximab vedotin (SGN-35), the investigational agent under study in this protocol, is an ADC consisting of the antibody cAC10, specific for human CD30; the potent antimicrotubule agent MMAE; and a protease-cleavable linker that covalently attaches MMAE to cAC10.

5.2 Investigational Study Drug

For injection: 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder in a single-use vial for reconstitution.

5.2.1 Dose and Administration

Brentuximab vedotin, 1.8 mg/kg (1.2 mg/kg in patients with grade 2 peripheral neuropathy at enrollment) will be administered by IV infusion given over approximately 30 minutes on Day 1 of each 21-day cycle. In the absence of infusion-related reactions, the infusion rate for all patients should be calculated in order to achieve a 30-minute infusion period. If an infusion reaction does occur, infusion rates should be adjusted as necessary and documented appropriately in source documents. Brentuximab vedotin must

not be administered as an IV push or bolus. Brentuximab vedotin should not be mixed with other medications.

Dosing is based on patient weight according to the institutional standard; however, doses will be adjusted for patients who experience a $\geq 10\%$ change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

5.2.2 Required Premedication and Postmedication

Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of brentuximab vedotin. However, patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent brentuximab vedotin infusions with premedication as described in Section 5.2.3. Patients who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with brentuximab vedotin at the discretion of the Investigator after discussion with the Sponsor.

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

5.2.3 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for at least 60 minutes following the first infusion of study treatment. During this observation period, an IV line should remain open for at least 60 minutes to allow administration of IV drugs, if necessary for infusion-related reactions. All supportive measures consistent with optimal patient care will be given throughout the study according to institutional standards. This includes adjusting the infusion time if necessary. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment infusions with premedication consisting of acetaminophen and diphenhydramine administered 30–60 minutes prior to each 30-minute infusion or according to institutional standards.

If anaphylaxis occurs, brentuximab vedotin administration should be immediately and permanently discontinued.

5.2.4 Management of Suspected PML

Signs and symptoms of progressive multifocal leukoencephalopathy (PML) may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. See the Investigator's Brochure for further details.

If PML is suspected, hold further brentuximab vedotin dosing and undertake a diagnostic work-up including (but not limited to):

- Neurologic examinations, as warranted
- Brain radiologic features by magnetic resonance imaging (MRI)
- PCR analysis: John Cunningham virus (JCV) DNA detectable in cerebrospinal fluid

If PML is confirmed, permanently discontinue treatment with brentuximab vedotin.

5.3 Concomitant Therapy

All concomitant medications and blood products will be collected from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent. All supportive measures consistent with optimal patient care should be provided throughout the study according to institutional standards.

5.3.1 Required Concomitant Therapy

Pneumocystis carinii (jiroveci) pneumonia (PCP) prophylaxis is required for human immunodeficiency virus (HIV)-positive patients. Medications that aggravate cytopenias (e.g., trimethoprim-sulfamethoxazole) should be avoided.

All patients should be up-to-date on any recommended vaccinations prior to study entry. Additional vaccination(s) during each cycle of study treatment must be approved by the medical monitor.

5.3.2 Allowed Concomitant Therapy

Routine premedication should not be administered prior to the first dose of brentuximab vedotin. However, patients who experience an infusion-related reaction may receive subsequent treatment with premedication as described in Section 5.2.3.

Prophylactic intrathecal therapy is allowed only after discussion with the Sponsor.

For HIV-positive patients, highly active anti-retroviral therapy (HAART) according to the institutional standard of care is permitted.

The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed. The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy. Prednisone (or equivalent) ≤ 20 mg/day may be used if for reasons other than malignant disease control and the patient has been on a stable dose for ≥ 30 days; doses > 20 mg are allowed for treatment of hypersensitivity reactions.

5.3.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications (excluding steroids as described in Section 5.3.2), radiotherapy, or systemic anti-neoplastic therapy during the study.

5.4 Drug Interactions

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5. *In vitro* data indicate that MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp).

5.4.1 Effect of Other Drugs on Brentuximab vedotin

CYP3A4 Inhibitors/Inducers: MMAE is primarily metabolized by CYP3A [see *Clinical Pharmacology (10.2)*]. 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 MMAE. Patients who are receiving P-gp inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse reactions.

5.4.2 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 [see *Clinical Pharmacology (10.2)*]. Brentuximab vedotin is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

5.5 Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays and Dose Modifications

Inpatient dose reduction will be allowed depending on the type and severity of toxicity. [Table 1](#) describes the recommended dose modifications for study treatment-associated

toxicity.

The start of the next cycle may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle. Delays of greater than 4 weeks are prohibited without approval of the Sponsor.

Doses reduced for treatment-related toxicity should not be re-escalated without discussion with the Sponsor.

Table 1 Recommended dose modifications for brentuximab vedotin-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral Neuropathy	Continue at same dose level.	Reduce treatment to 1.2 mg/kg	Withhold until toxicity resolves to \leq Grade 2 or has returned to baseline; resume treatment at 1.2 mg/kg	Discontinue treatment
Nonhematologic	Continue at same dose level.	Continue at same dose level, except in the event of Grade 2 neuropathy.	Withhold dose until toxicity is \leq Grade 2 or has returned to baseline, then resume treatment at the same dose level. ^a	Withhold dose until toxicity is \leq Grade 2 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the Investigator
Hematologic	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is \leq Grade 2, or has returned to baseline, then resume treatment at the same dose level. ^b Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles. If Grade 4 neutropenia recurs despite growth factor support, consider discontinuation or dose	

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
			reduction to 1.2 mg/kg.	

a. Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

b. Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

6.2 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in Section 6.1, a subject will also be discontinued from protocol therapy and followed up per protocol under the following circumstances:

- Evidence of disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
- In case a subject decides to prematurely discontinue protocol therapy (“refuses treatment”), the subject should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- Delays of greater than 4 weeks are prohibited without approval of the Sponsor.

Subjects will be removed from protocol therapy and the site investigator notified when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

6.3 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The treating investigator should contact the subject or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject’s study withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Procedure	Screening ¹ (≤ 28 days before 1 st dose)	Every Cycle (21 days ± 3 days)	Before cycle 3 & cycle 5	Before cycle 9 & then after every 4 cycles	Post Treatment Safety Assessments ⁶	Follow-Up ¹⁰
Informed consent and medical history	X					
Patient Registration	X					
Brentuximab vedotin administration ²		X				
ECOG Performance Status	X	X			X	
Physical exam ³ , vital signs	X	X			X	
Serum AFP and beta-hCG	X	X			X	X ¹²
CBC (differential & platelets)	X	X ^{4,11}			X	
Complete metabolic panel	X	X ⁴			X	
Magnesium and phosphorus	X	X ⁴			X	
Pregnancy test ⁵	X	X			X	
Concomitant medications	X	X			X	
Adverse event monitoring ⁷		X			X	
Radiologic evaluations ⁸	X		X	X		X ¹²
Archival tissue ⁹	X					
Survival						X

Footnotes:

- 1 All procedures are to be performed ≤ 28 days prior to study drug administration. Screening assessments may be used in place of the Cycle 1 Day 1 assessments if performed within 7 days prior to the Day 1 visit. Standard of care procedures may be used for screening requirements if performed within 28 days prior to study drug administration.
- 2 Brentuximab vedotin is administered on Day 1 of each Cycle. First dose must be administered within 7 days of registration.
- 3 Complete physical exam to be performed within 28 days of first study drug administration (for screening requirements), Day 1 Cycle 1 and at Final Safety Follow-up. At other time-points, a brief symptom-directed exam and ECOG performance evaluation are sufficient. At Screening, height is recorded and body surface area (BSA) calculated
- 4 Hematologic and chemistry parameters (including serum creatinine, AST, ALT, BUN, phosphate, bilirubin, calcium & magnesium) to be performed on Day -3 to Day 1 of every cycle.
- 5 Females of childbearing potential only. Pregnancy tests must be serum at screening and the post treatment safety assessment visit. Urine pregnancy tests are required on Day 1 of each Cycle. A positive urine pregnancy test must be confirmed by a serum pregnancy test and a pelvic US since some NSGCT can secrete beta-hCG. A pelvic US does not need to be repeated with each cycle unless the treating physician thinks it is necessary to do so.
- 6 The post-treatment safety assessment will be done 21 ± 7 days after the last dose of study drug.
- 7 All SAEs should be collected from C1D1 until the post-treatment safety assessment. SAEs related or possibly related to study treatment or a study procedure should be reported until the patient is off study. Any death occurring within 30 days after study treatment discontinuation must be reported as an SAE regardless of attribution.
- 8 Appropriate radiographic diagnostic procedures (CT scan of chest, abdomen & pelvis) for evaluation of measurable disease at baseline within 28 days of initiation of the study. CT scans and Chest X-ray will be performed as clinically indicated to follow disease per RECIST 1.1. A confirmation CT scan of response will be performed per RECIST as outlined in the protocol. Patients will be followed for progression every 2 months ± 2 weeks for first year from registration. NOTE: existing scans that are no older than 30 days may be used for the screening scan. RECIST 1.1 Guidelines will be used to evaluate response (see Section 9.0).
- 9 Previous surgical specimens or biopsy samples will be collected for CD30 staining. If none is available, the patient will be offered a repeat biopsy to determine CD30 status.
- 10 Follow up for disease progression and survival will be every 2 months ± 2 weeks for first year from registration. Patients who have progressed will be followed for resolution of all study related toxicity.
- 11 CBC should be done between Day 8 and Day 15 of Cycle 1. This lab can be done locally with results faxed to the study team. Detailed instructions and orders will be provided to patients.
- 12 This will be documented for all patients whenever possible as some patients will not have this information available.

7.1 Screening Evaluations

7.1.1 Within 28 days prior to registration for protocol therapy

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history and prior disease therapies including ECOG performance status
- Vital signs including height, weight, blood pressure, temperature, pulse and BSA
- Physical examination including testicular examination if appropriate
- Complete blood counts (CBC) with differential
- Chemistry panel (CMP) including serum creatinine, AST, ALT, BUN, phosphate, bilirubin, calcium & magnesium
- Tumor marker measurements including serum alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (BHCG)
- Serum pregnancy test for women of childbearing potential
- Concomitant medication use
- Appropriate radiographic diagnostic procedures (for example CT scan of chest, abdomen & pelvis) for evaluation of measurable disease at baseline within 28 days of initiation of the study. NOTE: Existing scans that are no older than 30 days may be used for the screening scan.
- Previous surgical specimens or biopsy samples will be collected for CD30 staining. If none are available, the patient will be required to do a repeat biopsy to determine CD30 status.

7.2 On Treatment Evaluations

7.2.1 Cycle 1 Day 1

- Complete physical examination including testicular examination if appropriate
- ECOG performance status
- Vital signs including weight, blood pressure, temperature and pulse
- Complete blood counts with differential
- Chemistry panel including serum creatinine, AST, ALT, BUN, phosphate, bilirubin, calcium & magnesium
- Tumor marker measurements including serum alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (BHCG)
- Urine pregnancy test for women of childbearing potential
- Concomitant medication use
- Adverse Event Assessment

7.2.2 Cycle 1 Day 8 (+7 days)

- Complete blood counts with differential

7.2.3 Cycle 2 Day 1 and all subsequent cycles

- Symptom-directed physical examination including testicular examination if appropriate

- ECOG performance status
- Vital signs including weight, blood pressure, temperature and pulse
- Complete blood counts with differential
- Chemistry panel including serum creatinine, AST, ALT, BUN, phosphate, bilirubin, calcium & magnesium
- Tumor marker measurements including serum alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (BHCG)
- Urine pregnancy test for women of childbearing potential
- Concomitant medication use
- Adverse Event Assessment

7.2.4 Before cycle 3 & cycle 5 (D-7 to D1)

- Appropriate radiographic diagnostic procedures (CT scan of chest, abdomen & pelvis) for assessment of response per RECIST 1.1 criteria. Assessments should be the same modality as used for screening.

7.2.5 Before cycle 9 & then after every 4 cycles (D-7 to D1)

- Appropriate radiographic diagnostic procedures (CT scan of chest, abdomen & pelvis) for assessment of response per RECIST 1.1 criteria. Assessments should be the same modality as used for screening.

7.3 Post Treatment Safety Assessment

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 21 days (± 7) after the last dose of study drug. This visit should include the following:

- Complete physical examination
- ECOG performance status
- Vital signs including weight, blood pressure, temperature and pulse
- Complete blood counts with differential
- Chemistry panel including serum creatinine, AST, ALT, BUN, phosphate, bilirubin, calcium & magnesium
- Tumor marker measurements including serum alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (BHCG)
- Serum pregnancy test for women of childbearing potential
- Concomitant medication use
- Adverse Event Assessment

7.4 Long Term Follow-up Evaluations

Patients who achieve a complete remission and are off treatment will be followed every 2 months ± 2 weeks for first year from date of registration. Follow up visits will be done per institutional standard of care. Patients who are discontinued from the treatment for other reasons and are not in remission will be followed for long-term survival and subsequent therapy.

8. BIOSPECIMEN STUDIES AND PROCEDURES

8.1.1 Source and Timing of Biospecimen Collections

Archival tumor tissue will be collected (orchiectomy and metastatic tumor) if available, and a fresh biopsy of tumor if archival tissue is not available will be attempted, for assessment of CD30 expression using immunohistochemistry with anti-CD30 BerH2. All tissues will be sent to the Indiana University Simon Cancer Center Clinical Trials Office Laboratory, 535 Barnhill Dr., RT 355, Indianapolis, Indiana, 46202 where it will be catalogued, and then transferred to the Department of Pathology and Laboratory Medicine at IU Health for IHC by Dr. Liang Cheng. The CD30 results from the original archival tissue pathology report will also be collected.

Please see Study Procedure Manual for additional processing and shipping information.

8.1.2 Storage of Biospecimens

Any remaining specimens will be stored for future research.

9. CRITERIA FOR DISEASE EVALUATION

Patients will be assessed every cycle by physical examination for response for disease progression and by serum AFP and beta-hCG. Patients will have appropriate radiographic diagnostic procedures (CT scan of chest, abdomen and pelvis) for evaluation of measurable disease at baseline within 28 days of initiation of the study. Imaging can be repeated if required to evaluate the disease (i.e. no elevation of serum tumor markers) before cycle 3, 5 and then every 4 cycles thereafter, at completion of treatment or as clinically indicated. Patients with stable disease or partial or complete response will be eligible for continued therapy.

9.1 The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) will be used as follows:

9.1.1 Measurable disease:

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

9.1.2 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.

9.1.3 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/pulmonis, inflammatory breast disease, and abdominal masses (not confirmed and followed by CT or MRI), are considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

9.2 Methods for Evaluation of Measurable Disease:

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed within 28 days before the beginning of the treatment.

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. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

9.3 Methods of Measurement:

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Baseline documentation of "Target" and "Non-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.

9.4 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.

9.5 Response Criteria

Evaluation of target lesions or serum tumor biomarker

- Complete Response (CR): Disappearance of all target and normalization of serum tumor markers (AFP and beta-hCG) for at least 4 weeks. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Complete Response must be confirmed four or more weeks after initial CR is observed.
In patients whose only evidence of disease is elevated serum tumor markers (AFP or beta-hCG), then values must fall below the upper limit of normal for the assay employed and remain at that level for at least 4 weeks.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. This should be present on at least 2 measurements 1 month apart. The serum tumor markers (AFP and beta-hCG) should be stable or decreasing. Partial Response must be confirmed four or more weeks after initial PR is observed.
In patients whose only evidence of disease is elevated serum tumor markers (AFP or beta-hCG), then values must fall $\geq 90\%$ below baseline pretreatment levels for beta-hCG or 50% decrease below baseline pretreatment levels for AFP and persist for 6 weeks. If both tumor markers are elevated and one falls below 90% the other should fall at least below 50% of baseline pretreatment levels.

- 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 OR the appearance of one or more new lesions OR unequivocal progression of non-target or non-measurable lesions (e.g. worsening bone pain requiring radiation or significant increase in pain medications) OR increase $\geq 50\%$ in serum tumor markers AFP or beta-hCG in 2 samples at least 1 week apart compared to nadir values
- 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 AND/OR stable serum tumor markers, or change that does not qualify as CR, PR or progressive disease. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks).

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).
- Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- 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.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Principal Investigator.

Note: In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.6 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). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Overall responses for all possible combinations of tumor responses in target and non-target lesions are summarized below

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/ Non-PD	No	PR	≥ 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/ Non-PD/ not evaluated	No	PR	
SD	Non-CR/ Non-PD/ not evaluated	No	SD	Documented at least once ≥ 4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

- * See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
 - ** Only for non-randomized trials with response as primary endpoint.
 - *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
- Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration.*” Every effort should be made to document the objective progression even after discontinuation of treatment.

9.7 Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

9.8 Duration of follow-up:

All patients, including those who discontinue protocol therapy early, will be followed for disease progression, and survival until death. Follow up for disease progression and survival will be every 2 months \pm 2 weeks for the first year from the date of registration, every 4 months \pm 2 weeks during year 2, and every 6 months \pm 4 weeks for years 3-5. Patients who progress will be followed for resolution of all study related toxicity.

9.9 Definitions of Response Evaluation:

9.9.1 Progression-Free Survival Time

Definition: A measurement from the start of the treatment until death or criteria for disease progression are met. Surviving patients without progression are treated as censored at last date known alive.

9.9.2 Overall Survival Time

Definition: A measurement from the start of the treatment until death. Patients surviving are treated as censored at last date known alive.

9.9.3 Time to Remission

Definition: A measurement from the start of the treatment until the confirmed criteria for disease remission (PR + CR) are met. Patients not in remission are treated as censored at last date known alive.

9.9.4 Duration of Remission (Among Remitters, PR + CR)

Definition: A measurement from the earliest time when confirmed remission criteria are met until death or progression. Patients continuing in remission at the end of the study are treated as censored.

9.9.5 Follow-Up Time

Definition: The time from start of treatment until last date known alive among surviving patients with patients considered censored at death.

10. DRUG INFORMATION

Please refer to the latest version of the Investigator's Brochure (IB), provided as a document separate from this protocol.

10.1 Brentuximab vedotin

Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder supplied by Seattle Genetics in single-use vials for reconstitution for IV administration. Each vial of the product contains brentuximab vedotin (SGN-35), trehalose, sodium citrate, and polysorbate 80.

10.2 Clinical pharmacology

10.2.1 Mechanism of Action

Brentuximab vedotin is an ADC. The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a microtubule disrupting agent. MMAE is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 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 cells.

10.2.2 Pharmacodynamics

QT/QTc Prolongation Potential

The effect of brentuximab vedotin (1.8 mg/kg) on the QTc interval was evaluated in an open-label, single-arm study in 46 evaluable patients with CD30-expressing hematologic malignancies. Administration of brentuximab vedotin did not prolong the mean QTc interval >10 ms from baseline. Small increases in the mean QTc interval (<10 ms) cannot be excluded because this study did not include a placebo arm and a positive control arm.

10.2.3 Pharmacokinetics

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 trials and in a population pharmacokinetic analysis of data from 314 patients. The pharmacokinetics of

three analytes were determined: the ADC, MMAE, and total antibody. Total antibody had the greatest exposure and had a similar PK profile as the ADC. Hence, data on the PK of the ADC and MMAE have been summarized.

Absorption

Maximum concentrations of ADC were typically observed close to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional from 1.2 to 2.7 mg/kg. Steady-state of the ADC was achieved within 21 days with every 3-week dosing of brentuximab vedotin, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule.

The time to maximum concentration for MMAE ranged from approximately 1 to 3 days. Similar to the ADC, steady-state of MMAE was achieved within 21 days with every 3 week dosing of brentuximab vedotin. MMAE exposures decreased with continued administration of brentuximab vedotin with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

Distribution

In vitro, the binding of MMAE to human plasma proteins ranged from 68–82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. *In vitro*, MMAE was a substrate of P-gp and was not a potent inhibitor of P-gp.16

In humans, the mean steady state volume of distribution was approximately 6–10 L for ADC.

Metabolism

In vivo data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. *In vitro* data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5. *In vitro* studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other CYP isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

Elimination

MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of brentuximab vedotin. Approximately 24% of the total MMAE administered as part of the ADC during a brentuximab vedotin infusion was recovered in both urine and feces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the feces and the majority of the excreted MMAE was unchanged.

10.3 Supplier

Brentuximab vedotin will be supplied by Seattle Genetics. Please see Study Procedures Manual for instructions on ordering initial and subsequent drug supply shipments.

10.4 Preparation

Brentuximab vedotin vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug disposal procedures.

Brentuximab vedotin should be reconstituted with the appropriate amount of Sterile Water for Injection, United States Pharmacopeia (USP) (or equivalent; see Pharmacy Manual for details). The vial should be gently swirled until the contents are completely dissolved. The vial must not be shaken or vigorously swirled; excess agitation may cause aggregate formation. The reconstituted drug product should be inspected visually for any particulate matter and discoloration.

The required volume of reconstituted drug product should be transferred to an infusion bag. There are no known incompatibilities between brentuximab vedotin and polyvinylchloride (PVC) ethylene vinyl acetate (EVA), polyolefin, or polyethylene bags. The reconstituted drug product should be diluted (see Pharmacy Manual for details) and the bag should be gently inverted to mix the solution. The bag must not be shaken; excess agitation may cause aggregate formation. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

Detailed drug preparation instructions are provided in the Pharmacy Manual.

10.5 Storage and Handling

Refrigeration should be set at 2-8°C for storage of vials and solutions containing brentuximab vedotin. The controlled location must be accessible only to the pharmacist, the investigator, or a designated person. Brentuximab vedotin (SGN-35) for Injection does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials of brentuximab vedotin 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 stored protected from direct sunlight until the time of use. Reconstituted vials must not be shaken.

Drug accountability instructions are provided in the Study Procedures Manual.

10.6 Packaging and Labeling

Vialed drug product may be labeled as brentuximab vedotin, the United States adopted name (USAN) and the International Nonproprietary Name (INN), or as SGN-35, the compound code; the 2 names can be used interchangeably.

10.7 Dispensing

Brentuximab vedotin must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Brentuximab vedotin should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.8 Adverse Events

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Peripheral Neuropathy [see *Warnings and Precautions (10.9.1)*]
- Anaphylaxis and Infusion Reactions [see *Warnings and Precautions (10.9.2)*]
- Hematologic Toxicities [see *Warnings and Precautions (10.9.3)*]
- Serious Infections and Opportunistic Infections [see *Warnings and Precautions (10.9.4)*]
- Tumor Lysis Syndrome [see *Warnings and Precautions (10.9.5)*]
- Increased Toxicity in the Presence of Severe Renal Impairment [see *Warnings and Precautions (10.9.6)*]
- Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment [see *Warnings and Precautions (10.9.7)*]
- Hepatotoxicity [see *Warnings and Precautions (10.9.8)*]
- Progressive Multifocal Leukoencephalopathy [see *Warnings and Precautions (10.9.9)*]
- Pulmonary Toxicity [see *Warnings and Precautions (10.9.10)*]
- Serious Dermatologic Reactions [see *Warnings and Precautions (10.9.11)*]
- Embryo-Fetal Toxicity [see *Warnings and Precautions (10.9.12)*]

Please refer to the most current IB or package insert(s) for the comprehensive list of adverse events.

10.9 WARNINGS AND PRECAUTIONS

10.9.1 Peripheral Neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative. In the HL and sALCL clinical trials, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCETRIS [see *Dose Modification (6.1)*].

10.9.2 Anaphylaxis and Infusion Reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related

reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

10.9.3 Hematologic Toxicities

Prolonged (≥ 1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with treatment with ADCETRIS. Complete blood counts should be monitored prior to each dose of ADCETRIS and more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses [see *Dose Modification (6.1)*].

10.9.4 Serious Infections and Opportunistic Infections

Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Patients should be closely monitored during treatment for the emergence of possible bacterial, fungal, or viral infections.

10.9.5 Tumor Lysis Syndrome

Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

10.9.6 Increased Toxicity in the Presence of Severe Renal Impairment

The frequency of \geq Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, \geq Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CL_{cr}) <30 mL/min].

10.9.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of \geq Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

10.9.8 Hepatotoxicity

Serious cases of hepatotoxicity, including fatal outcomes, have occurred in patients receiving ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCETRIS or after ADCETRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin.

Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

10.9.9 Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities.

Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

10.9.10 Pulmonary Toxicity

Pulmonary toxicity has been reported in patients receiving ADCETRIS. A causal association with single-agent ADCETRIS has not been established. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnea), perform a prompt diagnostic evaluation and institute appropriate medical therapy.

10.9.11 Serious Dermatologic Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

10.9.12 Embryo-Fetal Toxicity

There are no adequate and well-controlled studies of ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus.

11. ADVERSE EVENTS

11.1 Definitions of Adverse Events

11.1.1 Adverse Event (AE)

An **adverse event** is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0 (Appendix I).

11.1.2 Suspected Adverse Reaction (SAR)

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event.

Examples of types of evidence that would suggest a causal relationship between the drug and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

11.1.3 Adverse Reaction (AR)

An adverse reaction is any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

11.1.4 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered “serious” if it results in any of the following outcomes:

- Results in death
 - Is life-threatening. Life-threatening is defined as an adverse event or suspected adverse reaction that places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
 - Requires inpatient hospitalization or prolongation of existing hospitalization
- NOTE: Hospitalizations that are not considered SAEs are:
- Hospitalization planned prior to first administration of study drug
 - Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

Pregnancy

- Pregnancy of a patient or of the female partner of a male patient during the study or within 30 days after the last dose of study drug should be reported via an SAE report. Should pregnancy occur in a female participant during the treatment period, study drug should be discontinued and Seattle Genetics notified immediately. Should a pregnancy occur in a female companion of a male participant during the treatment period, the male participant can continue treatment and Seattle Genetics notified immediately. Any such pregnancy is to be followed until final outcome.

11.1.5 Unexpected Adverse 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. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

This definition relies entirely on the adverse events or suspected adverse reactions listed in the investigator brochure for the particular drug under investigation (or elsewhere in the general investigational plan if an investigator brochure is not required or available) as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is *unexpected*. This means that events not listed for the particular drug under investigation in the investigator brochure are considered “unexpected” and those listed are considered “expected.” When new adverse event information is

received, it is the sponsor's responsibility to determine whether the event is "unexpected" for IND safety reporting purposes. In the clinical trial setting, there has been some confusion with the term "expected" as it has been used to mean "anticipated" for the disease being treated or population being studied rather than "listed in the investigator brochure." For example, some adverse events can be anticipated to occur as a result of a disease or in an older population (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not "expected" because they are not listed in the investigator brochure (i.e., the test drug is not suspected or known to cause them).

Adverse events listed in the investigator brochure as occurring with members of the same class of drugs, or as anticipated from the pharmacological properties of the drug, would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the investigator brochure as a class effect, a case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes until it is included in the investigator brochure as occurring with the drug under investigation.

11.1.6 Determining Attribution to the Investigational Agent(s)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily "*caused by a therapeutic intervention*". After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly NOT related
	Unlikely	The AE is doubtfully related
Related to investigational agent/intervention	Possible	The AE may be related
	Probable	The AE is likely related
	Definite	The AE is clearly related

11.2 Adverse Event (AE) Reporting Requirements:

Adverse events (AEs) will be recorded from the time of first study drug administration and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. AEs occurring after the post-treatment safety assessment visit can be collected by telephone or other means of communication. All AEs considered related to trial

medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

11.2.1 Participating Site Reporting Responsibilities

11.2.1.1 Reporting to the IU Simon Cancer Center

Any serious adverse event or unanticipated problem occurring within 30 days of the last dose of study drug must be reported to the IU Simon Cancer Center within **1 business day** of notification or discovery of the incident, using the MedWatch Form 3500A (Mandatory Reporting). SAEs that occur greater than 30 days from last dose of study drug must be reported to the IU Simon Cancer Center if the event is possibly, probably, or definitely related to the study drug. This form must be accompanied by a cover letter which: identifies the event, is signed by the local principal investigator or treating physician, includes the applicable study number and title, and contains the following:

- Site assessment of the event attribution to investigational product or study procedure
- Site assessment of event expectedness (expected vs. unexpected)
- Assessment of whether or not the research places subjects at a greater risk of harm than was previously known or recognized
- Assessment of the event's affect on the risk to benefit ratio
- Statement as to whether the informed consent statement should reflect changes in the potential risks involved
- Statement as to whether the event has been reported previously, and if so, whether the frequency is considered unusually high

Send to: IUSCC Clinical Trials Office
 ATTN: Multicenter coordinator/ IUSCC-0568
 Fax: (317) 274-8022
 E-mail: IUSCCSAE@iu.edu

The Multicenter Network Associate Administrator, or designee, will distribute the reports to all participating sites, the FDA and to Seattle Genetics as per section 11.2.2 below. Copies of all serious adverse event reports or unanticipated problems reports will be kept on file in the IU Simon Cancer Center Clinical Trials Office.

11.2.1.2 Reporting to the IRB

Each participating site will report adverse events and unanticipated problems to their IRB per local guidelines. Any event that requires expedited reporting to the local IRB will also be submitted to the IU Simon Cancer Center for distribution to the Funder.

11.2.2 Coordinating Center Reporting Responsibilities

In addition to the responsibilities above, the Coordinating Center will also be responsible for reporting events to the Funder and the FDA.

11.2.2.1 Reporting to Seattle Genetics

SAEs

IUSCC will report to Seattle Genetics all SAEs that are sent to the FDA at the time of submission to the FDA. Follow-up information will be provided to Seattle Genetics as reasonably requested. Send SAE reports on the MedWatch Report Form to:

Seattle Genetics Drug Safety

Facsimile: (425) 527-4308 or (866) 333-6627

Email: drug.safety@seagen.com

A study-specific cumulative SAE line listing of all SAEs with assessment of causality to investigational product will be sent **monthly** to IST@seagen.com.

Study Initiation

IUSCC will provide the following to Seattle Genetics prior to initiation of Seattle Genetics support (provision of Product and/or funding):

- Final study protocol
- Fully executed IST Agreement
- Regulatory Response Documentation (IND or CTA documentation if applicable)
- IRB/IEC approval

Study Maintenance

Throughout the study, IUSCC will provide the following to Seattle Genetics:

- At least one safety study status update per year, to include information on enrollment and study completion dates.
- Notification of any amendment to the original protocol after the research has begun; and *immediate* notification of any amendments made due to safety reasons.

Study Closure

IUSCC will provide Seattle Genetics a copy of the IND Annual Report. Upon study closure, IUSCC will certify that all safety reporting obligations were met.

11.2.2.2 Reporting to the FDA

Per CFR 312.32 (c), the sponsor-investigator of the IND (Dr. Adra) must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any adverse experience that meets the criteria outlined below. There are two types of reports to the FDA: 7-day and 15-day reports.

7-Day Reports:

The investigator-sponsor of the IND must notify the FDA and all participating investigators in a written IND safety report of any adverse experience:

- **fatal or life-threatening experience** that is ***both***
- **suspected to be associated with use of the drug *and***
- **unexpected (as defined in 11.1.5)**

The FDA will be notified as soon as possible but no later than **7 calendar** days after the investigator-sponsor's initial receipt of the information.

15-Day IND Reports:

The investigator-sponsor of the IND must notify the FDA and all participating investigators in a written IND safety report of any adverse experience:

- **suspected to be associated with use of the drug** that is ***both***
- **serious** ***and***
- **unexpected** (as defined in 11.1.5)

The FDA will be notified as soon as possible but no later than **15 calendar** days after the investigator-sponsor's initial receipt of the information.

Report Content:

Each written notification may be submitted on FDA Form 3500A or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". For purposes of this protocol, the **MedWatch Report Form (FDA 3500A mandatory reporting), along with FDA Form 1571, and a cover letter** submitted to the appropriate FDA division, will serve as the written IND safety report. Follow-up information to a safety report should be submitted as soon as the relevant information is available. Submit to the FDA:

- MedWatch Report Form (FDA 3500A)
- FDA Form 1571
- Cover Letter

Notify the FDA via phone or fax using MedWatch 3500A (mandatory reporting form)

- Phone: 1-888-463-6332, option #1
- Fax: 1-800-FDA-0178

The IUSCC Protocol Development Coordinator should be contacted to assist with all FDA submissions and will be provided with a copy of all events that are reported to the FDA. All IND submissions will be maintained in a master file in the Clinical Trials Office of the IU Simon Cancer Center.

11.2.2.3 Reporting to Participating Sites

Seattle Genetics will send IND safety reports from external studies that involve the study drug to the Multicenter Network Associate Administrator, or designee. The Multicenter Network Associate Administrator, or designee, will forward the safety reports to the sponsor-investigator, or designee, who will review these reports and determine if revisions are needed to the protocol or consent. IUSCC will forward these reports to participating sites every 2 weeks.

For IND safety reports originating from this study, IUSCC will distribute reports which are serious, unexpected and associated with the study intervention (possibly, probably or definitely related) to all participating sites in the form of an Expedited Safety Report (external safety/IND safety report) within 15 calendar days from determination that the suspected adverse reaction qualifies for reporting. Copies of these External Safety Reports will be kept on file in the IU Simon Cancer Center

Clinical Trials Office. Upon receipt from IUSCC, site investigators, or designees, are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

This is an open label, single agent, multicenter, phase II study with 2 cohorts evaluating the efficacy of brentuximab vedotin in “CD30 positive” and “CD30 negative/unknown” relapsed/refractory NSGCT who are otherwise considered non-curable. Both cohorts will be treated similarly and in parallel but analyzed separately.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

Objective response rate is the proportion of patients who achieve either a partial or complete response

Complete response is defined as disappearance of all target lesions and normalization of serum tumor markers (AFP and beta-hCG) for at least 4 weeks. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Complete Response must be confirmed four or more weeks after initial CR is observed. In patients whose only evidence of disease is elevated serum tumor markers (AFP or beta-hCG), then values must fall below the upper limit of normal for the assay employed and remain at that level for at least 4 weeks.

Partial response is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. This should be present on at least 2 measurements 1 month apart. The serum tumor markers (AFP and beta-hCG) should be stable or decreasing. Partial Response must be confirmed four or more weeks after initial PR is observed.

In patients whose only evidence of disease is elevated serum tumor markers (AFP or beta-hCG), then values must fall $\geq 90\%$ below baseline pretreatment levels for beta-hCG or 50% decrease below baseline pretreatment levels for AFP and persist for 6 weeks. If both tumor markers are elevated and one falls below 90% the other should fall at least below 50% of baseline pretreatment levels.

12.2.2 Definition of Secondary Endpoints

Progression-free survival (PFS) is the time measured from the date of initiation of therapy until disease progression or death, whichever comes first. Patients alive and progression-free will be censored at their last disease assessment.

Overall survival (OS) is the time measured from the date of initiation of therapy until death, regardless of cause. Patients alive at the time of data analysis will be censored at their last date of contact.

12.3 Sample Size and Accrual

An optimal Simon two-stage design will be used for each cohort of patients to differentiate between the null hypothesis that the response rate P is $\leq 5\%$ ($P \leq 0.05$) and

the alternative hypothesis that the response rate is $\geq 20\%$ ($P \geq 0.20$). These values were chosen for both arms based on what is clinically relevant per the investigators' experiences. There is no available data at this time for CD30-negative/unknown patients as brentuximab vedotin has not been tested for such patients. Under this design, the probability of early termination under the null hypothesis is 0.599. This design yields a type I error rate, α (probability of concluding that the drug is not effective when it is actually effective) of 0.047 and a power of 0.801 (type II error rate 0.199) when the true response rate is $\geq 20\%$. In the first stage in each cohort, 10 patients will be enrolled. If there are no objective responses, then that cohort will terminate. If ≥ 1 response is observed, then an additional 19 patients will be enrolled in the second stage for a total sample size of 29 patients per cohort. If 3 or fewer responses are observed out of the 29 patients, then Brentuximab will be declared as not worthy of further study for that cohort. If ≥ 4 objective responses are achieved, then brentuximab vedotin will be deemed active in refractory/relapsed NSGCT and worthy of further study.

We estimate enrolling 2 patients/month for the CD30 negative cohort and 1 patient/month for the CD30 positive patients.

12.4 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Efficacy	The efficacy population comprises all patients who have received at least one dose of the study medication. This population will be used for efficacy analysis.
Safety	The safety population comprises all patients who have received at least one dose of the study medication. This set will be used for safety analysis.

12.5 Assessment of Safety

Toxicities will be assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The maximum grade of each toxicity will be recorded for each patient over the course of treatment (all cycles). Toxicities will be recorded up until 30 days after the last day of treatment. The incidence of treatment delays, dose reductions, and early discontinuations of treatment due to toxicity or patient choice, will also be recorded as a means of assessing the tolerability of treatment for each cohort.

12.6 Assessment of Efficacy

All subjects who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of objective response using the criteria for response detailed in Section 9.

12.7 Data Analysis Plans

12.7.1 Analysis Plans for Primary Objective

The ORR and its 95% exact CI will be summarized by cohort using the F distribution method (Collett 1991). This endpoint may also be tabulated by covariates, such as sex, age, race, categorized weight, categorized disease burden at baseline, prior treatment, and performance status. The maximum percent reduction in the sum of the products of the largest diameters of the nodes or nodal masses being followed for response assessment will be graphically displayed. ORR by intensity and pattern of CD30 expression will be tabulated by cohort.

12.7.2 Analysis Plans for Secondary Objectives

- Both PFS and OS will be estimates using the methods of Kaplan and Meier for each cohort separately.
- Toxicities will be summarized by cohort using frequencies and rates calculated as the proportion of patients in the safety population experiencing SAEs, and treatment delays, reductions, and discontinuations due to AEs, and SAEs. Two sets of tables will be generated: one for the overall toxicities and one for toxicities related to the study medication (possibly related, probably related and definitely related). Toxicities will be grouped by system using MedRA preferred terminology. Grade 1 to 4 will be reported individually and also as grade 3/4. Deaths will be reported individually.

12.7.3 Analysis Plans for Exploratory Objectives

- CD30 staining will be characterized by intensity (0 to 3+) and by localization (cell wall vs. cytoplasmic) using descriptive statistics and correlated with objective response using logistic regression and with PFS using proportional hazards regression.

12.8 Interim Analysis/Criteria for Stopping Study

Each cohort will be evaluated after 10 patients enroll on the study to that cohort. If no responses are seen then that cohort will be closed for lack of efficacy.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring

13.1.1 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) of the Indiana University Simon Cancer Center (IUSCC) is responsible for patient safety and privacy protection, compliance with required reporting, and study integrity for all trials conducted at IUSCC. Members are subject matter experts from multiple disciplines including medical oncology, pediatrics, biostatistics, behavioral oncology, radiation oncology, urology, surgery, gynecologic oncology, data and project management and research administration who are appointed by the DSMC Chair. The DSMC will provide independent oversight of the clinical trial so that study integrity is assured. However, the DSMC is not serving as a Data and Safety Monitoring Board (DSMB) for this study. The DSMC will meet per the currently approved

DSMP, led by the DSMC Chair and Coordinator, and will review all adverse events, monitoring and auditing reports, unanticipated problems and study non-compliance events that require expedited reporting. Meeting minutes will be maintained in the IUSCC Clinical Trials Office (CTO). Specifically the DSMC has the following responsibilities:

- Assessment of the adequacy of trial-specific Data Monitoring and Safety Plan (DSMP) of studies that are not subject to external monitoring, including investigator initiated studies, and establish risk based monitoring determination of trial specific DSMB.
- Review safety data for investigator initiated trials including all adverse events, unanticipated problems and study non-compliance events requiring expedited reporting.
- Conduct routine study monitoring and auditing in compliance with the IUSCC data quality control review process.

13.1.2 Data Safety Monitoring Plan

This trial will comply with the current requirements of the Data and Safety Monitoring Plan (DSMP) of the IUSCC. The CTO of the IUSCC will be the Coordinating Center for this multicenter phase 2 trial.

In accordance with the DSMP of the IUSCC, investigators will conduct continuous review of data and patient safety. **Monthly** review meetings for Phase 2 trials are required and will include the: principal investigator, clinical research specialist, and/or research nurse data manager and/or study coordinator, and other members as per the principal investigator's discretion. In addition, **conference calls** with investigators and staff at participating sites will be scheduled **at least monthly** (and more often as needed) to discuss study progress. If there are no patients on treatment or in follow-up, email communication will be used in lieu of a teleconference. **Monthly** meeting summaries will include and document review of data and patient safety by including for each dose level: the number of patients, significant toxicities as described in the protocol, dose adjustments, responses observed, eligibility of patients enrolled at each site, serious adverse events (SAEs) or unanticipated problems (UPs) (both IUSCC and those reported from other institutions), dose adjustments, and protocol deviations. Meeting minutes will be submitted and reviewed by the DSMC.

- **Study Auditing and Monitoring:** All trials are subject to auditing and/or monitoring per the currently approved DSMC Charter.
- **Reporting Guidelines:** The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed the direct view of reports within the Clinical Trial Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

- **Reporting Death:** Death will be captured in the Case Report Form and reported per local IRB reporting guidelines.
- **Study Accrual Oversight:** Accrual data will be entered into the IU Simon Cancer Center OnCore® system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.
- **Continuing Review:** All Continuing Reviews (CR) will be reviewed annually or as dictated by the Institutional Review Board. Participating sites will submit a copy of the CR with attachments to the IUSCC Multicenter Network Associate Administrator, or designee.
- **Protocol Deviations:** Investigators are required to submit protocol deviations to the DSMC via the OnCore® database.
- **Early Study Closure:** At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

13.1.3 Data Safety Monitoring Board

This study will have a Data and Safety Monitoring Board (DSMB) that will review and monitor study progress, toxicity, safety and other data from this trial. The board is chaired by an independent medical oncologist or another qualified individual external to this trial. Questions about participant safety or protocol performance will be addressed with the Principal Investigator, statistician and study team members. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the trial.

The DSMB will meet once a year to review accrual, toxicity, response and other information reported to the IRB. Information to be provided to the DSMB may include: participant accrual, treatment regimen information, adverse events and serious adverse events reported by category, summary of any deaths on study, audit and/or monitoring results.

The DSMB will provide a written recommendation to the PI and team after all information is reviewed. The report will indicate one or more of the following decisions:

- Continuation of the trial without change
- Continuation of protocol/project with modifications as outlined by the Board
- Immediate suspension of trial for safety reasons with recommended plan of follow up to minimize subject harm
- Study placed on clinical hold
- Termination of trial

The IUSCC will submit the DSMB report(s) to the participating sites as well. The DSMB report(s) should be provided to the local IRB at the time of continuing review.

13.1.4 Data Acquisition

Case Report Forms and Data Submission: This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore® at <https://cancer.iu.edu/oncore>. The OnCore® database is a comprehensive database used by the IUSCC CTO and supported by the Indiana University Cancer Center. Access to data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user which limits access to appropriate data.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Cancer Center per the DSMC Charter.

13.2 Changes to the Protocol and Informed Consent

Study procedures will not be changed without the mutual agreement of the sponsor-investigator and Seattle Genetics. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13.2.1 Emergency Modifications

Site investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IUSCC or their respective institution's IRB approval. As soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to IUSCC, and to the site's IRB for review and approval.

13.2.2 Other Protocol Deviations/Violations

If a deviation or violation occurs, the deviation should be reported in OnCore®. Any protocol violation that occurs must be reported to the IRB per institutional policies and reported to IUSCC as soon as possible. IUSCC will determine if the violation affects the safety of the study subject and integrity of the data.

13.2.3 Amendments

If it is necessary for the study protocol to be amended, the amended protocol will be generated by IUSCC and must be approved by the sponsor-investigator, Seattle Genetics prior to implementation (IST@seagen.com), the FDA (if applicable), and each site's IRB. If applicable, also the local regulatory authority. Local requirements must be followed.

The site investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

Seattle Genetics willingness to supply study drug is predicated upon the review of the protocol. IUSCC agrees to provide written notice to and approval from Seattle Genetics of any modifications to the protocol prior to implementation.

14. MULTICENTER GUIDELINES

14.1 Study Documents

Each participating site must submit regulatory documents (informed consents, 1572s, Financial Disclosures, IRB approval documents, Continuing Reviews, Amendments, patient brochures or recruitment material etc.) to the Coordinating Center. The Coordinating Center will provide each site with a comprehensive list of the required documents prior to study start-up, throughout the duration of the study and upon study close-out. It is the responsibility of the participating site to maintain copies of all documentation sent to the Coordinating Center.

14.2 Study Initiation

Before activating the clinical trial at each participating site, the IUSCC CTO Multicenter Network Associate Administrator, or designee will ensure that:

- Full **Institutional Review Board (IRB) approval** has been obtained.
- Research staff at the participating site has been trained in data entry into OnCore®
- A **start-up meeting** with each institution has taken place via telephone conference. The start-up meeting will cover protocol details (including eligibility criteria, treatment plan, etc.), responsibilities of the participating investigators, and reporting procedures.
- A financial **conflict of interest statement** from each investigator has been obtained.

14.3 Patient Enrollment

After eligibility is confirmed by the participating site staff, a completed eligibility checklist, supporting source documentation, and signed consent will be sent to IUSCC for verification. The Multicenter Network Associate Administrator, or designee, will assign the patient a study number and return the enrollment information to the site. The site staff will then register the patient in OnCore®. Additional details of this process can be found in the Study Procedure Manual.

14.4 Data Monitoring

All multicenter investigator initiated trials conducted at the IUSCC are subject to data monitoring by the Multicenter Network Associate Administrator, or designee. External sites will be notified of upcoming monitoring visits and will be expected to provide the Multicenter Network Associate Administrator, or designee, with de-identified source documents for remote monitoring of patients. Queries will be issued in OnCore® and a

detailed monitoring report will be provided to the participating site. The IUSCC will also forward any monitoring and/or auditing reports to the DSMC.

When a patient enrolled on this trial, or the trial itself, is selected for local monitoring or auditing, the participating site will forward the results to the Multicenter Network Associate Administrator, or designee. In addition, if a participating site patient is selected for local auditing by the IUSCC DSMC, the site will be responsible for sending IUSCC de-identified source documents.

14.5 Record Retention

All documentation of adverse events, records of study drug receipt, dispensation, destruction, and all IRB correspondence will be stored in accordance with all applicable federal guidelines.

Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

15. ETHICS

15.1 Institutional Review Board (IRB) Review

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to IUSCC before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

15.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, <http://www.clinicaltrials.gov>. The sponsor-investigator has delegated responsibility to IUSCC Clinical Trials Office for registering the trial and posting the results on [clinicaltrials.gov](http://www.clinicaltrials.gov). Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

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17. APPENDICES

Appendix 1

A copy of the Common Toxicity Criteria Version 4.0 can be obtained from the NCI website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Protocol 1601349135 IRB Approved - Do Not Enroll Subjects