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DEPARTMENT OF Hematology/HCT

TITLE: A Phase II Study of Brentuximab Vedotin as Salvage Therapy for Hodgkin Lymphoma Prior to Autologous Hematopoietic Cell Transplantation.

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DISEASE SITE: Hodgkin Lymphoma

MODALITY(IES): Chemotherapy

TYPE (*e.g., Pilot, Phase I, etc.*)**:** Phase 2

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A phase II study of brentuximab vedotin as salvage therapy for Hodgkin Lymphoma prior to autologous hematopoietic stem cell transplantation

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Study Sponsor, Monitor and Data Coordinating Center: City of Hope

PROTOCOL SUMMARY

Title: A phase II study of brentuximab vedotin as salvage therapy for Hodgkin lymphoma prior to autologous hematopoietic cell transplantation (AHCT).

Objectives

The primary objective of this study is to determine the anti-tumor activity as assessed by response rate.

The secondary objectives of this study are:

- To characterize stem cell mobilization and collection post brentuximab vedotin salvage therapy.
- To characterize the toxicity profile post brentuximab vedotin salvage therapy.
- Evaluate the biological markers of Hodgkin lymphoma patients treated with brentuximab vedotin as 1st line salvage therapy.
- To examine and characterize the outcomes of patients who receive brentuximab vedotin as 1st line salvage followed by AHCT (e.g., 2-year PFS/OS/relapse-progression incidence and NRM).

Objectives of the New Cohort

As part of a new cohort, up to 20 additional patients will be accrued to the phase II study. Those patients who do not achieve CR at the end of cycle 2 will receive a dose of 2.4 mg/kg of brentuximab vedotin during cycles 3 and 4. In addition to the objectives of the Phase II study, patients treated at the higher dose will be evaluated for the impact of the higher dose on response rate and toxicity after cycle 4.

Refer to specific inclusion and exclusion criteria detailed in protocol.

Number of patients

37 (Phase II Study)
Up to 20 (New Cohort)

Study design and methodology

Phase II, (efficacy) clinical trial

Treatments administered

For the primary study objective, brentuximab vedotin will be administered at a dose of 1.8 mg/kg on day 1, every 21 days for a total of 4 cycles prior to AHCT.

In the new cohort we will treat up to 20 additional patients at the 1.8 mg/kg dose of brentuximab vedotin on day 1, every 21 days for a total of 2 cycles and then evaluate their CR response rate. Patients who achieve a CR will continue getting 1.8 mg/kg for 2 more cycles. Patients who do not achieve a CR (e.g., PR or SD) after 2 cycles of treatment, will be treated at a dose of 2.4 mg/kg on day 1, every 21 days for 2 more cycles instead of 1.8 mg/kg.

Efficacy data collected

The following evaluations will be conducted to assess the efficacy of brentuximab vedotin

- CT/PET or CT of neck, chest, abdomen, and pelvis will be performed after every 2 cycles

of brentuximab vedotin prior to AHCT

- CT/PET scan to be performed at the end of 4 cycles but prior to AHCT.
- CT/PET and CT of the neck, chest, abdomen, and pelvis to be performed at baseline.
- Bone marrow biopsy will be performed at baseline. If positive at baseline, it will be performed after 4 cycles of brentuximab vedotin. If bone marrow biopsy was negative at baseline, it will not need to be repeated.
- Correlative studies of treatment effects on Hodgkin lymphoma biomarkers.
- Diagnostic lymph node samples will be examined for CD 68 expression and intensity.
- Repeat lymph node biopsy will be performed on patients who failed to achieve a partial remission if patient has an accessible node.

Safety data collected

- Specific safety measurements are detailed in section 3.6.3 and section 4.

Statistical procedures

Specific statistical procedures are detailed in section 5.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADC	antibody drug conjugate
AE	adverse event
AI	accumulation index
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the curve
β-hCG	beta human chorionic gonadotrophin
BMA	bone marrow aspirate
BUN	blood urea nitrogen
CBC	complete blood count
CHOP	cyclophosphamide, doxorubicin (hydrodoxorubicin), vincristine (Oncovin®), prednisone
CI	confidence interval
CL	total body clearance
Cmax	peak or maximum concentration
Cmin	minimum concentration
CRF	case report form
CR	complete remission
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	end of treatment
EU	European Union
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
G-CSF	granulocyte stimulating factor
GM-CSF	granulocyte macrophage colony stimulating factor
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Information Portability and Accountability Act
HL	Hodgkin lymphoma
HRS	Hodgkin-Reed-Sternberg
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRF	Independent Review Facility
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase

LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Affairs
mITT	modified intent-to-treat
MMAE	monomethylauristatin E
NCI	National Cancer Institute
NPM	nucleophosmin
NPT	non-protocol therapy
NYHA	New York Heart Association
ORR	overall objective response rate
OS	overall survival
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial remission
PTCL	peripheral T and NK/T cell lymphoma
REB	Research Ethics Board
SAE	serious adverse event
SAP	statistical analysis plan
sCD30	soluble CD30
SD	stable disease
SE	standard error
$T_{1/2}$	half-life
TARC	thymus and activation-regulated chemokine
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
USP	United States Pharmacopeia
Vss	volume of distribution at steady state

1 INTRODUCTION

CD30 is a cell surface antigen expressed on several malignancies including Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL), Kaposi's sarcoma (KS), cutaneous T-cell lymphomas (CTCL), a fraction of diffuse large B-cell lymphomas (DLBCL), some follicular lymphomas, and other lymphoproliferative diseases (Pizzolo et al. 1995; Horie et al. 1998; Chiarle et al. 1999; Younes et al. 1999; Gardner et al. 2001). SGN-35 is an antibody drug conjugate (ADC) directed against the CD30 antigen and is being developed to treat patients with CD30-positive hematologic malignancies. Hodgkin lymphoma and ALCL are among the most common CD30-positive malignancies.

1.1 Background on Relapsed or Refractory Hodgkin Lymphoma

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

Advances in the use of combined chemotherapy and radiotherapy in HL over the past half-century have resulted in a durable remission rate of approximately 70% (Connors 2005). However, these multi-agent regimens are associated with significant morbidity, including secondary malignancies, cardiac disease, pulmonary disease, and infertility (Loge et al. 1999; Swerdlow et al. 2000; van Leeuwen et al. 2000). Furthermore, approximately 30-40% of patients presenting with HL will become refractory to initial therapy or will relapse. The therapeutic options for patients with refractory or relapsed disease are very limited and carry a high morbidity rate (Horning et al 1977; Kleiner et al 1997.)

Patients presenting with advanced stage HL have an even less favorable prognosis than patients with early stage disease and have a much higher relapse rate (Duggan et al. 2003). For patients who do not respond to standard chemotherapy or who relapse, the only potentially curative therapy is high-dose chemotherapy in combination with autologous stem cell transplantation (ASCT) (Horning et al. 1997; Kleiner et al. 1997; Hasenclever et al. 1998; Baker et al. 1999; Connors 2005). This treatment is associated with morbidity and mortality, and a 5-year survival rate of less than 50% (Bartlett 2005). Five-year progression free survival (PFS) rates vary based on pre-transplant disease-related factors. Several retrospective studies have identified risk factors that stratify patients based on disease characteristics, such as the presence of B symptoms, extranodal disease and duration of remission from front line chemotherapy (Moskowitz et al. 2001). The 5-year event-free survival (EFS) rate for patients with low risk disease ranges from 65% to 80%, whereas EFS for patients with intermediate or high risk disease is less than 30%, with the majority of relapses occurring within the first 2 years post-ASCT (Moskowitz et al. 2001; Majhail et al. 2006).

Particularly for intermediate and high-risk patients, it is imperative to find more effective salvage therapies. In a recent phase II study, we have evaluated the response rates to single-agent Brenuximab vedotin, of patients with relapsed or refractory HL following ASCT. The overall objective response rate was 75%, with 34% complete remissions. Tumor regression was observed in 94% of the patients who were evaluable (98/102).

Limited data exist to support the utility of single-agent chemotherapy for treatment of relapsed/refractory HL. Gemcitabine has been evaluated alone, and in combination with rituximab, for the treatment of relapsed or refractory HL (see Table 1). In these small, single-arm, non-randomized, Phase 2 studies, both pre- and post-ASCT HL patients were assessed for response to therapy, although standardized criteria were not used across the studies. Observed overall response rates (ORR) ranged from 22% to 48% with varying durations of response, dependent upon the patient population mix (pre-or post-ASCT) (Santoro et al. 2000; Zinzani et al. 2000; Venkatesh et al. 2004; Oki et al. 2008). The highest response rates in these studies were observed in the pre-ASCT population (39%; Santoro, 2000) and in a mixed population of pre- and post-ASCT HL patients when gemcitabine was given in combination with rituximab (48%; Oki, 2008). Studies to evaluate single-agent vinblastine and vinorelbine treatment in patients with relapsed or refractory HL were also conducted in the 1990s (Devizzi et al. 1994; Little et al. 1998; Rule et al. 1998); see Table 1. From these single-arm studies, the highest response rates were observed in a retrospective series of 17 patients with relapsed HL, with 10 responses observed (Little et al. 1998). In summary, there continues to be an unmet medical need for HL patients with relapsed or progressive disease.

Table 1 Single-agent Phase 2 Studies in Relapsed/Refractory HL

Chemotherapy Dose (Reference)	N	Prior Regimens	Responses (criteria varied)	Durability	Survival
Brentuximab vedotin 1.8 mg/kg IV, D1 Q21d (Chen et al. 2011)	102	3.5 100% prior auto	ORR = (75%) CR = (34%)	mDUR = 6.7 months for all, for CR not reached	mOS not reached, 1-yr OS = 88%
Gemcitabine 1250 mg/m^2 D1,8,15 Q28d (Santoro, 2000)	23	Excluded prior auto Prior regimens: 2	ORR = 9 (39%) CR = 2 (9%)	mDUR = 6.4 months (1.1–21.9	OS = 26.9 months
Gemcitabine 1000–1250mg/m^2, D1,8,15 Q28d (Zinzani, 2000)	27	18/29 (62%) prior auto Prior regimens: (range 2-4)	PR = 6 (22%) CR = 0 (0%)	mTTP = 6.4 months)	mOS = 26.9 months
Gemcitabine 1200mg/m^2 D1,8,15 Q28d x 6d (Oki, 2008)	14	18/33 (55%) prior auto Prior regimens: 2	ORR = 6 (43%) CR/u = 5 (15%)	mFFS = 2.7	N/A
Gemcitabine 1250mg/m^2 D1, 8, Q21d **Rituximab** 375mg/m^2 Qwk x 6 d (Oki, 2008)	33	18/33 (55%) prior auto Prior regimens:, 3 (range 2-7)	ORR = 16 (48%) CR/u = 5 (15%)	mFFS = 2.7 months mDUR = 3.7months	N/A

Vinorelbine 30mg/m^2 Qwk (Devizzi, 1994)	22	At least 2 prior regimens	ORR = 11 (50%) CR = 3 (14%)	Median 6 months	N/A
Vinorelbine 25mg/m^2 IV D 1,8, Q21d (Rule, 1998)	8 HL	Prior regimens (range 2–8), 4 post-ASCT	ORR = 5 (59%) PR = 4 (50%)	Median 10.5	N/A
Vinblastine 4-6mg/m^2 Q1-2wk Retrospective review (Little, 1998)	17	All post-ASCT	ORR = 10 (59%) CR = 2 (11%) PR = 8 (48%)	mEFS = 8.3 months	mOS = 38.8 months

Monoclonal antibodies (mAb) that specifically target CD30 have been the focus of several therapeutic approaches. SGN-30, an antibody directed against the CD30 antigen, has been evaluated as monotherapy in Phase II clinical trials in patients with relapsed or refractory ALCL and HL; no objective responses were observed in patients with HL and an ORR of 17% was observed in heavily pretreated patients with systemic ALCL (Seattle Genetics, data on file). MDX-060, another antibody directed against CD30, has been evaluated in a Phase I/II study in patients with relapsed or refractory CD30-positive hematologic malignancies (Ansell et al. 2007). In this study, the ORR was 9.5% (6 out of 63) in HL patients and 28% (2 out of 7) in patients with systemic ALCL. Although unmodified antibodies exhibit modest efficacy as single agents, they have not been curative as monotherapy. Clinical studies are ongoing with SGN-30 and MDX-060 in combination with chemotherapy with the goal of improving clinical utility in patients with relapsed or refractory disease.

Antibody drug conjugates (ADCs), which consist of cytotoxic agents or toxins chemically conjugated to a mAb, potentially represent an advantage over treatment with chemotherapy because they are designed to deliver the cytotoxic agent specifically to tumor cells thereby resulting in an improved safety profile.

1.2 Brentuximab Vedotin

Brentuximab vedotin, previously known as SGN-35 is an ADC consisting of the chimeric antibody SGN-30 (cAC10) chemically conjugated to a synthetic analog (monomethylauristatin E [MMAE]) of the naturally occurring antitubulin agent, dolastatin10. Brentuximab vedotin is proposed to have a multi-step mechanism of action that is initiated by binding to CD30 on the cell surface and internalization of the ADC. Upon trafficking to lysosomes, MMAE is released from the conjugate through proteolytic degradation of the drug linker (Sutherland et al. 2006). Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis (Francisco et al. 2003).

Preclinical studies of brentuximab vedotin demonstrated antitumor activity in both *in vitro* and *in vivo* models. The toxicity of multiple doses of brentuximab vedotin has been assessed in rats and monkeys. In both species, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed. Histopathologic lesions were also observed in the spleen in monkeys and in the liver and testes in rats. In addition, decreases in peripheral blood counts were observed in both species, and elevations in

liver enzymes were seen in rats only. The most significant clinical toxicity was neutropenia, observed in monkeys, which resulted in secondary bacterial infections leading to early deaths at the 6 mg/kg dose. Toxicity was dose-dependent, with a no-observable-adverse-effect level of 0.5 mg/kg in rats and 1 mg/kg in monkeys. See the brentuximab vedotin SGN-35 Investigator's Brochure for details of the nonclinical data.

1.3 Study Rationale

Most patients diagnosed with HL respond to front-line chemotherapy. However, 30% to 40% of these patients will eventually relapse, and approximately 10% of patients will have refractory disease. Salvage chemotherapeutic regimens and ASCT are secondary options for these patients, but both are associated with a significant morbidity rate.

Brentuximab vedotin is a novel ADC directed against the CD30 surface antigen expressed on hematologic malignancies including HL tumor cells. A Phase 1, single-arm, open-label, dose-escalation study of brentuximab vedotin (SGN-35) has been conducted in patients with CD30-positive hematologic malignancies (SGN35-0001). In this study, patients received brentuximab vedotin on Day 1 of each 21-day cycle and tumor response assessments were performed on Days 15–21 of the second cycle. Brentuximab vedotin was generally well-tolerated at doses of up to 1.8 mg/kg and induced multiple objective responses in these heavily pretreated patients. As reported by Younes et al 2010, 50% of the patient treated at the 1.8 mg/kg dose level achieved an objective response, and tumor regression was observed in 36 out of 42 patients who could be evaluated (86%). Of the 17 patients with objective responses, 88% achieved response within 4 cycles. The median duration of response is 9.7 months. These encouraging results suggest that brentuximab vedotin should be further evaluated in Phase II studies for patients with HL.

To date, over 400 patients have been treated with Brentuximab vedotin. In the Phase 1 dose-escalation study of brentuximab vedotin administered IV every 21 days (SGN35-0001), 45 patients were treated. The dose-limiting toxicity (DLT) experienced in the first cycle of therapy was more common at the 2.7 mg/kg dose level than at the 1.8 mg/kg dose level. DLT observed in 3 of 12 patients treated at the 2.7 mg/kg dose level included Grade 4 neutropenic fever, Grade 3 prostatitis, Grade 3 hyperglycemia, and 1 case of unrelated acute renal failure. One occurrence of Grade 4 thrombocytopenia qualified as a DLT at the 1.8 mg/kg dose level. The maximum tolerated dose (MTD) was defined as 1.8 mg/kg IV administered every 3 weeks.

The clinical safety data observed in the Phase 1 dose-escalation study of brentuximab vedotin administered once every 3 weeks support the 1.8 mg/kg dose level as the MTD and this dose and schedule has been selected for Phase 2 studies. Overall, the most frequent adverse events related to SGN-35 treatment have been constitutional (fatigue), gastrointestinal (diarrhea, nausea), respiratory (cough), and hematologic (neutropenia). In general, there were fewer related and less severe adverse events in patients treated at the 1.8 mg/kg dose level compared to patients treated at the 2.7 mg/kg dose level. Fewer cases of hematologic toxicity, specifically neutropenia, thrombocytopenia, anemia, and neutropenic fever, were observed in the 1.8 mg/kg cohort compared to the 2.7 mg/kg cohort.

Concentration-time profiles for both brentuximab vedotin and MMAE given at 1.8 mg/kg every 21 days for 6 cycles of treatment were simulated in pediatric (12 years) and adult

patients using a population pharmacokinetic model. Within each gender, brentuximab vedotin exposure (median and 90% prediction intervals) was comparable between pediatrics and adults. Exposure to MMAE in the pediatric population (40 kg body weight) was significantly lower than in adults. Based on these simulations, the exposure to brentuximab vedotin and MMAE was comparable or significantly lower in pediatrics. Therefore pediatric and adult patients, regardless of gender, can be administered the same dose of brentuximab vedotin.

Phase II experience: 102 patients were treated in a multicenter pivotal phase II study of brentuximab vedotion. The dosing level and schedule was 102 patients relapsed post ASCT, using brentuximab vedotin 1.8 mg/kg intravenously every 3 weeks. The overall response rate was 75% (Chen et al.), with 34% complete response rate and tolerable toxicity. The toxicity profile is similar to the phase I experience published by Younes et al. (2010). Here we propose to use brentuximab vedotin as single agent salvage therapy, prior to AHCT, in an attempt to more effectively bring disease under control with minimal toxicity before transplant. We will be using the same dose of 1.8 mg/kg intravenously every 3 weeks since this dosing already has established efficacy and safety profile. We will use a maximum of 4 cycles in this study prior to AHCT

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

1.4 Rationale for New Cohort :

With 30 evaluable patients to date, data from the phase II portion of this study show an ORR of 75% and a CR rate of 33.3%. Among patients who achieved CR after 2 cycles of treatment, all remained in CR after 2 additional cycles of treatment and were able to proceed to AHCT without further intervening therapy. For patients who only achieved PR or SD after 2 cycles of therapy, 2 additional cycles of brentuximab vedotin, given at the 1.8mg/kg dose, did not change the response rate in any patient, either from PR to CR or SD to PR. Ultimately all patients, with the exception of one went on to AHCT after additional therapy. Although it is medically acceptable and allowed as part of the COH standard operating procedure to take a patient with PR to AHCT, retrospective data from Memorial Sloan Kettering show better PFS when patients enter AHCT with CR as disease status (Moskowiz et al.). For that reason, the majority of our patients in PR or SD received combination chemotherapy such as ICE (ifosphamide, Cyclophosphamide, Etoposide) to convert from PR to CR or SD to PR/CR before AHCT.

Because data from the phase II portion of this study showed that the observed conversion

rate to CR, among patients who were in PR or SD after 2 cycles of treatment, was 0, a new cohort of ~20 patients is now proposed to evaluate the impact of treating non-CR patients with a higher brentuximab vedotin dose of 2.4 mg/kg) during cycles 3 and 4 – within dose levels shown to be safe in previous studies. In the phase I dose escalation study of brentuximab vedotin (SG035-0001) by Younes et al. 2010, 2 dose levels were explored; 12 patients each were treated at dose levels 1.8 mg/kg and 2.7 mg/kg, with brentuximab vedotin administered on an every-3rd-week schedule. Of the patients treated at 2.7 mg/kg, 3 of 12 (25%) had a dose limiting toxicity compared to 1 of 12 (8%) treated at 1.8 mg/kg. DLT were grade 3 hyperglycemia, grade 3 prostatitis, and grade 3 febrile neutropenia. Due to similar rates of overall response and lower toxicity, 1.8 mg/kg given every 3 weeks was the dose and schedule chosen to move forward in phase 2 studies of Hodgkin and systemic anaplastic large cell lymphoma. Furthermore, in a recent phase II study, COH IRB#12282, a dose of 2.4 mg/kg was administered safely to patients with non-lymphomatous cancers, so we have chosen this same dose level. Although the phase I study did not show differences in response between 1.8 mg/kg and 2.7 mg/kg, we hypothesize that there may be a dose response. There are some reports of dose response relationship anecdotally in the initial pivotal trial where patients were given up to 16 cycles of BV at 1.8 mg/kg. One or two patients developed progressive disease when dose was reduced to 1.2 m/kg for toxicities and went into partial remission again when dose was increased to 1.8 mg/kg.

Based on these data and data from the phase II portion of this study, we now propose to enroll a new cohort study of up to 20 additional patients until we have 10 non-CR patients (after two cycles of therapy) that are treated at the increased dose of 2.4 mg/kg of brentuximab vedotin. The goal of this study is to evaluate the impact of treating non-CR patients (after two cycles of therapy) at an increased dose (from 1.8 mg/kg to 2.4 mg/kg) during cycles 3 and 4. We have decided not to treat everyone at 2.4 mg/kg from cycle 1, since 33% of patients already achieve CR with 1.8 mg/kg; only patients who do not achieve CR require increased dosing. We believe that the 2.4 mg/kg dose will be well tolerated in cycles 3 and 4 and that treating the non-CR patients at this dose would increase the CR rate. If the 2.4 mg/kg dose in cycles 3 and 4 allows patients to convert to CR, it could spare patients a harsher salvage treatment such as ICE and also potentially improve the likelihood of a successful autologous transplant. Combination ICE chemotherapy yields a neutropenic fever rate of over 20% and all patients require 3 days of hospitalization. The DLTs experienced (3/12 patients, 1 grade 3 hyperglycemia, 1 g3 prostatis, and 1g3 febrile neutropenia) at the 2.7 mg/kg dose in the Phase I trial are far less severe than those typically seen with ICE. Also, among the37 patients treated in this phase II study, no patient has required dose reduction from 1.8 mg/kg, therefore, we believe the 2.4 mg/kg dose will be well tolerated and have included dose-modification criteria to reduce to 1.8 mg/kg if necessary.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the activity of salvage brentuximab vedotin in Hodgkin lymphoma prior to autologous hematopoietic stem cell transplantation, as measured by overall response rate.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To characterize the safety, toxicity and tolerability of brentuximab vedotin as a salvage regimen.
- To summarize the stem cell mobilization results of patients receiving brentuximab vedotin as salvage therapy (e.g., total CD34+ cell yield, number of apheresis days, proportion of patients who achieve $\geq 3 \times 10^6$ CD34+ cells/kg)
- To evaluate potential changes in Hodgkin lymphoma biological markers of patients treated with brentuximab vedotin as 1st line salvage therapy.
- To examine and characterize the outcomes of patients who receive brentuximab vedotin as 1st line salvage followed by AHCT (e.g., 2-year PFS/OS/relapse-progression incidence and NRM).

2.3 Objectives of the New Cohort

As part of a new cohort, 20 additional patients will be accrued. ,Patients treated as part of the new cohort who do not achieve CR at the end of cycle 2, will receive an escalated dose of 2.4 mg/kg of brentuximab vedotin during cycles 3 and 4. In addition to the original objectives of the Phase II study, patients treated at the higher dose will also be evaluated for the impact of the higher dose on response rate and toxicity after cycle 4.

3 INVESTIGATIONAL PLAN

This is an open label, phase II study of brentuximab vedotin in patients with Hodgkin lymphoma prior to autologous hematopoietic stem cell transplantation (AHCT). Patients must have either primary refractory disease (failed to achieve complete remission after ABVD chemotherapy) or have relapsed after ABVD. Patients cannot have had another line of treatment after ABVD. Patients may have had BEACOPP as upfront induction chemotherapy instead of ABVD. Patients also can have consolidative radiotherapy in conjunction with ABVD. Patients will start treatment with brentuximab vedotin as salvage therapy prior to AHCT. Brentuximab vedotin will be given at dose of 1.8 mg/kg on D1 every 21 days for a total of 4 cycles.

The primary efficacy endpoint of this study is response rate. This is a phase II efficacy trial. Response will be assessed according to modified criteria for malignant lymphoma, based on (Cheson *et al.* 1999) and (Cheson, *et al.* 2007). Response assessment will be performed after every two cycles.

4 SELECTION OF PATIENTS

The total number of patients to be enrolled on this study is 37. Enrollment date is defined as the first day of brentuximab vedotin treatment (i.e., Day 1 of Cycle 1).

4.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Patients must have histologically documented or cytologically confirmed Hodgkin lymphoma with CD 30 expression.
- Patients must have ANC ≥1000/μL and Plt ≥ 50,000/μL. Neupogen can be given prior to start of SGN-35 and during SGN-35 treatment to achieve target ANC ≥ 1000/uL. Platelet transfusion can also be given prior to the start of SGN-35 and during SGN-35 treatment to achieve a target plt ≥ 50,000/uL.
- Patients must have measurable disease > 1.5 cm evidenced by CT scan of the neck/chest/abd/pelvis or CT/PET scans.
- Patient must be either primary refractory to one frontline induction therapy or relapsed after one frontline induction therapy. Patients who do not achieve complete remission after induction therapy are also eligible.
- Patients cannot have had a second line salvage treatment (chemotherapy, biologic agents, investigational drugs, or radiation) or have had an autologous or allogeneic hematopoietic stem cell transplantation. Patients can have had mixed frontline therapy such as 2-4 cycles of ABVD followed by 2-4 cycles of BEACOPP as long as the induction chemotherapy is not more than 8 cycles in total length.
- Radiation use as part of induction regimen or consolidation (within 90 days after completion of induction chemotherapy) is allowed.
- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
- Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.
- Male subject agrees to use an acceptable method of contraception for the duration of the study.
- Age > 10 years old. Life expectancy of greater than 3 months.
- Karnofsky performance status of > 60%.
- Patients must have normal organ and marrow function as defined below:
  - ANC ≥ 1000/μL
  - Plts ≥ 50,000/μL

- Total bilirubin within 1.5x of the upper limit of normal institutional limits, patients with elevation of unconjugated bilirubin alone, as in Gilbert's disease, are eligible.
- AST/ALT < 2.5 X institutional upper limit of normal (unless demonstrated Hodgkin lymphoma involvement of the liver).
- Calculated creatinine clearance > 30 ml/min (unless demonstrated Hodgkin lymphoma involvement of the kidney).

4.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

- Patient has > 1.5 × ULN total bilirubin, unless history of Gilbert's syndrome.
- Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.4), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at Screening has to be documented by the investigator as not medically relevant.
- Patient has hypersensitivity to brentuximab vedotin
- Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
- Patient has received other investigational drugs within 14 days before treatment of treatment with brentuximab vedotin
- Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
- Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
- Patients with other active malignancies (no evidence of other cancer or life expectancy greater than 5 years) are ineligible for this study.
- Patients with active CNS disease or history of brain mets are excluded from study.
- Patients may be on steroids prior to initiation of treatment as long as by cycle 1 day 1 steroids use was tapered down less than or equal to 20 mg of prednisone.

4.3 Eligibility for 2.4 mg/kg dosing in the new cohort

- In addition to the inclusion/exclusion criteria as outlined above, to be eligible for treatment with the higher 2.4 mg/kg dose of brentuximab vedotin in the new cohort of 20 additional patients, best response after 2 cycles of brentuximab

vedotin administered at the 1.8 mg/kg dose, must be PR or SD as determined by radiographic imaging.

4.4 Registration Processes

Eligible patients will be given the opportunity to participate in the study. The goals of the study will be described and the patient will be given a copy of the informed consent to review. The interested patient will sign the consent form and retain a copy.

Registration Process (City of Hope patients)

- Registrations for this protocol must be made through the CTO office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m., Monday through Friday (except holidays).
- Patients must be registered prior to initiation of protocol therapy.
- A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact (626) 256-4673 ext. 62468 and ask for the CRA in charge of this study.
- Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to the study calendar.
- Patients must sign an informed consent prior to registration.
- Confirm that the patient meets all inclusion and exclusion eligibility criteria for the protocol.
- Completion of the Eligibility Checklist (per institutional guidelines).
- Verify that all required prestudy tests were performed.
- Fax the completed Eligibility Checklist and the signed, dated informed consent to CTO. The FAX number is (626) 301-8393.
- Call CRA at (626) 256-4673 x 62468 to confirm the FAX arrival. If the CRA is not in the office, have him/her paged.
- If the patient qualifies, the CRA will assign the patient's study ID number.
- Once a patient has been registered, CRA will confirm registration of the patient.

The outside institution patient registration process will be handled by the Department of Clinical Research Information Support (CRIS) Data Coordinating Center (DCC) at City of Hope. Documentation of current IRB approval must be on file with the DCC prior to registration of patients on this study for participating institutions.

The steps below are to be taken when registering a **patient at a participating institution**:

Registration Process (Participating Institutions)

- The participating institution's research staff must assure they have the most current and updated version of the protocol and informed consent

prior to enrolling a patient. If a question arises, please contact the Data Coordinating Center at 626-256-4673 extension 63968 or via pager at 626-423-6486.

- The participating institution must assure that all prestudy laboratory tests, scans and x-rays have been completed prior to registration according to the study calendar.
- The participating institution must assure that the patient has signed an approved informed consent prior to registration, including Experimental Subject Bill of Rights (if applicable) and appropriate HIPAA authorization.
- The participating institution must confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol. The eligibility checklist must be completed in its entirety.
- A patient failing to meet all protocol requirements may not be registered. Patients must be registered prior to initiation of protocol therapy. \
- Once a patient is eligible, all the pre-study requirements have been fulfilled, and the informed consent obtained, the research nurse or the data manager (study coordinator) at the participating center will inform the Data Coordinating Center (626-256-4673, ext 63968; pager 626-423-6486) and FAX (fax number 626-301-8422) a copy of the signed informed consent, patients' Bill of Rights, signed HIPPA consent, completed eligibility checklist and corresponding source documentation confirming eligibility (including pathology reports, lab reports, x-ray reports, etc.).

The City of Hope Data Coordinating Center will:

- Review all materials received to ensure the patient is eligible.
- Ensure the consent form is valid and is signed correctly by all parties. If additional information is needed or should there be any questions, the Data Coordinating Center will immediately contact the participating institution and registration will not occur until all issues are resolved. No exceptions will be granted.
- The patient will be registered centrally at City of Hope.
- Confirmation of Registration will be emailed/faxed to the participating institution noting study number as well as assigning the dose (if applicable) within 24 hours via fax or email.
- The Data Coordinating Center will call the research nurse or data manager (study coordinator) at the participating site and verbally confirm registration.
- If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Data Coordinating Center should be notified of cancellations as soon as possible.

4.5 Procedures for On-Study and Treatment Deviations

Any amendments to the study protocol need to be approved by the IRB at the study sponsor site, City of Hope, and then at the participating center. All deviations or single subject exceptions to the study protocol must be reported to the primary IRB of the participating site, and to Dr. Robert Chen, the study PI at the sponsor institution.

5 STUDY TREATMENTS

5.1 Investigational Study Drug Description

SGN-35, the investigational agent under study in this protocol, is an antibody-drug conjugate consisting of the anti-CD30 antibody cAC10 conjugated to MMAE, an anti-tubulin agent.

SGN-35 is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. SGN-35 is supplied by Seattle Genetics in single-use, Type 1 borosilicate glass vials with FluroTec®-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains SGN-35, trehalose, sodium citrate, and polysorbate 80.

5.2 Dose and Administration

SGN-35 will be administered on Day 1 of each 21-day cycle. The dose of SGN-35 is 1.8 mg/kg and is administered by outpatient IV infusion given over approximately 30 minutes. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute infusion period. SGN-35 must not be administered as an IV push or bolus. SGN-35 should be administered through a dedicated IV line. SGN-35 cannot be mixed with other medications.

Dosing should be based on baseline weight; doses will be adjusted for patients who experience a ≥10% change in weight during the study. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. SGN-35 dose should be rounded to the nearest whole number of milligrams.

5.3 Required Premedication and Postmedication

Routine premedication should not be administered prior to the first dose of SGN-35. However, patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent SGN-35 infusions with premedication as described in Section 5.4 below. Patients who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with SGN-35 at the discretion of the Investigator after discussion with Seattle Genetics.

5.4 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of SGN-35. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for 60 minutes following the first infusion of SGN-

35.

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

Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent SGN-35 infusions with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25–50 mg orally or 10–25 mg IV) or according to institutional standards, administered 30–60 minutes prior to each 30-minute SGN-35 infusion. The routine use of steroids as premedication is discouraged.

5.5 Dose Modifications

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

Neutropenia: Neutropenia should be managed by dose delays and reductions. The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. In patients with recurrent Grade 4 neutropenia despite the use of growth factors, discontinuation or dose reduction of ADCETRIS to1.2 mg/kg may be considered.

Anemia and thrombocytopenia: For Grade 1 or 2, continue at same dose. For Grade 3 and 4, withhold dose until toxicity is $\leq$ Grade 2 or has returned to baseline, then resume treatment at the same dose level. For second occurrence of Grade 4, withhold until toxicity $\leq$ Grade 1 or has returned to baseline, then resume treatment at 1.2 mg/kg. If patient was already at 1.2 mg/kg, then discontinue treatment

Other Non-hematological toxicities: For Grade 1 or 2, continue at same dose. For Grade 3, withhold dose until toxicity is $\leq$ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For Grade 4, withhold until toxicity $\leq$ Grade 1 or has returned to baseline, then resume treatment at 1.2 mg/kg. If patient was already at 1.2 mg/kg, then discontinue treatment.

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

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

5.5 Dose Modifications for the New Cohort 2.4 mg/kg-treated patients

So far among the37 patients treated in this phase II study, no patient has required dose reduction from 1.8 to 1.2 mg/kg.

Peripheral Neuropathy: Peripheral neuropathy should be managed using a combination of dose delay and reduction to 1.8 mg/kg. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.8 mg/kg. For Grade 4 peripheral neuropathy, ADCETRIS should be discontinued.

Neutropenia: Neutropenia should be managed by dose delays and reductions. The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. In patients with recurrent Grade 4 neutropenia despite the use of growth factors, discontinuation or dose reduction of ADCETRIS to1.8 mg/kg may be considered.

Anemia and thrombocytopenia: For Grade 1 or 2, continue at same dose. For Grade 3 and 4, withhold dose until toxicity is $\leq$ Grade 2 or has returned to baseline, then resume treatment at the same dose level. For second occurrence of Grade 4, withhold until toxicity $\leq$ Grade 1 or has returned to baseline, then resume treatment at 1.8 mg/kg. If patient was already at 1.8 mg/kg, then discontinue treatment

Other Non-hematological toxicities: For Grade 1 or 2, continue at same dose. For Grade 3, withhold dose until toxicity is $\leq$ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For Grade 4, withhold until toxicity $\leq$ Grade 1 or has returned to baseline, then resume treatment at 1.8 mg/kg. If patient was already at 1.8 mg/kg, then discontinue treatment.

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

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

5.6 Storage and Handling

Vials containing SGN-35 must be refrigerated at 2–8 °C in an appropriate locked room

accessible only to the pharmacist, the investigator, or a duly designated person. Reconstituted SGN-35 should not be stored at room temperature. The effect of light on SGN-35 has not been assessed; therefore, it is recommended that SGN-35 vials and solutions be stored in the dark until the time of use. Reconstituted vials must not be shaken.

Drug accountability instructions are provided in the Study Manual.

5.7 Packaging and Labeling

Refer to the Pharmacy Manual for information regarding packaging and labeling.

5.8 Preparation

SGN-35 vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug disposal procedures.

SGN-35 should be reconstituted with the appropriate amount of Sterile Water for Injection, USP (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 appropriate amount of reconstituted SGN-35 should be withdrawn from the vial(s) and diluted in a 250-mL infusion bag containing 0.9% Sodium Chloride Injection, USP (see Pharmacy Manual for details).

There are no known incompatibilities between SGN-35 and polyvinylchloride bags. 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. Refer to the Pharmacy Manual for stability information.

5.9 Selection and Timing of Doses for Each Subject

All patients will receive 1.8 mg/kg SGN-35 administered as a single outpatient IV infusion on Day 1 of each 21-day treatment cycle.

5.10 Concomitant Therapy

All concomitant medications and blood products administered during the patient's participation in the study until the End of Treatment (EOT) visit must be recorded in the source document and on the CRF. All supportive measures consistent with optimal patient care should be provided throughout the study according to institution standards.

5.10.1 Required Concomitant Therapy: None

5.10.2 Allowed Concomitant Therapy

Patients may receive concomitant prednisone (or equivalent) or hormonal therapy, provided the prednisone dose (or equivalent) does not exceed 20 mg per day. The use of intermittent corticosteroid treatment to manage hypersensitivity reactions is allowed. The use of steroids to treat other medical conditions such as bleomycin lung toxicity, radiation

pneumonitis, or COPD exacerbation is also allowed. The use of benadryl or tylenol to manage infusion reaction is allowed starting from cycle 2 of treatment. Prophylactic use of Benadryl or Tylenol is not necessary at cycle 1 but can be given if patient demonstrated infusion reaction during cycle 1. 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. For patients that have achieved a response after 2 cycles of therapy and go on to receive an autologous hematopoietic stem cell transplant, patients are allowed to receive neupogen in order to collect stem cells.

5.10.3 Prohibited Concomitant Therapy:

No other approved anti-cancer treatment will be permitted during the treatment period, including chemotherapy, biological response modifiers, hormone therapy, surgery, palliative radiation therapy, or immunotherapy. No other investigational drug may be used during treatment on this protocol and concurrent participation in another clinical trial of a medical intervention is not allowed. Prednisone (or equivalent) doses of greater than 20 mg per day are not allowed.

5.11 Treatment Compliance

Subject compliance with treatment is not an issue for this trial as study drug will be administered at the study site by the investigator or investigator designee. Treatment administration data will be captured and reviewed to ensure site compliance with the treatment protocol.

6 STUDY ACTIVITIES

6.1 Schedule of Events

Concomitant medications and adverse events will be collected from the time of informed consent until the End of Treatment (EOT) visit or 30 days after the last dose, whichever is later. Other study activities are listed by visit in this section and descriptions of study assessments are presented in Section 7. A schedule of events is provided in Appendix Section 14.1.

6.2 Screening/Baseline: Days -28 to -1

- Informed consent
- Study eligibility per inclusion/exclusion criteria (see Section 4.1 and 4.2)
- Medical history
- Prior disease therapies
- Dedicated CT of chest, neck, abdomen and pelvis and CT/PET (allow up to 5 day window. Days -33 to -1)
- Bone marrow aspirate and biopsy (Note: may not need to be performed if patient had a bone marrow biopsy done at diagnosis and there was no bone marrow involvement. If a prior history of bone marrow involvement at diagnosis, a repeat

bone marrow biopsy must be done to document bone marrow status 30 days prior to 1st dose of SGN-35. If the patient had undergone another bone marrow biopsy at the time of relapse with positive involvement, and no other intervening therapy was given prior to SGN-35, no additional bone marrow biopsy is needed in the screening /baseline period).

- B symptom assessment

6.3 Screening/Baseline: Days -7 to Day 1

- Physical examination (see Section 7.3)
- Height
- Electrocardiogram
- Serum chemistry panel (see Section 7.2)
- Complete blood count (CBC) with differential (see Section 7.2)
- Pregnancy test
- Karnofsky performance status (Appendix Section 14.2)

6.4 Treatment Period: (Day 1 to Day 21)

6.4.1 Day 1 of each cycle

- Serum chemistry panel (within 1 day before dosing)
- CBC with differential (within 1 day before dosing)
- SGN-35 administration (see Section 5.2)
- Vital signs
- Weight
- Physical examination (see Section 7.3)
- Karnofsky performance status (Appendix Section 14.2)
- B symptom assessment

6.4.2 Disease Response Assessments

Responses will be assessed (between Days 15 and 21) as follows as defined in Section 7.1:

- Dedicated CT of chest, neck, abdomen, and pelvis or CT/PET: Cycles 2 and 4
- PET: Cycle 4

In addition, bone marrow aspirate and biopsy are required to confirm responses in patients who have bone marrow involvement at baseline (see Section 7.1). The follow-up bone marrow aspirate and biopsy must be done within 2 weeks of documentation of response. Once the bone marrow is negative no further bone marrow evaluations are required.

6.5 End of Treatment (21 ± 7 days after last dose of SGN-35)

Note: End of Treatment (EOT) evaluations should be obtained before initiation of non-protocol therapy.

- Electrocardiogram
- Serum chemistry panel
- CBC with differential
- Pregnancy test
- Weight
- Physical exam
- Karnofsky performance status (Appendix Section 14.2)
- Response assessment (if a radiologic assessment has not been performed within the prior 6 weeks)
- B symptom assessment

7 STUDY ASSESSMENTS

Only patients who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled onto this study.

7.1 Response Assessments

Treatment response will be assessed by dedicated spiral CT scan of chest, neck, abdomen, and pelvis and PET scans performed at protocol-specified time points (see Appendix Section 14.1 and Section 6). The determination of antitumor efficacy will be based on objective response assessments made according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007) and treatment decisions by the investigator will be based on these assessments. Clinical response of progressive disease (PD), stable disease (SD), partial remission (PR), or complete remission (CR) will be determined at each assessment. Selection of up to 6 of the largest dominant nodes or nodal masses to follow for response assessment must be PET FDG-avid at baseline. Investigator evaluation of baseline radiographic assessment will enable study enrollment per Inclusion Criteria based on the presence of measurable disease > 1.5 cm evidenced by CT scan of the neck/chest/abd/pelvis or CT/PET scans. In addition, per the Revised Response Criteria for Malignant Lymphoma, these nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

If the bone marrow was positive at baseline, a follow-up bone marrow aspirate and biopsy is required and must be negative for assessment of a CR. If the follow-up

morphology is indeterminate, the biopsy tissue must be negative by immunohistochemistry or the patient will be assessed as a PR.

Tumor imaging will be performed at screening, cycle 2, and 4.

7.2 Clinical Laboratory Evaluations

Samples will be drawn for local labs. All clinical decisions will be based on local lab results. The following laboratory assessments will be performed to evaluate safety at scheduled timepoints (see Appendix Section 14.1) during the course of the study:

- Chemistry panel, including sodium, chloride, potassium, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), creatinine, calcium, albumin, glucose (fasting levels are to be assessed at baseline; non-fasting levels are to be assessed at other timepoints), total bilirubin, alkaline phosphatase, ALT, AST, ESR, and uric acid.
- The hematology panel includes the following tests: white blood cell count, hemoglobin/hematocrit, platelets and the differential includes: neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

7.3 Other Study Assessments

Other study assessments include the following:

- Biopsies for CD30 expression: Results of CD30 expression from the most recent post-diagnostic biopsy of relapsed/refractory disease may be obtained from pathology reports of an archived tumor block or slides or a fresh biopsy to enable study enrollment (per inclusion criteria). The archived tumor block or slides must be submitted for central pathology review. In addition, a tumor block or slides from the original diagnostic biopsy should be submitted when available. These should be submitted to the pathology department
- Patient medical history, including a thorough review of:
  - The patient's current and previous conditions.
  - Disease status after each previous systemic therapy received prior to entering this study.
  - Concomitant medications and prior therapies.
- Physical examination, including evaluation of skin, HEENT (head, eyes, ears, nose, and throat), nodes, heart, lungs, abdomen, back, extremities, and neurology.
- Karnofsky performance status (see Appendix section 14.2).
- B symptom assessment (unexplained fevers greater than 38°C, drenching night sweats and/or weight loss greater than 10% of body weight).
- Electrocardiogram.
  - FACT/GOG Neurotoxicity questionnaire to be done at screening, before every cycle and at the end of study visit.

- Tumor biopsies for patients who develop progressive disease during the course of brentuximab vedotin therapy as long as medically safe (optional)

7.4 Pharmacodynamic/Pharmacogenomic/Correlative Studies

A paraffin block from the representative diagnostic section or 12 unstained paraffin slides will be obtained from diagnostic materials and also at the time of relapse (if available). We will analyze for CD 30 and CD 68 expression. We will confirm CD 30 expression prior to enrollment in trial. Patients must have CD 30 expression in original diagnostic material or relapsed material. We will examine the CD 68 expression in the original and relapsed material and attempt to correlate with response. For patients who have biopsy material available at relapse or progression, we will collect DNA/RNA from the tumor specimen and perform microarray analysis and compare with before and after treatment.

7.5 Safety Measurements

Safety measurements will consist of monitoring and recording all adverse events, including serious adverse events, the regular monitoring of hematology, serum chemistry, routine monitoring of vital signs (heart rate, blood pressure, and body temperature) and physical condition. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, Version 4.0.

8 STATISTICAL PROCEDURES.

8.1 Sample size calculations.

The aim of this study is to estimate the efficacy of this salvage bretuximab vedotin treatment for Hodgkin lymphoma prior to autologous hematopoietic stem cell transplantation. Treatment will be given once every three weeks in a 21 day cycle. Based on historical data, the assumed ORR in this patient population is 60%. The objective of this study is to be able to detect an ORR of at least 60%. The study will utilize a Simon two-stage optimal design. Twenty three (23) subjects will be enrolled in the first stage. If 12 or more subjects respond, an additional 14 subjects will be enrolled (for a total sample size of 37). The null hypothesis will be rejected if 23 or more of the total sample size of 37 respond. This design is based on the use of a two sided test at the 5% level of significance and provides 80% power.

Analysis: Response rates will be calculated as the percent of evaluable patients that have confirmed CR or PR by radiographic response including CT and/or PET scans, and exact 95% confidence intervals will be calculated for this estimate. Time to response, duration of response, and survival will be estimated using the product-limit method of Kaplan and Meier. Toxicity information recorded will include the type, severity, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity. Baseline information (e.g. the extent of prior therapy) and demographic information will be presented, as well, to describe the patients treated in this study.

Based on the current referral patterns it is expected that 37 patients will enrolled in this study over the course of 3 years.

In accordance with the primary study objectives, we will perform descriptive statistical analyses on these data after the study is complete. With adequate follow-up time, the endpoints of PFS, overall survival (OS) will be assessed by Kaplan-Meier survival analysis and 95% confidence intervals will be calculated using Greenwood's formula. PFS will be defined as the time from first treatment day (post AHCT) until objective or symptomatic relapse or death as a result of lymphoma or acute toxicity of treatment. OS will be defined as the time from first treatment day (post AHCT) until death. The cumulative incidence of relapse/progression and non-relapse mortality will be calculated as competing risks.

8.2 New Cohort to Test Increased Dosing for Patients Not Achieving CR after Two Cycles

Based on previously published brentuximab vedotin response/toxicity data and data from the phase II portion of this study (see protocol section 1.3), we now propose to accrue up to 20 additional patients in a new cohort that will enroll until we have 10 patients who do not attain CR after two cycles of therapy, and are treated at the increased dose of 2.4 mg/kg of brentuximab vedotin for cycles 3 and 4. The goal of this study is to evaluate the impact of treating non-CR patients (after two cycles of therapy) at an increased dose (from 1.8 mg/kg to 2.4 mg/kg) during cycles 3 and 4. We believe that the 2.4 mg/kg dose will be well tolerated (defined as $\leq$33% of patients with $\geq$ grade 3 non-hematologic toxicity that is assigned an attribution level of at least possibly related to the study drug during cycle 3 or 4) and that treating these patients at the increased dose will increase the CR rate.

With a CR rate of 33.3% -after two cycles of therapy, we expect to achieve 10 patients without CR (in the first 2 cycles) after 15 patients are enrolled (maximum enrollment 20, which has >90% chance of having 10 patients without CR in first two cycles). With 10 patients treated at the escalated dose of 2.4 mg/kg, with a conversion rate of 25%, the probability of not getting at least one response is less than 6%. If the first 2 cycle response data are pending, accrual will not hold. Accrual will only hold based on stopping due to toxicity, or when 10 patients are treated at the escalated dose of 2.4mg/kg. Patients who are treated with at least one cycle at 2.4 mg/kg will be evaluable at that dose level, even if later dose reduced or discontinued.

8.3 Randomization and Stratification

Randomization and stratification will not be used in this study.

8.4 Populations for Analysis

Hodgkin lymphoma patients refractory to induction chemotherapy or 1st relapsed after induction therapy.

8.5 Statistical methods

The toxicities observed will be summarized in terms of type (e.g. organ affected or ANC) severity (by NCI CTCAE 4.0 and nadir or maximum values for the laboratory measures), date of onset, duration, reversibility, and attribution. Table will be created to summarize these toxicities and side effects. Baseline information (e.g., the extent of prior therapy) and demographic information will be presented for all patients.

In accordance with the primary study objectives, we will perform descriptive statistical analyses on the data after the study is complete. Response will be assessed by Cheson 2007 criteria and reported as percentage of the evaluable study population. With adequate follow-up time, the secondary endpoints of PFS, overall survival (OS) will be assessed by Kaplan-Meier survival analysis and 95% confidence intervals will be calculated using Greenwood's formula.

9 PROTOCOL DEVIATIONS

9.1 Deviation policy

Brief interruptions and delays may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illnesses not related to disease progression. These delays of up to three days will not be considered protocol deviations.

Planned deviations may be permitted in accordance with the COH policy on "Clinical Research Protocol Planned Deviations and Single Subjects Exception." These planned deviations, considered Single Subject Exceptions, are considered an amendment to the protocol. In addition, if contractually obligated, the sponsor must also approve any planned deviations.

9.2 reporting of unplanned deviations

All unplanned deviations will be reported to the COH DSMB who will forward to the IRB follow review.

9.3 Resolving disputes.

If there is a dispute among the persons involved in the provision of research treatment, in regard to whether a treatment deviates from the protocol, resolution will be resolved in accordance with the Clinical Research Protocol Planned Deviations and Single Subject Exception policy.

10 RESULTS REPORTING

The COH, as sponsor of IND #pending, will submit reports annually to the FDA within 60 days of the anniversary date that the IND went into effect in accordance with 21 CFR 312.33.

11 HUMAN SUBJECTS PROTECTION

11.1 Data and Safety Monitoring

11.1.1 Definition of Risk Level

This is a Risk Level 4 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx involving COH as IND holder.

11.1.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA/protocol nurse, and statistician is

responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy.

Data and safety will be reported to the COH DSMC using the PMT report and submitted quarterly from the anniversary date of activation. Protocol specific data collection will include the following items: hematological response, and toxicities of treatment. Reporting of data and safety to the DSMB will occur at the time of planned endpoints or unanticipated problems and at least once per year using the PMT report. The planned endpoint is overall response rate as determined by radiographic imaging after 2nd and 4th cycle of treatment. We will perform interim analysis after 17 patients have accrued on study and report to the DSMB and also after 37 patients have accrued on study.

11.2 Adverse Event Definitions

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

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

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event* that results in any of the following outcomes:

- Death
- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary Malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical

intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience or outcome that **meets all three** of the following criteria:

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

11.3 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the continuation reports and PMT reports (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

Externally Sponsored Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED[1]**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 1 and 2	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

ADDITIONAL REPORTING REQUIREMENTS

SAEs meeting the requirements for expedited reporting to the FDA, as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting which can found at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the following:

- any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];

- any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]

- any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

11.4 Adverse Events Reporting – Reporting of City of Hope Patients

In addition to reporting to COH DSMB and IRB, SAEs must be reported to Seattle Genetics. The procedures are as follows:

AEs which are serious must be reported to Seattle Genetics from first dose of brentuximb vedotin up to and including 30 days after administration of the last dose of brentuximb vedotin. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Any SAE that occurs at any time after completion of brentuximb vedotin treatment or after the designated follow-up period that the investigator and/or sub-investigator considers to be related to any study drug must be reported to Seattle Genetics. Planned hospital admissions or surgical procedures for an illness or disease that existed *before the patient was enrolled in the trial* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

This is an investigator-initiated study. The principal investigator (who may also sometimes be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

Sponsor-investigator must report all SAEs, regardless of expectedness or relationship with any study drug, to Seattle Genetics as soon as possible, but no later than 5 calendar days from the sponsor-investigator's observation or awareness of the event. In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Seattle Genetics from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to Seattle Genetics, unless otherwise agreed between the sponsor-investigator and subinvestigator(s). Seattle Genetics (or designee) may request follow-up information to a reported SAE, which the sponsor-investigator will be responsible for providing to Seattle Genetics (or designee).

Seattle Genetics will provide a sample SAE Report Form representative of the information Seattle Genetics may request in follow-up (see Appendix Section 14.10.).

The SAE report must include event term(s), serious criteria, and the investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration.

Intensity for each SAE, including any lab abnormality, will be determined by using the NCI CTCAE, version 4.0, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Seattle Genetics with a copy of all communications with applicable regulatory authorities related to the study or study drug(s), including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of such communication.

Seattle Genetics will send to the sponsor-investigator a monthly listing of the SAE reports received for SAE verification. Sponsor-investigator will be responsible for forwarding such reports to any subinvestigator(s).

Seattle Genetics
SAE and Pregnancy Reporting Contact Information:
North America
PPD, Inc.
Safety and Medical Management, US
Fax: 425-527-4308
Hotline number (available 24/7): 866-333-6627
Product complaints call number: 425-527-4000

11.5 Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

11.6 Safety Reporting Requirements and Timelines – Participating Sites

The guideline is to provide a procedure for accurate and timely reporting of serious adverse events (SAEs) from the participating institution to the Principal Investigator (PI) at City of Hope (COH). The participating institution, participating PI and/or study coordinators are responsible for reporting all serious adverse events immediately (within 24 hours after learning of the event) to their local IRB, the PI at City of Hope, and the Data Coordinating Center at COH.

The participating investigator must report each serious adverse event, regardless of attribution, to the Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

Report to City of Hope all serious adverse events by telephone (to Dr. Robert Chen and the DCC) and send via fax a copy of the following forms:

- Participating sites internal serious adverse event form.
- Seattle Genetics Serious Adverse Event Form (located at end of the protocol)
- Notification of Toxicity Form (located at end of the protocol)

SAE Notification Contact Numbers:

Dr. Robert Chen	Phone: 626-256-4673x65298	Fax: 626-301-8116
Data Coordinating Center	Phone: 626-256-4673x63968	Fax: 626-301-8422

The Data Coordinating Center at City of Hope will send a copy of the participating institutions serious adverse event (Seattle Genetics Form) to the following internal departments:

- City of Hope IRB and DSMC (as appropriate)
- City of Hope Office of IND Development and Regulatory Affairs
- Seattle Genetics (PPD, Inc. Safety and Medical Management)

Any supporting documentation to the reports (i.e., laboratory, pathology, progress notes, discharge summary, autopsy, etc.) explaining the adverse event should also be submitted to the Data Coordinating Center at City of Hope. The Data Coordinating Center will then submit to our COH IRB as well as submit to Seattle Genetics in a timely manner.

11.7 Participation of Children

Participants under the age of 10 will be excluded from study because no dosing or adverse event data are currently available for the use of brentuximab vedotin in participants < 10 years of age.

11.8 Evaluation of benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrences of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in protocol Appendix Section 14.5. If patients suffer any physical injury as a result of participation in this study, immediate medical treatment is available. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

12 ADMINISTRATIVE REQUIREMENTS

12.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see section 14.5). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Seattle Genetics requests that informed consent documents be reviewed by Seattle Genetics or designee prior to IRB/IEC submission.

12.3 Patient Information and Informed Consent

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

12.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Seattle Genetics or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.5 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Seattle Genetics and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Seattle Genetics and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

12.6 On-site Audits

Regulatory authorities, the IEC/IRB and/or Seattle Genetic's clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

12.7 Drug Accountability

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Seattle Genetics or disposal of the drug (if applicable and if approved by Seattle Genetics) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing brentuximab vedotin will be treated and disposed of as hazardous waste in accordance with governing regulations.

12.8 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Seattle Genetics, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Seattle genetics by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to patients
2. Failure to enter patients at an acceptable rate
3. Insufficient adherence to protocol requirements
4. Insufficient complete and/or evaluable data
5. Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study materials must be returned to Seattle Genetics.

12.9 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

12.10Product Complaints

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Seattle Genetics and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Seattle Genetics quality representative.

For Product Complaints, call 425-527-4000

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