Brentuximab Vedotin (SGN-35) in Transplant Eligible Patients with Relapsed or Refractory Hodgkin Lymphoma

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program. Memorial Sloan-Kettering Cancer Center

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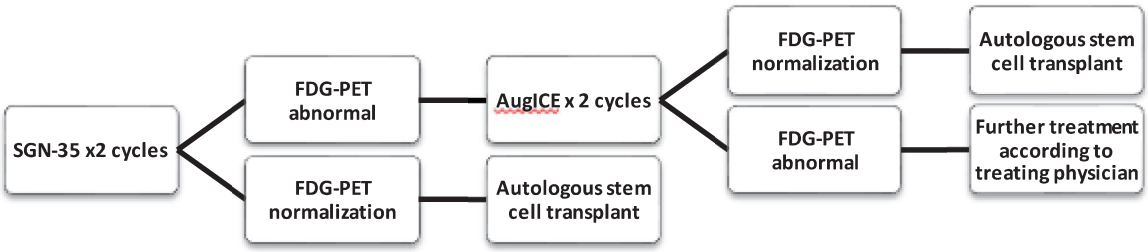
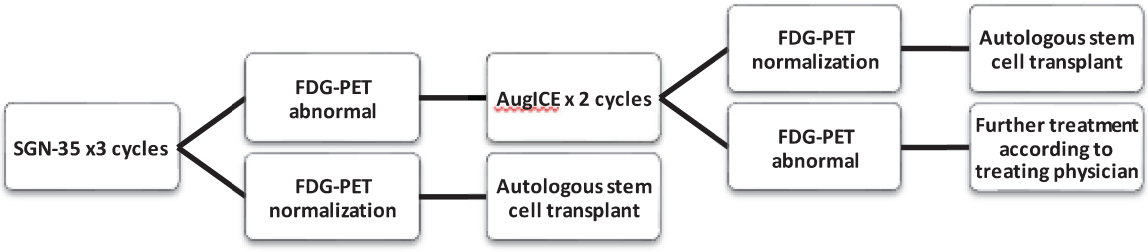
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

In this study, we plan to treat patients with 2 cycles of weekly brentuximab vedotin (SGN-35); patients who achieve FDG-PET/CT normalization will proceed directly to autologous stem cell transplant (ASCT) and avoid salvage treatment with ifosfamide, carboplatin, and etoposide (ICE). Patients with persistent FDG-PET/CT abnormalities will receive 2 cycles of augmented ICE chemotherapy followed by repeat FDG-PET/CT. We aim to evaluate the rate of FDG-PET/CT normalization following 2 cycles of weekly brentuximab vedotin with or without augmented ICE in transplant eligible patients with relapsed or refractory HL. This study will enroll 46 patients.



Expansion Cohort

We will expand this study to include 20 additional patients. The expansion would again enroll patients who fail their front-line therapy for HL; however they will receive 3 cycles of weekly BV followed by reassessment by FDG-PET. Those who score Deauville 2 or better will proceed to ASCT while all others will receive 2 cycles of augmented ICE prior to consideration for ASCT. We aim to evaluate the rate of FDG-PET/CT normalization following 3 cycles of weekly brentuximab vedotin with or without augmented ICE in transplant eligible patients with relapsed or refractory HL.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objectives

1. Determine the rate of FDG-PET/CT normalization following salvage therapy with brentuximab vedotin (SGN-35) alone or followed by augmented ICE chemotherapy

Secondary objectives

1. Rate of FDG-PET/CT normalization with respect to the presence of previously determined prognostic factors: extranodal disease, bulk ≥ 5cm, relapse within previously radiated fields, relapse within 1 year of initial treatment, and presence of B symptoms at relapse
2. Determine overall response rate (CR and PR) rate to brentuximab vedotin alone
3. Toxicity from brentuximab vedotin alone and followed by augmented ICE chemotherapy
4. Evaluate progression free survival (PFS) and overall survival (OS) with this treatment program and their correlation with: ΔSUVmax, expression of CD68, FoxP3, and TIA-1 by immunohistochemistry, serum cytokine levels, and the clinical factors listed in secondary objective #1.
5. Determine number of CD34 cells collected following this treatment program.

3.0 BACKGROUND AND RATIONALE

Introduction

We have reported that patients with relapsed or refractory Hodgkin lymphoma (HL) who achieve FDG-PET/CT normalization prior to autologous stem cell transplant (ASCT) have an excellent outcome with 5 year progression free survival of 75%. Current standard salvage regimens for relapsed and refractory HL include ICE or DHAP chemotherapy. These regimens are associated with significant hematologic toxicity and therefore effective and less toxic treatments are needed. Brentuximab vedotin (SGN-35) is well tolerated and highly active in patients with relapsed or refractory HL who have failed ASCT. Weekly administration of this agent has yielded complete responses in patients after only 2 cycles (8 weeks) making this an attractive agent to test as a pre-ASCT salvage regimen.

Pre-transplant FDG-PET in Hodgkin lymphoma

The majority of patients with Hodgkin's Lymphoma (HL) are cured with radiation therapy and/or combination chemotherapy. However, patients who relapse after attaining a complete remission with chemotherapy and those with primary refractory disease have a poor outcome with conventional salvage regimens. Randomized studies have established high dose chemotherapy followed by autologous stem cell transplant (ASCT) as the standard treatment for relapsed or refractory (rel/ref) HL[1, 2] following response to salvage chemotherapy (ST). Unfortunately, about 50% of patients with rel/ref HL will fail ASCT and the prognosis for these patients is grim[3]. Since 1994, 4 consecutive phase II studies have been performed at

MSKCC using ICE (ifosfamide, carboplatin, and etoposide)-based salvage therapy (ST) followed by ASCT for patients demonstrating chemosensitivity. In the earliest studies, protocols 94-68 and 97-51, all patients with rel/ref HL received uniform ST with ICE followed by ASCT and multivariate analysis identified 3 factors that predicted for outcome: B symptoms, extranodal disease, and complete remission less than 1 year from induction therapy[4]. The next study, 98-71, employed risk stratified salvage therapy based upon the presence of the 3 risk factors (RFs) identified in the earlier studies. Patients with 0-1 RFs received standard ICE, 2 RFs received increased dose ICE ("augmented ICE") and patients with all three RF received tandem transplants. This risk stratified approach diminished the prognostic difference between low risk and higher risk patients. Furthermore, an important finding from this study was that functional imaging (gallium or FDG-PET) status before ASCT strongly predicted outcome following transplant. A combined analysis of patients from protocols 94-68, 97-51, and 98-71 revealed a 5 year EFS of 75% for patients with functional imaging (FI)–normalization compared to 31% for patients with persistent abnormalizations on FI-suggesting that normalization of FI following ST should be a goal for patients proceeding to ASCT for rel/ref HL.[5] These findings led to the design of our most recent study in rel/ref HL, 04-047, in which patients are again treated with risk stratified ST; however those with persistent abnormalities on FI (FDG-PET/CT primarily used in this study) receive additional non-cross resistant gemcitabine-based (GND) chemotherapy before ASCT. FDG-PET/CT was repeated after GND and those with responding disease proceeded to ASCT. Of 98 patients enrolled on this study, 33 received GND for persistent FDG-PET/CT abnormalities; 17 subsequently achieved FDG-PET/CT normalization following GND and had similar favorable outcomes to those who achieved FDG-PET/CT normalization from ICE alone[6]. These findings confirm the notion that normalization of FDG-PET/CT should be the goal of ST prior to ASCT in rel/ref HL. Our combined analysis of the 3 protocols, 94-68, 97-51, and 98-71 also revealed that patients with persistent pre-ASCT FI abnormalities who are ineligible for involved field radiation (due to previous radiation therapy or extranodal disease) have particularly poor outcomes suggesting that alternatives to autologous stem cell transplant (such as allogeneic stem cell transplant) should be evaluated.[5]

Factors that predict response to ICE salvage therapy

All patients have received ICE-based ST for rel/ref HL at our institution since 1994; therefore we recently pooled this data to identify factors predictive of FI normalization following ICE. Between 9/1994 and 4/2010, 277 patients with rel/ref HL were treated on 1 of 4 studies described above. Two hundred and seventy-one patients underwent evaluation with FI before and after ST; 62% of these patients were evaluated with FDG-PET/CT. One hundred sixty-five (60%) patients achieved normalization of functional imaging following ST. Univariate and multivariate analysis to identify factors associated with failure to normalize FI was performed and four factors remained significant by multivariate analysis: bulk ≥ 5cm, relapse within previously radiated fields, relapse within 1 year of initial treatment, and presence of B symptoms at relapse. The numbers of patients with 0, 1, 2, 3, or 4 risk factors were 31, 100, 83, 38, and 4 and the rate of FI normalization by risk factor group was 87%, 76%, 50%, 34%, and 0% respectively. Patients with 0-1 risk factors have a high rate of FI normalization with ICE ST and may be candidates for less intense therapy. In contrast, patients with 3-4 risk factors are at high risk for persistent FI abnormalities following ICE treatment and therefore may benefit from more novel salvage therapy, such as an antibody-

drug conjugate. As described below, brentuximab vedotin (SGN-35) is a highly effective treatment in rel/ref HL that is generally well tolerated and therefore may represent a better option for patients both at low risk and high risk of failing to normalize FI following ICE-based treatment, therefore we plan to treat all risk cohorts with brentuximab vedotin with or without augmented ICE and analyze the results according to risk group.

The majority of patients enrolled on the MSKCC studies described above had 0-2 risk factors (risk factors = b symptoms, extranodal disease, and relapse within 1 year). Since 2004, patients with all 3 risk factors were enrolled on a different study evaluating allogeneic stem cell transplant and therefore are not well represented in our ICE database. The true rate of FDG-PET/CT normalization following ICE chemotherapy is therefore likely lower than 60%. On this protocol, we will enroll patients with 0-3 risk factors and therefore we assumed a lower rate of FDG-PET/CT normalization from ICE chemotherapy in our biostatistics.

Brentuximab vedotin (SGN-35)

Antibody-drug conjugates (ADCs), which consist of cytotoxic agents or toxins chemically conjugated to a monoclonal antibody, 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.

Brentuximab vedotin (cAC10-vcMMAE [4]) is a novel ADC that binds to the cell-surface marker CD30. After binding to CD30-positive cells, brentuximab vedotin is internalized releasing free MMAE that leads to cell death. CD30 was originally identified on RS cells, the malignant cell in HL, and is now used as a diagnostic marker for the disease. Brentuximab vedotin induces growth inhibition of HL cell lines in vitro and inhibits disease progression in both disseminated and subcutaneous HL xenograft models in immunodeficient mice.

Two phase I studies (evaluating different treatment schedules) and a phase II study demonstrated high efficacy with acceptable toxicity for brentuximab vedotin in rel/ref HL. The first phase I study enrolled 45 patients (42 with HL, 2 with systemic ALCL, 1 with angioimmunoblastic T-cell lymphoma) treated at dose levels of 0.1 to 3.6 mg/kg administered intravenously every 3 weeks[7]. The most common adverse events were fatigue, pyrexia, diarrhea, nausea, neuropathy peripheral, and neutropenia. Dose related peripheral neuropathy and neutropenia were observed. Notable serious adverse events considered at least possibly related to treatment included anaphylaxis, myocardial infarction, and peripheral neuropathy. One patient treated with 3.6 mg/kg died of septic shock (no organism identified) and febrile neutropenia that were considered treatment related. The maximum tolerated dose of brentuximab vedotin was 1.8 mg/kg administered every 3 weeks. Evidence of objective responses in this study led to the phase II study with brentuximab vedotin 1.8 mg/kg q3week in relapsed or refractory HL[8]. This study enrolled 102 patients with relapsed and refractory HL following ASCT. The overall response rate was 75% and complete response rate 34%, establishing brentuximab vedotin as a highly effective therapy in rel/ref and heavily pre-treated HL.

The second phase I study evaluated weekly administration of brentuximab vedotin (day 1, 8, and 15 of 28 day cycles)[9]. The study enrolled 44 patients, 86% with HL. The maximum tolerated dose was determined to be 1.2mg/kg and the dose limiting toxicities were diarrhea and hyperglycemia. The incidence of peripheral neuropathy seen with this dosing schedule

was similar to that seen with every 3 week dosing. About 50% of patients experienced peripheral neuropathy, mostly grade 1 or 2. Five patients experienced grade 3 peripheral neuropathy, 3 with motor neuropathies after 4-9 months of treatment with brentuximab vedotin. Thirteen CRs and 9 PRs were seen with an overall response rate of 56%. Most notable was that the majority of the complete responses were seen at the first restaging performed 8 weeks into treatment (following 2 cycles). The tolerability, efficacy, and early responses seen with this dosing schedule make this an attractive agent to test as a salvage therapy prior to ASCT in rel/ref HL.

Rationale for salvage therapy with brentuximab vedotin

Standard salvage regimens administered before ASCT, such as ICE or DHAP, are inpatient therapies, associated with significant hematologic toxicity, and risk of myelodysplastic syndrome and infertility. A therapy that is less toxic but can still achieve the same rate of response is desirable. In particular, avoiding ICE chemotherapy, but achieving a similar rate of chemosensitivity using less toxic therapy would be considered a success. Weekly brentuximab vedotin is an attractive regimen to test in this setting because it is associated with encouraging response rates, and complete responses are seen after only 8 weeks, which is desirable for a salvage therapy leading to ASCT. In this study, transplant-eligible patients with rel/ref HL will receive 2 cycles of weekly brentuximab vedotin. FDG-PET/CT will be performed following 2 cycles and patients with PET-normalization will proceed to transplant. Patients with persistent abnormalities on FDG-PET/CT will receive standard salvage treatment with 2 cycles of augmented ICE chemotherapy prior to proceeding to ASCT.

Rationale for expansion cohort in patients who fail front-line therapy with brentuximab vedotin

As of April 2013, this study had accrued 37 of the planned 46 patients and 32 patients were evaluable for response. Of the 32 evaluable patients enrolled on this study, 9 (28%) achieved normalization of FDG-PET (referred to as “excellent responders”) and proceeded to ASCT. The remainder of the patients went on to receive augmented ICE. Although most patients did not score Deauville 2 on their post-BV PET, the majority of them achieve marked reduction in their disease burden following 2 cycles of BV (see table). In fact, 4 of the 4 patients who scored Deauville 3 and 10 of the 17 who scored Deauville 4 achieved greater than 66% reduction in SUV max on PET or had residual FDG-avidity of SUV 4 or less (referred to as “good responders”). Overall, there were 14 “good responders” and they represent a group of patients who may have achieved normalization of FDG-PET following BV if they were given an additional cycle of weekly BV.

We therefore propose an expansion to our current study for 20 additional patients. The expansion would again enroll patients who fail their front-line therapy for HL; however they will receive 3 cycles of weekly BV followed by reassessment by FDG-PET. Those who score Deauville 2 or better will proceed to ASCT while all others will receive 2 cycles of augmented ICE prior to consideration for ASCT. We hypothesize that administration of 3 cycles of BV will convert more “good responders” into “excellent responders” and allow more patients to avoid ICE chemotherapy prior to consolidation with ASCT.

Deauville score	n=32	Delta SUV (%) range*	Post-BV SUV max**	Excellent responders	Good responders
1	5	-95 to -84	1	5	0
2	4	-90 to -80	2.3	4	0
3	4	-77 to -67	2.9-3.7	0	4
4	17	-86 to -32	2.2-6.2	0	10
5	2	-63 to -13	n/a	0	0

*calculated for patients with baseline PET SUV max of ≥ 10
**shown only for patients with baseline PET SUV max of <10

Rationale for correlative studies

Immunohistochemical studies

All patients enrolled on this study will be required to have biopsy proven relapsed or refractory HL. This gives us the opportunity to prospectively analyze several markers on the biopsy specimens by immunohistochemistry. Based upon the recent report of the prognostic significance of CD68 (a marker of tumor associated macrophages)[10] on outcome in newly diagnosed HL, we will look at this marker in our relapsed/refractory population. In addition, immunohistochemical analysis of HL biopsy specimens have shown high expression of TIA-1 (markers of cytotoxic t cells) and low expression of FOXP3 (markers of regulatory T cells) to be associated with poor prognosis both following primary treatment[11] and in the relapsed/refractory setting[12]. We aim to confirm these observations and evaluate differences following treatment failure by analyzing these markers in both initial biopsies and relapsed/refractory biopsies for each patient.

ΔSUVmax analysis

For the purpose of this study, FDG-PET/CT scans will be interpreted by visual analysis where areas with uptake greater than the mediastinal blood pool will be considered positive. Visual analysis of early interim FDG-PET/CT may not represent the most accurate method of interpretation. Evaluation of changes in FDG uptake over time, rather than assessment of findings at a single time point, has been proposed as an alternative assessment. Intensity of FDG uptake can be measured as standardized uptake value, SUV, usually measured as highest activity concentration per lesion, or SUVmax. Treatment induced changes in SUV over time are referred to as ΔSUVmax. In patients with previously untreated diffuse large B-cell lymphoma, it has been suggested that these changes in SUV from baseline to interim scan after 2 cycles of chemotherapy may be more accurate than visual assessment of a single scan[13]. These authors founds that a ΔSUVmax of -67.5% between FDG-PET/CT scans performed before and after 2 cycles of chemotherapy reduced the number of false positive results and improved the prognostic value of FDG-PET/CT compared to visual

analysis. We plan to explore ΔSUVmax between FDG-PET/CT scans performed before brentuximab vedotin, after two cycles of brentuximab vedotin and after augmented ICE (if given) as a predictor of outcome. This will be done by retrospective analysis of the data set. No ΔSUVmax will be defined a priori for determination of treatment strategy.

Serum cytokines

Serum levels of various cytokines and TNF receptor family members in patients with HL have been shown to have prognostic influence on disease outcome. Sarris et al. reported the prognostic significance of serum IL-10 levels in previously untreated HL patients. Among 101 patients evaluated, 3 year failure free survival (FFS) for patients with high verse normal serum IL-10 levels was 60% and 91% respectively[14]. Casasnovas et al. described a cytokine prognostic index that predicted disease related outcome in HL[15]. They evaluated serum levels of TNF receptors (TNFα, TNF-R1, TNF-R2, CD30), and cytokines (IL-6, IL-10, IL1-RA) in 519 patients with untreated classical HL. Elevated levels of TNFα, TNF-R1, TNF-R2, IL1-RA, IL-10, IL6, and soluble CD30 (sCD30) were associated with inferior event-free survival (EFS) and overall survival (OS). Furthermore, a cytokine prognostic index which stratified patients based upon elevated serum levels of sCD30, IL-6, and IL1-RA was a strong independent predictor of EFS. The prognostic significance of cytokine and TNF expression has not been evaluated in patients with relapsed and primary refractory HL. We will evaluate serum levels of IL-10, IL-6, IL-1, and TNFα before and after 2 cycles of brentuximab vedotin.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Patients with relapsed or refractory HL who are eligible for ASCT will be enrolled. Patients will receive 2 cycles of weekly brentuximab vedotin and then undergo evaluation with FDG-PET/CT. Patients with pre-treatment positive bone marrow biopsies will have repeat bone marrow biopsies if the PET scan is negative. Patients with normalization of FDG-PET/CT and negative bone marrow biopsies will proceed to ASCT. Patients with persistent abnormalities on FDG-PET/CT will receive 2 cycles of augmented ICE chemotherapy followed by repeat FDG-PET/CT prior to ASCT. Following augmented ICE, patients with negative FDG-PET/CT will proceed to ASCT. Those with persistent abnormalities on FDG-PET/CT will be treated according to their physician's recommendations.

4.1.1 Design: Expansion Cohort

Patients with relapsed or refractory HL who are eligible for ASCT will be enrolled. Patients will receive 3 cycles of weekly brentuximab vedotin and then undergo evaluation with FDG-PET/CT. Patients with pre-treatment positive bone marrow biopsies will have repeat bone marrow biopsies if the PET scan is negative. Patients with normalization of FDG-PET/CT and negative bone marrow biopsies will proceed to ASCT. Patients with persistent abnormalities on FDG-PET/CT will receive 2 cycles of augmented ICE chemotherapy followed by repeat FDG-PET/CT prior to ASCT. Following augmented ICE, patients with negative FDG-PET/CT will proceed to ASCT. Those with persistent abnormalities on FDG-PET/CT will be treated according to their physician's recommendations.

4.2 Intervention

Patients will receive 2 cycles of weekly brentuximab vedotin, 1.2mg/kg on days 1, 8, and 15 of each 28 day cycle. FDG-PET/CT will be repeated after 2 cycles of treatment within 1 week of the last dose of cycle 2. Patients with normalization of FDG-PET/CT (and negative bone marrow biopsy) after brentuximab vedotin will proceed to arm A. Patients with persistent FDG-PET/CT abnormalities will proceed to arm B.

Arm A: Patients with normalization of FDG-PET/CT following 2 cycles of brentuximab vedotin will undergo stem cell mobilization in preparation for ASCT.

Stem cell mobilization and collection will be performed as per standard MSKCC guidelines.

Arm B: Patients with persistent abnormalities on FDG-PET/CT following 2 cycles of brentuximab vedotin will receive 2 cycles of augmented ICE. The first cycle of augmented ICE will be initiated 7-14 days after the last dose of SGN-35. FDG-PET/CT will be repeated within 21 days following the second cycle of augmented ICE. Stem cell mobilization can be performed following the first or second cycle of augmented ICE.

4.2.1 Intervention: Expansion Cohort

Patients will receive 3 cycles of weekly brentuximab vedotin, 1.2mg/kg on days 1, 8, and 15 of each 28 day cycle. FDG-PET/CT will be repeated after 3 cycles of treatment within 1 week of the last dose of cycle 3. Patients with normalization of FDG-PET/CT (and negative bone marrow biopsy) after brentuximab vedotin will proceed to arm A. Patients with persistent FDG-PET/CT abnormalities will proceed to arm B.

Arm A: Patients with normalization of FDG-PET/CT following 3 cycles of brentuximab vedotin will undergo stem cell mobilization in preparation for ASCT.

Stem cell mobilization and collection will be performed as per standard MSKCC guidelines.

Arm B: Patients with persistent abnormalities on FDG-PET/CT following 3 cycles of brentuximab vedotin will receive 2 cycles of augmented ICE. The first cycle of augmented ICE will be initiated 7-14 days after the last dose of SGN-35. FDG-PET/CT will be repeated within 21 days following the second cycle of augmented ICE. Stem cell mobilization can be performed following the first or second cycle of augmented ICE.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Brentuximab vedotin (SGN-35)
SGN-35, the investigational treatment 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. See the Pharmacy Manual for further information (Appendix 1).

Dose and Administration

SGN -35 will be administered on Day 1, 8, and 15 of each 28-day cycle. The dose of SGN-35 is 1.2 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 actual weight 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 according to institutional standards.

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 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.

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

A patient who experiences 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.

Dose Modifications

Intrapatient dose reduction to 0.8 mg/kg will be allowed depending on the type and severity of toxicity. The following table 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. Doses reduced for drug-related toxicity should generally not be re-escalated. However, intrapatient re-escalation to the previous dose level may be permitted at the discretion of the treating physician.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at same dose level.	Continue at same dose level, except in the event of Grade 2 neuropathy. For Grade 2 neuropathy, reduce dose to 0.8mg/kg. For the second occurrence of Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume at 0.8 mg/kg.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level [a]. For Grade 3 or higher neuropathy, discontinue treatment at the discretion of the investigator.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce dose to 0.8 mg/kg and resume treatment, or discontinue at the discretion of the investigator [a].
Hematologic	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is ≤ 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.	Withhold dose until toxicity is ≤ Grade 2, then resume treatment at the same dose level. Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles. For the second occurrence of Grade 4 toxicity (if neutropenia, while receiving growth factor support), withhold dose until toxicity is ≤ Grade 2, then reduce the dose to 0.8 mg/kg and resume treatment[b].

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.

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 logs must be maintained. .

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. 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 an infusion bag containing 0.9% Sodium Chloride Injection, USP.

There are no known incompatibilities between SGN-35 and polyviny1chloride 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.

Ifosfamide (Ifex®)
Mechanism of action: Ifosfamide is activated in the liver by microsomal enzymes and the subsequent ifosfamide mustard causes direct alkylation of DNA.
Formulation: Ifosfamide is supplied in single dose vials for constitution and administration by IV infusion. Each contains 1 gram or 3 grams of sterile ifosfamide.
Preparation: Injections are prepared by adding sterile water to the vial. The 1-gram dose is mixed with 20 mL and the 3-gram dose with 60 mL for a final concentration of 50 mg/mL.
Storage: The dry powder may be stored at room temperature.
Supplier: Bristol-Myers Squibb

Carboplatin (Paraplatin®)
Mechanism of action: Carboplatin binds to DNA and causes cross-linking with a non-cell cycle dependent tumor cell lysis. It inhibits DNA synthesis by altering the template via the formation of intrastrand cross-links.
Formulation: Paraplatin® is supplied as a sterile lyophilized powder available in single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by IV infusion. Each vial contains equal parts of carboplatin and mannitol.
Preparation: Immediately before use the content of each vial must be reconstituted with sterile solution: 50 mg strength with 5 mL, 150 mg with 15 mL and 450 mg with 45 mL. These solutions produce a concentration of 10 mg/mL. The solution is stable for 8 hours at room temperature.
Storage: Unopened vials are stable for the life indicated on the insert if protected from light.
Supplier: Bristol-Myers Squibb

VP-16 (etoposide, VePesid®)

Mechanism of action: Induction of an irreversible blockade of cells in the premitotic phases of the cell cycle leading to accumulation of cells in late S or G2 phases. This mechanism is secondary to interference of the scissors-reunion reaction of the enzyme topoisomerase II.
Formulation: VP-16 injection is available in 100-mg (5-mL) sterile multiple-dose vials. The pH is 3-4. Each mL contains 20-mg etoposide, 2-mg citric acid, 30-mg benzyl alcohol, 80-mg polysorbate 80, 650-mg polyethylene glycol 300 and 30.5% alcohol.
Preparation: The computed dose is diluted in 500 mL of normal saline and given by intravenous infusion over 1 hour.
Storage: Unopened vials of VP-16 are stable for 24 months at room temperature. Vials are diluted as recommended to a concentration of 0.2 or 0.4 mg/mL and are stable for 96 and 48 hours respectively, at room temperature under normal light in both plastic and glass containers.
Supplier: Bristol-Myers Squibb

Mesna (Mesnex®)
Mechanism of action: Mesna was developed as a prophylactic agent to inhibit hemorrhagic cystitis induced by ifosfamide and is analogous to the cysteine-cystine system; mesna is rapidly metabolized to mesna disulfide and acts as a free radical scavenger.
Formulation: Mesna is a sterile preservative free aqueous solution of clear, colorless appearance in clear glass ampules for IV administration. Mesna injection contains 100 mg/ml Mesna, 0.25 mg/ml acetate disodium, and sodium hydroxide to maintain pH 6.5-8.5.
Preparation: For IV administration the drug is diluted in sterile solution to make a final concentration of 20 mg/ml.
Storage: Diluted solutions are chemically and physically stable for 24 hours at room temperature. It is recommended that solutions be refrigerated and used within 6 hours.
Supplier: Bristol-Myers Squibb

G-CSF (Neupogen, Filgrastim)
Mechanism of action: Filgrastim is a human protein, which is involved in the promotion of the growth and maturation of neutrophil/granulocyte progenitors.
Formulation: Available as a recombinant DNA product supplied as 1 or 1.6 ml vials containing clear colorless sterile protein solution.
Storage: It can be stored at 2-6°C and is stable for at least 30 months.
Supplier: Amgen, Inc.

G-CSF (Neulasta, Pegfilgrastim)
Mechanism of action: Pegfilgrastim is a human protein, which is involved in the promotion of the growth and maturation of neutrophil/granulocyte progenitors.
Formulation: Available as a recombinant DNA product supplied as 6 mg/0.6 ml containing clear colorless sterile protein solution.
Storage: It can be stored at 2-6°C and is stable for at least 30 months.
Supplier: Amgen, Inc.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Histologic diagnosis of cd30 positive classical Hodgkin's lymphoma.
- Primary refractory or relapsed disease proven by biopsy or fine needle aspiration (cytology) of an involved site. Pathology must be reviewed at MSKCC.

- Relapse or refractory disease following doxorubicin or nitrogen mustard containing front-line therapy
- Fluorodeoxyglucose (FDG)-avid disease by FDG-PET/CT and measurable disease of at least 1.5 cm by spiral CT, as assessed by the site radiologist.
- Cardiac ejection fraction of greater than 45%, measured since last chemotherapy.
- Hemoglobin-adjusted diffusing capacity for carbon monoxide of greater than 50% on pulmonary function testing, measured since last chemotherapy
- Serum creatinine $\leq$1.5 mg/dl; if creatinine >1.5 mg/dl then the measured 12- or 24-hour creatinine clearance must be >60 ml/minute.
- ANC>1000/µl and Platelets>50,000/µl
- Total bilirubin < 2.0 mg/dl in the absence of a history of Gilbert's disease.
- Females of childbearing age must be on an acceptable form of birth control.
- Age between 12 and 72
- HIV I and II negative.

6.2 Subject Exclusion Criteria

- Received more than 1 prior treatment (combined modality therapy represents 1 treatment) for Hodgkin Lymphoma
- Hepatitis B surface antigen positive or hepatitis B core antibody positive.
- Known pregnancy or breast-feeding.
- Medical illness unrelated to Hodgkin's Lymphoma, which, in the opinion of the attending physician and/or principal investigator, makes participation in this study inappropriate.
- Peripheral neuropathy > grade 1

7.0 RECRUITMENT PLAN

Patients seen in the inpatient or outpatient setting who meet eligibility criteria will be recruited to this study. An attending physician of the Lymphoma or Hematology service will evaluate all patients.

8.0 PRETREATMENT EVALUATION

Prior to initiating treatment:

- Obtain tissue blocks or unstained slides (10) to confirm relapsed or refractory disease and to stain for CD68, TIA-1, and FOXP3
- Obtain tissue block or unstained slides (10) from initial diagnostic biopsy to stain for CD68, TIA-1, and FOXP3

- Bone marrow biopsy to be performed after the most recent treatment for Hodgkin lymphoma. Bilateral bone marrow biopsies to be performed if previously positive unless there was a bone marrow biopsy performed since the last treatment that was positive (then the unilateral bone marrow biopsy is sufficient).

Within 2 weeks prior to initiating treatment:

- CBC
- ESR
- Electrolytes (Na, K, Cl, CO2), BUN, Cr, bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase, uric acid, and LDH
- Hemoglobin (Hgb) A1c
- Serum ß-HCG (premenopausal females only) to assess for pregnancy
- Creatinine clearance by 12- or 24-hr urine collection if serum Cr>1.5 mg/dl
- Modified Total Neuropathy Score (mTNS) and European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire for chemotherapy-induced peripheral neuropathy (CIPN-20)

Within 4 weeks prior to initiating treatment:

- CT scan of the chest, abdomen, and pelvis
- 18F-fluorodeoxyglucose-PET/CT scan
- Echocardiogram or MUGA scan
- Pulmonary Function Testing

Within 6 months of initiating treatment

- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis C serology
- HIV I/II antibodies

9.0 TREATMENT/INTERVENTION PLAN

Patients will receive 2 cycles of weekly brentuximab vedotin, 1.2mg/kg on days 1, 8, and 15 of each 28 day cycle. See section 5.0 for dosing and administration of brentuximab vedotin. FDG-PET/CT will be repeated after 2 cycles of treatment within 1 week of the last dose of cycle 2. Patients with pre-treatment positive bone marrow biopsies will have repeat bone marrow biopsies if the PET scan is negative. Patients with normalization of FDG-PET/CT

and negative bone marrow biopsies after brentuximab vedotin will proceed to arm A. Patients with persistent FDG-PET/CT abnormalities will proceed to arm B.

Arm A: Patients with negative FDG-PET/CT following 2 cycles of brentuximab vedotin will undergo stem cell mobilization in preparation for ASCT.

Stem cell mobilization and collection will be performed as per standard MSKCC guidelines.

Arm B: Patients with persistent abnormalities on FDG-PET/CT following 2 cycles of brentuximab vedotin will receive 2 cycles of augmented ICE. The first cycle of augmented ICE will be initiated 7-14 days after the last dose of SGN-35. FDG-PET/CT will be repeated within 21 following the second cycle of augmented ICE. Stem cell mobilization can be performed following the first or second cycle of augmented ICE.

Augmented ICE will be administered as follows:

Ifosfamide (5,000 mg/m2) mixed with Mesna (5,000 mg/m2) IVCI x 2 starting on day 1
Carboplatin (AUC 5 [maximum dose 800 mg]) IVPB x 1 on day 3
Etoposide (200 mg/m2) IVPB Q 12 hours x 3 doses starting on day 1

The second cycle of augmented ICE will be initiated no sooner than 17 days after the first cycle. ANC must be ≥1000/µl and platelet count must be ≥50,000/µl for ICE to be administered. Treatment will be held until these criteria are met. No dose reductions will be allowed.

For **non-collection cycles**, either pegfilgrastim 6 mg on day after hospital discharge (completion of chemotherapy) or filgrastim 300 mcg (for patients under 70 kg) or 480 mcg (for patients over 70 kg) on days +5 to +12 will be given.

For **collection cycles**, Filgrastim at 10 mcg/kg/day will be given on day +5 and continue until stem cell collection completed (approximated to the nearest increment of Filgrastim 600 mcg, 780 mcg, 960 mcg, 1260 mcg, or 1,440 mcg).

Stem cell mobilization and collection will be performed as per standard MSKCC guidelines.

Pediatric patients will be treated in the Pediatric Day Hospital.

9.0.1 EXPANSION COHORT: TREATMENT INTERVENTION/PLAN

Patients will receive 3 cycles of weekly brentuximab vedotin, 1.2mg/kg on days 1, 8, and 15 of each 28 day cycle. See section 5.0 for dosing and administration of brentuximab vedotin. FDG-PET/CT will be repeated after 3 cycles of treatment within 1 week of the last dose of cycle 3. Patients with pre-treatment positive bone marrow biopsies will have repeat bone marrow biopsies if the PET scan is negative. Patients with normalization of FDG-PET/CT and negative bone marrow biopsies after brentuximab vedotin will proceed to arm A. Patients with persistent FDG-PET/CT abnormalities will proceed to arm B.

Arm A: Patients with negative FDG-PET/CT following 3 cycles of brentuximab vedotin will undergo stem cell mobilization in preparation for ASCT.

Stem cell mobilization and collection will be performed as per standard MSKCC guidelines.

Arm B: Patients with persistent abnormalities on FDG-PET/CT following 3 cycles of brentuximab vedotin will receive 2 cycles of augmented ICE. The first cycle of augmented ICE will be initiated 7-14 days after the last dose of SGN-35. FDG-PET/CT will be repeated within 21 days following the second cycle of augmented ICE. Stem cell mobilization can be performed following the first or second cycle of augmented ICE.

Augmented ICE will be administered as follows:

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Etoposide (200 mg/m2) IVPB Q 12 hours x 3 doses starting on day 1

The second cycle of augmented ICE will be initiated no sooner than 17 days after the first cycle. ANC must be ≥1000/µl and platelet count must be ≥50,000/µl for ICE to be administered. Treatment will be held until these criteria are met. No dose reductions will be allowed.

For **non-collection cycles**, either pegfilgrastim 6 mg on day after hospital discharge (completion of chemotherapy) or filgrastim 300 mcg (for patients under 70 kg) or 480 mcg (for patients over 70 kg) on days +5 to +12 will be given.

For **collection cycles**, Filgrastim at 10 mcg/kg/day will be given on day +5 and continue until stem cell collection completed (approximated to the nearest increment of Filgrastim 600 mcg, 780 mcg, 960 mcg, 1260 mcg, or 1,440 mcg).

Stem cell mobilization and collection will be performed as per standard MSKCC guidelines.

Pediatric patients will be treated in the Pediatric Day Hospital.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Tests to be performed day 1 of each cycle of brentuximab vedotin

- History and physical exam
- CBC (may be drawn within 24 hours pre-treatment)
- Comprehensive metabolic panel
- ESR
- Cytokine levels (one 8.5 mL SST speckled red top tube - IL-10, IL-6, IL-1, TNFα): ***cycle 1 only**
- Modified Total Neuropathy Score (mTNS) and European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire for chemotherapy-induced peripheral neuropathy (CIPN-20): ***cycle 2 only**

Tests to be performed day 8 and 15 of each cycle of brentuximab vedotin

- History and physical exam
- CBC (may be drawn within 24 hours pre-treatment)

Tests to be performed at the completion of 2 cycles of brentuximab vedotin:

- FDG-PET/CT (1-7 days after the last dose of brentuximab vedotin, between days 44 and 50). All studies will be obtained on dedicated PET/CT cameras. Patients must fast for 6 hrs prior to PET imaging, but intake of water or other non-caloric beverages is encouraged. When the patient arrives at one of the nuclear medicine imaging sites, a fingerstick blood glucose measurement will be obtained; patient with blood glucose levels > 200mg/dl are ineligible. Approximately 12 mCi of 18F FDG will be injected intravenously. Following an approximately 60-80 min uptake time, CT and PET images will be obtained from skull base to upper thigh using standard clinical imaging protocols. For a given patient, all serial PET/CT scans will be obtained on the same camera model.
- CT chest, abdomen, pelvis (1-7 days after the last dose of brentuximab vedotin, between days 44 and 50)

Within 1 week of last dose of SGN-35 (+/- 4 days)

- Hemoglobin A1c
- Cytokine levels (one 8.5 mL SST speckled red top tube - IL-10, IL-6, IL-1, TNFα)
- Modified Total Neuropathy Score (mTNS) and European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire for chemotherapy-induced peripheral neuropathy (CIPN-20)
- Bone marrow biopsy (if BM was involved before treatment and post-SGN-35 PET scan is negative)

Interventions while receiving brentuximab vedotin (SGN-35)

	Treatment days								
Test/treatment	**Pretreatment**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**44-50**
SGN-35		x	x	x		x	x	x	
History and Physical		x	x	x		x	x	x	
CBC	x	x*	x*	x*		x*	x*	x*	
Comprehensive Metabolic Panel	x	x				x			
ESR	x	x				x			
Uric acid	x								
Lactate dehydrogenase	x								
Creatinine clearance**	x								

Hemoglobin A1c	x								x
Serum β-HCG***	x								
Hep B, C, HIV	x								
Cytokines		x							x
Neuropathy Questionnaire	x					x			x
BM Bx	x								x****
FDG-PET/CT and CT CAP	x								x
Echo or MUGA	x								
PFTs	x								

*may be drawn within 24 hours pre-treatment; ** if creatinine >1.5; ***premenopausal females; ****if previously positive

The following applies to patients receiving augmented ICE:

- A CBC and basic metabolic panel will be obtained upon each admission for chemotherapy and a 12-hour urine collection for creatinine clearance will be obtained prior to receiving carboplatin. Other laboratory evaluations during admission for ICE chemotherapy may be performed at the discretion of the inpatient attending physician. When receiving ifosfamide, urine will be monitored for hematuria by urinalysis.

The following will be performed within 21 days following the completion of augmented ICE:

- CT scan of the chest, abdomen, and pelvis
- FDG-PET/CT scan
- Bone marrow biopsy (if BM was involved before treatment and post-ICE PET scan is negative)

10.0.1 EXPANSION COHORT: EVALUATION DURING TREATMENT/INTERVENTION

Tests to be performed day 1 of each cycle of brentuximab vedotin

- History and physical exam
- CBC (may be drawn within 24 hours pre-treatment)
- Comprehensive metabolic panel
- ESR

- Cytokine levels (one 8.5 mL SST speckled red top tube - IL-10, IL-6, IL-1, TNFα): ***cycle 1 only**

- Modified Total Neuropathy Score (mTNS) and European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire for chemotherapy-induced peripheral neuropathy (CIPN-20): *** **cycle 3 only**

Tests to be performed day 8 and 15 of each cycle of brentuximab vedotin

- History and physical exam

- CBC (may be drawn within 24 hours pre-treatment)

Tests to be performed at the completion of 3 cycles of brentuximab vedotin:

- FDG-PET/CT (1-7 days after the last dose of brentuximab vedotin). All studies will be obtained on dedicated PET/CT cameras. Patients must fast for 6 hrs prior to PET imaging, but intake of water or other non-caloric beverages is encouraged. When the patient arrives at one of the nuclear medicine imaging sites, a fingerstick blood glucose measurement will be obtained; patient with blood glucose levels > 200mg/dl are ineligible. Approximately 12 mCi of 18F FDG will be injected intravenously. Following an approximately 60-80 min uptake time, CT and PET images will be obtained from skull base to upper thigh using standard clinical imaging protocols. For a given patient, all serial PET/CT scans will be obtained on the same camera model.

- CT chest, abdomen, pelvis (1-7 days after the last dose of brentuximab vedotin)

Within 1 week of last dose of SGN-35 (+/- 4 days)

- Hemoglobin A1c
- Cytokine levels (one 8.5 mL SST speckled red top tube - IL-10, IL-6, IL-1, TNFα)
- Modified Total Neuropathy Score (mTNS) and European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire for chemotherapy-induced peripheral neuropathy (CIPN-20)
- Bone marrow biopsy (if BM was involved before treatment and post-SGN-35 PET scan is negative)

Interventions while receiving brentuximab vedotin (SGN-35)

	Treatment days												
Test/treatment	**Pretreatment**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**72-78**
SGN-35		x	x	x		x	x	x		x	x	x	
History and Physical		x	x	x		x	x	x		x	x	x	
CBC	x	x*	x*	x*		x*	x*	x*		x*	x*	x*	
Comprehensive Metabolic Panel	x	x				x				x			
ESR	x	x				x				x			

Uric acid	x												
Lactate dehydrogenase	x												
Creatinine clearance**	x												
Hemoglobin A1c	x												x
Serum β-HCG***	x												
Hep B, C, HIV	x												
Cytokines		x											x
Neuropathy Questionnaire	x									x			x
BM Bx	x												x****
FDG-PET/CT and CT CAP	x												x
Echo or MUGA	x												
PFTs	x												

*may be drawn within 24 hours pre-treatment; ** if creatinine >1.5; ***premenopausal females; ****if previously positive

The following applies to patients receiving augmented ICE:

- A CBC and basic metabolic panel will be obtained upon each admission for chemotherapy and a 12-hour urine collection for creatinine clearance will be obtained prior to receiving carboplatin. Other laboratory evaluations during admission for ICE chemotherapy may be performed at the discretion of the inpatient attending physician. When receiving ifosfamide, urine will be monitored for hematuria by urinalysis.

The following will be performed within 21 days following the completion of augmented ICE:

- CT scan of the chest, abdomen, and pelvis
- FDG-PET/CT scan
- Bone marrow biopsy (if BM was involved before treatment and post-ICE PET scan is negative)

11.0 TOXICITIES/SIDE EFFECTS

Brentuximab vedotin: Fatigue, fever, diarrhea, nausea, peripheral neuropathy, neutropenia, alopecia, rash

Ifosfamide: Alopecia, nausea and vomiting, hematuria, gross hematuria, CNS toxicity, infection, renal dysfunction, allergic reactions and at high doses, cardiotoxicity, and myelosuppression.

Carboplatin: Myelosuppression, nausea, vomiting, peripheral neuropathy, ototoxicity, hepatic toxicity, electrolyte abnormalities, hypomagnesemia, hypocalcemia, and allergic reactions.

Etoposide: Myelosuppression, mucositis, alopecia, nausea, vomiting, headache, fever, hypotension, anorexia, and allergic reactions. Possible secondary leukemia.

Mesna: Nausea, vomiting, diarrhea.

Neupogen® (Filgrastim): Bone pain; exacerbation of preexisting autoimmune disorders; transient and reversible changes in alkaline phosphatase, uric acid and LDH; peripheral edema.

Neulasta® (Pegfilgrastim): bone pain, flu-like symptoms, nausea/vomiting, adult respiratory distress syndrome, sickle cell crises, splenic rupture (rare)

Placement of leukapheresis catheter: pneumothorax, deep venous thrombosis, infection, and bleeding.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Criteria for interim FDG-PET/CT assessment

Patients enrolled in this study will receive salvage treatment with brentuximab vedotin and those who achieve FDG-PET/CT normalization will proceed directly to ASCT without receiving standard salvage chemotherapy such as ICE or DHAP. Because this treatment strategy represents, for some patients, a departure from standard practice, or de-escalation of treatment, stringent criteria are required to designate those most appropriate for avoiding ICE chemotherapy. A five-point scale for assessing response on interim FDG-PET/CT scans, referred to as the "London criteria", was developed by international experts in Nuclear Medicine and Oncology for use in diffuse large B cell lymphoma and HL[17] and validated for use as interim assessment in HL patients.[18] The 5-point scale is displayed in the following table.

Score	FDG-PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately more than liver uptake, at any site
5	Markedly increased uptake at any site or new sites of disease

The score on this scale used to define a normal or abnormal scan depends upon the particular clinical strategy planned. For example, when escalation of treatment is planned based upon FDG-PET/CT results, defining an abnormal FDG-PET/CT by a score of 4 or 5 is appropriate to avoid overtreating patients. Conversely, when de-escalation of treatment is planned based upon FDG-PET/CT results, defining a persistently abnormal FDG-PET/CT by a score of 3, 4, or 5 is appropriate in order to avoid undertreating patients.

For the purpose of this study, a score of 1 or 2 will be considered a "normal" FDG-PET/CT scan because de-escalation of treatment is anticipated. All scores (1 through 5) will be recorded for each FDG-PET/CT scan and scans will be reviewed by either Dr. Grewal or Dr. Schöder.

Progression free survival (PFS) and overall survival (OS) will be calculated from the time of initiation of brentuximab vedotin.

The response criteria developed by the International Harmonization Project for response assessment in lymphoma will be used to define complete response, partial response, and progression of disease in this study[19]. The definitions for response are detailed in the table below.

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be followed on study until progression of disease or 2 years following autologous stem cell transplant.

The following patients will be removed from study:

• Patients who have progression of disease while on treatment. These patients may be offered alternate treatments.
• Patients who develop unacceptable toxicity.
• Patients who request that they be removed from study. This will not compromise the care they receive at this institution.
• Patients who are non-compliant with treatment or follow-up.

14.0 BIOSTATISTICS

For the primary objective of this study, we will employ a Simon two stage design. Currently, the FDG-PET/CT normalization rate for ICE alone is between 50-60% therefore for a new treatment regimen, we would consider a normalization rate of 40% unacceptable. The goal of this study is to replace an intense inpatient regimen with an effective, less toxic regimen without impacting efficacy. Thus, we will set the desirable FDG-PET/CT normalization rate aa 60% for the new treatment regimen (i.e., SGN-35 with or without ICE) and we will use 40% as our null hypothesis in employing the Simon two stage design. In the first stage, we will enroll 18 relapsed or refractory Hodgkin lymphoma patients who meet the criteria in Section 6. If 7 or fewer patients achieve FDG-PET/CT normalization either after SGN-35 alone or after SGN-35 combined with ICE, no additional patients will be enrolled and the regimen will be considered not promising in this cohort of patients. If 8 or more patients are FDG-PET/CT negative either after SGN-35 alone or after SGN-35 with ICE, then an additional 28 patients will be enrolled for the second stage. Among the total 46 patients, If 23 or more patients achieve FDG-PET/CT normalization either after SGN-35 alone or after SGN-35 with ICE, this treatment regimen will be declared effective. This decision rule has both type I error (declaring the new treatment regimen promising while it is actually not) and type II error (declaring the new treatment regimen not promising while it actually is) rate as 0.10. The early stopping (i.e., stop after the first stage with 18 patients) probability is 0.56 when the FDG-PET/CT normalization rate is 40%, and is 0.06 when the FDG-PET/CT normalization rate is 60%. We expect it will take 2-3 years to enroll 46 patients.

Furthermore, additional stopping rules are in place if we observe an unacceptable amount of toxicity due to SGN-35 or an unacceptable rate of relapse following transplant in the SGN-35-only group among the first 18 patients. We have defined an unacceptable rate of toxicity as grade 3 or more neuropathy occurring in 5 of the first 18 patients enrolled. We have defined an unacceptable relapse rate as a 50% rate of relapse within 3 months of transplant among the SGN-35-only patients.

As an additional criterion, we require that at least 7 out of the total 46 patients (15%) achieve FDG-PET/CT normalization after SGN-35 to call this new regimen a success. The purpose of this criterion is to exclude the situation that all patients may fail SGN-35 (i.e., persistent PET abnormalities) and hence must receive ICE salvage therapy, yet accidently pass the above two-stage design. The threshold 15% was chosen because the previous phase I data show that about 30% of patients may achieve CR with SGN-35, and thus we believe it would be clinically meaningful to require at least 15% of patients to achieve PET normalization after SGN-35 to call it a success.

For the secondary objectives, we will report the stratified FDG-PET/CT normalization rates as sample proportions with their confidence intervals. Overall response rate to SGN-35 alone will be reported similarly. Toxicities will be summarized and tabulated. PFS and OS (see

definition in Section 12) will be analyzed using standard survival tools such as Kaplan-Meier estimation, log-rank tests and/or Cox regression models to incorporate various factors (such as ΔSUVmax, CD68, FoxP3, TIA-1, serum cytokine, etc.) and assess their correlation with PFS and/or OS. Competing risks analysis will be conducted if competing risk(s) exists (such as death without progression). Lab results including CD34 cell yield following mobilization will be reported as summary statistics.

14.0.1 EXPANSION COHORT: BIOSTATISTICS

This study would be an expansion of our current study and therefore the data will ultimately be analyzed along with the data from our current study in which patients are receiving 2 cycles of BV. The goal of this expansion study is to determine whether the rate of FDG-PET normalization is improved with 3 cycles of BV when compared to 2 cycles. So far, we have observed a 28% rate of FDG-PET normalization following 2 cycles of BV; however an additional 14 patients (44%) were "good responders" to 2 cycles of BV and likely had the potential to achieve FDG-PET normalization had they received an additional cycle of BV. Based upon this, we estimate that the rate of FDG-PET normalization following 3 cycles of BV will be around 50%.

Allowing for type I and type II error rates of 0.2, and assuming a FDG-PET normalization rate of 28% with 2 cycles of BV, the number of patients required to show an improvement in FDG-PET normalization rate to 50% is 20.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

Data to be collected will include:

1. Patient related features:

- age

- sex

2. Disease related features

- prior therapy

- disease status- relapsed vs. primary refractory

- results of all tests related to the study

- disease status at long-term follow-up

3. Treatment related

- duration of treatment

- stem cell yields

- response to treatment

- toxicities of treatment

16.1 Quality Assurance

Registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

Retention of Records: All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be retained for at least 3 years after the investigation is completed.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data

and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb5.mskcc.org/intranet/html/99073.cfm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

Section 16.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

17.0 PROTECTION OF HUMAN SUBJECTS

Potential Risks

Traditionally, we have used ICE chemotherapy as the initial salvage therapy in relapsed/refractory HL. In this study, ICE chemotherapy is either eliminated or delayed until treatment with SGN-35 is completed. In the phase II studies described above, SGN-35 was associated with tumor reduction in over 90% of patients with relapsed/refractory HL. While delaying or eliminating ICE chemotherapy represents a potential risk for patients enrolled in this protocol, this potential risk is minimal given the high activity of SGN-35.

Potential Benefits

While ICE-based salvage treatment is commonly administered for relapsed/refractory HL it is associated with significant toxicity. Patients enrolled on this trial who achieve FDG-PET/CT negativity following 2 cycles of SGN-35 will proceed directly to ASCT. Therefore, a portion of patients enrolled on this study may avoid ICE-based treatment. Furthermore, Seattle Genetics is supplying SGN-35 free of charge.

Provisions for preventing and treating adverse events

Assessment for neuropathy will be performed before each cycle of brentuximab vedotin. Treatment of febrile neutropenia, cytopenias, ifosfamide-related gross and microscopic

hematuria, and catheter related sepsis, thrombosis, and pneumothorax will be in accordance with standard medical practices employed at MSKCC.

Patients will receive standard anti-emetics as prophylaxis against nausea and vomiting.

Alternatives/Options for treatment

For patients eligible, alternative therapy would consist of ICE-based salvage therapy or DHAP chemotherapy.

Costs

The patient will be responsible for all costs related to treatment and complications of treatment, including G-CSF, pegfilgrastim, FDG-PET scans, and all hospitalizations.

SGN-35 will be supplied by Seattle Genetics free of charge. The patient will not be responsible for the cost of correlative studies.

Participation in this study is voluntary and patients will not be paid for participation.

Privacy and confidentiality

Confidentiality will be maintained within the limits of the law. Only qualified individuals from MSKCC; the National Cancer Institute; the FDA; Seattle Genetics; will be able to review patients' medical records. Neither the patients' names nor other identifying information will be used in reports or publications arising from this study. After all patients have completed treatment on study and primary data analysis is complete, FDG-PET/CT scans will be de-identified (only patient weight and study ID number will be shared) and sent on a CD via mail to LYSA Imaging at Hôpitaux Universitaires Henri Mondor, France for data analysis.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number

- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 SAE reporting information to Seattle Genetics

- **Reporting Timeframe:** The Principal Investigator will report to Seattle Genetics Drug Safety by facsimile (425) 527-4308 or (866) 333-6627 (USA only toll free) any Serious Adverse Event (SAE) that occurs in a study subject within 24 hours of first awareness of the event.
- **Reporting Forms:** The Principal Investigator will report such SAEs using the Seattle Genetics SAE Report Form or the approved local regulatory form SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.
- **Reporting Period:** The reportable events that are subject to this provision are those that occur from the start of administration of the first dose of the Product through thirty (30) days after discontinuation of the Product. SAEs occurring more than thirty (30) days after discontinuation of the Product that are assessed by the Investigator as related to the Product should also be reported.

- **Follow-up Information:** The Principal Investigator will assist Seattle Genetics in investigating any SAE and will provide any follow-up information reasonably requested by Seattle Genetics.
- **Regulatory Reporting:** Reporting an SAE to Seattle Genetics does not relieve the Principal Investigator conducting the study of the responsibility for reporting it to the FDA, local regulatory authority, or IRB/IEC as required.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1: Pharmacy manual

Appendix 2: mTNS questionnaire

Appendix3: EORTC neuropathy questionnaire