A Phase II Trial of Sequential SGN-35 Therapy With Adriamycin, Vinblastine, and Dacarbazine (S-AVD) for Older Patients with Untreated Hodgkin Lymphoma

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PROTOCOL SUMMARY

Title	A Phase II Trial of Sequential SGN-35 Therapy With Adriamycin, Vinblastine, and Dacarbazine (S-AVD) for Older Patients with Untreated Hodgkin Lymphoma
Version Date	May 31, 2018
Objectives	The primary objective of this study is to evaluate the complete remission (CR) rate with SGN-35/AVD sequential therapy in older subjects with untreated Hodgkin lymphoma. The secondary objectives of this study are to determine the progression-free survival, time to treatment failure, freedom from progression, and overall survival rates following SGN-35/AVD sequential therapy and to examine the ORR, CR rate, and prognostic relevance of FDG-PET following 2 cycles of SGN-35. Further, we will evaluate the safety of sequential SGN-35/AVD/SGN-35 therapy.
Patient population	Older patients (i.e., age =/> 60 years of age) with newly diagnosed classical Hodgkin lymphoma.
Number of patients	45 evaluable patients (48 total)
Duration	The study will last approximately 3 years.
Study design and methodology	A Simon optimal 2-stage design, with interim efficacy analysis (after 22 patients [21 evaluable]) followed by 26 patients (24 evaluable) in the second stage if 12 more of the 21 evaluable in the 1st stage obtain complete remission for a total of 48 patients (45 evaluable).
Treatment	Therapy on this protocol is divided into 3 phases: 1) SGN-35 “lead in” given as a single-agent for 2 cycles (doses); this will be followed by a repeat FDG-PET scan among the first 22 patients enrolled on trial. All non-progressing patients will proceed to the second phase. 2) AVD chemotherapy for 6 cycles. Patients after 6 cycles of AVD with CR or PR will proceed to the third phase. Patients who do not complete 6 cycles of AVD (due to toxicity: designated ‘chemotherapy intolerant’), but have achieved PR or CR may also proceed to the third phase. 3) SGN-35 consolidation with SGN-35 given as a single-agent once every 3 weeks for 4 total doses with starting dose dependent on prior treatment-related neurotoxicity.
Safety data collected	All patients who receive treatment will be included in the safety summaries and analyses. The safety and tolerability will be examined by: Extent of exposure to therapy (dose, duration, and number of patients), detailed summary of deaths by time to death (using Kaplan-Meier methods) and by cause of death, detailed examination of adverse events (adverse events will be classified by body system and preferred term using the NCI CTCAE v4. Frequency tables at the patient level will summarize events. Frequency tables by category of event (serious, related), and by NCI CTCAE grade (version 4.03) will be presented by dose regimen, laboratory test results, and vital signs or other physical findings.

1 INTRODUCTION AND STUDY RATIONALE

1.1 Background.

In the modern era of combination chemotherapy, Hodgkin lymphoma (HL) is a malignancy considered to have a favorable prognosis with consistently improving survival rates. Outcomes for older HL patients (often defined as >60 years of age), however, remains poor.[1-7] Older HL is a disease entity where 1) it has been difficult to investigate in classical trial format (due to relative rarity of the disease, advanced age, under-representation in clinical trials); 2) there are large numbers of subjects who are frail or have frequent co-morbidities; 3) the approach to curative treatment has been absent or inconsistent; and 4) there remains no agreed/standard treatment approach.[8,9] In addition, several sources of evidence suggest a different biology in older HL patients compared with younger populations.[7,9-12]

Survival rates for older patients with HL are disproportionately inferior to those achieved by younger patients. Five-year progression-free survival (PFS) or freedom from treatment failure (FFTF) rates for older HL patients ranges from 30-50% (Table 1) compared with >75-80% for younger patients.[6-8,13-15] There are several potential explanations for the poor outcome of older HL patients. Suboptimal staging and inadequate treatment delivery for older HL patients may compromise the rate of cure,[16,17] while co-morbidities may preclude the delivery of standard intensity of chemotherapy.[18,19] In addition, treatment-related toxicities in this patient population are often prohibitive including high rates of infectious complications[2,4,17,20] and other toxicities such as bleomycin-related lung toxicity.[4,21-23] More tolerable and effective therapeutic regimens need to be developed for older patients with newly diagnosed HL.

1.2 Epidemiology

In population-based studies, the proportion of HL patients older than 60 years ranges between 15–40%.[1,4-7,24] However, the proportion of older HL patients participating in clinical trials has been considerably lower, typically constituting <5% of study populations.[6,14,17] In terms of biologic epidemiology, Epstein-Barr virus (EBV) is a factor with potential etiologic and prognostic importance. Approximately 30%-50% of all HL cases are EBV-positive, as identified by LMP-1 or EBER immunostaining of malignant cells.[25,26] The highest percentages of EBV-positive cases are seen in HL patients < age 10 years and > age 55 years.[10,25,26] Moreover, several large population-based studies have shown that the survival of older patients with EBV-positive tumors is significantly inferior compared with EBV-negative tumors.[7,10,12]

1.3 Chemotherapy: outcomes

Efforts to improve outcomes in elderly HL have included decreased intensity of chemotherapy and use of regimens with individualized dosing. However, results

have been overall disappointing with modest remission rates and high relapse rates.[1,2,20,24,27]

Two prospective trials for older HL were recently reported. Levis and colleagues studied the VEPEMB regimen (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone and bleomycin),[28] while Ballova and colleagues examined COPP-ABVD and $BEACOPP_{baseline}$.[29] Outcomes were modest with complete remission rates of 54-76% (for advanced stage patients) with associated long-term failure-free survival rates <50% (Table 1).

We recently presented data of cases of HL >/= age 60 years diagnosed and treated at 3 Chicago academic centers from December 1999 through December 2009.[30] We assessed co-morbidities using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) scale and classified patients if they were "fit" (i.e., preserved activities of daily living (ADLs), <3 grade 3 CIRS-G, no grade 4, and no geriatric syndrome [dementia, delirium, incontinence, falls, neglect/abuse and/or failure to thrive]). Among 56 patients (24F:32M), median age was 67 years (range 61-84).. Disease characteristics included: B symptoms present in 56%, PS of 2-3 In 27%, marrow involvement in 25%, and presence of other (non-marrow) extra-nodal disease 20% (most common: bone n=6 and lung n=5).

Sixty-four percent of patients had advanced-stage (stage III/IV), of which 61% had an international prognostic score (IPS) ≥4. For co-morbidities, 38% had grade a 3-4 CIRS-G in at least 1 category. Additionally, 29% were classified as "not fit" at HL diagnosis, while 16% had a geriatric syndrome. 54/56 received chemotherapy; most common were ABVD (n=34), BCVPP (n=7), ChlVPP (n=6). The ORR to chemotherapy was 88% (75% CR) and with 51-month median follow-up (7-120), the 4-year PFS and OS for all patients were 36.8% and 57.6%, respectively (early-stage: 61.6% and 80.5%; advanced-stage: 21.7% and 43.4%; p=0.03 and p=0.04, respectively). In multivariate analyses, ADL loss was borderline for inferior OS (HR 4.44 [0.83-23.71], p<0.08), while < than a CR to initial therapy predicted significantly inferior OS (HR 9.32 [1.81-47.92], p=0.008).

Table 1. Survival rates for older patients with advanced stage HL.

Author, year	No. pts	Study type	Stage, median age (years)	Treatment	Outcome
Levis, 1996	25	Prospective	All stage II-IV (24% IV), 72	CVP/CEB	5-year EFS 32%
Weeks, 2002	56	Retrospective	73% III/IV, NR	ChlVPP (n=31) or ChlVPP/ABV (n=25)	ChlVPP: 5-year EFS 24%; ChlVPP/ABV: 5-year EFS 52%
Macpherson, 2002	55	Retrospective	82% III/IV, 72	MOPP/ABV (n=17) or ODBEP (n=38)	MOPP/ABV: 5-yr DFS 37%; ODBEP: 5-year DFS 49%
Landgren, 2003	88	Retrospective	69% III/IV, 72	MOPP-based (n=46), ABVD-based (39), other (n=3)	5-year CSS 39%
Levis, 2004	105	Prospective	54% IIB-IV, 71	VEPEMB	Stage IIB-IV: 5-year FFS 34%
Ballova, 2005	68	Prospective	All IIB-IV, 69	COPP/ABVD (n=26) vs BEACOPP baseline (n=42)	COPP/ABVD: 5-year FFTF 46%
Evens, 2010	56	Retrospective	64% III/IV, 67	Heterogenous	All pts: 4-year EFS 37% and 58% (stage III/IV EFS 22% and OS 43%)

Abbreviations: RT, radiation; FFTF, freedom from treatment failure; RT, radiation therapy; DSS, disease specific survival; FFS, freedom from treatment failure; PFS, progression free survival; CSS, cause specific survival; No, number; pts, patients.

1.4 Treatment toxicity in elderly HL

A high incidence of chemotherapy-related toxicity has been reported in older HL patients.[2,4,17,20] The German Hodgkin Lymphoma Study Group showed that severe toxicity (WHO grade 4) was more common in older patients vs younger HL patients,[17] including increased incidence of grade 3/4 infections in older vs younger patients as well as fatal treatment-related toxicity. The incidence of bleomycin lung toxicity (BLT) in the literature is variable, though has been reported to be up to 46% in some reports.[25-27] Older age has been a consistent risk factor associated with BLT.[25-27] The Mayo Clinic reported an incidence of BLT of 33% for patients > age 40 years compared with 11% for younger

patients.[14] Furthermore, they noted a BLT-associated mortality rate of 40%. We noted a BLT incidence rate of 31% with an associated fatality rate of 27%.[30] Of note, retrospective data has shown that the omission of bleomycin does not appear to adversely affect HL survival rates.[28]

1.5 Recent prospective elderly HL data.

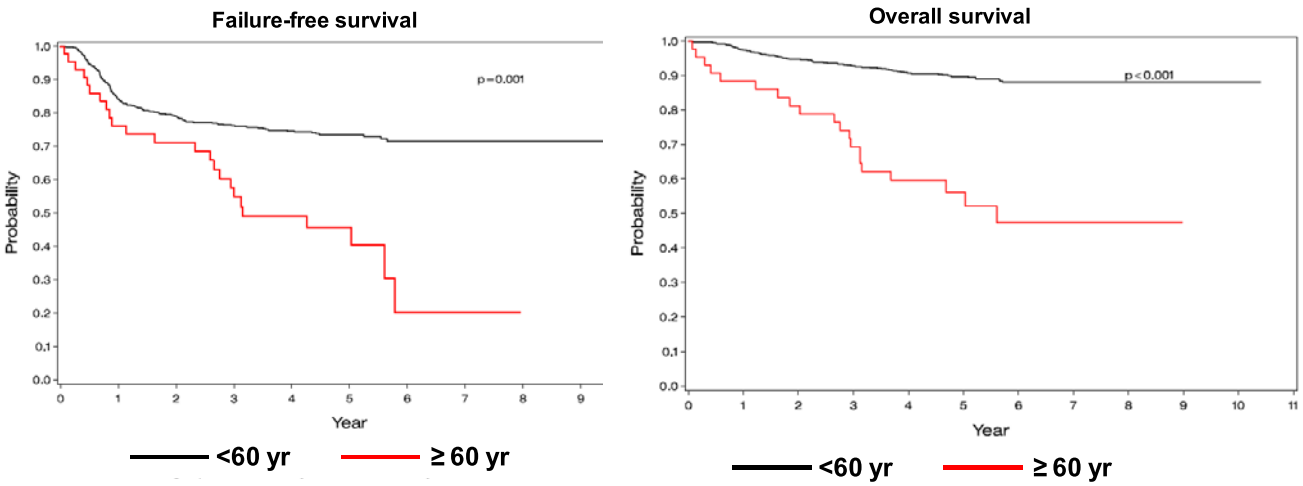
Evens et al recently presented data regarding the tolerability and outcomes of Stanford V and ABVD chemotherapy for patients ≥ age 60 years with advanced-stage HL treated in the National (and Intergroup) E2496 study.[31] All patients were randomized to receive 'standard' chemotherapy with ABVD x 6–8 cycles vs the Stanford V regimen (12 weeks of CT). Of 812 eligible patients enrolled, 43 were ≥ 60 years of age (n=23 ABVD and n=20 Stanford V). Patient characteristics between chemotherapy arms were balanced. Several differences were noted comparing patients ≥ 60 vs < 60 years including mixed cellularity cell type being more common in elderly patients (35% vs 13%, respectively, p=0.0004, OR=3.52) and ECOG performance status of 0 (ie, asymptomatic) being less common in older vs younger patients (35% vs 58%, respectively, p=0.004, OR=0.38). There were no statistically significant differences of grade 3 and 4 toxicities between older and younger patients, however the incidence of the severe toxicity of BLT occurred in 26% of HL patients ≥ 60 years, which had an associated mortality rate of 18%. Furthermore, the treatment-related morality rate was 9.3% for patients ≥ 60 years (2 deaths in each chemotherapy arm; 2 deaths due to BLT- both in the ABVD arm) compared with 0.3% for patients <60 years (p<0.0001).

We found among the 43 patients ≥ 60 years, there was no difference in outcome between the two chemotherapy arms.[31] Further, the overall response rate (ORR) and complete remission (CR) rates appeared overall similar comparing patients ≥ 60 years vs < 60 years (70% vs 78%, respectively, p=0.19) and CR rates (65% vs 71%, respectively, p=0.49). However, the failure-free survival (FFS) and overall survival (OS) were significantly inferior for patients ≥ 60 years (see Figure and Table below). These observations show the difference in disease biology and continued poor outcome for elderly HL underscoring the need for new/novel therapeutic approaches.

Table 2 (and corresponding Figure 1). Survival comparing older vs younger HL patients.[31]

		< 60 years	**=/> 60 years**	**P**
FFS	**3-year**	**76%**	**55%**	**0.0014**
	5-year	**74%**	**46%**	
OS	**3-year**	**93%**	**69%**	**<0.0001**
	5-year	**90%**	**56%**	

Figure 1. Survival comparing older vs younger HL patients.



1.6 Targeted therapy: SGN-35

1.6.1 Mechanism of Action of SGN-35

SGN-35 (brentuximab vedotin) is an antibody-drug conjugate (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. SGN-35 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.[32] Binding of released MMAE to tubulin disrupts the microtubule network, leading to G2/M phase cell cycle arrest and apoptosis.[33]

1.6.2 Preclinical Experience of SGN-35

Preclinical studies of SGN-35 demonstrated antitumor activity in both in vitro and in vivo models. The toxicity of multiple doses of SGN-35 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 SGN-35 Investigator's Brochure for details of the

nonclinical data.

1.6.3 Rationale for SGN-35, Clinical Safety and Efficacy

SGN-35 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 SGN-35 was conducted in patients with CD30-positive hematologic malignancies (SG035-0001).34,35 In this study, patients received SGN-35 on Day 1 of each 21-day cycle and tumor response assessments were performed on Days 15–21 of the second cycle. SGN-35 was generally well-tolerated at doses of up to 1.8 mg/kg, the maximally tolerated dose (MTD), and induced multiple objective responses in these heavily pretreated patients. The most common adverse events (occurring in 20% of patients) were fatigue, pyrexia, nausea, and diarrhea. Objective responses, including 11 complete remissions (CRs), were observed in 17 patients. Of 12 patients who received the 1.8 mg/kg dose, 6 (50%) had an objective response. Furthermore, the majority of patients (86%) had reductions in target lesion size, while the median response duration to date was 22 weeks (range, 0.1+ to 38+ weeks). Bartlett et al reported results of a phase I trial using weekly SGN-35 for relapsed/refractory HL or anaplastic large cell lymphoma.36 MTD was exceeded at 1.4 mg/kg (grade 4 hyperglycemia and grade 3 diarrhea dose limiting toxicity). Among 27 evaluable patients, ORR was 48% including a CR rate of 37%.

Of note, a pivotal phase II trial in relapsed/refractory HL was completed with single-agent SGN-35 (1.8 mg/kg q 3 weeks).[37] More than 70% of the 102 patients had primary refractory disease, defined as failure to achieve a CR or progression within 3 months of completing frontline therapy. The median duration of brentuximab vedotin treatment on this study was 27 weeks with a median number of cycles on therapy of 9. The ORR was 75% with 95% of patients experiencing some degree of tumor shrinkage and 83% of patients had resolution of their B symptoms. Therapy was overall well tolerated. Grade 3 treatment-related AEs (reported in >1 patient) were neutropenia (14%), peripheral sensory neuropathy (5%), thrombocytopenia and hyperglycemia (3% each), and fatigue (2%). The only grade 4 treatment-related events were neutropenia (4%), and thrombocytopenia, abdominal pain, and pulmonary embolism (1% each).

1.6.4 Experience with SGN-35 in Elderly HL

Among the 3 clinical trials SG035-0001, SG035-0002, and SG035-0003 for patients with relapsed/refractory lymphoma, 12 patients ≥ age 65 years were enrolled of which 7 were evaluable for response. There did not appear to be a significant difference in toxicity between older and younger patients. Treatment-emergent adverse events (TEAE) ≥ grade 3 occurred in 80/143

(56%) patients ages 18-64 compared with 9/12 (75%) of patients ≥ age 65 years (P=0.2382). Treatment-related serious AEs occurred in 21/143 (15%) patients ages 18-64 compared with 3/12 (25%) of patients ≥ age 65 years (P=0.4013). Further, any treatment-emergent grade 2 peripheral neuropathy events occurred in 43/143 (29%) patients ages 18-64 compared with 4/12 (33%) patients ≥ age 65 years, while any treatment-emergent grade 3 peripheral neuropathy events occurred in 16/143 (11%) patients ages 18-64 vs 2/12 (17%) patients ≥ age 65 years.

Clinical efficacy appeared similar between these age groups. Overall response rate (ORR) in the 3 aforementioned single-agent SGN-35 clinical trials was 61% for (107/175) for patients ages 18-64 vs 57% (4/7) for patients ≥ age 65 years. Nevertheless, patients will be followed closely through this clinical trial including routine objective assessments of potential neurotoxicity through formal GOG-based neurotoxicity assessments.

In addition, there is an ongoing contemporaneous phase II clinical trial using consecutive doses (q 3 weeks 1.8mg/kg) of 'single-agent' SGN-35 for elderly Hodgkin lymphoma patients. As of May 1st 2013, 11 out of 30 planned patients have been enrolled. Ten of the 11 patients have received at least 2 cycles of SGN-35, while 4 patients have received at least 6 SGN-35 cycles. Among these patients, there have been 2 SAEs identified (grade 3 orthostatic hypotension and weakness in patient with pre-existing resected astrocytoma; and grade 3 alkaline phosphatase elevated in patient with baseline fatty liver disease and baseline abnormal LFTs).

1.6.5 Pancreatitis and SGN-35.

Seattle Genetics performed an internal qualitative review of all cases of acute pancreatitis received to date. As of June 30, 2013, Seattle Genetics has received reports of acute pancreatitis associated with brentuximab vedotin resulting in an incidence of 0.27% from clinical trials and compassionate use programs, and 0.07% from other patient exposures. The occurrence of acute pancreatitis contributed to a fatal outcome in 2 patient reports. Most of the cases of acute pancreatitis were reported within the first or second cycle of dosing. Some of the cases were confounded by other possible contributory factors, including concomitant administration of medications known to be associated with pancreatitis and possible alternate etiologies (including cholelithiasis and pancreatic lymphoma progression).

Re-challenge experiences with subsequent dose(s) after resolution of the acute pancreatitis were documented in 3 patients. Two of these patients did not experience recurrent acute pancreatitis on re-challenge. In the third patient, 2 re-challenge doses were administered without an elevation in

pancreatic enzyme; however, following the third re-challenge dose, the patient experienced a recurrence of acute pancreatitis.

Based on this information, Seattle Genetics considers acute pancreatitis to be an important potential risk associated with brentuximab vedotin dosing, and will be updating the Investigator's Brochure accordingly.

1.7 Emerging role of PET

Thus far, the most important prognostic tool in advanced stage HL has been the International Prognostic Score (IPS).[3] Fluorodeoxyglucose-positron emission tomography (PET) has become a standard imaging modality complementing CT scans in the management of HL.[38-41] Gallamini and colleagues reported on the prognostic importance of early PET after two of six planned chemotherapy cycles (ABVD in 96%) for 108 patients with advanced-stage HD.[42] The 2-year PFS rate for patients with a negative PET-2 compared with a positive PET-2 were 96% and 6%, respectively (P<0.01). Furthermore, PET-2 remained significantly associated with PFS irrespective of the IPS. These data support the concept of early risk assessment using PET imaging in the study of newly-diagnosed HL.

Although, several key issues regarding PET response-adapted therapy need to be considered including consistent definitions of PET-negativity versus positivity and strategy of trial design with appropriate control arms. In addition, the majority of the prognostic early PET data has been examined in younger HL patients. The median age of the aforementioned PET-2 studies was 32 to 36 years.[43-45] It is not clear if the prognostic results of early PET seen in younger HL patients will translate into similar outcomes for older patients and/or for patients who receive novel targeted therapy as a component of treatment.

1.8 Functional status/co-morbidities.

The presence of co-morbidity as an independent prognostic factor is particularly relevant for older patients. Levis et al reported results of a trial including 105 elderly HL patients in which all patients received a lower intensity regimen, VEPEMB (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, and bleomycin).[28] Thirty-seven percent of patients had a co-morbidity, defined as the presence of a concomitant disease requiring specific treatment. On multivariate analysis, in addition to stage and presence of B symptoms, presence of co-morbidity was independently associated with inferior survivals (DSS 59% vs 74%, respectively, p<0.01; FFS 40% vs 64%, respectively, p<0.02; and OS 54% and 69%, respectively, p<0.01*).* Note that the effect on DSS was as significant as OS, which suggests ineffective treatment and/or biology related to co-morbidity rather than death from other causes.

In a population based study, van Spronsen et al reported on 194 HL patients diagnosed between 1993-1996.[19] Among patients <60 years, 13% had a serious

co-morbid condition compared to 56% for older patients (p<0.0001). The prevalence of co-morbidity among HL patients was similar among early vs advanced stage. The most common co-morbid conditions were cardiovascular disease (18%), hypertension (13%), chronic obstructive pulmonary disease (13%), and diabetes (10%). Of note, the proportion of elderly patients who received chemotherapy was 50% lower among those with co-morbidity vs no co-morbidity (*p*=0.01). Furthermore, elderly patients with early-stage HL and a co-morbid condition received chemotherapy much less often (90% vs 33%, p=0.05).

Guinee et al compared the outcomes of HL patients aged 60-79 years with that of patients aged 40-59 years from 1977-1983. The older group experienced twice the risk of dying from HL and four times the risk of dying from other causes compared with the younger group. Of note, older patients responded to therapy with similar CR rates in their analysis (84% vs 88% in the younger group).[46] As proposed by Levis et al[28] and Proctor et al,[47] documentation of co-morbid conditions and objective assessment of functional status such as the Comprehensive Geriatric Assessment (CGA)[19] should be included in prospective studies. It may be possible to modify regimens and/or dosing based on objective criteria that predict for prohibitive morbidity and mortality. In addition, as we noted in our retrospective elderly HL series, assessment of activities of daily living (ADLs) may be an important consideration when evaluating and treating elderly HL patients. This needs to be validated in a prospective clinical trial.

1.9 Summary/hypothesis

Our *hypothesis* is that the addition of the novel anti-CD30 drug-conjugate, SGN-35, sequentially to AVD systemic chemotherapy will improve the outcomes of older patients with newly diagnosed HL as assessed by improved CR rates. This hypothesis is based on the notable single-agent activity of SGN-35 in heavily pre-treated relapsed/refractory HL patients, as well as a modest toxicity panel. In addition, the drug bleomycin, which may be associated with significant toxicity in older patients, will be removed from ABVD therapy. We expect to learn the response rate to SGN-35 in an untreated HD patient population with the lead-in SGN-35 therapy. It is not expected that only 2 total doses of this therapy will be adequate to improve efficacy, thus we will administer 4 additional doses of SGN-35 as “consolidation” after AVD chemotherapy. To test our hypothesis, we will complete a multi-center phase II clinical trial for older patients with untreated HL who will receive 2 ‘lead in’ cycles of SGN-35 alone, followed by 6 cycles of AVD chemotherapy, then followed by 4 cycles of SGN-35 alone as consolidation therapy.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this clinical study is to evaluate the complete remission (CR) rate with SGN-35/AVD sequential therapy in patients ≥ 60 years old with untreated Hodgkin lymphoma (HL).

2.2 Secondary Objectives

The secondary objectives of this study are to:

a) To examine the ORR, CR rate, and prognostic relevance of FDG-PET following 2 cycles of SGN-35.

b) To evaluate the safety of sequential SGN-35/AVD/SGN-35 therapy.

c) To determine the 2-year progression-free survival (PFS), time to treatment failure (TTF), freedom from progression (FFP), and overall survival (OS) rates following SGN-35/AVD sequential therapy.

d) To evaluate patient-reported outcomes at baseline and during treatment to determine potential symptom palliation (of baseline/pre-treatment symptoms), treatment-related symptoms, and overall health-related quality of life (HRQL).

e) To examine the association between baseline and end-of-treatment patient co-morbidities as assessed by the Cumulative Illness Rating Scale (CIRS) with outcome (CR, TTF, FFP, PFS, and OS) and toxicity.

f) To collect peripheral blood for proposed future studies of tumor and host characteristics that may predict for clinical outcome and enhance existing prognostic indices.

3 SELECTION OF PATIENTS

3.1 Inclusion Criteria

3.1.1 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.

3.1.2 ≥ 60 years old.

3.1.3 Previously untreated classical Hodgkin lymphoma (i.e., nodular sclerosis, mixed cellularity, lymphocyte depleted, lymphocyte-rich, and NOS). Nodular lymphocyte predominant Hodgkin lymphoma is not eligible.

3.1.4 Stage II, III, and IV disease by Ann Arbor classification.

3.1.5 ECOG performance status score of 0, 1, or 2.

3.1.6 Patients must have bi-dimensional measurable disease (as defined in section 6.1) within 60 days prior to starting treatment (at least 1.5 cm). Patients with non-measurable disease (defined in Section 6.1) in addition to measurable disease must have been assessed within 60 days prior to starting treatment.

3.1.7 Patients must have a bone marrow biopsy (bilateral preferred, unilateral acceptable) within 90 days prior to starting treatment.

3.1.8 Patients must have a MUGA or echocardiogram within 90 days prior to starting treatment and the ejection fraction must be =/> 45%.

3.1.9 Adequate organ function including an ANC > 1000/mm^3, platelet count > 75,000/mm^3, creatinine < 2.5 mg/dl, and bilirubin < 3.0 mg/dl. Patients with documented marrow involvement by lymphoma at the time of registration are not required to meet the above hematologic parameters.

3.1.10 Patients must not have received prior chemotherapy or radiation therapy for the treatment of Hodgkin lymphoma.

3.1.11 Both females and males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 30 days following the last dose of study drug.

3.1.12 Patients must sign the informed consent form before registration.

3.2 Inclusion of Women and Minorities.

3.2.1 Both men and women and members of all races and ethnic groups are eligible for this trial.

3.3 Exclusion criteria.

3.3.1 Previous treatment with SGN-35 or any other prior anti-CD30-based antibody therapy.

3.3.2 No currently active other (second) malignancy, other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed anti-cancer therapy and are considered by their physicians to be at less than 30% risk of relapse.

3.3.3 Known cerebral/meningeal disease.

3.3.4 Any active systemic viral, bacterial, or fungal infection requiring IV treatment with antimicrobial therapy within 1 week prior to first dose.

3.3.5 Patients with known HBsAg positive HBV infection. Patients with prior history of Hepatitis B infection, but immune, with only IgG Hepatitis core antibody + (HBcAb +) must receive anti-viral prophylaxis (e.g., lamivudine 100mg po daily) for at least 1 week prior to cycle 1 and throughout induction and continuation therapy and for at least 6 months after the last SGN-35 dose. In addition, consultation with a hepatologist is recommended.

3.3.6 Patients with a known hypersensitivity to any excipient contained in the drug formulation.

3.3.7 Patients with dementia or an altered mental state that would preclude the understanding and rendering of informed consent.

3.3.8 Patients with a prior history of documented pancreatitis.

3.3.9 Patients with severe renal impairment (CrCL <30 mL/min). A calculated CrCl is acceptable.

4 PATIENT REGISTRATION

NOTE: Patients *may not* begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

4.1 Access to the Registration Program

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

4.2 Registering a Patient

4.2.1 BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:
:

4.2.1.1 Eligibility eCRF (complete in NOTIS)

4.2.1.2 Patient's signed and witnessed informed consent form (upload to NOTIS).

4.2.1.3 Copy of pathology report (upload to NOTIS)

4.2.1.4 Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)

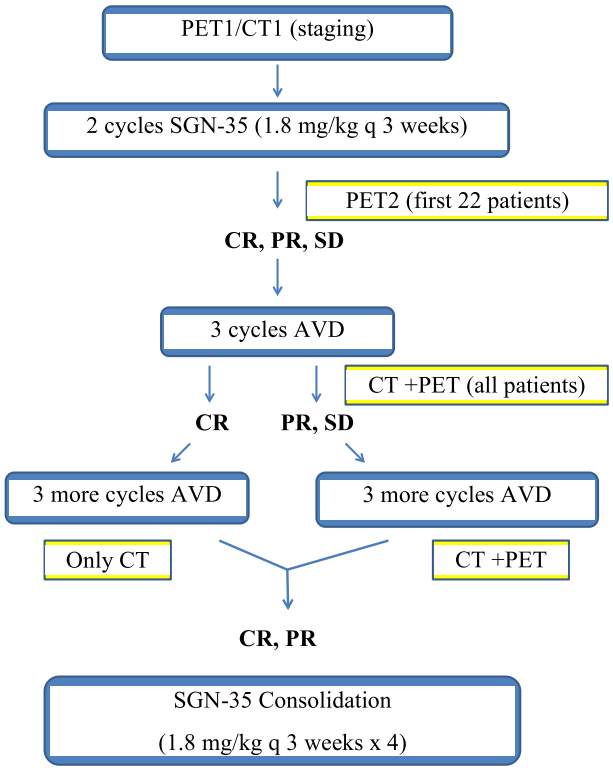
4.2.2 Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CRO website for additional instructions on registering a patient. The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

5 TREATMENT PLAN

5.1 Overall description.

Therapy on this protocol is divided into 3 phases: 1) SGN-35 "lead in" as a single-agent for 2 cycles/doses (1.8 mg/kg q 3 weeks x 2 doses); 2) AVD chemotherapy for 6 cycles; and 3) SGN-35 consolidation with SGN-35 given as a single-agent once every 3 weeks for 4 total doses (see Figure 2).

Figure 2. Trial schema.



* Any patient who has not achieved a CR or PR after 6 cycles of AVD should be taken off study and not proceed with SGN35 consolidation therapy; however patients who do not complete 6 cycles of AVD (due to toxicity: designated 'chemotherapy intolerant'), but have achieved PR or CR may proceed with SGN35 consolidation therapy.

5.2 SGN-35 "lead in".

5.2.1 SGN-35 Description

SGN-35 (brentuximab vedotin) is an antibody-drug conjugate consisting of the anti-CD30 antibody cAC10 conjugated to MMAE, an anti-tubulin agent.

5.2.2 Dose and Administration

Study treatment must not be administered as an IV push or bolus. Study treatment will be administered by outpatient IV infusion given over approximately 30 minutes on Day 1 of each 21-day cycle. For this "lead in" phase, there are a total of 2 cycles. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute infusion period. Study treatment will be administered through a dedicated IV line and cannot be mixed with other medications.

The dose of SGN-35 for lead-in is: **1.8 mg/kg.** Dosing is based on patient weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

5.2.3 Required Premedication and Postmedication

Routine premedication should not be administered prior to the first dose of study treatment. However, patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment with premedication as described immediately below.

5.2.4 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of study treatment. The infusion is to be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for at least 60 minutes following the first infusion of study treatment. During this observation period, 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 study according to institutional standards. This includes adjusting the infusion time if necessary. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment infusions with premedication consisting of acetaminophen (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 infusion. Additionally, steroids may be administered at the physician discretion.

5.2.5 Dose Modifications

Intra-patient dose reduction to 1.2 mg/kg will be allowed depending on the type and severity of toxicity. Table 3 on the following page describes the recommended dose modifications for study treatment-associated toxicity. The start of the next cycle may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle. Delays of greater than 3 weeks are generally prohibited; if a delay of greater than 3 weeks is anticipated, the QAM and the PI should be contacted for consideration. Approval of such delays will be on a case-by-case basis.

NOTE: SGN-35 doses reduced for treatment-related toxicity should not be re-escalated.

NOTE: Please use CTCAE version 4.0 for all treatment-associated toxicities.

NOTE: Additional dose reductions (in addition to Table 3) may be warranted on a case-by-case basis at the discretion of the PI. If the treating physician feels this is necessary, due to recurrent toxicity or other reasons, the treating physician must contact the PI and the QAM to discuss.

5.2.5.1 Dose modifications regarding pancreatitis.

- Asymptomatic elevated amylase and lipase (for patients with amylase elevation >3x upper limit of normal, but no abdominal pain):
    - Grade 1 – continue at same dose level
    - Grade 2 – continue at same dose level
    - Grade 3 – hold dose until toxicity resolves to ≤ Grade 2 and then resume treatment at the same dose level
    - Grade 4 – hold dose until toxicity resolves to ≤ Grade 2 and then resume treatment at reduced dose level or discontinue at the discretion of the treating investigator

If a 2nd episode of asymptomatic hyperamylasemia occurs, SGN-35 must be reduced by 1 dose level. If a 3rd episode occurs, SGN-35 must be permanently discontinued.

- Mild to moderate pancreatitis (hyperamylasemia syndrome – characterized by abdominal pain of <72 hours duration with amylase and/or lipase elevation): Hold SGN-35. May consider resuming, with 1 dose level reduction, when signs, symptoms and laboratory values (i.e., amylase and lipase) return to baseline/normalize. If a 2nd episode of mild to moderate pancreatitis occurs, SGN-35 must be permanently discontinued.

- Severe pancreatitis (abdominal pain of > 72 hours with lipase and/or amylase elevation of >3x normal for >72 hours duration): Permanently stop SGN-35.

Table 3. Recommended SGN35 Dose Modifications for SGN35 Treatment-Associated Toxicity.

• Toxicity	• Grade 1	• Grade 2	• Grade 3	• Grade 4
• **Non-Hematologic (pancreatic[c])**	• Withhold dose until toxicity is has returned to baseline, then resume treatment at the same dose level	• Withhold dose until toxicity is has returned to baseline, then resume treatment at the same dose level	• Withhold dose until toxicity has returned to baseline, then reduce dose, as described in section 5.2.5.1.	• Withhold dose until toxicity has returned to baseline, then reduce dose, as described in section 5.2.5.1.
• **Non-Hematologic; Other**	• Continue at same dose level.	• Continue at same dose level, except in the event of Grade 2 neuropathy. • For Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1, then reduce the dose to 1.2 mg/kg (or to 0.8 mg/kg if already on 1.2 mg/kg) and resume treatment	• 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.	• Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce dose to 1.2 mg/kg (or to 0.8 mg/kg if already on 1.2 mg/kg) and resume treatment and resume treatment [a] • For Grade 3 or higher neuropathy, discontinue treatment.
• **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 (eg, G-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 (eg, G-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 1.2 mg/kg (or to 0.8 mg/kg if already on 1.2 mg/kg) and resume treatment and resume treatment [b]

[a] Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities or nausea/vomiting that respond to treatment may continue study treatment without interruption.

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

[c] See Section 5.2.5.1 above regarding specific modifications for pancreatitis.

5.2.6 Treatment Compliance.

Subject compliance with treatment is anticipated to be well controlled for this trial as study treatment 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 regimen.

5.2.7 Other directions.

See **Section 8.1** for Preparation, Packaging and Labeling, and Concomitant Therapy and other information regarding SGN35.

5.2.8 Re-staging.

The first 22 evaluable patients entered onto the trial will have an "early" FDG-PET scan performed after the 2 'lead in' cycles of SGN35. The recommended timing for this FDG-PET scan is to be completed between days 14 and 18 after the 2nd cycle of SGN35. See **Section 6.6** for further details regarding completion and interpretation of FDG-PET and see Table 3 Schedule of Activities in Section 7.0 for additional details.

5.2.8.1 Re-staging for evaluable patients 23 through 45.
Patients 23 through 45 are not required to have a restaging PET or CT scan after the first 2 'lead in' cycles of SGN35. PET and/or CT scans may be obtained at the investigators discretion at this time point. If there is documented progressive disease after SGN35 (i.e., prior to initiation of AVD), patients may still remain 'on trial' and proceed to AVD chemotherapy, however they will not receive SGN35 consolidation.

5.2.8.2 Re-staging for chemotherapy intolerant patients.
See Section 5.3.3.8 for this definition. Chemotherapy intolerant patients may proceed with consolidation SGN35 therapy if they have achieved either a PR or CR at time of chemotherapy intolerant designation. These patients should have repeat staging CT scans performed prior to initiation of SGN35 consolidation therapy (if not done within the preceding 30 days).

5.3 AVD chemotherapy.

5.3.1 Dosing.

Chemotherapy	**Dose**	**Infusion**	**Timing**
Doxorubicin (adriamcyin)	25 mg/m^2	IV	Days 1 and 15
Vinblastine (velban)	6 mg/m^2	IV	Days 1 and 15
Dacarbazine	375 mg/m^2	IV	Days 1 and 15

(DTIC)			

NOTE: A cycle is 28 days. Use actual weight to calculate body surface area. For further information regarding drug administration, please see Section 8.2.

5.3.2 Number of cycles.

Patients will receive 6 cycles of AVD chemotherapy, unless judged by the treating physician to be chemotherapy intolerant (see section 5.3.3.8). Each cycle is scheduled to be repeated every 28 days.

5.3.3 Dose modifications.

NOTE: All toxicities should be graded according to the CTC (version 4.0).

5.3.3.1 Hematologic Toxicity.

Dose delays and reductions of AVD chemotherapy only are to be done at the discretion of the treating physician and must be clearly documented on the Treatment eCRF in NOTIS along with the CTC (version 4.0) grade. Delays of greater than 3 weeks due to AVD toxicity must be approved by the PI and the QAM must be included on this correspondence. The following are only recommendations (are not mandatory) for modifications for AVD; SGN modifications are mandatory and are described above in Table 3. Some guidelines to be considered are for absolute neutrophil count of <500 on the day of treatment would be to consider addition of G-CSF (filgrastim) therapy. This is strongly preferred due to the long half-life of pegfilgrastim.

Patients with persistent severe neutropenia, especially despite use of granulocyte growth factor, could have reduction of doxorubicin and vinblastine by 25%.

5.3.3.2 Hepatic Dysfunction

Reduce the dose of vinblastine and doxorubicin as follows*:

Bilirubin	**% of full dose****
=/< 1.5	100
> 1.5 but < 3.0	50
=/> 3.0 but < 5.0	25
=/> 5.0	0

*Gilbert's syndrome is excluded from this guideline;

**May give full dose with recovery of bilirubin < 1.5.

5.3.3.3 Peripheral Nervous System Toxicity (Vinblastine).

Vinblastine may be dose reduced at the discretion of the treating physician. Consideration for dose reduction (e.g., by 50%) should

be given for grade 2 neuropathy (i.e., limiting instrumental ADL), especially if pain is present. Vinblastine should be stopped for grade 3 neuropathy (i.e., limiting self care ADL). If neuropathy improves, re-escalation may be considered.

NOTE: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5.3.3.4 Gastrointestinal Toxicity

5.3.3.4.1 Nausea and Vomiting

All patients should receive prophylactic anti-emetic therapy as noted in section 8.2 (e.g., ondansetron + decadron).

5.3.3.4.2 Mucositis and Diarrhea

For Grade 3-4 oral ulceration or diarrhea, hold all chemotherapy (i.e., doxorubicin, vinblastine, and dacarbazine) until symptoms clear, then may reinstate at 75% full dose. Doses may be re-escalated as tolerated.

5.3.3.4.3 Constipation

Vinblastine may cause severe hypomotility with constipation or ileus. Inform patients prior to administration and advise the patient to maintain regular bowel function. Decrease vinblastine dose by 50% for Grade 4 constipation, then re-escalate on a vigorous bowel regimen.

5.3.3.5 Cardiotoxicity

Doxorubicin may result in congestive heart failure. MUGA scans (or echocardiogram) should be repeated routinely s/p cycle 4 of AVD as described in the Schedule of Activities (Table 3), or earlier and more frequently, if clinically indicated.

Treatment with doxorubicin should be **discontinued** if there is cardiac dysfunction as indicated by:

- symptomatic arrhythmia or congestive heart failure, **or**
- a decrease in LVEF to below the institutional lower limit of normal **and** at least a 5% absolute decrease from the baseline LVEF value (e.g., 45% to 40%), **or**
- any absolute decrease of 15% or more from the patient's baseline value (e.g. 60% to 45%).

NOTE: If there is a return/improvement in LVEF back to the baseline level (or higher) prior to the next doxorubicin and/or if an arrhythmia has been controlled, then the remaining doxorubicin infusion(s) may be administered if it is felt by the managing physician to be in the best interest of the patient.

5.3.3.6 Creatinine clearance (as determined by Cockcroft-Gault equation): relating to Dacarbazine dosing.

Cl_{cr} 46-60 mL/minute: Administer 80% of dose

Cl_{cr} 31-45 mL/minute: Administer 75% of dose

Cl_{cr} <30 mL/minute: Administer 70% of dose

5.3.3.7 Other considerations

There may be other toxicities whereby the treating physician believes it would be 'best medical practice' to dose reduce a particular chemotherapy agent. This should be discussed with the study PI on a case-by-case basis and the QAM should be included on all such correspondence.

5.3.3.8 Chemotherapy intolerance.

If any of the above grade 3 or 4 non-hematologic toxicities or grade 4 hematologic toxicities last > 2 weeks or if the severe toxicity is 'recurrent', the patient may be deemed "chemotherapy intolerable" and stop further chemotherapy. This designation should be discussed with the study PI. In addition, this designation may be applicable for any other grade 3 or 4 non-hematologic toxicities not listed above and it is deemed by the treating physician that the patient should not continue further chemotherapy.

Chemotherapy intolerable patients may still proceed with consolidation SGN35 therapy if they have achieved either a PR or CR at time of chemotherapy intolerable designation. These patients should have repeat staging CT scans performed prior to initiation of SGN35 consolidation therapy.

5.3.4 AVD supportive care measures.

5.3.4.1 Antibiotic use

Prophylactic antibiotic use (e.g., levaquin) is at the discretion of the treating physician. It is encouraged that patients receive a form of oral thrush prophylaxis (e.g., diflucan 100mg po daily or nystatin swish

and spit twice daily) and also a form of PCP prophylaxis (e.g., Bactrim DS once on Monday, Wednesdays, and Fridays or Dapsone 50-100 mg once daily).

5.3.4.2 Growth factor

Granulocyte colony stimulating factor (e.g., G-CSF) may be used at the discretion of the treating physician as above and in accordance with ASCO guidelines; however as noted in Section 5.3.3.1, G-CSF would be advocated (filgrastim) vs pegfilgrastim. Please record all granulocyte (or erythrocyte) colony stimulating factors on the treatment forms.

5.3.5 Re-staging.

All patients will have re-staging FDG-PET and re-staging CTs of the neck/chest/abdomen/pelvis performed after the 3rd cycle of AVD. Recommended timing of these scans are between days 22 and 25 of the 3rd cycle. All patients will also have re-staging CTs of the neck/chest/abdomen/pelvis performed at the completion of AVD (i.e., after the 6th cycle).

FDG-PET will only be repeated at this time (end of AVD) if the patient has not entered into complete remission (CR). See **Section 6.0** for further details regarding assignment of response and see Table 3 Schedule of Activities in Section 7.0 for additional details. Any patient who has not achieved a CR or PR after the 6 cycles of AVD should be taken off study at this point and not proceed with SGN-35 consolidation therapy.

5.4 SGN-35 consolidation.

5.4.1 Overall

See Section 5.2 above for SGN-35 Description, Administration, Required Premedication and Post-medication, and Management of Infusion Reactions.

5.4.2 Dosing

Dosing of SGN-35 in this consolidation phase will start at **1.8 mg/kg or 1.2 mg/kg (depending in part on presence of neurotoxicity during SGN-35 lead-in and AVD chemotherapy)**.

5.4.2.1 The intent is to start all SGN-35 consolidation 2 weeks after the last dose/administration of AVD therapy. Furthermore, irrespective of dose, SGN-35 consolidation therapy will be given once every 3 weeks for 4 doses.

5.4.2.2 Patients who had **no neurotoxicity-related dose reductions** during the lead-in SGN-35 or vinblastine therapy may start SGN-35 consolidation at **1.8 mg/kg**.

5.4.2.3 Patients who had **any neurotoxicity-related dose reduction(s)** (or discontinuation) of the lead-in SGN-35 and/or vinblastine therapy will start SGN-35 consolidation at **1.2 mg/kg**.

5.4.2.4 If patients have **"ongoing"** grade 2, 3, or 4 neurotoxicity at the time of initiation of SGN-35 consolidation, therapy **must be delayed** until recovery to grade 1 (delay up to 8 weeks after completion of last AVD dose are permitted). If neurotoxicity does not recover to grade 1 within 8 weeks, then SGN-35 consolidation will not be given.

5.4.2.5 ***Additionally,*** if there are **other toxicities** whereby the treating physician believes it would be best medical practice to delay SGN-35 consolidation (up to 6 weeks) and/or initiate at the lower 1.2 mg/kg dose level, such decisions may be evaluated on a case-by-case basis, but should be discussed with the study PIs; the QAM should also be included on all such correspondence.

5.4.3 Dose modifications.

Intra-patient dose reduction to 1.2 mg/kg or to 0.8 mg/kg will be allowed depending on the type and severity of toxicity. Table 2 describes the recommended dose modifications for study treatment-associated toxicity. Additionally, the start of a subsequent SGN35 cycle may be delayed for up to 4 additional weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle.

NOTE: ***SGN-35 doses reduced for treatment-related toxicity should not be re-escalated.***

6 RESPONSE ASSESSMENT

6.1 Measurability of Lesions

6.1.1 Measurable disease

Lesions that may be accurately measured in two dimensions by CT, MRI, plain x-ray, or other conventional technique and have a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters 2 cm or greater. Splenomegaly alone is not sufficient to qualify as measurable disease.

NOTE: PET scans are insufficient for evaluation of measurable disease.

6.1.2 Non-measurable disease

All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not cofirmed or followed by CT or disease documented only by PET imaging or indirect evidence (e.g., lab values).

Lymphoma Response Criteria

NOTE: These criteria are based upon the criteria from the Revised Response Criteria for Malignant Lymphoma, (Cheson et al.), Journal of Clinical Oncology, 2007, Vol. 25:579-586.

The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks.

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant.
- If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features: a) they should be clearly measurable in at least two perpendicular measurements; b) they should be from as disparate regions of the body as possible; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required.

- The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1cm, 2.2 cm, etc.).

- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.

6.2 Complete Response

Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

6.2.1 For lymphomas for which the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.

6.2.2 If the pretreatment PET scan was negative: all lymph nodes and extranodal masses must have regressed on CT to normal size ($\leq$ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to treatment must have decreased to $\leq$ 1 cm in their short axis after treatment.

6.2.3 The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.

6.2.4 If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology,

it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

NOTE: Complete Remission/unconfirmed (CRu): Using the above definition for CR and that below for PR eliminates the category of CRu.

6.3 Partial Response (PR)

The designation of PR requires all of the following:

6.3.1 A $\geq$ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; (b) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

6.3.2 No increase in the size of other nodes, liver or spleen.

6.3.3 Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment.

6.3.4 No new sites of disease.

6.4 Stable Disease (SD)

6.4.1 Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease (see below).

6.4.2 Typically FGD-avid lymphomas: The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

6.4.3 For variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pretreatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

6.5 Progression (PD) and Relapse

For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes $\leq$ 1 x $\leq$ 1 cm will not be considered as abnormal for relapse or progressive disease.

Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single PET scan without histologic confirmation.

6.5.1 Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

6.5.2 At least a 50% increase from nadir in the SPD of any previously involved nodes or extranodal masses, or in a single involved node or extranodal mass, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node or extranodal mass with a diameter of the short axis of less than 1.0 cm must increase by $\geq$ 50% and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.

6.5.3 At least a 50% increase in the longest diameter of any single previously identified node or extranodal mass more than 1 cm in its short axis.

6.5.4 Lesions should be PET positive if the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

6.5.5 Measurable extra-nodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

6.6 FDG-PET guidelines.

6.6.1 **Overall.** FDG-PET/CT scans with ^{18}Fluorine- fluorodeoxyglucose (FDG) will be performed at baseline in all patients. An "early" FDG-PET/CT will be repeated after the 2 SGN-35 "lead-in" cycles for the first 22 patients (21 evaluable) patients enrolled on the study (funding is currently only available for these first 22 patients, which comprises the 1st stage of the Simon 2-stage study, for this investigational early FDG-PET scan). For all patients, FDG-PET/CT will then be repeated until a patient achieves CR status, then only CTs will be obtained. See the sections below for further description of recommended FDG-PET scanning procedure and interpretation; also see Table 4 Schedule of Activities in Section 7.

6.6.2 **Baseline FDG-PET/CT scan.** All patients should have a pre-treatment FDG-PET/CT scan as a baseline to compare with subsequent scans to assess response. This should be performed no more than 60 days before starting chemotherapy.

6.6.3 **"Early" FDG-PET/CT scan.** To assess the response to the first two (2) cycles of SGN-35 lead-in. This will be completed only for the first 22 patients (21 evaluable) patients enrolled on the Simon 2-stage study.

6.6.4 **Standard repeat FDG-PET/CT scans.** All patients will have FDG-PET/CT scans completed after the 3rd cycle of AVD. FDG-PET/CT scans will be repeated until a patient achieves CR status, then only CTs will be obtained. See Table 4 Schedule of Activities for other times of response assessments.

6.6.5 Scanning Facilities.

6.6.5.1 Only full-ring integrated FDG-PET/CT scanners are acceptable (coincidence cameras are not acceptable). The CT of the FDG-PET/CT is used for attenuation correction of PET data and anatomic localization. CT settings should follow institutional guidelines.

6.6.6 Scanning Protocol guidelines.

6.6.6.1 Patient preparation.

Non-diabetic patients should fast for at least 8 hours prior to the scan. Plain (unflavored water) should be taken during the period of fasting and the uptake period to ensure good hydration.

Diabetic patients should ideally be given a morning appointment. They should take their usual antidiabetic medication (oral or insulin) and eat a light meal (lighter than they normally would) on that morning. The time interval between that morning meal and PET/CT scan should be approximately 3-4 hours.

Blood glucose of all patients should be measured on arrival and consideration given to rescheduling if the blood glucose level is higher than 200 mg/dl. Insulin should not be administered to reduce glucose level when the blood glucose is > 200mg/dl at the time of arrival in the PET clinic. Oral diazepam or beta blockers may be given if desired to reduce brown fat uptake one hour prior to tracer injection.

Oral diluted contrast (e.g., Gastografin or 2% barium sulfate) may be administered, according to institutional guidelines. Intravenous contrast may also be administered, provided this is done in a technique that avoids deterioration of the CT images by streak artifacts from high-concentration intravenous contrast bolus.

6.6.6.2 Scanning protocol guidelines.

1. Administer 260 - 555 MBq (7-15mCi) ^{18}F- FDG
2. Emission part of the scan should start no earlier than 60 and no later than 80 minutes after injection.
3. The exact same period of uptake must be used for staging and response scans – within 15 minutes.
4. Perform attenuation corrected PET-CT scan to cover the area from the base of the skull to mid-thigh. This should be done with the arms above the head.
5. Perform a separate head and neck scan, with arms down, ONLY IF this is the only site of disease.
6. Attenuation correction of PET emission data will be based on the low dose CT from the FDG-PET/CT.

   Acquisition should be performed using the institution's standard protocol, i.e. with regard to time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc. Images should be reconstructed using OSEM or a similar iterative reconstruction algorithm. Both attenuation-corrected and non attenuation-corrected images should be reconstructed. The proposed data acquisition/reconstruction protocol (including details of all the parameters above) must be agreed with the core lab prior to the start of the study

6.6.6.3 Reporting guidelines.

Visual interpretation will be used. The PET response scans will be scored with reference to sites of presumed lymphomatous involvement on the PET staging scan.

Negative

1 no uptake
2 uptake ≤ mediastinum
3 uptake > mediastinum but ≤ liver

Positive

4 uptake > liver in some sites even if uptake ≤ liver or mediastinum at other sites
5 uptake > liver in over 90% of sites or development of new uptake consistent with progressive disease

For the purpose of this study, scores 1, 2, 3 with uptake in sites abnormal on the staging scan equal or less than liver uptake will be regarded as 'negative' for disease and scores 4, 5 with uptake greater than liver will be regarded as 'positive' for disease. A separate analysis will be performed on patients with a score of 3 whose scan findings are analogous to the concept of 'minimal residual disease' (MRU) referred to in earlier published data on the use of PET in lymphoma. However for the purposes of treatment, patients with a score of 3 on the interim PET scan will be regarded as negative for disease.

Absolute and relative standard uptake values (SUVs) should not be used to determine scan positivity (because of inter-institution variations in scan performance and the acknowledged lack of standardization for SUV values).

Radiation Dosimetry

The whole body dose for FDG is about 0.10 rad/mCi, and the effective dose equivalent about 0.10 rem/mCi (0.03mSv/MBq). For the suggested activity range of 7-15mCi, the effective dose equivalent will be 0.7-1.5 rem (7.8 – 16.6mSv). (ARSAC Notes for Guidance 2006). The target organ is the urinary bladder wall, which will receive 0.22rad/mCi with a realistic one hour voiding interval (ICRP Publication 53). The dose from a low dose (140kV, 80mA) CT as part of a PET/CT is about 0.9 rad (rem) or 9mSv (Wu et al. Eur J Nucl Med Mol Imaging 31:38-43, 2004).

6.7 Cumulative Illness Rating Scale.

6.7.1 The modified CIRS will be collected for assessment of co-morbidities. Please see Appendix III for further details/methods for completion (and Section 9.11).

6.8 Activities of Daily Living.

The basic ADL and instrumental ADL scales as well as classification for 'fit' vs 'unfit' are described fully in Appendix VI.

6.9 Quality of Life Measurement.

6.9.1 Quality of life materials must be submitted at the time points listed below. Please refer to the table below and see Appendix V.

6.9.2 **Hypothesis:** We hypothesize that HRQL will provide a meaningful comparison of the different novel targeted therapy in the lead in and consolidation phases with AVD chemotherapy. HRQL data will complement the standard assessment of treatment-related toxicity. Prospective data will be informative to clinicians and patients in providing descriptive data on what to expect with regard to these domains during and following treatment. Long-term follow-up will provide valuable descriptive data on patients' HRQL as they transition from active treatment to survivorship. In addition, these results will be used to identify the most relevant endpoints for potential follow-up phase III trials, to calculate power estimates to adequately address follow-up HRQL questions, and to establish minimally important differences to evaluate clinically meaningful changes over time and between treatment arms.

6.9.3 **Study Design:** We will prospectively measure HRQL (physical, functional, emotional and social well-being) using the Functional Assessment of Cancer Therapy – General (FACT-G).[48] Disease-related symptoms and concerns specific to lymphoma will be assessed using the FACT-Lymphoma subscale (FACT-Lym).[48,49] The FACT-Lym used in this study will encompass of the parameters of the FACT-G. While limited research has examined HRQL among patients with HL,[50,51] emotional function is significantly impacted and is therefore an important endpoint for this trial. Fatigue and neurotoxicity are anticipated to be the most commonly experienced side effects from SGN35 and AVD sequential therapy. Treatment-emergent symptoms will be assessed using the FACT-Fatigue subscale and neurotoxicity will be assessed using the FACT/GOG-Neurotoxicity subscale.

Quality of Life Studies.

QOL Form	Baseline	Induction	Consolidation
FACT-L and FACT-Fatigue	X	C1D1 of AVD	C1D1 of SGN consolidation • at completion of consolidation;

			12 months after completion of consolidation
FACT/GOG Neurotoxicity	X	C1D1 of AVD C4D1 of AVD	C1D1 of SGN consolidation at completion of consolidation; 6 months after completion of consolidation 12 months after completion of consolidation

6.9.4 Quality of Life Studies to be Performed

(1) FACT-Lymphoma subscale (FACT-Lym) - 42 items.
(2) FACT-Fatigue scale - 13 items.
(3) FACT/GOG-Neurotoxicity scale - 11 items.

6.9.5 Administration Instructions

6.9.5.1 The questionnaires must be administered at the time points listed above. The patient should be instructed to respond to the questionnaires in terms of his/her experience during the time frame specified on each questionnaire.

6.9.5.2 The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the completion of the questionnaires as long as the staff person does not influence the patient's responses.

6.9.5.3 The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how he/she is feeling. If a question was not answered, the patient should be asked if he/she would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the questionnaire that he/she declined to answer the item.

6.9.5.4 If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be notedon the questionnaire. .

6.9.5.5 If a patient misses an appointment on the scheduled date, the questionnaires may be completed by telephone on the appointed date or they may be completed at the time the appointment is rescheduled. If the missed scheduled date is on a treatment date, the quality of life assessment will be done when the patient comes for the rescheduled treatment.

6.9.5.6 If a patient cannot complete the questionnaire because he/she is too sick, this should be documented onthe questionnaire. .

7 STUDY PARAMETERS

7.1 Schedule of Study Activities. See *Table 4 below* for the Study Activities.

7.1.1 **Pre-cycle testing.** Laboratory assessments must be done within 30 days before beginning study treatment (testing may be completed on day 1 of each cycle, but must be done prior to treatment). Measurements of measurable disease (as in Section 6.1.1) or non-measurable disease (as in Section 6.1.2) must be completed within 60 days prior to starting treatment. Staging bone marrow and cardiac testing (e.g., echocardiogram) may have been done within the prior 90 days before starting treatment. A window of +/- 2 days is permitted for all scheduled visits, tests, and procedures.

7.1.2 **Treatment Schedule.** Patients will be seen by a physician every 3 weeks during the SGN-35 “lead in” phase, every 4 weeks during AVD therapy, and every 3 weeks during SGN-35 consolidation. A window of +/- 2 days is permitted for all scheduled visits, tests, and procedures.

7.1.3 **Follow-Up Visit Schedule.** Patients with CR, PR, or SD will return for a follow-up examination 30 days after their last treatment dose. Early termination patients and patients with PD will return for a final study visit (including imaging) 30 days after their last respective treatment dose.

7.1.4 **Concomitant Medications.** All concomitant medications will be recorded from screening through study discontinuation.

7.1.5 **Eastern Cooperative Oncology Group (ECOG) Performance Status Assessment.** The patient’s ECOG performance status will be assessed during screening (within 14 days before beginning study treatment). To be eligible for enrollment, patients must have a score of 0, 1, or 2, according to the ECOG scale (see Appendix I).

7.1.6 **CT scan and PET scan.** Patients will undergo CT scans of the chest, abdomen and pelvis +/- neck and FDG-PET scanning prior to cycle 1. Scans must be done within 60 days prior to day 1, cycle 1. The baseline CT scan may be done concurrently with the PET scan, however oral contrast needs to be used (use of intravenous contrast for the diagnostic CT is encouraged, but not mandatory).

Table 4. Schedule of Activities.

		SGN-35 lead-in	AVD[15]	SGN-35 consolidation[15]	Post-Therapy Follow-up
Parameter	**Pre-study**	**Cycles[1]**	**Cycles[2]**	**Cycles[3]**	
Assignment of IPS score	X				
History and Physical examination	X	X	X	X	X[13]
Performance Status	X	X	X	X	X[13]
Tumor Measurements by Physical Exam (if applicable)	X	X	X	X	X[13]
CBC and Differential[4]	X	X	X	X	X[13]
Serum Chemistries (electrolytes, SGOT, SGPT, total bilirubin, direct bilirubin,[5] LDH, creatinine, glucose, alkaline phos, and calcium)	X	X	X	X	X[13]
Serum amylase and lipase[17]	X	X		X	
ESR	X	X	X	X	
Uric acid[16]	X				
Bone marrow biopsy (bilateral preferred, unilateral acceptable)[6]	X				
EBV PCR[16]	X		Day 1, cycle 1	On start of cycle 1	At end of and 6 months after consolidation
TSH and Hemoblogin A1c[16]	X			On start of cycle 1	
HIV screening[7]	X				
Echo or MUGA	X		X[8]		
CT Chest, Abdomen, and Pelvis[9, 10, 15]	X	X	X[15]	X[10]	X[13]
PET/CT Scan[9, 10]	X	X	X		
Co-morbidity/ADL assessment[11]	X				X[11]
Quality of life assessments[12]	X		X	X	X
SGN-35 PK sample[18]		X			

Correlative science blood studies[14]	X	X		X	

1. Two cycles of therapy given 21 days apart (+/- 7 days). Patients may be evaluated in the office more frequently, if needed, at physician discretion. If there is documented progressive disease after SGN35 (i.e., prior to initiation of AVD), patients may still remain 'on trial' and proceed to AVD chemotherapy, however they will not receive SGN35 consolidation. Study visits, tests, and procedures should be completed Day 1 (+/- 2 days) of each cycle.
2. Six cycles of therapy. Cycles are every 28 days (+/- 7 days), though treatments are given day 1 and day 15 of each cycle. Patients may be evaluated in the office more frequently, if needed, at physician discretion. Study visits, tests, and procedures should be completed Day 1 (+/- 2 days) of each cycle.
3. Four cycles of therapy. Cycles are every 21 days (+/- 7 days). Patients may be evaluated in the office more frequently, if needed, at physician discretion. Study visits, tests, and procedures should be completed Day 1 (+/- 2 days) of each cycle.
4. CBC at baseline and as clinically indicated to capture nadir: please record the absolute lymphocyte count.
5. Direct bilirubin is recommended, but required only if total bilirubin is elevated.
6. Baseline bone marrow biopsy is mandatory within 90 days prior to starting treatment. Repeat bone marrow biopsy at time of CR and relapse **ONLY** if positive at baseline (bilateral biopsy is preferred, but unilateral is acceptable). **.**
7. Not mandatory, but recommended.
8. Repeat after 4th cycle of AVD. May be repeated earlier or more frequently as clinically indicated.
9. Combined PET/CT scan will be sufficient if the PET/CT is performed with oral contrast (intravenous contrast is encouraged, but not mandatory); if PET/CT is without oral contrast, then separate/dedicated CTs of chest/abdomen/pelvis (in addition to PET/CT) must be obtained. Please see Section 6.6 for further guidelines on recommended interpretation of PET scans.
10. The first 22 evaluable patients entered on the study will have a repeat FDG-PET after the 2 "lead in" cycles of SGN35. This should be completed the week prior to planned initiation of AVD chemotherapy. All patients entered on study will have FDG-PET and CTs performed prior to day 1 of cycle 4 of AVD therapy (after day 15 of cycle 3). Thereafter, once a patient enters complete remission (CR), then only CT's (chest/abdomen/pelvis) should be obtained (not both PET/CT and dedicated CTs). All patients will have re-staging scans performed at the end of AVD chemotherapy (i.e., prior to start of SGN35 consolidation therapy).
11. See Appendix III and Appendix IV for further details/methods for completion. This includes Co-morbidity assessment (Appendix III) and Activity of Daily Living (ADL) assessment (Appendix VI). Obtain once at baseline (pre-treatment) and then repeat once at the completion of all therapy.
12. **See Section 6.9 for exact timing and description and Appendix IV for Quality of Life forms.**
13. 30 days (+/- 2 days) after the last dose of treatment, patients should have repeat re-staging CTs +/- FDG-PET completed. Thereafter, the follow-up schedule will be office visits with blood tests q 3 months and re-staging CTs q 6 months for 3 years, then per local institutional guidelines. Patients who stop treatment early due to AEs or PD will also follow this schedule.
14. See Table 4 in Section 12.3.3 for full explanation of which blood tubes (i.e., ACD/yellow, EDTA/purple, and red top) and timing (e.g., baseline/pre-SGN35, after 2 cycles of SGN35 lead-in, and after completion of AVD chemotherapy) of correlative blood studies.
15. Any patient who has not achieved a CR or PR after the 6 cycles of AVD should be taken off study and not proceed with SGN consolidation therapy. However, patients who do not complete 6 cycles of AVD (due to toxicity: designated 'chemotherapy intolerable'), but achieve PR or CR may proceed with SGN35 consolidation therapy. See **Section 5.3.3.8** regarding designation of chemotherapy intolerance. Patients who are designated as 'chemotherapy intolerant' should have restaging CTs of the chest, abdomen, and pelvis performed prior to the start of SGN35 consolidation (if they have not been performed within the preceding 30 days).

16. Encouraged, but not required.

17. Amylase and lipase levels must be drawn 72 hours prior to the dosing of SGN-35. See **Section 5.2.5.1** regarding dose modifications for pancreatitis.

18. 2.7 mL of whole blood to be collected in a 3 mL Na Citrate (blue top) tube 48-72 hours post the first dose of SGN-35. The properly frozen plasma should be shipped overnight to the Lurie Cancer Center Pathology Core Facility. Should an unexpected SAE arise with a dose/cycle of SGN-**35 other than the 1st dose/cycle**, samples should be drawn and sent on a case-by-case basis to the Lurie Cancer Center Pathology Core Facility. This should be discussed with the study P.I & QAM. See section 12.4 for specimen processing and storage requirements.

8 DRUG FORMULATION AND PROCUREMENT.

8.1 SGN-35.

8.1.1 **Other names.** Brentuximab vedotin.

8.1.2 **Classification.** SGN-35 is an antibody-drug conjugate consisting of the anti-CD30 antibody cAC10 conjugated to MMAE, an anti-tubulin agent.

8.1.3 **Mode of Action.** Induction of apoptosis and cytotoxic cell death.

8.1.4 **Storage and stability.** SGN-35 is supplied as sterile, preservative-free, white to off-white lyophilized cakes for reconstitution for IV administration and are supplied by Seattle Genetics in single-use glass vials. Each vial of SGN-35 product contains SGN-35, trehalose, sodium citrate, and polysorbate 80.

Vials containing study treatment must be refrigerated at 2–8°C in a secure location (e.g., locked room) accessible only to the pharmacist, the investigator, or a duly designated person. Study treatment does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used on the same day when stored under refrigeration at 2–8°C. Reconstituted SGN-35 should not be stored at room temperature. It is recommended that study treatment vials and solutions be protected from direct sunlight until the time of use. Reconstituted vials must not be shaken.

8.1.5 **Dose specifics.** Dosing is based on patient weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

8.1.5.1 Dosing for the first 2 cycles of the SGN-35 lead-in are administered at 1.8 mg/kg given 3 weeks apart.

8.1.5.2 Dosing for the 4 cycles of consolidation (i.e., after induction AVD chemotherapy), SGN-35 dosing is 1.8 mg/kg or 1.2 mg/kg given every 3 weeks apart for 4 doses. See **Section 5.4.2** for details.

8.1.5.3 For SGN-35 dose modifications, see **Sections 5.2.5 and 5.4.3** as well as Table 2.

8.1.6 **Preparation.** Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published (see manufacturer's prescribing information insert). Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

8.1.6.1 Reconstitution

Calculate the dose (mg) and number of vials of brentuximab vedotin required. The dose for patients with a weight of >100 kg should be calculated for 100 kg. Reconstitute each 50 mg vial of brentuximab vedotin with 10.5 mL of Sterile Water for Injection, USP, to yield a single-use solution containing 5 mg/mL brentuximab vedotin. Direct the stream toward wall of vial and not directly at the cake or powder. Gently swirl the vial to aid dissolution. DO NOT SHAKE. Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates. Following reconstitution, dilute immediately into an infusion bag, or store the solution at 2-8˚C (36-46˚F) and use within 24 hours of reconstitution. DO NOT FREEZE. Discard any unused portion left in the vial.

8.1.6.2 Dilution

Calculate the required volume of 5 mg/mL reconstituted brentuximab vedotin solution needed and withdraw this amount from the vials. The dose for patients with a weight of >100 kg should be calculated for 100 kg. Immediately add the reconstituted solution to an infusion bag containing a minimum volume of 100 mL to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin. Brentuximab vedotin can be diluted into 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection. Gently invert the bag to mix the solution. Brentuximab vedotin contains no bacteriostatic preservatives. Following dilution, infuse the brentuximab vedotin solution immediately, or store the solution at 2-8˚C (36-46˚F) and use within 24 hours of reconstitution. DO NOT FREEZE.

8.1.7 **Administration. Study treatment must not be administered as an IV push or bolus.** Study treatment will be administered by outpatient IV

infusion given over approximately 30 minutes on Day 1 of each 21-day cycle. For this "lead in" phase, there are a total of 2 doses/cycles. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute infusion period. Study treatment will be administered through a dedicated IV line and cannot be mixed with other medications.

- **Avoid use in patients with severe renal impairment**
- **Avoid use in patients with moderate or severe hepatic impairment.**

Required Premedication and Postmedication. Routine premedication is not mandated prior to the first dose of study treatment. However, patients at clinical risk of nausea or who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment with premedication as described below (e.g., prochlorperazine, ondansetron, etc).

8.1.8 **Incompatibilities.** No other anti-cancer treatment will be permitted during the treatment period, including chemotherapy, investigational therapies, radiation, biological response modifiers, hormone therapy, or immunotherapy.

8.1.9 **Compatibilities.** Best supportive care is expected. All concomitant medications and blood products administered during the patient's participation in the study from the time of informed consent through the End of Treatment visit or 30 days after the last dose, whichever is later, must be recorded in the source document and on the CRF. Supportive measures consistent with optimal patient care should be provided throughout the study according to institutional standards.

8.1.10 **Availability.** This study drug will be supplied by Seattle Genetics. Drug orders should be emailed to Seattle Genetics drug supply at IST@seagen.com or faxed to 425-527-2016.

8.1.11 **Side effects.** In the initial SGN-35 phase I dose escalation study (administered once every 3 weeks) for patients with relapsed or refractory CD30-positive lymphomas (73% of patients had received prior autologous stem cell transplant), besides lymphocytopenia (47%) and neutropenia (16%), the incidence of grade 3/4 laboratory abnormalities was ≤15%. Thirty-one percent experienced SGN35-related therapy delay, primarily

neutropenia seen at higher doses. The dose limiting toxicities were neutropenic fever (prostatitis), hyperglycemia, and unrelated acute renal failure, which were seen at the SGN35 dose of 2.7 mg/kg.

Following are some of the side effects noted:

Likely (>20%): diarrhea, nausea, fatigue, fever, upper respiratory infection, decreased neutrophil count, peripheral sensory neuropathy.

Less Likely (<=20%): Allergic reaction; Cough, Dyspnea; Anxiety; Depression; Insomnia; Anemia; Blood and lymphatic system disorders - Other (lymphadenopathy); Dry skin; Alopecia, Hyperhidrosis; Dyspepsia; Abdominal pain; Constipation; Vomiting; Chills, Edema; Pain in administration site; Hyperhidrosis; Infections and infestations - Other (herpes zoster); lung infection; decreased WBC and platelet count; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Pain(back, bone, extremity); Arthralgia; Myalgia; Weight loss; Anorexia; Pruritus; Maculo-papular rash; Dizziness; Headache; Paresthesia; Peripheral motor neuropathy;

Rare but Serious (<3%):Anaphylaxis; Pancreatitis; Hepatobiliary disorders - Other (hepatotoxicity); Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity); Nervous system disorders-other(progressive multifocal leukoencephalopathy); Stevens Johnson Syndrome; Toxic epidermal necrolysis ;Tumor lysis syndrome .

Also Reported on SGN-35 Trials But With the Relationship to SGN-35 Still Undetermined: Acute kidney injury; Adult respiratory distress syndrome; Alanine aminotransferase increased; Aspartate aminotransferase increased; Dehydration; Encephalopathy; Generalized muscle weakness; Hot flashes; Hyperkalemia; Hypertension; Hypocalcemia; Hypophosphatemia; Hypotension; Infections and infestations - Other (oral candidiasis); Investigations - Other (blood LDH increased); Lymphocyte count decreased; Meningitis; Myelodysplastic syndrome; Myositis; Neck pain; Non-cardiac chest pain; Pericardial effusion; Pharyngitis; Pleural effusion; Pneumothorax; Productive cough; Renal and urinary disorders - Other (Pyelonephritis); Reproductive system and breast disorders - Other (groin pain); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Sinus tachycardia; Sinusitis; Skin infection; Syncope; Urinary tract infection

Please refer to current Investigator's brochure for detailed information on all side effects.

8.1.12 **Nursing/patient implications.** Please see above under administration in Section 8.1.7. In addition, avoid the use of SGN35 in patients with moderate (Child-Pugh B) or severe (Child –Pugh C) hepatic impairment. Regarding management of infusion reactions, infusion-related reactions

may occur during the infusion of study treatment. The infusion is to be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for at least 60 minutes following the first infusion of study treatment. During this observation period, 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 study according to institutional standards. This includes adjusting the infusion time if necessary. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment infusions with premedication consisting of acetaminophen (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 infusion.

8.2 Doxorubicin.

8.2.1 **Other names.** Adriamycin, Rubex, Adriamycin RDF, Adriamycin PFS, hydroxydaunorubicin, hydroxydaunomycin, ADR.

8.2.2 **Classification.** Anthracycline antibiotic.

8.2.3 **Mode of Action.** Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

8.2.4 **Storage and stability.** Rubex or Adriamycin RDF intact vials are stable protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

8.2.5 **Dose specifics.** Doxorubicin will be given intravenously at a dose of 25 mg/m^2 on days 1 and 15 of each AVD chemotherapy cycle. A cycle will be repeated every 28 days. Use actual weight to calculate body surface area

and doses. See section 5.3.3 regarding dose modifications (toxicity-related).

8.2.6 **Preparation.** Add 5, 10, 25, 50, or 75 ml of preservative-free normal saline to the 10, 20, 50, 100, or 150 mg vial to produce a solution containing 2 mg/ml.

8.2.7 **Administration.** Intravenously as a bolus injection. Peripheral vein administration is allowed.

8.2.8 **Incompatibilities.** Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

8.2.9 **Compatibilities.** Stable with vincristine in normal saline for 5 days at room temperature protected from light. Also compatible in solution with cyclophosphamide.

8.2.10 **Availability.** Commercially available as powder for injection in 10, 20, 50, 100, 150 mg vials, and as 2 mg/ml solution for injection in 10, 20, 50, and 200 mg vials.

8.2.11 **Side effects.** Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days. Dermatologic: Alopecia, usually complete; hyperpigmentation of nail beds and dermal creases; radiation recall. Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia, diarrhea; mucositis, especially with daily x 3 schedule. Cardiovascular: Arrhythmias, ECG changes; rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose; risk is greater with total doses > 550 mg/m2, mediastinal irradiation pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens. Other: Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity. Local effects: Vesicant if extravasated; flush along vein, facial flush.

8.2.12 **Nursing/patient implications.** Monitor CBC, platelet counts. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration

occurs. Advise patient of alopecia. Instruct on how to obtain wig, hairpiece, etc. Hair loss generally occurs 2-4 weeks after injection and is usually complete. Advise patient of red discoloration of urine for 24 hours after administration of the drug. Administer antiemetics as indicated. Assess for stomatitis and treat symptomatically. Generally occurs 7-10 days after injection. Be aware of "Adria" flare - most common reaction consists of an erythematous streak up the vein. It is associated with urticaria and pruritus. Occasionally the use of corticosteroids and/or antihistamines has been useful. Monitor for signs and symptoms of cardiomyopathy. Calculate total cumulative dose with each administration.

8.3 Vinblastine.

8.3.1 **Other names.** Velban, vinblastine sulfate, vincaleukoblastine, VLB, Velsar, Alkaban AQ.

8.3.2 **Classification.** Vinca alkaloid (tubulin inhibitor).

8.3.3 **8.3.3 Mode of Action.** Vinblastine binds to tubulin, a protein that forms microtubules, thus interfering with spindle formation during metaphase and causing cessation of cellular mitosis.

8.3.4 **Storage and stability.** Drug vials are stored in the refrigerator. Reconstituted vinblastine, 1 mg/ml, is stable for 30 days in the refrigerator. Further diluted to a concentration of 0.01 mg/ml in normal saline or 5% dextrose, vinblastine is stable for 24 and 72 hours, respectively, at room temperature.

8.3.5 **Dose specifics.** Patients will receive Velban intravenously at a dose of 6 mg/m^2 on days 1 and 15 of each AVD chemotherapy cycle. A cycle will be repeated every 28 days. Use actual weight to calculate body surface area and doses. See section 5.3.3 regarding dose modifications (toxicity-related).

8.3.6 **Preparation.** The 10 mg vial is reconstituted with 10 ml of bacteriostatic normal saline, yielding a concentration of 1 mg/ml. Doses for continuous infusion may be further diluted with 50 ml or more of normal saline or 5% dextrose in water.

8.3.7 **Administration.** Intravenously as a bolus injection.

8.3.8 **Incompatibilities.** Furosemide, heparin; Infusaid pumps.

8.3.9 **Compatibilities.** Vinblastine is physically stable in normal saline solutions for at least 5 days, alone or mixed with doxorubicin, at 8, 25, and 32°C. Vinblastine is also compatible in solution with metoclopramide and bleomycin.

8.3.10 **Availability.** Vinblastine is commercially available in 10 mg vials, as a lyophilized powder and as a 1 mg/ml solution.

8.3.11 **Side effects.** Hematologic: Leukopenia, thrombocytopenia, anemia. Dermatologic: Alopecia, epilation; skin and soft tissue damage if extravasated (the manufacturer recommends subcutaneous injection of hyaluronidase and application of heat to help disperse the drug); rash, photosensitivity. Gastrointestinal: Nausea, vomiting (preventable); constipation (see neurological side effects); abdominal pain (cramps), anorexia, diarrhea, mucositis, gastrointestinal hemorrhage. Neurologic: Peripheral neuropathy (loss of deep tendon reflexes, paresthesias, paralysis); autonomic neuropathy (constipation, paralytic ileus, urinary retention, orthostasis); vocal cord paralysis; myalgias; Raynaud's phenomenon; headache, seizures, depression, dizziness, malaise; may be enhanced by concomitant use of interferon. Pulmonary; Bronchospasm (acute shortness of breath), more common when administered with mitomycin; pulmonary edema. Other: Severe pain in the jaw, pharynx, bones, back or limbs following injection; syndrome of inappropriate antidiuretic hormone (SIADH); fever; ischemic cardiotoxicity; enhanced interferon toxicity.

8.3.12 **Nursing/patient implications.** Premedicate with antiemetics as needed. Administer by slow IV push. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs. Assess for neurotoxicity. Assess for constipation. Monitor CBC and platelet count.

8.4 Dacarbazine.

8.4.1 **Other names.** DTIC, DTIC-Dome,, DIC, imidazole carboxamide, dimethyl triazeno imidazole carboxamide.

8.4.2 Classification. Alkylating agent.

8.4.3 **Mode of Action.** Activity may be the result of at least 3 mechanisms: 1) alkylation; 2) antimetabolite activity as a purine precursor; and 3) interaction with sulfhydryl (SH) groups in proteins. Dacarbazine appears to be more active in G2 phase but is not particularly cell cycle phase specific.

8.4.4 **Storage and stability.** Store vials under refrigeration and protected from light. In solution, dacarbazine is stable for 96 hours if refrigerated and protected from light, 24 hours if not refrigerated but protected from light. When further diluted in 500 ml D5W or NS, it is stable for 24 hours if refrigerated, and 8 hours at room temperature and protected from light. Photodegradation: The manufacturer of dacarbazine states that the drug does not decompose when left at room temperature under normal lighting conditions for eight hours.

NOTE: A change in color of solution from pale yellow to pink is indicative of decomposition of the drug.

8.4.5 **Dose specifics.** Patients will receive Dacarbazine intravenously at a dose of 375 mg/m^2 on days 1 and 15 of each cycle of AVD chemotherapy. Cycles will be repeated every 28 days. Use actual weight to calculate body surface area and doses. See section 5.3.3 regarding dose modifications (toxicity-related).

8.4.6 Preparation. Dilute the 100, 200, and 500 mg vials with 9.9, 19.7, and 49.5 ml of sterile water, respectively, resulting in a concentration of 10 mg/ml. Protect the drug from direct light. Do not freeze. Discard if solution turns pink/red. The drug can be further diluted in 50-500 ml of 5% dextrose or normal saline.

8.4.7 **Administration.** Usually administered by intravenous infusion over 30 minutes or longer; has also been given IV push.

8.4.8 **Incompatibilities.** Metabolism of dacarbazine may be induced by phenytoin or phenobarbital. Toxicity may be enhanced if given concomitantly with allopurinol, azathioprine, or mercaptopurine. Dacarbazine is physically incompatible with hydrocortisone sodium succinate and heparin.

8.4.9 **Availability.** Commercially available in vials containing 100 mg, 200 mg, or 500 mg of lyophilized drug.

8.4.10 **Side effects.** Hematologic: Myelosuppression; nadir of WBC and platelet depression occurs approximately 21-25 days after treatment. Dermatologic: Alopecia; facial flushing; extravasation may result in severe pain but has not resulted in tissue damage. Rapid IV push may result in pain along injection site or thrombophlebitis. Gastrointestinal: Severe nausea and vomiting which characteristically lessens with each subsequent daily dose. Hepatic: Increased AST, ALT. Renal: Increased serum creatinine, BUN. Neurologic: Facial paresthesia. Other: Flu-like syndrome (with fever, malaise, myalgia) rarely occurs about 7 days after treatment and lasts 1-3 weeks. Rarely Anaphylaxis.

8.4.11 Nursing/patient implications. Administer prophylactic and prn antiemetics. Monitor CBC, platelet count. May cause pain, burning of the vein with rapid administration. This can be minimized by decreasing the rate of infusion.

9 9.0 STATISTICAL CONSIDERATIONS

9.1 This is a phase II study.

9.2 Analysis of the Conduct of the Study.

9.2.1 Data from patients who do not receive the three cycles of AVD chemotherapy or follow-up through 30 days after the last study drug dose due to termination, death, or noncompliance will be tabulated and described. Protocol violations during treatment and follow-up will be listed. Additional analyses will include summaries of patient demographics, baseline characteristics, compliance, and concurrent treatments.

9.2.2 The definition of an evaluable patient will be as follows: patients who complete/receive a minimum of at least the 2 initial SGN-35 lead-in doses of therapy and at least 3cycles of AVD chemotherapy will be considered evaluable for efficacy (response).

9.3 Phase II Efficacy Analysis.

9.3.1 The sample size for this study was calculated using a Simon's two-stage design. If the study completes both stages, with an approximate 5-10% loss to follow-up rate, approximately 48 patients will be enrolled, for a total of 45 evaluable patients.

9.3.2 The primary endpoint of the phase II portion of this study is the complete remission (CR) rate among older patients with Hodgkin Lymphoma receiving sequential SGN-35 therapy with adriamycin, vinblastine, and dacarbazine chemotherapy (S-AVD). This CR rate for the primary endpoint will be assessed at the completion of AVD chemotherapy (i.e., prior to SGN35 consolidation). Patients who are deemed 'chemotherapy intolerant' (i.e., do not complete 6 cycles of AVD chemotherapy) and have achieved a PR or CR may continue to SGN35 consolidation. Of note, all patients will be 'counted' towards the primary objective of CR rate at the end of AVD chemotherapy on an intent-to-treat basis. Patients who are designated chemotherapy intolerant (i.e., stop AVD chemotherapy prematurely), will have their remission rate analyzed for the primary objective at the time of stopping chemotherapy. These patients will still be followed for other/secondary study endpoints.

9.3.3 A true CR rate of 70% would be considered promising in this population, whereas a true complete response (CR) rate of 50% would not be

considered worthy of further study. A two-stage Simon optimal design will be used with 22 patients (21 evaluable patients who are eligible and begin protocol therapy) in the first stage and 26 patients (24 evaluable patients who are eligible and begin protocol therapy) in the second stage. Maximal type I error = 0.05, type 2 error = 0.2.

9.3.3.1 If 12 or more CRs are observed in the first stage among the 21 evaluable patients, accrual will continue to the second stage (n=24 evaluable patients in the 2nd stage of the Simon 2-stage).

9.3.3.2 If the 21st evaluable patient has enrolled to this study and fewer than 12 CRs have been observed/confirmed, then subsequent accrual to the study will be suspended for lack of adequate response. Once 12 CRs have been confirmed, then the trial may proceed (re-open to accrual if suspended) to the 2nd stage of the Simon 2-stage trial.

9.3.3.3 This treatment will be considered promising for further study if 27 or more of the 45 evaluable patients demonstrate CR.

9.3.3.4 The probability of stopping at the first stage is 0.07 if the true CR rate is 70% and is 0.67 if the true CR rate is 50%. With 45 evaluable patients, the probability of concluding this treatment is promising for further study is 0.9 and 0.1 assuming a true underlying CR rate of 70% and 50%, respectively. The maximum 90% two-stage confidence interval width for response is 0.26.

9.3.4 The incidence of overall response rate (CR and PR) and CR rate to induction SGN35 x 2 cycles will be reported for the initial 22 patients where PET is being employed. In exploratory analysis, outcome measures of PFS and OS will be analyzed for early responder vs non-responders at this timepoint. Patients will be dichotomized for CR/PR vs <PR and PET - vs. PET +.

9.3.5 We will also investigate time to progression free survival (PFS), defined as the time from registration to the earlier of disease progression or death from any cause without documentation of disease progression. The exponential Wald test will be used for the PFS analysis. With 45 evaluable patients, an accrual duration of 15 months and an additional follow-up duration of 3 years, there will be approximately 90% power to detect an

improvement in 2-year PFS rate from 45% (corresponding to median PFS 1.7 years) to 65% (corresponding to median PFS 3.2 years), using a one-sided type I error rate of 0.08. We assumed an exponential distribution for PFS and a uniform distribution for patient's entry to the study. The expected PFS event number would be about 20 at the time of analysis.

9.3.6 Estimates of the response rate based on CR rate, overall response rate (CR and PR) and the tumor control rate (CR, PR, and stable disease (SD)) will be provided together with the exact two-sided 95% confidence intervals. FDG-PET scanning will be incorporated as a component to assess response rate according to current/updated lymphoma restaging guidelines. The probability of a response in each category will be estimated using the proportion of subjects falling into the response category, that is, (number of subjects with response in that category)/(number of subjects evaluated). For progression-free survival and duration of response the Kaplan-Meier procedure will be used to characterize the survivorship function. Median time-to-events and the corresponding two-sided 95% confidence intervals will be provided for each of these variables. In all estimation we will consider using estimators and confidence intervals appropriate for sequential trials along the lines outlined in Cheng and Shen (Biometrics 60, 910-918) and G Yin and Y Shen (Biometrics 61, 2005).

9.4 Safety Analysis.

9.4.1 All patients who receive SGN-35 treatment will be included in the safety summaries and analyses. The safety and tolerability of therapy will be examined by: Extent of exposure to SGN-35 (dose, duration, and number of patients), Detailed summary of deaths by time to death (using Kaplan-Meier methods) and by cause of death, Detailed examination of AEs, Laboratory test results, Vital signs or other physical findings.

9.5 Adverse Events.

9.5.1 Adverse events will be classified by body system and preferred term using NCI CTCAE v4. Frequency tables at the patient level will summarize events. Frequency tables by category of event (serious, related), and by NCI CTCAE grade will be presented by dose regimen.

9.6 Laboratory Parameters.

9.6.1 Descriptive statistics (mean, standard deviation, mean change from baseline) of laboratory values will be presented. Individual patient graphs

will be displayed and reviewed for clinically relevant changes. Laboratory values of WBC, hemoglobin, absolute neutrophils, platelets, ALT, AST, bilirubin, and creatinine will also be summarized by NCI CTCAE grade.

9.7 Overall survival

9.7.1 Overall survival is defined as the date of study entry to the date of death.

9.7.2 Patients will followed for a total of 3 years for survival and then per local institutional guidelines.

9.8 Progression-Free Survival

9.8.1 Progression-free Survival (PFS) is defined as the time from entry onto study until lymphoma progression or death from any cause. PFS reflects tumor growth and, therefore, occurs prior to the endpoint of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. Whether a prolongation of PFS represents direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit ratio of the therapy under investigation. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. Where there is missing information, censoring of the data may be defined as the last date at which progression status was adequately assessed or the first date of unscheduled new anti-lymphoma treatment.

9.9 Time to treatment failure.

9.9.1 Time to treatment failure (event-free survival) is measured from the time from study entry to any treatment failure including discontinuation of treatment for any reason, such as disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death.

9.4 Freedom from progression.

9.9.2 Freedom from progression is measured form the time of study entry to the progression of disease. Other causes of treatment failure as noted above in

time to treatment failure are not included in freedom from progression. This end point pertains to the control of disease.

9.10 Quality of life (QoL) assessments.

9.10.1 Although the study is designed as two-stage optimal design study for effectiveness outcome = percent CR rate, QoL analysis will also be powered to show reasonable QoL effect. From literature we gather that functional well being measures have an SD = 6, while FACT-G has SD=16. Looking at After-Before measures, with correlation = 0.5 and equal SD's, for a null hypothesis of no difference between After and Before, and a two sided alternative hypothesis, at apha=5%, with n=21 patients in the first stage, we have 69% power to reject the null hypothesis in favor of alternative = 9 points for FACT-G. Similarly, if the study goes into second stage, n=42 patients gives 82% power to reject H0 in favor of H1 if the observed difference is 7 points for FACT-G. Similar results hold for functional well being measures.

9.11 Co-Morbidity assessment.

9.11.1 We will collect the number of co-morbidities for each patient at baseline and at the end of completion of all therapy utilizing the Cumulative Illness Rating Scale and assess the relationship between CIRS score and outcome (CR, DFS, PFS).

The comprehensive geriatric assessment (CGA) has been developed as a procedure to assess the objective health status of elderly persons.[52-55] The CGA is considered to be more effective than standard medical evaluation for the care of the elderly. Initially, use of a CGA was based on its ability to predict morbidity and mortality in the general geriatric population, although accumulating data show the benefits of using the CGA specifically in patients with cancer.[53,54,56] Comorbidity is an essential part of the CGA. Several comorbidity scales have been used in research, although the Cumulative Illness Rating Scale (CIRS) is one of the more prominent tools utilized in geriatrics.[53,57] The CIRS measures chronic medical illness burden while taking into account the severity of chronic diseases. The CIRS has been revised to reflect common problems of elderly people and was renamed the Cumulative Illness Rating Scale for Geriatrics (CIRS-G);[58] this version has subsequently been validated.[59] Furthermore, several recent cancer related studies have validated the relevance of the CIRS to define comorbidities among oncology patient populations, some of which correlated with survival.[60,61]

For binary outcomes such as CR, logistic regression will be used to assess the relationship with CIRS score; for time-to-event outcomes, the method of Kaplan and Meier and the log rank test, as well as Cox proportional hazards models, will be used to assess the association with co-morbidity.

10 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high intensity monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations and as required by the NCI AdEERS Reporting Guidelines.

10.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 7 for timepoints). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

10.2 Definitions & Descriptions

10.2.1 Adverse Event.

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions

that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation

10.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

10.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.
An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- Results in *death*.

  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- Is life-threatening.

  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

- Results in persistent or significant disability or incapacity.

- Is a congenital anomaly/birth defect.

- Is an important medical event.

  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

10.2.4 Unanticipated Problems Involving Risks to Subjects or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

10.3 Adverse Event Reporting

10.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

10.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1. Identify the type of adverse event using the NCI CTCAE v 4.0.
2. Grade the adverse event using the NCI CTCAE v 4.0.
3. Determine whether the adverse event is related to the protocol therapy.

   Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4. Determine the prior experience of the adverse event.

   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

10.3.3 Expedited Reporting of SAEs/Other Events

10.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:
- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics

- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

10.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 10 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

10.3.3.3 Reporting to the FDA (completed by NU QAM)

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

All other SAEs will be reported on an annual basis as part of

10.3.3.4 Reporting to Seattle Genetics

All serious adverse events that occur during this study, regardless of the relationship to the study drug, must be reported by the Investigator using the MedWatch form to the following parties within 24 hours of

being made aware of the SAE:

* Sponsor-Investigator – via notification to the QAM
* IRBs of individual institutions per local reporting requirements
* Seattle Genetics, Inc., the manufacturer of Investigational

Product, by faxing the SAE Report form and any copies of relevant source documentation (e.g., hospital admission or discharge summary, laboratory or other test results, etc.) that pertain to the event to:

Seattle Genetics Drug Safety Department at 425-527-4308.

Relevant follow-up information is to be submitted to the Sponsor-Investigator and Seattle Genetics Drug Safety (at the fax number above) as soon as it becomes available.

10.4 Scheduled Assessment of Safety

10.4.1 Safety Data: Safety data will be collected on Day 1 of each cycle of chemotherapy and then at 3 month intervals for a total of 24 months. Analysis will also include MUGA scan studies done at baseline.

10.4.2 Efficacy endpoints: Efficacy endpoints data will be analyzed (primarily: CT scans and PET scans) at baseline and after 3 cycles of the above regimen and at completion of chemotherapy; and then every 3 to 6 months for 2 years total.

10.5 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients study treatment for any of the following reasons:

- Intercurrent illness
- Occurrence of an unacceptable adverse event
- Patient request (follow-up may still be permitted unless patient withdraws consent from the study as a whole)
- Protocol violations
- Non-compliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
- Progressive disease at any time

If treatment is ongoing at the time of termination, patients should return 30 days after the last study treatment for a "termination visit" that includes the assessments specified for the 30-day follow-up visit. If this is not possible or if the patient has completed study treatment more than 30 days before, these assessments should be done at the time of termination.

If a patient has terminated the study as a whole (withdraws consent), no further data collection and submission is permitted, except for follow-up of AE's present at the time of termination. If, however, a patient is withdrawn from treatment (but not the study as a whole), follow-up for survival endpoints will continue.

Patients may choose to stop study treatment and/or withdrawn from the study as a whole for any reason without jeopardizing their relationship with their health care providers.

10.5.1 **Accountability for Study Drug.** Seattle Genetics Clinical Affairs (the Supporter) or its designee will ship vials of SGN-35 directly to each study center.

The individual receiving the shipment must verify the quantities received. The Clinical Supplies Shipping Receipt contained in the shipment must be signed, dated, and returned to the Supporter or its designee. An overall summary of all clinical supplies received, used, and returned per patient must be maintained by each study center. Seattle Genetics will provide full accountability for shipments of drug to individual sites. Seattle Genetics will NOT assume accountability of drug within the individual sites.

The Supporter will supply the center with the necessary forms. Records should contain the dates of receipt, dispensing, and return or destruction of unused study drug. Each vial of used in the study must be documented on the Investigational Drug Accountability Log by recording the lot number and the patients' initials and number. Explanations for any broken vials will be recorded on the Investigational Drug Accountability Log form. Empty drug vials are to be kept until the Supporter or its designee has performed a drug reconciliation at the study center. Destruction of empty vials will be recorded on the Investigational Drug Accountability log by the Supporter or its designee. If the empty vials cannot be destroyed at the study center, the Supporter or its designee will complete a Returned

Investigational Drug/Device Inventory form and return the vials to the Supporter. The investigational therapeutic agent may only be used in patients enrolled specifically in this research investigation, and may not be used in other persons or released to any third party, laboratory, or clinic for use in humans, or for in vivo or in vitro laboratory research, or any other use, without the express written consent of Seattle Genetics.

No investigative procedures other than those detailed in this protocol may be undertaken with on enrolled patients or otherwise without prior written consent from the Supporter. At the completion of the study, the Supporter, or its designee, will conduct a final Investigational Drug Accountability review. At that time, the study center will be instructed to either destroy the unused study drug in accordance with provided instructions and consistent with applicable local, state, FDA, national, and ICH guidelines or return the drug to the Supporter or its designee. Destruction of unused study drug must be documented on the Study Drug Accountability Log and a copy of the study center's drug destruction policy must be forwarded to the Supporter. If the unused study drug is being returned to the Supporter, a completed Returned Investigational Drug/Device Inventory form must be included with the shipment. All original Investigational Drug Accountability Log forms will be returned to Seattle Genetics. The study will be considered complete only after the final drug accountability procedures are completed.

11 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Janssen Scientific Affairs. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

Patients may not begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

Prior to registration, eligibility criteria must be confirmed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the web-based application NOTIS (Northwestern Oncology Trial Information System), which is available at: https://notis.nubic.northwestern.edu. Please note that a username and

password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CRO website for additional instructions on registering a patient.

The QAM will review the registration, register the patient, assign a subject identification number, and send a confirmation of registration to study personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.
- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires High Intensity

Monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the Appendices for additional data submission instructions.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Promptly Reportable Non-Compliance (PRNC) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. The assigned QAM will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

12 PATHOLOGY REQUIREMENTS

12.1 Pathologic confirmation of classical Hodgkin lymphoma is required. If diagnosis was made at an outside institution, pathology slides must be reviewed by one of the hematopathology departments at the institutions directly participating in this clinical trial.

12.2 Mandatory SGN-35 Pharmacokinetic Sample.

12.2.1 Blood samples should be collected 48-72 hours after the **first dose** of SGN-35 for provisional safety PKs collection. Sample collection and processing information is found in Table 5, below.

12.2.2 Should an unexpected SAE arise with a dose/cycle of SGN-35 other than the 1st dose/cycle, properly frozen samples should be drawn and sent on a case-by-case basis to the Lurie Cancer Center Pathology Core Facility (see Table 5). This should be discussed with the study P.I and QAM.

Table 5. Provision Safety PK Collection and Processing Instructions.

Assay and time points	Sample requirements	Destination lab/contact info
For Free MMAE (fMMAE) collect sample 48-72 hours after brentuximab vedotin dosing	• 2.7 mL of whole blood collected into a 3 mL Na Citrate tube (blue top) tube. • Immediately after the blood draw, carefully mix the blood with the anticoagulant by gently inverting the tube 8-10 times. DO NOT SHAKE. • Immediately after mixing the specimen, place the vacutainer tube into a container with cold water and ice for 1-2 minutes. If your site does not a have a refrigerated centrifuge, leave the specimen in the ice mixture for 5-6 minutes before processing. The samples should be processed within 1 hour of collection. • Centrifuge blood at 800-1000 g for 15 minutes to separate the plasma from blood cells. • Transfer the plasma into one appropriately labeled 2 mL cryogenic vial. Be careful not to include any of	**Shipping destination information for participating sites:** Samples from all participating sites will be shipped to the Pathology Core Facility at Northwestern University. See section 12.4.4 for mailing address and instructions. **Shipping destination information for NU only:** For questions or to arrange testing, email IST@seagen.com for shipping instructions.

	the separated cells. Label tube with date and time of last infusion, and date and time of sample collection. • Samples must be frozen and stored immediately at -20ºC or -80ºC preferably. **Do not use liquid nitrogen to flash freeze the specimen.** If it is impossible to place the specimen immediately at < -20ºC, it may be refrigerated up to 8 hours prior to storage at < -20ºC.	

12.3 Correlative blood studies.

12.3.1 An optional part of this study includes blood to be drawn and stored for future use. Funding is currently not available to complete the studies, however applications are being actively submitted for grant funding to fund the correlative tissue studies described below. Thus, at this time- blood will only be collected and stored (please see Table 6 below).

12.3.2 Background: correlative studies.

There are multiple emerging pathologic and genetic factors with prognostic importance in HL. Epstein-Barr virus (EBV) is associated with a variety of hematopoietic malingnancies including HD. Approximately 30%-50% of all HL cases are EBV-positive, often identfied by LMP-1 immunostaining of the tumor tissue.[7,10] Further, according to age groups, the highest percentages of EBV-positive cases are seen in HL patients < 10 years and > age 55. Older studies regarding the prognostic importance of EBV yielded mixed results, but many of these studies included selected patient groups, most not considering age as a modifying factor. Two population-based studies showed that survival of patients with EBV-positive tumors was significantly inferior compared with EBV-negative tumors.[7,10] Keegan and colleagues studied 922 classical HL patients with biopsy specimens assayed for EBV.[12] They showed that the presence of EBV predicted inferior survival only for older adults (defined as 45-96 years of age) where the OS and HL-specific mortality were significantly increased (hazard ratio for death 2.5; 95% CI, 1.5 to 4.3).

Other factors that have been shown to have prognostic importance in HL that warrant further investigation include MUM1/IRF4,[62] HGAL,[63] galectin-1,[64] cytokine plasma levels, H-RS genetic alterations, and host genetics (e.g., IL-6, IL-10, MDC, and TARC).[65-67] Ribrag et al showed that patients who carried 1 or 2 UGT1A1*28 allele had a significantly

better FFP, TTTF, and OS compared with patients homozygous for the UGT1A1 allele.[68] In addition to influencing risk of HL, at least one GST deletion (*GSTM1* or *GSTT1*) associated with improved DFS.[69] Inferior freedom from treatment failure (FFTF) was found in patients harboring the IL- 10-597AA genotype (p = 0.026), the IL-10-824TT genotype (p = 0.026) or the IL-10-1087AA genotype (p = 0.033).[65] Carriers of the IL-10-592AA and the IL-6-174GG genotypes; Patients carrying the high-producing homozygous IL-6-174G allele had a poorer treatment outcome.

Other pathologic and genetic factors have emerged as potential important prognostic factors in HL. Kelley and colleagues showed that HD patients with more intra-tumor T-cell regulatory cells (Tregs, as determined by FOXP3 epxression) in addition to less activated cytotoxic T/NK lymphocytes (as determined by granzyme B cells, GrB+) were associated with significantly superior survival.[70] Interestingly, older age (>45 years) in their analysis was associated with decreased FOXP3+ Tregs and increased GrB+ cells compared with younger patients. Deipstra and colleagues showed that the lack of HLA class II cell-surface expression on HRS cells was associated with inferior FFS and OS.[71] This factor was significant on multivariate analysis with a relative risk of death of 2.55 (95% CI, 1.22-5.31). Of note, the only other factor associated with increased risk of death was age (patients >age 65 risk 6.47, 95% CI 2.81-14.90). In addition, gene expression profiling of H-RS cells as well as the HD microenvironment is feasible.[72] Steidl and colleagues recently showed through gene expression profiling that a signature of tumor-associated macrophages was associated with treatment failure.[73] Further, with immunohistochemical studies, an increased number of CD68+ macrophages in the tumor microenvironment correlated with inferior PFS and OS. Moreover, in multivariate analysis, this prognostic factor was a more robust predictor of DFS compared with the International Prognostic Score.[3]

12.3.3 Correlative aims.

12.3.3.1 To determine the frequency of EBV-related HL, and moreover to examine the different EBV phenotypes from tumor tissue of untreated older HL patients.

12.3.3.2 To examine the tissue microenvironment for the cellular signatures using immunohistochemical analysis with attention to T-cell regulatory cells and tumor associated macrophages.

12.3.3.3 To determine host genetic SNPs that are associated with specific tumor cellular/molecular markers (including EBV) and the tissue microenvironment among untreated older HL patients.

Table 6. Blood to Be Collected for Correlative Studies.

Tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes)[1]	Blood product being processed[1]	Component being harvested	Baseline (Pre-SGN35)	After 2 cycles of SGN35 lead in (i.e., before AVD)	After AVD chemo-therapy
ACD (yellow)	10 mL (1)	Whole blood	Plasma Cells for DNA/RNA, Protein	X		
EDTA (purple) [2]	10 mL (2) [2]	Whole Blood	Plasma Cells for DNA/RNA, Protein	X[2]	X	X
Red top	10 mL (1)	Whole Blood	Serum	X	X	X

1. All specimens should be frozen and batched at each local institution for shipment to the lead institution (Northwestern) at the end of the study.
2. At baseline, 4 (four) EDTA tubes (10 mL each) will be obtained; at all other time points, only 2 EDTA tubes will be needed.

12.4 Blood Processing & Shipping

12.4.1 Red top tubes:

a. Red top tube should sit upright after the blood is drawn at room temperature for a minimum of 30 minutes to a maximum of 60 minutes to allow the clot to form.
b. Centrifuge the blood sample at the end of the clotting time for 15 minutes at room temperature at 1500g. If the blood is not centrifuged immediately after the clotting time, the tubes should be refrigerated (4 degrees Celsius) for no longer than 4 hours
c. Pipette serum into the labeled cryovials, Close caps on the vials tightly. Note: Be careful not to pick up red blood cells when aliquoting. This can be done by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube

d. Place all aliquots upright in a specimen box or rack in an -80C or colder freezer. All specimens should remain at -80C prior to shipping. The samples should not be thawed prior to shipping.

12.4.2 Purple top tubes:

1) Gently mix tubes by inverting 8-10 times. Store tubes upright at 4C until centrifugation. Blood samples should be centrifuged within four hours of blood collection.
2) Centrifuge the blood samples at 1500g for 15 minutes at 4C.
3) After centrifugation, plasma layer will be at the top of the tube. Collect the plasma layer with a pipette without disturbing the buffy coat layer. Pipette plasma into labeled cryovials. Close caps on the vials tightly. This should be completed within 1 hour of centrifugation.
4) Place all aliquots upright in a specimen box or rack in an -80C or colder freezer. All specimens should remain at -80C prior to shipping. The samples should not be thawed prior to shipping.

12.4.3 Plasma samples are to be labeled with the study participant's study ID number. The following parameters must be recorded for each specimen collection:

- Date and time of blood draw
- Time of specimen processing
- Time specimen was snap frozen

12.4.4 Frozen samples and associated paperwork from both the mandatory SGN-35 pharmacokinetic (PK) sample and optional correlative should be shipped to the Lurie Cancer Center Pathology Core Facility. Specimens must be shipped via overnight FedEx on dry ice. Email Pathcore staff with details of shipment using the email listed below. It is important that samples do not thaw, therefore all packages should be sent Monday-Thursday only; batch shipping of specimens for both mandatory PK and optional correlative is allowable. All packages should be sent to:

Robert H. Lurie Comprehensive Cancer Center
Northwestern University
Clinical Trials
Attention: NU 11H01
Olson 8-412
710 North Fairbanks Court
Chicago, IL 60611
312-908-0603
CTPathcore@northwestern.edu

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14 APPENDIX

14.1 APPENDIX I

Eastern Cooperative Oncology Group Scale

ECOG Performance Status Scale

Score	Criteria	Equivalent KPS Score
0	Fully active, able to carry out all pre-disease performance without restriction	90 - 100
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	70 - 80
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours	50 - 60
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	30 - 40
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair	10 - 20
5	Dead	0

Abbreviations: ECOG = Eastern Cooperative Oncology Group;
KPS = Karnofsky Performance Status.

14.2 APPENDIX II

DATA FOR FDG-PET/CT SCAN

Patient's initials: _____

Patient's study number: _____

Hospital name: _____

Date of PET scan: _____

Timing of PET (circle): baseline | s/p SGN-35 lead-in | s/p 3 cycles AVD | s/p 6 cycles AVD

RESULT OF PET-CT SCANS according to 5-point scale:

1 : no uptake

2 : uptake ≤ mediastinum

3 : uptake > mediastinum but ≤ liver

4 : uptake > liver at some sites even if uptake ≤ liver or mediastinum at other sites

5 : uptake > liver in > 90% of initial sites or development of new sites consistent with progressive disease

Score	**1**	**2**	**3**	**4**	**5** (please circle)

List sites of residual uptake (score 4 and 5):

……

……

……

Comments e.g. positive sites elsewhere in the body:

Name:…… Date:

Signature:

14.3 APPENDIX III

Modified Cumulative Illness Rating Scale (CIRS)

The Modified Cumulative Illness Rating Scale (CIRS).

	Body system	Score				
1.	Cardiac (heart only)	0	1	2	3	4
2.	Hypertension (rating is based on severity; organ damage is rated separately)	0	1	2	3	4
3.	Vascular (blood, blood vessels and cells, bone marrow, spleen, lymphatics)	0	1	2	3	4
4.	Respiratory (lungs, bronchi, trachea below the larynx)	0	1	2	3	4
5.	EENT (eye, ear, nose, throat, larynx)	0	1	2	3	4
6.	Upper GI (esophagus, stomach, and duodenum; pancreas; do not include diabetes)	0	1	2	3	4
7.	Lower GI (intestines, hernias)	0	1	2	3	4
8.	Hepatic (liver and biliary tree)	0	1	2	3	4
9.	Renal (kidneys only)	0	1	2	3	4
10.	Other GU (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
11.	Muscolo-skeletal-integumentary (muscle, bone, skin)	0	1	2	3	4
12.	Neurological (brain, spinal cord, nerves, do not include dementia)	0	1	2	3	4
13.	Endocrine-Metabolic (includes diabetes, thyroid; breast; systemic infections; toxicity)	0	1	2	3	4
14.	Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation/delirium, psychosis)	0	1	2	3	4

PHILOSOPHY AND DEVELOPMENT OF THE SCALE

Compiling and quantifying medical problems in the elderly population will allow meaningful comparison of medical burden and treatment outcomes in elderly patients with variable and complex medical problems.

The Cumulative Illness Rating Scale (CIRS) was initially developed by Linn et al. and published in JAGS 1968 (1); it appeared immediately a user friendly but comprehensive review of medical problems by organ systems, based on a 0 thru 4 rating, yielding a cumulative score. This scale was successively revised by Miller et al. to reflect common problems of the elderly with an emphasis on morbidity using specific examples and was renamed CIRS for Geriatrics (CIRS-G) (2); moreover, Miller and Towers provided also a manual of guidelines for scoring their version (3).

Then, in 1995, Parmelee et al. validated a Modified CIRS version, based on a 1 thru 5 rating and with some differences in categories, in a geriatric residential population (4). Finally, Mistry et al. used this

latter Modified CIRS version with a 0 thru 4 rating to measure medical burden in psychogeriatric participants of the UPBEAT program, showing that inclusion of acute medical conditions did not undermine the usefulness of the CIRS (5). Based on the version of Miller and Towers, current guidelines were adapted to the Modified CIRS version and updated.

RATING SUGGESTIONS (GENERAL PRINCIPLES)

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: for a patient suffering from mild diet-controlled diabetes (Grade 1) and hyperthyroidism in pharmacologic treatment (Grade 2), only the higher rated condition would be scored in the Endocrine system (e.g. rating is 2).

The spread of a cancer may lead to rate the condition in more than one category. For example, lymphoma with bone involvement treated with nonsteroidal anti-inflammatory drugs (NSAID) is Rated 4 in Respiratory and 2 in Musculoskeletal.

General rules for severity rating:

0 - No problem affecting that system or past problem without clinical relevance.
1 - Current mild problem or past significant problem.
2 - Moderate disability or morbidity and/or requires first line therapy.
3 - Severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen).
4 - Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

LEVEL 0

No problem or healed minor injuries; past childhood illnesses (chickenpox); minor surgery (carpal tunnel completely healed, caesarean); uncomplicated healed fractures; other past problems healed without sequel, residual or complication (pneumonia).

LEVEL 1

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations, having only minor impact on morbidity (asthma controlled with PRN bronchodilators, occasional heartburn relieved with PRN antiacids). Medical problems that are not currently active but were significant problems in the past (passage of a kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy).

LEVEL 2

Medical conditions that require daily treatment or first line therapy (asthma controlled with inhaled steroids, gastro-esophageal reflux treated with daily medication, osteoarthritis requiring daily NSAID, etc.) and/or have moderate disability or morbidity.

LEVEL 3

Chronic conditions that are not controlled with first line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, heart failure with symptoms or uncontrolled hypertension despite complex therapeutic regimen) and/or constant significant disability, but not severe disability.

LEVEL 4

Any acute condition that requires immediate treatment or hospitalization (unstable angina, acute myocardial infarction, stroke, but also bladder outlet obstruction) and/or extremely severe problems; organ failure (end-stage renal disease needing dialysis, oxygen-dependent chronic obstructive pulmonary disease, terminal heart failure); severe sensory impairment (almost complete blindness or deafness, being wheelchair bound) and/or severely affected quality of life, severe impairment in function; delirium by medical (organic) conditions.

ORGAN SPECIFIC CATEGORIES

The following organ specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the "judgement strategy" that can be applied to other problems not listed.

If there are several problems in the same system, only the most severe is rated.

HEART

In this category only heart and coronary disease have to be considered (not vascular): coronary arteries disease, heart failure, valvular heart diseases, heart disease secondary to hypertension, endocardities, miocardities, pericardities, arrhythmias (extrasystoles, bundle-branch blocks, atrial fibrillation, PMK placement), heart malignancies. Functional impact must be considered too, e.g. NYHA II heart failure has different value between dependent and independent persons.

0. No problems
1. Remote MI (>5 years ago); occasional [exertion] angina; asymptomatic valvular disease
2. CHF compensated with meds (NYHA I-II); daily anti-angina meds; left ventricular hypertrophy; atrial fibrillation, bundle branch block, daily anti-arrhythmic drugs (even for prophylaxis); PMK placement for asymptomatic bradycardia (relieved by Holter EKG monitoring); valvular disease requiring medical treatment
3. Previous MI (<5 years ago); abnormal stress test; status post (previous) percutaneous coronary angioplasty, coronary artery bypass graft surgery or other cardiac surgery (valve replacement); moderate CHF (NYHA II-III) or complex medical treatment; bifascicular block; PMK placement for cardiogenic syncope; pericardial effusion or pericarditis
4. Acute coronary syndrome, unstable angina or acute MI; intractable CHF (NYHA III-IV acute or chronic); marked restriction to the normal activity of daily living secondary to cardiac status

HYPERTENSION

Consider only hypertension severity; organ damage (complications) should be considered into the respective categories.

0. Normotension
1. Borderline hypertension; hypertension compensated with salt restriction and weight loss, drug free (when drug therapy is indicated, but the patient does not take meds, the score is at least 2)
2. Daily antihypertensive meds: hypertension controlled by 1 pill therapy (even fixed doses combinations)
3. Hypertension requiring two or more pills for control
4. Malignant hypertension, or hypertension non controlled by complex therapeutic regimen

VASCULAR-HEMATOPOIETIC

Artery disease: carotid atherosclerosis, peripheral arteries disease (PAD), aneurysms (every site);

Venous disease: venous insufficiency, varices, deep venous thrombosis (DVT), pulmonary embolism, primary pulmonary hypertension;
Hematopoietic disease: anemia, leucopenia, thrombocytopenia, hematological malignancy;
Lymphopoietic disease: chronic lymphatic edema, lymphoma, spleen and thymus disease;
Immunologic disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity

0. No problem
1. Venous insufficiency, varices, lymphedema; carotid stenosis <70%; hemoglobin 10-12 g/dl (in females), 12-14 g/dl (in males); anemia of chronic "inflammatory" disease
2. Previous DVT; one symptom of atherosclerosis disease (claudication, bruit, amaurosis fugax, absent pedal pulses) or daily meds (e.g. anti-platelets drugs); PAD IIa-IIb by Fontaine; carotid stenosis >70%; aortic aneurysm <4 cm; hemoglobin 8-10 g/dl (in females), 10-12 g/dl (in males); anemia secondary to iron, B12 vitamin or folate deficiency, or to chronic renal failure; total white blood cell (WBC) 2000-4000/mmc; mild thrombocytopenia (50000-150000/mmc)
3. DVT or recent DVT (<6 months ago); two or more symptoms of atherosclerosis (see above); PAD Fontaine III or recent/previous angioplasty (with or without stenting); hemoglobin <8g/dl (in females), <10 g/dl (in males); dyserythropoietic anemia; WBC <2000/mmc; severe thrombocytopenia (<50000/mmc)
4. Pulmonary embolism (acute or recent/previous); atherosclerosis requiring surgical intervention (e.g. aortic aneurysm >4 cm, symptomatic carotid stenosis >70%, PAD Fontaine IV or amputation for vascular causes, etc.); recent/previous vascular surgery; any hematological or vascular malignancy (including multiple myeloma)

In case of immunological disease, score should be assigned by considering blood abnormalities, stadium of organ damage and/or functional disability (2: symptoms controlled by daily meds; 3: symptoms not well controlled; 4: symptoms impossible to be controlled or short time poor prognosis).

RESPIRATORY

In this category we consider COPD, asthma, emphysema, restrictive pulmonary interstitial lung diseases, malignancies of lung and pleura, pneumonia, and smoking status too.

0. No problem
1. Recurrent episodes of acute bronchitis; currently treated asthma with prn inhalers when required; cigarette smoker >10 but <20 pack years
2. Instrumental diagnosis of COPD or pulmonary interstitial disease (x-ray, TC, spirometry); daily prn inhalers (≤2 pharmacological classes); two or more episodes of pneumonia in the last 5 years; cigarette smoker <20 but <40 pack years
3. exertion dyspnea secondary to limited respiratory capacity, not well controlled by daily meds; required oral steroids for lung disease; daily prn inhalers (3 pharmacological classes); acute pneumonia treated as an outpatient
4. Chronic supplementation of oxygen; respiratory failure requiring assisted ventilation, or previous (at least one episode); any lung or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered as a disease, and it is rated according to *lifetime pack years*:

Number of cigarette packs smoked per day X Number of years smoked in their lifetime

e.g. 1 pack year = 20 cigarettes/die (1 pack) X 1 year

Ex-smokers should be rated too, but those who have been smoke free for the most recent 20 years would merit a lower rating than currently smoking

Examples:

A. Patient smoking 20 cig/die (1 pack) for 25 years = 25 pack years - CIRS score: 2

B. Patient smoking 40 cig/die (2 packs) for 25 years = 50 pack years – CIRS score: 3

C. Ex-smoker of 20 cig/die (1 pack) for 25 years, he stopped 5 years ago – CIRS score: 2

D. Ex smoker of 20 cig/die (1 pack) for 25 years, he stopped 20 years ago – CIRS score: 1

Classification of COPD could be more specific when instrumental data (objective evidence) are available: blood gases, forced expiratory volume in 1 second (FEV1), etc.

EYES, EARS, NOSE & THROAT, and LARYNX

To simplify the potential complexity of this category it was decided to score according to the severity of the disability created by sensory diseases (degree of limited autonomy and communication), and avoid rating each type of pathology. Sensory impairments should be rated **after** instrumental correction (corrective lenses, hearing aid, etc.).
Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology
Ears: otitis, dizziness, any cause of hearing impairment
Nose & Throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignancies
Larynx: dysphonia, acute and chronic laryngitis, malignancies

0. No problems
1. Corrected vision with glasses; mild hearing loss; chronic sinusitis
2. Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily meds
3. Severe low vision, partially blind (required an escort to venture out, unable to read newspaper); severe ear impairment (conversational heading still impaired with hearing aid); laryngeal dysphonia (not neurological dysarthria)
4. Functional blindness/deafness: unable to read, recognize a familiar face, unable to conversational heading, even if “organically” he is not completely blind or deaf; laryngectomy (every cause, especially malignancies); required surgical intervention for vertigo; aphonia secondary to laryngeal impairment.

UPPER GASTROINTESTINAL SYSTEM

This category is comprehensive of the intestinal tract from esophagus to duodenum, and pancreatic trees: dysphagia, GERD, hiatal hernia, esophageal diverticula, any type of gastritis (consider also H. Pylori eradication or not), gastric/duodenal ulcer, acute or chronic pancreatitis, malignancies (comprehensive of gastric lymphoma).
Pay attention that type 1 diabetes is rated under “metabolic”.

0. No problem
1. Hiatal hernia, GERD or gastritis requiring prn meds; previous ulcer (>5 years ago); previous H. Pylori eradication therapy (>5 years ago)
2. Daily proton pump inhibitor/anti-acid meds; documented gastric or duodenal ulcer or H.P. eradication therapy within 5 years

3. Active gastric or duodenal ulcer; positive fecal occult blood test; any swallowing disorder or dysphagia; chronic pancreatitis requiring supplemental pancreatic enzymes for digestion; previous episode of acute pancreatitis
4. Any type of malignancies (see "*Rating Malignancies*"); previous gastric surgery because of cancer; history of perforated ulcer (gastric surgery not because of cancer, ulcorrhaphy); melena/heavy bleeding from upper GI source; acute pancreatitis

LOWER GASTROINTESTINAL SYSTEM

Comprehensive of the rest of the G.I. system, from small bowel to anus: Whipple's disease, diverticulosis, irritable bowel, malignancies. Constipation is rated, too, by type and frequency of laxatives required, or by history of impaction.

0. No problems, previous appendectomy, previous hernia repair (without complications)
1. Constipation managed with prn meds; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adherences, laparocele, etc.); irritable bowel syndrome (few symptoms)
2. Constipation requiring daily bulk laxatives (psyllium, policarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with meds (>5 years ago)
3. Bowel impaction/diverticulitis within the last year; daily use of stimulant (irritant) or osmotic laxatives (bysacodil, senna, glycerol, sodium docusate; lactulose, polyethylene glycol) or enemas; chronic bowel inflammation in remission with meds (<5 years ago)
4. Diverticulitis flare up; active inflammatory disease; current impaction; hematochezia/active bleeding from lower GI source; bowel carcinoma

LIVER AND BILIARY TREES

Comprehensive of liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, autoimmune, idiopathic), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignancies. As the hepato-biliary system is difficult to assess through the physical examination, therefore, laboratory results must be used.

0. No problem
1. History of hepatitis (actually normal values of transaminases); cholecystectomy
2. Cholelithiasis; chronic hepatitis or previous hepatitis (<5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with mildly elevated transaminases (within 3-times normal values); heavy alcohol use within 5 years (to rate in "psychiatric", too)
3. Chronic hepatitis or any other liver disease with marked elevation of transaminases (>3-times normal values); elevated bilirubin
4. Acute cholecystitis; any biliary obstruction; active hepatitis/liver cirrhosis; any liver or biliary tree carcinoma

RENAL

This category is exclusive of kidney: kidney stones, acute/chronic renal failure, glomerulonephritis; nephrosic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma.
Bence-Jones proteinuria in multiple myeloma should not be considered.

0. No problem
1. Asymptomatic kidney stone; kidney stone passage within the last ten years; pyelonephritis within 5 years; kidney cysts without hematuria
2. Serum creatinine >1.5 but <3 mg/dl without diuretic or antihypertensive medication (particularly ACE-inhibitors or SRAA blockers); kidney calculi requiring daily meds
3. Serum creatinine >3 mg/dl or >1.5 mg/dl in conjunction with diuretics, antihypertensive, or bicarbonate therapy; active pyelonephritis; nephrosic syndrome; colic symptoms treated as an outpatient
4. Required dialysis; renal carcinoma; colic symptoms requiring hospitalization

GENITOURINARY

Ureters, bladder, urethra.
Genitals, prostate, testicles, penis, seminal vesicles.
Uterus, ovaries. *Mammary gland is rated under "metabolic".*
This category is comprehensive of all GU tract impairments: ureteral or bladder stones, benign prostate hypertrophy (BPH), urinary tract infections (UTI's), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

0. No problem
1. Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)
2. Pathological pap smear (or 2 consecutives abnormal); frequent UTI's (3 or more in the past year) in female or current UTI's; urinary incontinence (not stress) in females; BPH with urinary symptoms (frequency, urgency, hesitancy); status post TURP; any urinary diversion procedure; indwelling catheter; bladder calculi
3. Prostatic cancer in situ (e.g. incidentally found during TURP); vaginal bleeding; cervical carcinoma in situ; hematuria (any cause); urinary incontinence (not stress) in males; bladder polyps
4. Acute urinary retention; current urosepsis; any GU malignancies except as above

MUSCULOSKELETAL/INTEGUMENT

This is a very wide category, including: osteoarthritis, osteoporosis, any bone fracture; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized skin cancers; rheumatoid arthritis and polymyalgia rheumatica; muscular injuries (rotator cuff, long head of the biceps); pressure sores; any dermatological disease.
The scores of this category are strictly correlated to the disability they cause; for the evaluation of the level of disability, refer to BADL and IADL.

NOTICE: score the severity of each illness according to the level of disability caused by the same illness in this category, without considering the disability caused by other diseases. For example: a patient affected both by osteoarthritis and hemiplegia from a previous stroke has a high level of disability, but you have to score 2 for disability by osteoarthritis (in this category) and 4 for disability by stroke (in the neurological category); for a patient with both a deforming rheumatoid arthritis and a previous stroke without remaining outcomes you have to score 4 for disability from arthritis (in this category) and 2 for disability from stroke (in the neurological category).

0. No problem
1. Requires PRN meds for osteoarthritis (NSAID) or has mildly limited IADL from joint pathology; excised skin cancers (except melanoma); skin infections requiring antibiotics within a year
2. Daily anti-osteoarthritis meds (NSAID) or use of assisitive devices or little limitation in ADL (previous arthroprosthesis or treated fracture with a low level of remaining disability); osteoporosis without vertebral fractures; daily meds for chronic skin diseases (even local, as psoriasis or pressure sores); non metastatic melanoma; daily meds for rheumatoid arthritis (except steroids) with a low level of disability
3. Osteoarthritis with a moderate level of disability in ADL; requires chronic treatment with steroids for arthritic conditions or joints' deformities or severely impaired; osteoporosis with vertebral compression fractures
4. Wheelchair bound for osteomuscular disease; severe joint deformities or severely impaired usage; osteomyelitis; any bone or muscle or connective tissue neoplasm (see "Rating Malignancies"); metastatic melanoma.

Fractures and/or arthroprosthesis (both recent and old) have to be scored according to the level of disability they cause (considering outcomes too), in order to avoid confusion about possible classifications of different fractures or joints. The same for muscular diseases.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

This category includes the "somatic" pathologies of the central and peripheral nervous system: any kind of stroke, neurodegenerative diseases (Parkinson's disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological outcomes, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. It must carefully estimate the severity and prognosis of the illness but also the functional impairment that the illness causes.

0. No problem (or fewer convulsions in childhood)
1. Frequent headaches requiring PRN meds without impairment in Advanced ADL; previous TIA (one event); previous epilepsy, actually not treated, without crisis since more than 10 years ago.
2. Chronic headache requiring daily meds (even for prophylaxis) or with regularly functional impairment in Advanced ADL (bed rest, job withdrawal, etc.); actual TIA or more than one previous TIA; previous stroke without significant residual; mild severity neurodegenerative diseases (see above), treated and well controlled; epilepsy controlled with drugs.
3. Previous stroke with mild residual dysfunction (hemiparesis, dysarthria); any neurosurgical procedure; moderate severity neurodegenerative diseases (see above), not well controlled by meds; epilepsy in treatment but with periodic crisis.
4. Acute stroke or previous stroke with severe residual dysfunction (hemiplegia, aphasia, severe vascular dementia) or more than one previous stroke (multi-infarct encephalopathy); severe neurodegenerative diseases (see above) causing disability in ADL; neurological coma.

Alzheimer's disease and dementia should not be rated into this category (Psychiatric and behavioral diseases): Alzheimer's disease should be listed only under psychiatric disorders; if dementia stems from vascular and/or mixed dementia and/or other neurological condition (e.g. Parkinson's Disease), both "neurologic" and "psychiatric" categories should be endorsed at the appropriate level for severity, considering in this category the stroke and the multi-infarct encephalopathy responsible for the

cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

ENDOCRINE-METABOLIC SYSTEM AND BREAST (systemic infections and poisonings too)

Type 1 and type 2 diabetes (organ damage should be considered into the respective categories, like for hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; it includes also hypo- and hyper-thyroidism, hypo- and hyper-parathyroidism, adrenal pathologies (Cushing' or Addison' disease), hypogonadism, hypopituitarism, etc. Malignancies of these glands, both benignant (like thyroid nodules) and malignant (like thyroid or adrenal cancer, vipoma, etc.) are included too.

Even if it is an exocrine gland, breast was included in this category because the authors didn't find a more appropriate one; so it includes the breast cancer too.
Moreover, it includes: electrolyte disorders, sepsis, systemic infections (like tuberculosis, syphilis, AIDS) scored according to their severity and the functional impairment they cause (see general indications) and poisonings (chronic by metals or acute by pesticides or carbon monoxide).

0. No problem
1. Diabetes and/or dyslipidemia compensated with diet; mild obesity (BMI 30-35 kg/m^2); hypothyroidism in replacement therapy (L-thyroxin); hyperthyroidism caused by Plummer' adenoma surgically treated.
2. Diabetes compensated with oral hypoglycemic drugs or insulin (hemoglobin A1c <7%); dyslipidemia well controlled by daily meds (c-LDL lower than the recommended target according to the individual global cardiovascular risk); moderate obesity (BMI 35-45 kg/m^2); hyperthyroidism (Basedow, Plummer) in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease.
3. Diabetes not well compensated by therapy (hemoglobin A1c 7-8.5%, presence of complications); dyslipidemia not well controlled (c-LDL higher than the recommended target according to the individual global cardiovascular risk; for instance, c-LDL>100 mg/dl in patients with previous myocardial infarction or stroke); severe obesity (BMI >45 kg/m^2); symptomatic hyperparathyroidism (for instance, hypercalcaemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization.
4. Uncontrolled diabetes (hemoglobin A1c >8.5%) or one diabetic ketoacidosis or nonketotic hyperosmolar coma during the past year; genetic uncontrolled dyslipidemia; acute adrenal failure during hormonal replacement therapy; any neoplasm of thyroid, breast, adrenal gland (see "Rating Malignancies").

NOTICE: when the patient is not treated with drug therapy for diabetes or dyslipidemia but he should be for the optimal control of the pathology (for instance, hemoglobin A1c >7%, total cholesterol >250 mg/dl), score the pathology according to the laboratory values, which really define its severity.

PSYCHIATRIC AND BEHAVIORAL DISEASES

This category includes both dementia and related behavioral disorders (psychosis, anxiety, depression, agitation) and all the pre-existing and/or not related to dementia psychiatric disorders. Since this is the only item analyzing patient's mental status (all the others refer to physical status), it is very important to evaluate it considering carefully further information derived from the Comprehensive Geriatric

Assessment (MMSE; Geriatric Depression Scale, Neuro-Psychiatric Inventory if available) (8, 9).

0. No psychiatric problem or history thereof
1. Minor psychiatric condition or history thereof: previous (occasional) psychiatric treatment without hospitalization; major depressive event and/or use of antidepressants more than 10 years ago without hospitalization; occasional use of minor tranquilizers (e.g. BDZ; even if as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25-28).
2. A history of major depression (according to DSM-IV criteria) within the last 10 years (treated or untreated); mild dementia (MMSE 20-25); previous admission to Psychiatric Department for any reason; history of substance abuse (more than ten years ago, including alcoholism).
3. Current major depression (according to DSM-IV criteria) or more than two previous major depression episodes in the past 10 years; moderate dementia (MMSE 15-20); current and usual usage of daily anti-anxiety meds (even as hypnotherapy for insomnia); current or within the past ten years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.
4. Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management (psychiatric emergency, as attempt at suicide or severe depression with suicide purpose, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse; severe agitation from dementia); severe dementia (MMSE <15); **delirium** (acute confusion or altered mental status for medical (organic) reasons: in this case you have to codify also the medical cause in its own category with the appropriate level of severity).

It could be requested psychiatric consult for this category; dementia and depression, the most frequent diseases in the elderly, can be scored in details using the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse and all the others) has to be scored according to the level of functional impairment or disability they cause.

DRUG LIST

Medical history

1. Drugs list (*fundamental*), including laxatives and tranquilizers (drug doses not needed- but list of each medication here):

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Appendix IV References

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14.4 APPENDIX V

HRQL Forms

SEE SEPARATELY ATTACHED PDF DOCUMENT CONTAINING APPENDIX IV.

14.5 APPENDIX VI

Activities of Daily Living (ADLs) and Fit vs Unfit

At each required timepoint, please print Appendix VI, complete, sign, and upload into the eCRF system.

All patients should have recorded once at baseline (pre-treatment) and then repeat once at the end of consolidation therapy (at the end of SGN-35 consolidation) if they have: a) loss of any ADLs, b) loss of instrumental ADLs, and c) if they are fit (vs unfit), as defined below.

Loss of Activities of daily living (ADL) is defined by loss in any activity including: bathing, dressing, toileting, transferring, feeding and/or continence. Please record if the patient at baseline has any loss of ADLs.

Instrumental activities of daily living (IADLs) are defined as being able to complete each of the following. Please record if the patient at baseline has any loss of instrumental ADLs.

- Housework
- Meal Preparation
- Taking medications
- Managing money
- Shopping (for groceries or clothing)
- Doing laundry
- Using the telephone
- Using transportation

Patients are "Fit" if they have: 1) no loss of ADLs, 2) have less than three grade 3 CIRS-G comorbidities and no grade 4 comorbidities, and 3) none of the criteria defining the presence of geriatric syndrome (see below). All other patients classified as "unfit".

[Geriatric syndromes: Dementia, Delirium, Depression, Incontinence, Falls, Osteoporosis, Neglect and abuse and/or Failure to thrive)

Treating Physician Assessment (please circle one): FIT UNFIT

Time point Assessed (circle one): BASELINE POST SGN-CONSOLIDATION

Signature: _____

Date:_____

14.6 Appendix VII

Protocol History of Changes

Original Protocol – January 31, 2011			
Amendment 1 – June 23, 2011 *Scientific Review Committee Approval: October 7, 2011*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Throughout	n/a	Adds protocol number for lead institution (NU 11H01) to all headers and version date to all footers; corrects formatting, numbering, and grammar.	Administrative
Throughout	Different versions of the NCI CTCAE referenced.	Corrects all references to reflect NCI CTCAE version 4.0.	Administrative correction
Cover-page	1. n/a 2. Lists Johns Hopkins University and Dr. Richard Ambinder as an affiliate/sub-investigator. 3. Dr. Julie Vose listed as the sub-PI for University of Nebraska. 4. n/a 5. No IND information provided.	1. Adds Ohio State University and Dr. Kristie Blum as an affiliate/sub-investigator. 2. Removes Johns Hopkins University and Dr. Richard Ambinder as an affiliate/sub-investigator 3. Replaces Dr. Vose with Dr. Gregory Bociek as the sub-PI for University of Nebraska. 4. Clarifies that the lead institution is Northwestern University. 5. Adds the IND Holder (Dr. Gordon) and IND #.	Administrative updates
Protocol Summary	n/a	Clarifies that this will be a Simon **optimal** 2-stage design.	Clarity
Table of Contents, Appendices	n/a	Adds Appendix VI (Activities of Daily Living) and Appendix VII (Protocol History of Changes) and clarifies that Appendix IV (HRQL Forms) and Appendix V (Disease Staging Forms) are attached	Administrative

		separately as PDF documents.	
1.0 (Introduction and Study Rationale)	1. n/a 2. Background lacking in recent data on elderly HL patients. 3. Protocol lacking in data on experience with SGN-35 in elderly HL patients. 4. Data on functional status and co-morbidities not included in background. 5. The summary/hypothesis section did not clearly explain the rationale for the dosing design of SGN-35.	1. Removes unnecessary statement in Section 1.3. 2. Adds Section 1.5 regarding recent prospective elderly HL patient data, including a tabular summary of survival data and figures. 3. Adds Section 1.6.4 detailing the experience of SGN-35 in elderly HL patients. 4. Adds Section 1.8 discussing functional status and co-morbidity data, including references. 5. Adds statements clarifying that it is not expected that efficacy will be improved with only 2 lead-in doses of SGN-35, hence the additional 4 doses of "consolidation" SGN-35 therapy.	All additions made as part of initial review at various affiliate institutions and to provide additional clarity and information regarding the rationale for this study.
5.1 (Treatment Plan – Overall Description)	Dose description not given for SGN-35 "lead-in" period.	Clarifies that the dose and schedule for the SGN-35 "lead in" period will be 1.8 mg/kg q 3 weeks x 2 doses.	Added for clarity
Trial Schema, 5.3.5 (Re-Staging), Table 4 – Schedule of Activities.	n/a	Clarifies that patients who do not achieve a CR or PR after the 6 cycles of AVD chemotherapy will be taken off study and will not undergo consolidation therapy with SGN-35.	Added for clarity.
5.2.5 (Dose Mondifications – SGN-35 Lead In)	States that delays of greater than 3 weeks are prohibited unless approved by the Sponsor and that intra-patient dose reductions are at the discretion of the treating	Revises language to indicate that such delays will be considered on a case-by-case basis by the PI and that the QAM should be included in the correspondence.	Added to comply with study monitoring activities.

	physician.		
5.3.3.1 (Dose Modifications – AVD Modifications for Heme Toxicity)	1. States that dose delays or reductions are at the discretion of the investigator. 2. G-CSF administration indicated as preferred for ANC > 500.	1. Revises language to indicate that such delays will be considered on a case-by-case basis by the PI and that the QAM should be included in the correspondence. 2. Clarifies that G-CSF is **strongly** preferred.	1. Added to comply with study monitoring activities. 2. Added for clarity.
5.3.3.6 (Dose Modifications – AVD Modifications for Other Considerations), 5.4.2.5 (SGN-35 Dosing – Consolidation Period)	The role of the treating physician v. PI not clear regarding dose reductions of particular agents when considered "best medical practice."	Revises language to indicate that such decisions should be discussed on a case-by-case basis with the PI and that the QAM should be included in the correspondence.	Revised for clarity.
5.3.4 (AVD supportive care)	States that G-CSF may be used at the discretion of the treating physician and in accordance with ASCO guidelines.	Stresses that G-CSF (filgrastim) is preferred v. pegfilgrastim.	Added for clarity.
5.4.2 (SGN-35 Dosing – Consolidation Period)	Not clear **after which point** SGN-35 consolidation therapy should be delayed for ongoing neurotoxicity.	Clarifies that therapy must be delayed up to 6 weeks **after completion of last AVD cycle (i.e. 8 weeks)**.	Added for clarity.
5.4.3 (SGN-35 Dose Modifications – Consolidation Period)	Delays of 4 weeks for subsequent SGN-35 cycles mentioned but not clear whether this is "in addition to" or "including" previous delays.	Clarifies that "the start of a subsequent SGN-35 cycle may be delayed for up to 4 **additional** weeks…"	Added for clarity.
6.0 (Measurement of Effect)	n/a	Adds reference to the ADL scales in appendices.	Administrative
Table 4 – Schedule of Activities	1. Requires Hep B surface antigen and core antibody testing at baseline. 2. n/a 3. HIV screening	1. Removes these tests from baseline assessments – this was a copy/paste error. 2. Clarifies footnotes. 3. Clarifies that this is not	Administrative updates and corrections

	included in baseline tests.	mandatory but recommended.	
9.0 (Statistical Considerations)	1. Definition of evaluable not clearly stated. 2. Explanation of the MiniMax Design included in sample size justification. 3. Not clearly stated when the CR rate for the primary endpoint will be assessed. 4. Details regarding the analysis of the first 22 patients who have PET scans left out of statistical section. 5. Type 1 and 2 error calculations not given. 6. No planned stopping/suspension point given for efficacy analysis prior to stage 2 enrollement.	1. Adds definition of evaluable patient for efficacy endpoints. 2. Removes statement regarding MiniMax Design. 3. Adds that CR rate for the primary endpoint will be assessed at the completion of AVD therapy. 4. Adds a description of the planned analyses to be conducted on the first 22 patients who also receive PET scans. 5. Adds maximal type 1 and 2 error calculations. 6. Adds stopping/suspension rule after the 21st evaluable patient for interim efficacy analysis.	All changes/additions made to increase clarity and to ensure appropriate design and planning.
10.0 (Data Reporting & Regulatory Considerations)	Form/method for SAE reporting not clearly indicated.	Adds reference to the MedWatch form to be utilized for reporting of SAEs.	Administrative
11.0 (Records to be Kept)	Data recording/reporting language outdated and referenced paper CRFs.	Updates language to indicate the use of NOTIS to record and submit data via eCRFs.	Administrative
12.0 (Pathology Requirements – Table 5)	Only mentions storage of samples at Northwestern Pathology Core Facility.	Revises language to indicate that samples will be frozen and batched at each local institution for future shipment to the lead site (Northwestern) at study completion.	Added for clarity.
Amendment 2 – March 20, 2012 *Scientific Review Committee Approval – April 4, 2012*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Throughout	n/a	Adds/corrects captions and	Administrative

		locations of figures and tables, corrects some sections to match table of contents.	
Protocol Summary, 5.0 (Treatment Plan – Overall Description), 7.0 (Study Parameters), 8.1.5 (SGN-35 Dose Specifics)	These sections erroneously stated that consolidation therapy with SGN-35 would occur every 4 weeks or 28 days.	Corrects errors to accurately reflect that consolidation therapy with SGN-35 will occur every 3 weeks or 21 days.	This was done to correct mistakes make these sections consistent with the rest of the protocol.
5.2.8 (Re-staging), 7.0 Table 4 (Study Parameters)	Stated that the "early" FDG-PET scan would be done on the first 22 patients enrolled.	Clarifies that this "early" scan will be done on the first 22 *evaluable* patients. Adds that this "early" scan is not required for patients 23-45, but may be obtained at the investigator's discretion. Notes that if there is documented progressive disease after SGN35 (i.e., prior to initiation of AVD), patients may still remain 'on trial' and proceed to AVD chemotherapy, however they will not receive SGN35 consolidation.	Changes made to improve clarity concerning the "early" FDG-PET scan requirements.
7.0 Table 4 (Study Parameters)	1. Uric acid, EBV PCR, TSH and HgbA1c tests all required. 2. Unclear whether direct bilirubin is required or not.	1. Makes uric acid, EBV PCR, TSH, and HgbA1c recommended but not required. 2. Adds clarification that direct bilirubin is recommended but only required if total bilirubin is elevated.	1. This was done to accommodate participating sites for whom these research-related tests are not funded. 2. This was done for clarity.
7.0 Table 4 (Study Parameters)	Reference is made to bone marrow biopsy "and aspirate."	Removes references to bone marrow aspirate and clarifies that although bilateral biopsy is preferred, unilateral is acceptable.	This was done to ensure consistency with the rest of the protocol.

7.0 Table 4 (Study Parameters), 9.3 (Phase II Efficacy Analysis), 9.7 (Overall Survival)	Length of follow-up inconsistently stated as 2, 3, or 5 years.	Revises to state that follow-up with blood tests and CT will be for 3 years, after which it should be per local institutional practice guidelines.	This was done for clarity and to correct errors.
Amendment 3 – January 13, 2013 *Scientific Review Committee Approval – January13, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Table 4; footnote 10	The <u>first 22 patients</u> entered on the study will have a repeat FDG-PET	Adds the word “evaluable” that was previously omitted.	Administrative

Amendment 4 – April 16, 2013 *Scientific Review Committee Approval –April 18, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Table of Contents, Protocol Summary, Throughout		Formatting was changed throughout. An updated and linked Table of Contents was added. The Protocol Summary was put into a table format.	Formatting and spacing was adjusted throughout to match the new Northwestern University template.
Protocol Summary; Treatment Plan (Sections 5.1, Figure 2; 5.2.8.2 [new section added]; 5.3.2; 5.3.3.8 [new section added]); Section 7.0, Table 4 footnote 15; Section 9.3.2 Statistical Considerations, Phase II Efficacy Analysis	All 6 cycles of AVD treatment needed to be completed into order for patients to continue on the SGN-35 maintenance.	Patients who are determined to be chemotherapy intolerant may be discontinued from AVD, but may still move on the SGN-35 maintenance. Chemotherapy intolerance is now defined in section 5.3.3.8.	It has been appreciated with the initial several patients treated that there is extreme heterogeneity in this patient population including “very elderly” patients who cannot tolerate 6 cycles of chemotherapy.
Treatment Schema (section 5.1)	Indicated PET/CT was due after cycle 6 and again after consolidation.	Clarifies PET/CT is done every 3 cycles. Also clarifies PET/CT is only required for those in PR/SD. CT only is required for this in CR.	Administrative, to match the protocol parameters (Section 7.0).
Section 5.3.3 AVD chemotherapy	This section did not include dose modifications related to changes in creatinine clearance.	Section 5.3.3.6 was added, providing dose adjustments for decreasing creatinine clearance.	This was updated for safety.
Section 7.2 Pre-cycle testing.	Required all pre-study tests to be done within 4 weeks on beginning	Clarifies that the staging bone	These are not critical factors

	study treatment.	marrow and cardiac testing may be done within 3 months prior to starting treatment.	that are not likely to change within 3-4 months of study entry.
Section 7.7 Ct scan and PET scan; Table 4	Required scans to be done within 4 weeks of starting treatment. CT of the neck was required.	Allows scans to be done within 6 weeks of starting treatment. The CT of the neck is no longer a requirement.	This is a more clinically realistic time parameter and the neck may be assessed clinically.
Section 8.1.6 (SGN-35 Preparation)	Requires drug to be diluted into at 150ml infusion bag.	Removes requirements for 150ml bag.	NMH Pharmacy does not carry 150ml infusion bags, and the size of the infusion bag does not impact the drug.
Section 8.1.7 (Required Premedication and Postmedication)	It was advised that anti-emetics are not to be given prior to the 1st cycle.	Allows anti-nausea medications as needed.	This was done for standard clinical practice.
Amendment 5 – May 31, 2013 *Scientific Review Committee Approval – June 5, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Cover Page		Adds Tufts University as a site.	An additional site is being added to aid in enrollment to the trial.
Section 1.0 (Introduction and Study Rationale)	Section 1.6.5 was not included.	Adds background on the incidence of pancreatitis seen with SGN-35. Also adds a description of the ongoing other trial of SGN-35 for elderly patients.	Additional background and safety information is now available and has been added.
Section 3.3.2	Excluded patients with a history of	Excludes patients	This protocol

(Selection of Patients)	another primary cancer that has not been in remission for at least 3 years, with exceptions indicated.	with no currently active other malignancy other than melanoma. "Currently active" is clearly defined.	includes older patients who often have a prior cancer history. This revision is for clarity.
Section 3.0 (Selection of Patients)	Section 3.3.8 did not exist.	Excludes patients with a history of pancreatitis.	This is being done for patient safety, after a severe, unexpected case of pancreatitis was seen on the study.
Section 3.2 (Exclusion Criteria)	Excludes patients with "any active systemic viral, bacterial, or fungal infection requiring IV treatment with antimicrobial therapy within 1 week prior to first dose."	Clarifies that this must be infection requiring "***IV*** treatment."	Clarification
Section 5.2.5 (Dose Modifications), including Table 3	Did not include dose modifications specifically related to pancreatic toxicity.	Add dose modifications specifically related to pancreatic toxicity (SGN-35 is to be held until the toxicity resolves).	This is being done for patient safety, after a severe, unexpected case of pancreatitis was seen on the study.
Section 7.0 (Study Parameters)	Did not require amylase or lipase testing.	Amylase and lipase testing was added.	This is being done for safety, due to the pancreatitis case seen on the study. These labs will be used for monitoring for toxicity.
Section 7.0 (Study Parameters); Section 12.0 (Pathology Requirements)	Safety PK specimens were not collected.	Safety PK sample collection has been added.	This is being added as a safety measure in the event a study participants

			experiences an adverse drug reaction.
Section 7.0 (Study Parameters) & Table 4 (Schedule of Activities)	1. No windows given for scheduled tests, assessments, and procedures. 2. Table listed tests as being completed "every cycle."	1. Allows a window of +/- 2 days for all scheduled tests, assessments, and procedures. Allows a window of +/- 7 days between cycles. 2. Changed to "X" with footnotes clarifying "Day 1 (+/- 2 days) of each cycle."	1. Added to avoid protocol deviations for slight changes in scheduling due to weekends, holidays, etc. 2. Clarity
Section 11.0 (Records To Be Kept)	Required treatment eCRFs, including the summary, to be completed at the end of therapy.	Summary eCRFs are no longer required. Treatment data must now be submitted each cycle.	DMC requires more frequent review of data for compliance and safety. In addition, the new eCRFs negate the needs for a treatment summary sheet, as all data is collected on treatment forms.
Amendment 6 – July 30, 2013 *Scientific Review Committee Approval – August 7, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
1.6.5 (Pancreatitis and SGN-35)	Information regarding SGN-35 and pancreatitis based on data available as of May 9, 2013.	Updates data based on more recent internal review of	Updated for safety reasons per memo from

		data by Seattle Genetics (as of June 30, 2013) and indicates the intention to update the Investigator's Brochure in the upcoming version, as acute pancreatitis is now considered. an important potential risk associated with SGN-35 dosing.	Seattle Genetics.
Section 5.2.5.1 (Dose modifications regarding pancreatitis)	Instructions referenced drawing lipase depending on results of amylase.	Revises dose modifications to require action based on elevation of *either* lipase or amylase.	Updated for clarity.
Table 4 (Schedule of Activities)	Only amylase listed on the table for pancreatic monitoring.	Adds lipase.	Lipase was left off by mistake in the last version.
Section 10.5 (Termination of Treatment and/or Study Participation)	Language unclear about follow-up for survival endpoints.	Clarifies that patients who terminated study treatment may be followed for survival endpoints, *unless they also withdrawn consent from the study as a whole*.	Clarity.
Amendment 7 – November 18, 2014 *Scientific Review Committee Approval – November 19, 2014*			
Section(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
Cover page		Contact information for sub-investigator Andrew M. Evans, DO, MSc updated	Administrative
Cover page		Sub-investigators Kristie A.Blum,	Administrative

		MD and Andreas Klein, MD deleted	
3.1.6	Patients must have bi-dimensional measurable disease documented within 30 days prior to registration and documented in tumor assessment form. Non-measurable disease must have been assessed within 60 days prior to registration.	Revised to 60 days prior to starting treatment, and removed documentation on the tumor assessment form. Non-measurable disease must have been assessed within 60 days prior to starting treatment.	
3.1.7	Patients must have a bone marrow biopsy (bilateral preferred, unilateral acceptable) within 60 days prior to registration.	Revised to 90 days prior to starting treatment.	
3.1.8	Patients must have a MUGA or echocardiogram within 60 days prior to registration…	Revised to 90 days prior to starting treatment	
3.3.2	No “currently active” other (second) malignancy	Quotation marks removed	Administrative
3.3.5	Patients with HBsAG positive HBV infection	Revised to known HBsAG positive HBV infection	Clarification
4.0	Registration procedures	Patient registration information revised to include most current registration procedures	Administrative
5.2.2	For “lead in phase”, there are a total of 2 doses/cycles	Revised to delete the term “doses”	Clarification
5.2.5.1	Dose modification for asymptomatic hyperamylasemia	Revised to “Asymptomatic elevated amylase and lipase (for patients with amylase elevation >3x upper limit of normal, but no abdominal pain): • Grade 1 – continue at same dose level	

		• Grade 2 – continue at same dose level • Grade 3 – hold dose until toxicity resolves to ≤ Grade 2 and then resume treatment at the same dose level • Grade 4 – hold dose until toxicity resolves to ≤ Grade 2 and then resume treatment at reduced dose level or discontinue at the discretion of the treating investigator"	
5.4.2.1 (Dosing)	The intent is to start all SGN-35 consolidation 4 weeks after the last cycle of AVD therapy	Revised to "The intent is to start all SGN-35 consolidation 2 weeks after the last dose/administration of AVD therapy	Clarification of treatment procedures
5.4.2.4	If patients have **"<u>ongoing</u>"** grade 2, 3, or 4 neurotoxicity at the time of initiation of SGN-35 consolidation, therapy **<u>must be delayed</u>** (up to 6 weeks after completion of last AVD cycle ie, 8 weeks after last dose). If neurotoxicity does not recover to grade 1, then SGN-35 consolidation will not be given.	Revised to "If patients have "ongoing" grade 2, 3, or 4 neurotoxicity at the time of initiation of SGN-35 consolidation, therapy **<u>must be delayed</u>** until recovery to grade 1 (delay up to 8 weeks after completion of last AVD dose are permitted. If neurotoxicity does not recover to grade 1 within 8 weeks, then SGN-	Clarification of treatment procedures

		35 consolidation will not be given."	
6.6.2	Baseline scan performed no more than 4 weeks before starting chemotherapy	Revised to "Baseline scan performed no more than 60 days before starting chemotherapy".	Clarification of treatment procedures
6.6.4	"Thus if a patient had an "early" FDG PET/CT that showed CR status, then only CTs will be obtained therafter."	Deleted	Removed to prevent confusion
6.9.3 "Quality of life Studies" table	n/a	Wording in table simplified	Clarification of QOL procedures
6.9.5.4 & 6.9.5.6	Patient "refuses to complete the questionnaire, the reason should be noted on the Assessment Compliance Form."	Revised to "reason should be noted on the questionnaire".	Administrative
7.2 (Pre-cycle testing)	Laboratory assessments must be done within 4 weeks	Laboratory assessments must be done within 30 days	Revised for consistency of protocol
7.2 (Pre-cycle testing)	n/a	Measurements of measurable disease (as in Section 6.1.1) or non-measurable disease (as in Section 6.1.2) must be completed within 60 days prior to starting treatment.	Timeframe previously not noted.
7.2 (Pre-cycle testing)	Staging bone marrow and cardiac testing (e.g., echocardiogram) may have been done within the prior 3 months before starting treatment.	Revised to "Staging bone marrow and cardiac testing (e.g., echocardiogram) may have been done within the prior 90 days before starting treatment."	Revised for consistency.
7.4 (Follow-Up Visit Schedule)	Patients with CR, PR, or SD will return for a follow-up examination 30	Revised to "Patients with CR,	Revised for clarity.

	days after their last treatment cycle. Early termination patients and patients with PD will return for a final study visit 30 days after their last respective treatment cycle.	PR, or SD will return for a follow-up examination 30 days after their last treatment dose. Early termination patients and patients with PD will return for a final study visit (including imaging) 30 days after their last respective treatment dose."	
7.5 (Concomitant Medications)	All concomitant medications will be recorded from screening through study termination.	Revised to "All concomitant medications will be recorded from screening through study discontinuation."	Revised for clarity.
7.6 (ECOG Performance Status Assessment)	(within 7 days before beginning study treatment)	(within 14 days before beginning study treatment)	Revised for accuracy
7.7 (CT and PET scan)	Scans must be done within 6 weeks prior to day 1, cycle 1.	Scans must be done within 60 days prior to day 1, cycle 1.	Revised for consistency.
7.0 (Table 4. Schedule of activities)	Co-morbidity/ADL assessment row	"X" in "SGN-35 consolidation" column moved to "Post-Therapy Follow-up"	Revised for accuracy
7.0 (Table 4. Schedule of activities, footnote 6)	Repeat biopsy only if positive at baseline; bilateral biopsy is preferred, but unilateral is acceptable**. Bone marrow biopsy should also be obtained at time of CR and relapse.**	Reworded to "Baseline bone marrow biopsy is mandatory within 90 days prior to starting treatment. Repeat bone marrow biopsy at time of CR and relapse **ONLY** if positive at baseline (bilateral biopsy is	Revised for clarity.

		preferred, but unilateral is acceptable)."	
7.0 (Table 4. Schedule of activities, footnote 11)	Obtain once at baseline (pre-treatment) and then repeat once at the end of consolidation therapy (at the end of SGN consolidation).	Obtain once at baseline (pre-treatment) and then repeat once at the completion of all therapy.	Revised for accuracy
7.0 (Table 4. Schedule of activities, footnote 13)	After completion of SGN-35 consolidation, patients should have repeat re-staging CTs +/- FDG-PET completed.	Revised to "30 days (+/- 2 days) after the last dose of treatment, patients should have repeat re-staging CTs +/- FDG-PET completed". Added "Patients who stop treatment early due to AEs or PD will also follow this schedule."	Revised for clarity.
7.0 (Table 4. Schedule of activities, footnote 17)	Amylase and lipase levels may be drawn 72 hours prior to the dosing of SGN-35	Amylase and lipase levels must be drawn 72 hours prior to the dosing of SGN-35	Revised to clarify mandatory testing schedule
7.0 (Table 4. Schedule of activities, footnote 17)	n/a	Revised to include "The properly frozen plasma should be shipped overnight to the Lurie Cancer Center Pathology Core Facility."	Revised to clarify shipping procedures
7.0 (Table 4. Schedule of activities, footnote 17)	"…properly frozen samples should be drawn and sent on a case-by-case basis to the Lurie Cancer Center Pathology Core Facility. This should be discussed with the study PI."	Revised to "…samples should be drawn and sent on a case-by-case basis to the Lurie Cancer Center Pathology Core Facility. This should be discussed with the study P.I & QAM.	Revised to clarify shipping procedures
8.1.10 (Availability)	Seattle Genetics drug supply contact information	Revised to "Drug orders should be emailed to Seattle Genetics drug supply at IST@seagen.com or	Administrative

		faxed to 425-527-2016."	
9.2.1	"Data from patients who do not receive the three cycles of study treatments…"	"Data from patients who do not receive the three cycles of AVD chemotherapy…"	Revised for clarity.
9.2.2	"The definition of an evaluable patient will be as follows: patients who complete/receive a minimum of at least the 2 initial SGN-35 lead-in doses of therapy and at least 2 cycles of AVD chemotherapy will be considered evaluable for efficacy (response)."	Revised to "The definition of an evaluable patient will be as follows: patients who complete/receive a minimum of at least the 2 initial SGN-35 lead-in doses of therapy and at least 3 cycles of AVD chemotherapy will be considered evaluable for efficacy (response)."	Revised for accuracy
9.5.1(Adverse Events) & Protocol Summary	"Adverse events will be classified by body system and preferred term using the COSTART or MedDRA Thesaurus."	Revised to "Adverse events will be classified by body system and preferred term using NCI CTCAE v4."	Revised for accuracy
9.12.1	"We will collect the number of co-morbidities for each patient at baseline and at the end of therapy (i.e., at the end of 2 years of continuation therapy)…"	Revised to "We will collect the number of co-morbidities for each patient at baseline and at the end of completion of all therapy."	Revised for accuracy
Section 10.0 (Data Reporting/Regulatory Considerations)	Data Reporting/Regulatory Considerations	This entire section has been replaced with the updated protocol template language entitled "Adverse Events".	Revised for accuracy
10.4 (Scheduled assessment of Safety)	"Analysis will also include MUGA scan studies done at baseline." in	This sentence moved to Section	Revised for accuracy

	section 10.4.2	10.4.1 under Safety Data.	
10.4.2	"Efficacy endpoints data will be analyzed (primarily: CT scans and PET scans) at baseline and after 2 cycles…"	Revised to "Efficacy endpoints data will be analyzed (primarily: CT scans and PET scans) at baseline and after 3 cycles…"	Revised for accuracy
11.0 (Study Management)	"Records to be kept" section	This entire section has been replaced with the updated protocol template language entitled "Study Management".	Revised for accuracy
12.2	n/a	The Section entitled "Mandatory SGN-35 Pharmacokinetic Sample" has been moved to section 12.2, the remaining sections have been renumbered accordingly	Revised to highlight mandatory PK procedures
Table 6 in Section 12.0 and footnote 2	2. At baseline, 3 (three) EDTA tubes (10 mL each) will be obtained; at all other time points, only 1 EDTA tube will be needed.	2. At baseline, 4 (four) EDTA tubes (10 mL each) will be obtained; at all other time points, only 2 EDTA tube will be needed.	Additional EDTA tube needed to collect sufficient amount of plasma
12.4 (Blood Processing & Shipping)	n/a	Blood processing for red and purple top tubes added	Blood processing information was previously missing from protocol
12.4.4	"Frozen samples and associated paperwork should be shipped to the Lurie Cancer Center Pathology Core	Revised to "Frozen samples and associated	Revised to clarify shipping of PK

	Facility. Specimens must be shipped via overnight FedEx on dry ice. It is important that samples do not thaw, therefore all packages should be sent Monday-Thursday only; batch shipping of specimens is allowable"	paperwork from both the mandatory SGN-35 pharmacokinetic (PK) sample and optional correlative should be shipped to the Lurie Cancer Center Pathology Core Facility. Specimens must be shipped via overnight FedEx on dry ice. Email Pathcore staff with details of shipment using the email listed below. It is important that samples do not thaw, therefore all packages should be sent Monday-Thursday only; batch shipping of specimens for both mandatory PK and optional.correlative is allowable". Also added pathcore email for notification.	and correlative samples
Appendix V	Disease Staging Forms	Disease Staging Forms have been removed	
Appendix VI	n/a	Form revised to add "At each required timepoint, please print Appendix VI, complete, sign, and upload into the eCRF system." Also included timepoint designation and	Instructions added for proper use and submission of form

		signature/date fields.	
Appendix VIII (Data Submission)	2nd sentence "In addition, instructional videos on data entry using NOTIS and eCRFs are available on the CRO's website at: https://www.cancertrials.northwestern.edu/working-with-the-cro."	Sentence deleted	Revised for accuracy
Appendix VIII (Data Submission)	"Disease Measurement form"	Replaced with "Cheson Assessment Form"	Revised for accuracy
Appendix VIII (Data Submission)	n/a	ADL instructions added	Revised for accuracy
Appendix VIII (Data Submission)	"Survival Form"	Revised to "Follow-Up Form"	Revised for accuracy
Amendment 8 – March 4, 2015 *Scientific Review Committee Approval – March 04, 2015*			
Section(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
1.6.3 (Rationale for SGN-35, Clinical Safety and Efficacy) & 8.1.11 (Side effects)	***n/a***	Clarified that safety data are based on oncology studies and that 1.8 mg/kg is the recommended dose for the approved indications. Added toxic epidermal necrolysis and pulmonary toxicity with monotherapy as notable adverse events. Added results of studies in patients with hepatic or renal impairment..	Updated Version 12 of SGN-35 IB released.
3.3.9 (Exclusion Criteria)	n/a	Added exclusion "Patients with severe renal impairment (CrCL <30 mL/min). A calculated CrCl is acceptable."	Updated prescribing information released
8.1.7(Administration)	n/a	Revised to add: • Avoid use in patients with severe renal impairment	Updated prescribing information released

		Avoid use in patients with moderate or severe hepatic impairment.	
8.1.12 (Nursing /patient implications*)*	n/a	Avoid the use of SGN35 in patients with moderate (Child-Pugh B) or severe (Child – Pugh C) hepatic impairment.	

Amendment 9 – July 12, 2016		
Prior Version	***Amendment 9 Changes***	***Rationale***
Brief description of side effects	New information on side effects listed .Side effects have been categorized into Likely, Less likely, Rare and Undetermined.	As per Action letter for Brentoximab Vedotin received from ECOG-ACRIN Operations Office

Amendment 10 – December 15, 2017			
Section	***Prior Version***	***Amendment 10 Changes***	***Rationale***
Cover Page	Andrew Evans listed as PI at Tufts	Andreas Klein listed as PI at Tufts	Administrative - Dr. Evans no longer at Tufts.
	n/a	Added version date of protocol	Administrative
Section 10	n/a	Inserted ‘high intensity monitoring’	Level of monitoring had not been entered in previous versions of the protocol.
Section 10.1	Schedule of events in section 5	Schedule of events in Section 7	Corrected error in numbering.

Amendment 11 -			
Section	***Prior Version***	***Amendment 10 Changes***	***Rationale***
All sections	n/a	General formatting updates	To align with the NU IIT Template

Cover Page	Michelle Fanale, MD listed as PI at MD Anderson	Hun Ju Lee MD listed as PI at MD Anderson	Administrative

14.7 Appendix VIII

Data Submission

Study-specific instructions regarding the entry and submission of data using eCRFs through NOTIS will be provided at the time of training prior to study activation. The Internal and Affiliate Data Compliance Policies of the Lurie Cancer Center's DMC regarding will be strictly enforced.

Study Chart & eCRFs

In addition to the regular hospital chart, a separate patient folder will be kept which includes the patient's signed, dated informed consent document. Once a subject is confirmed and enrolled to the study, the following eCRFs should be submitted to the QAM through NOTIS.

Forms to be submitted prior to registration:

Please see Section 4.0 for all forms/documentation to be submitted prior to registration.

Forms to be submitted within 5 days of registration:

- Concomitant Medications Form: updated to reflect the patients' information at the time of registration.
- Adverse Event Forms: update to reflect the adverse events that were present at baseline
- • On-Study Form: dates and results of all baseline exams/tests/labs required to be performed prior to registration will be entered here. Bone Marrow Biopsy Report: upload scanned report under "Bone Marrow Report" in eCRF system
- Cheson Assessment Forms: Enter Measurements for baseline assessment.
- PET/CT Data Form: upload fdg-PET scan (appendix II) under PET/CT Data Form in eCRF system
- FACT-Lym & FACT-Fatigue Forms: upload completed FACT Lym and FACT Fatigue Forms completed at baseline under FACT-Lym & FACT-Fatigue section in the eCRF system
- Cumulative Illness Rating Scale (CIRS): upload completed CIRS form completed at baseline under CIRS section in eCRF system.FACT/GOG Neurotoxicity Form: upload completed FACT/GOG neurotoxicity form completed at baseline under the FACT/GOG Neurotoxicities section in the eCRF system.

ADLs: Print Physician's assessment of ADLs (appendix VI) and upload into the eCRF system.

Forms to be submitted after each cycle of SGN-35 lead-in, after each cycle of AVD therapy, and after each cycle of SGN-35 consolidation therapy:

- Labs Order Form
- Adverse Events Form
- Patient Vitals Form

- Concomitant Medications Form: Should be updated as necessary.
- Treatment Log

Forms to be submitted after SGN-35 lead-in therapy completed (for first 22 patients), after C3D15 of AVD induction, after completion of AVD induction, after completion of SGN-35 consolidation, and every 6 months after patient goes off-treatment:

- Cheson Assessment Form
- PET/CT Data Form: upload fdg-PET scan (appendix II) under PET/CT Data Form in eCRF system

Forms to be submitted after Cycle 1 and Cycle 4 of induction (AVD therapy):

- FACT-Lym & FACT-Fatigue Forms: upload completed FACT Lym and FACT Fatigue Forms completed at Induction C1D1 and Induction C4D1 under FACT-Lym & FACT-Fatigue section in the eCRF system
- FACT/GOG Neurotoxicity Form: upload completed FACT/GOG neurotoxicity form completed at Induction C1D1 and Induction C4D1 under the FACT/GOG Neurotoxicity section in the eCRF system.

Forms to be completed at the end of consolidation:

- Cumulative Illness Rating Scale (CIRS): upload completed CIRS form completed at end of consolidation under CIRS section in eCRF system.
- ADLs: Print physician's assessment of ADLs (appendix VI) and upload into eCRF system.

Forms to be submitted after Cycle 1 of SGN-35 Consolidation, after the completion of SGN-35 consolidation, and 12 months after the completion of SGN-35 consolidation:

- FACT-Lym & FACT-Fatigue Forms: upload in eCRF system.
- FACT/GOG Neurotoxicity Form: upload in eCRF system.

Forms to be completed 6 months after the completion of SGN-35 consolidation:

- FACT/GOG Neurotoxicity Form: upload in eCRF system.

Forms to be submitted when a patient goes off-treatment:

- **Off-treatment Form: Complete part of this form within 1 week the subject's last day of treatment.**

Forms to be completed during Post-Therapy Follow-Up Period:

Labs Order Form: Complete this form every 3 months for 3 years after patient completes therapy
Cheson Assessment Form: Complete this form every 6 months for 3 years after patient completes therapy
FACT-Lym & FACT-Fatigue Forms: upload completed FACT Lym and FACT Fatigue Forms completed under FACT-Lym & FACT-Fatigue section in the eCRF system at 6 months after patient completes therapy and 12 months after patient completes therapy

FACT/GOG Neurotoxicity Form: upload completed FACT/GOG neurotoxicity form under the FACT/GOG Neurotoxicities section in the eCRF system at 6 months after patient completes therapy and 12 Months after patient completes therapy
Follow-Up Form: Complete q 6 months for a period of 3 years after therapy.

Data Submission Table

	Prior to registration	Within 5 days of registration	SGN-35 Lead-In		AVD Induction Therapy						SGN Consolidation Therapy				Follow-up
			C1	C2	C1	C2	C3	C4	C5	C6	C1	C2	C3	C4	
Eligibility Form	X														
Informed Consent Form	X														
Pathology Report	X														
Eligibility Checklist	X														
On-Study Form		X													
Concomitant Medications Form		X[1]	X[5]		X[5]						X[5]				
Patient Vitals Form			X[3]		X[3]						X[3]				X[11]
Labs Order Form			X[3]		X[3]						X[3]				X[11]
AE Form		X[2]	X[4]		X[4]						X[4]				X[11]
Treatment form			X[6]		X[6]						X[6]				
Bone Marrow Biopsy Report Upload		X[7]													
CIRS Form Upload		X												X[13]	
FACT/GOG Neurotoxicity Upload		X			X[12]			X[12]			X[15]			X[13]	X[16]
FACT-Lymp and FACT-fatigue upload		X			X[12]			X[12]			X[15]			X[13]	X[17]
ADL Assessment		X[20]												X[20]	
PET/CT Data Form Upload		X		X[8]			X[9]			X[10]				X[13]	X[18]
Cheson Assessment Form				X[8]	X[7]		X[9]			X[10]				X[13]	X[18]
Off-Treatment Form											X[14]				

Follow-Up Form		X[19]

1 Should reflect medications taken at baseline
2 Should reflect all AEs present at baseline
3Enter by end of each cycle, for assessments conducted on D1 of each cycle.
4 Update after each physical exam and labs done on D1 of each cycle, and as needed.
5 Update as required
6 To be entered at the end of each cycle
7 Should reflect bmbx results required at baseline. If bmbx is positive at baseline, repeat biopsies should be done, and reports uploaded at time of CR and relapse.
8Upload completed forms after end of SGN lead-in cycle 2, PET/CT Data Form only for the first 22 patients.
9 Upload completed forms by at the end of cycle 3 (for assessment required C3D15).
10 Uploaded completed forms for assessment required at the end of AVD therapy.
11 Enter q 3 months for a period of three years after pt completes therapy.
12 Submit by end of C1 and C4 for assessments conducted at D1 of C1 and C4.
13 To be completed and uploaded at the end of consolidation.
14 To be completed 1 week within 1 week of when subject goes off-treatment.
15 To be completed and uploaded by the end of C1 of consolidation.
16 To be completed and uploaded 6 months and 12 months after completion of consolidation.
17To be completed and uploaded 12 months after the completion of consolidation.
18 To be completed and uploaded q 6 months for a period of 3 years.
19 Complete follow-up form for a period of 3 years after pt goes off treatment.
20 Print physician's assessment of ADLs (appendixVI) and upload into the eCRF system.