BRENTUXIMAB VEDOTIN (SGN-35)

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EXECUTIVE SUMMARY

Seattle Genetics, Inc. is seeking regular approval for brentuximab vedotin, a CD30-directed antibody-drug conjugate (ADC) for the treatment of patients with relapsed or refractory Hodgkin lymphoma (HL). HL is a neoplasm of lymphoid tissue histopathologically defined by the presence of Hodgkin Reed-Sternberg cells, which are characterized by the cell surface antigen CD30.

The recommended clinical dose of brentuximab vedotin is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Continued treatment until disease progression or unacceptable toxicity is recommended.

A total of 357 patients in 6 studies were evaluated in the brentuximab vedotin clinical development program supporting two proposed indications. As part of this program, a pivotal study assessing objective response rate (ORR) was conducted in 102 patients with relapsed or refractory HL. Patients in this pivotal study had disease progression subsequent to autologous stem cell transplant, a state for which there is no clear standard of care and for which a median survival of 12 months has been reported. A second indication of relapsed or refractory systemic anaplastic large cell lymphoma (ALCL), which is a rare form of non-Hodgkin lymphoma characterized by uniform expression of the cell surface antigen CD30, is also being sought by the sponsor. The indication of relapsed or refractory ALCL is supported by a registrational study assessing ORR in 58 patients. Both indications were included in the original Biologics License Application (BLA) submitted to the U.S. Food and Drug Administration (FDA) by the sponsor. The FDA administratively separated the original BLA submission and will act individually on the application for each indication.

Efficacy

In a multicenter, international, phase 2 pivotal study in 102 HL patients with relapsed or refractory disease post autologous stem cell transplant, treatment with brentuximab vedotin 1.8 mg/kg every 3 weeks resulted in a clinically meaningful ORR as assessed by IRF according to the Revised Response Criteria for Malignant Lymphoma. Supporting the primary endpoint of ORR are the clinically meaningful complete remission (CR) rate and median response durations for ORR and CR (Table 1).

Table 1: Summary of key efficacy results in Hodgkin lymphoma

Efficacy endpoint	N = 102	
	Original BLA August 2010	Durability Update[a] March 2011
ORR (95% CI)	75% (64.9, 82.6)	75% (64.9, 82.6)
Median duration of response (95% CI)	6.7 months (3.6, 12.0)	6.7 months (3.6, 14.8)
CR (95% CI)	34% (25.2, 44.4)	34% (25.2, 44.4)
Median duration of response (95% CI)	not reached (8.8 months, NE)	20.5 months (10.8, NE)

NE, not estimable

a Updated durability includes response duration through 04 March 2011.

Objective responses were accompanied by symptomatic resolution in most patients with disease symptoms at baseline. B symptoms resolved in 77% of patients with B symptoms at baseline. Patients in the pivotal HL study received a median of 27 weeks treatment (9 cycles) with a median relative dose intensity of 96%.

Subgroup analyses included age, gender, race, baseline tumor volume, relapsed versus refractory disease status, primary refractory disease, postbaseline antitherapeutic antibody development. Analyses of efficacy by subgroups did not reveal any group of patients that failed to achieve clinically meaningful antitumor activity. Additionally, the demographics, baseline disease characteristics, and prior therapy data were compared between those patients who achieved CR per IRF compared to those without CR per IRF. CRs were observed both in patients with relatively low volume disease as well as some presenting with relatively high baseline SPD values (>60 cm^2).

In two phase 1 studies, an ORR of 30% was achieved in a subgroup of relapsed or refractory HL patients without prior autologous stem cell transplant (ineligible for or refused transplant) with a CR rate of 10%. Most of these responses were durable with no disease progression by the time of study closure. This represents a clinically meaningful response in patients with no curative therapy option.

Efficacy in Another CD30-Positive Hematologic Malignancy

In a multicenter, international, phase 2 study in 58 patients with relapsed or refractory systemic ALCL, treatment with brentuximab vedotin 1.8 mg/kg every 3 weeks resulted in a clinically meaningful ORR as assessed by IRF according to the Revised Response Criteria for Malignant Lymphoma. Supporting the primary endpoint of ORR are the clinically meaningful CR rate and clinically meaningful median response durations for ORR and CR (Table 2).

Table 2: Summary of key efficacy results in systemic ALCL

Efficacy endpoint	N = 58	
	Original BLA[a] August 2010	Durability Update[b] January 2011
ORR (95% CI)	86% (74.6, 93.9)	86% (74.6, 93.9)
Median duration of response (95% CI)	not reached (8.3 months, NE)	12.6 months (5.7, NE)
CR (95% CI)	53% (39.9, 66.7)	57% (43.2, 69.8)
Median duration of response (95% CI)	not reached (8.3 months, NE)	13.2 months (10.8, NE)

NE, not estimable

a Interim data through 11 August 2010 are included, the date the last patient was assessed for the primary endpoint. At the time of the data cut, 18 patients continued to receive treatment in the study.

b Interim data through 14 January 2011 are included; the durability update includes a minimum of 6 months follow up since the first response assessment for all patients.

The results observed in the two registrational studies in two types of hematologic malignancies characterized by the CD30 cell surface antigen provide supportive evidence for each other. These studies demonstrate a consistency of response with similar ORR and a substantial CR rate.

Safety

Safety data were pooled for the phase 2 registrational studies in HL and ALCL. This approach enabled safety evaluations to include 160 patients receiving the recommended clinical dose. Treatment-emergent adverse events occurring in ≥20% of patients were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily Grade 1 or 2, with the exception of neutropenia, for which Grade 3 and Grade 4 events were reported for 13% and 7% of patients, respectively. The main safety findings were as follows:

- Treatment-emergent peripheral neuropathy occurred in 53% of patients. Events were predominantly sensory in nature with an onset and severity pattern consistent with a cumulative effect. Among the peripheral neuropathy Standardized MedDRA Query SMQ terms, there were no Grade 4 or Grade 5 events. Grade 3 peripheral neuropathy occurred in 11% of patients with a median time to onset of approximately 33 weeks. Peripheral neuropathy was managed by dose delays and reductions. At the time of last follow up, 31% of patients had resolution of all events and 31% had resolution of some events or improvement of at least 1 grade level.

- Consistent with nonclinical toxicology observations, neutropenia was a relatively common treatment-emergent adverse event occurring in 21% of patients with Grade 3 events in 13% and Grade 4 events in 7%. Temporally associated infections occurred in 39% of patients with neutropenia (9% [14 of 160] patients overall). The majority of infections were mild to moderate. Neutropenia was well managed with the protocol-specified recommendations for hematologic toxicity (e.g., dose delay, growth factor support).

- Infusion-related reactions (IRR) occurred in 11% of patients and were typically managed by dose interruptions for IRR treatment. In most cases, the dose was subsequently completed. IRR prophylaxis in later treatment cycles was instituted at the discretion of the investigator. In phase 2 studies, all IRRs were Grade 1 or 2. In phase 1 studies, 2 patients had serious events of anaphylaxis with the Cycle 2 dose.

- Persistently positive antitherapeutic antibody development, categorized as >2 positive titers postbaseline, developed in 6% of patients overall. Of the small percentage of persistently positive patients, 30% (3 of 10) patients had an IRR. The incidence of IRRs in persistently positive patients was higher than that observed in transiently positive 12% (5 of 42) or never positive 7% (7 of 96) patients. There were no other discernible associations between adverse events and postbaseline antitherapeutic antibody development.

In a multicenter study, intense electrocardiogram monitoring was conducted to assess the effect of brentuximab vedotin on the duration of cardiac ventricular repolarization. No clinically significant prolongation in the duration of ventricular repolarization as measured

by Fridericia's corrected QT interval (QTcF) was observed in patients treated with brentuximab vedotin. The mean QTcF change (increase) from baseline was <10 ms at all evaluated timepoints.

In summary, based on compelling evidence of clinical benefit consisting of objective responses in 75% of HL patients, a high percentage of complete remissions (34%), prolonged durations of response (>6 months for responders; >20 months for CR), resolution of B symptoms in a substantial proportion of patients with B symptoms at baseline (77%), and the manageable toxicity profile of brentuximab vedotin, there is a strong benefit versus risk profile for treatment of relapsed or refractory HL, a disease with substantial unmet need.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALT	alanine transaminase
AST	aspartate transaminase
ATA	antitherapeutic antibodies
CALGB	Cancer and Leukemia Group B
CHOP	cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin®), prednisone
CI	confidence interval
CR	complete remission
CSR	clinical study report
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FDA	Food and Drug Administration
GVD	gemcitabine, vinorelbine, and pegylated liposomal doxorubicin
hERG	human ether-a-go-go related gene
HL	Hodgkin lymphoma
HR	hazard ratio
ICE	ifosfamide, carboplatin, etoposide
ICH	International Conference on Harmonisation
IRF	independent review facility
IRR	infusion-related reaction
IV	intravenous
MMAE	monomethyl auristatin E
NE	not estimable
ORR	objective response rate
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PN	peripheral neuropathy
PR	partial remission
QTcF	Fridericia's corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
SMQ	Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query
SPA	Special Protocol Assessment

1 INTRODUCTION

1.1 Proposed Indication and Product Description

Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC) indicated for the treatment of patients with relapsed or refractory Hodgkin lymphoma (HL).

Brentuximab vedotin is a CD30-directed ADC consisting of three components: 1) the antibody cAC10, specific for human CD30, 2) the potent antimicrotubule agent monomethyl auristatin E (MMAE), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

1.1.1 Hodgkin Lymphoma and Therapeutic Paradigm

Hodgkin lymphoma is a neoplasm of lymphoid tissue that is histopathologically defined by the presence of Hodgkin Reed-Sternberg cells in a background of inflammatory cells. The characteristic surface antigen expressed on Hodgkin Reed-Sternberg cells is CD30. It was estimated that in 2010, approximately 8490 new cases of HL would be diagnosed in the United States and 1320 patients would die of their disease (Jemal 2010).

Advances in the use of combined chemotherapy and radiotherapy in HL over the past half century have dramatically improved outcomes for these patients overall. The most commonly used frontline therapy is ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), resulting in responses in greater than 90% of all patients presenting with HL (Connors 2005). For patients presenting with advanced HL, approximately 30% to 40% are refractory to initial therapy or will relapse (Kuruvilla 2009). Primary refractory disease is associated with particularly poor outcomes. The 5-year overall survival from initiation of salvage therapy was 26% in patients with primary refractory HL, compared with 71% in patients with late relapse (>12 months) (Josting 2000; Josting 2002).

A salvage approach consisting of multi-agent chemotherapy followed by autologous stem cell transplant (SCT) remains widely advocated for patients who have failed frontline or initial therapy; however, more than half eventually relapse again and die of their disease. These relapsed patients fare dismally and represent a clear unmet need (Sureda 2005; Horning 2008). A pooled analysis from 5 international transplant centers of 756 patients who experienced relapsed HL after autologous SCT revealed a median survival of only 2.4 years with fewer than 10% alive at 5 years. When the collected data were analyzed by decade in which treatment was received (before 1990, 1990–2000, after 2000), no difference in treatment outcome was apparent, suggesting that introduction of novel treatment approaches has not meaningfully improved overall survival in the relapsed/refractory setting. Sureda et al identified similarly poor outcomes among patients whose lymphoma recurred

after autologous SCT, reporting that such patients had a median life expectancy of only 12 months (range 1 to 76) from the time of first post-autologous SCT relapse, reinforcing the unmet need in this relatively young population. In the set of patients whose lymphoma is refractory to salvage therapy, autologous SCT is not an option and the prospects for long-term survival are bleak. In a study assessing the effectiveness of high dose chemotherapy plus autologous SCT in 75 consecutive patients with biopsy-proven primary refractory disease, the 7 patients who were refractory to second-line chemotherapy (ICE: ifosfamide, carboplatin, etoposide) had a median survival of 4 months (Moskowitz 2004).

Collectively, the goals for treatment in the post-autologous SCT relapsed/refractory HL setting range from palliation of symptoms in relatively young (yet end-stage) patients to near-complete eradication of lymphoma cells to enable durable remissions. With regard to the goal of attaining sustained, disease-free survival, no clear standard of care has emerged. For some patients with a matched donor, a graft-versus-lymphoma effect provided by allogeneic SCT has been employed with some success (Kuruvilla 2011). Two reports describing clinical outcomes of salvage allograft have identified attainment of complete remission (CR) prior to allogeneic transplant to be strongly associated with prolonged survival (Claviez 2009; Sarina 2010). However, because allogeneic SCT is associated with substantial risks of chronic morbidity and treatment-related mortality and is limited in availability by the need to find a human leukocyte antigen matched donor, it is also defensible to utilize other agents in this setting, including investigational drugs. Such treatment may provide meaningful responses, delay progression or symptoms of disease, or provide complete remissions that may be durable on their own or enable SCT.

There are currently no U.S. Food and Drug Administration (FDA)-approved agents and no randomized, controlled studies to guide the care of patients with recurrent HL after failure of autologous SCT (Kuruvilla 2011). No specific recommendations are provided by the National Comprehensive Cancer Network, Inc. for these patients. Few prospective studies in a limited number of patients have evaluated single agents in the setting of recurrent disease (see Table 3). The reported response criteria varied considerably in these manuscripts, and few explicitly employed the International Working Group criteria reported by Cheson et al. in 1999 and subsequently revised in 2007 (Cheson 1999; Cheson 2007).

Table 3: Summary of single-agent therapies and activity in relapsed/refractory HL

Agent	Reference	Total N	N with Prior SCT	Objective Responses[a]	Study Type
Gemcitabine	(Aurer 2005)	14	9	9/14	retrospective chart review
Gemcitabine	(Venkatesh 2004)	29	18	6/27	phase 2
Gemcitabine	(Zinzani 2000)	14	6	6/14	phase 2
Vinorelbine	(Devizzi 1994)	24	4	11/22	phase 2
Vinorelbine	(Rule 1998)	8	4	4/8	phase 2
Vinblastine	(Little 1998)	17	17	10/17	retrospective chart review

a All patients, irrespective of prior SCT

While a number of multiagent regimens have been studied in relapsed/refractory HL, few have specifically analyzed the post-autologous SCT population segment. A large prospective evaluation of multi-agent chemotherapy (GVD: gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) in relapsed/refractory HL conducted by the Cancer and Leukemia Group B (CALGB) did evaluate this subgroup of patients (Bartlett 2007). Of the 91 patients treated, 40 had previously received autologous SCT. Of these patients, 70% had received 3 or more prior chemotherapy regimens and 89% had chemosensitive disease. Per Cheson 1999 criteria as assessed by the investigators, the objective response rate (ORR) in the post-autologous SCT patients was 75% (95% CI: 57.8, 87.9) and the CR rate was 17% (95% CI: 6.4%, 32.8%). The GVD chemotherapy regimen was associated with cytopenias and infections. Grade 3 and 4 neutropenia occurred in 27% and 24%, respectively, of post-autologous SCT patients, with Grade 3 and 4 febrile neutropenia observed in 8% and 3%, respectively. Thrombocytopenia occurred in 43% of patients.

In summary, the majority of patients with newly diagnosed HL enjoy an excellent prognosis. For patients with relapsed disease that is sensitive to salvage chemotherapy, autologous SCT can represent a curative approach. Patients with chemotherapy sensitive disease that achieve remission may proceed to a high dose chemotherapy regimen followed by autologous SCT. For patients who are not candidates for autologous SCT or who relapse following autologous SCT, no therapies have consistently resulted in substantive rates of durable remission or extension of overall survival. An unmet need exists, and effective therapy for patients with relapsed HL would be particularly impactful given the relative youth of affected patients.

1.2 Development Approach and Regulatory Guidance/Advice

Current oncology research standards and input from FDA and European Medicines Agency informed the clinical development of brentuximab vedotin. Clinical studies were conducted in accordance with Good Clinical Practice (GCP) regulations and guidelines (21 CFR Parts 11, 50, 54, 56, 312; ICH E6).

In the setting of relapsed or refractory HL, which lacks specifically approved therapies and consistent standards of care, a randomized comparator trial was not considered feasible. Therefore brentuximab vedotin was evaluated in a single-arm trial with ORR as the primary endpoint. ORR is a direct measure of antitumor activity and is one of the endpoints

recommended by FDA for approval of anticancer drugs based on single-arm trials (FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007). Durable CRs have been especially important evidence of benefit in hematologic malignancies. Response durability and CR rate were evaluated as secondary endpoints to further assess clinical benefit. Standardized and internationally accepted criteria were employed to evaluate responses. As suggested in the guidance, the primary and secondary endpoints were assessed by an independent review facility (IRF) to avoid introducing bias and ensure consistency of evaluation.

The BLA submission is based on the results from a phase 2 single-arm study in HL (SG035-0003) conducted under a Special Protocol Assessment (SPA) agreement. As part of the development program, a second study in systemic anaplastic large cell lymphoma (ALCL) (SG035-0004) with the same registrational design elements has been completed through the primary endpoint determination for all patients. The results observed in these studies of hematologic malignancies characterized by the CD30 cell surface antigen provide supportive evidence for each other. Both studies demonstrate a consistency of response with similar ORR and a substantial CR rate. The overall brentuximab vedotin clinical program supporting the BLA, comprising 6 studies with a total of 357 patients exposed to brentuximab vedotin, allowed for an adequate safety evaluation in support of product licensure.

A summary of key interactions with FDA guiding the clinical development of brentuximab vedotin in relapsed or refractory HL is as follows:

- The proposed pivotal phase 2 study (SG035-0003) was described as a single-arm, single-agent, open-label study of brentuximab vedotin in patients who had received an autologous SCT and had progressive or relapsed HL, with ORR as determined by IRF as the primary endpoint. Protocol SG035-0003 was submitted to FDA for SPA review on 11 September 2008. Agreement that the protocol design (SG035-0003 Amendment 2) and the statistical analysis plan (version 2) adequately address the objectives necessary to support a regulatory submission was received from FDA on 16 January 2009.

- Orphan drug designation for brentuximab vedotin for the treatment of patients with HL was received on 30 January 2007 and Fast Track designation was granted on 13 March 2009.

- Based on feedback from a 27 March 2009 meeting with FDA to discuss clinical pharmacology and nonclinical development plans, two phase 1 clinical pharmacology trials were initiated. The first was a study to investigate the effects of brentuximab vedotin on cardiac ventricular repolarization. The second was a study encompassing the assessment of drug-drug interactions between brentuximab vedotin and a CYP3A4 inhibitor, inducer, and substrate, and the determination of the primary route of excretion of MMAE. The study also included the evaluation of brentuximab vedotin pharmacokinetics in special populations with hepatic or renal impairment;

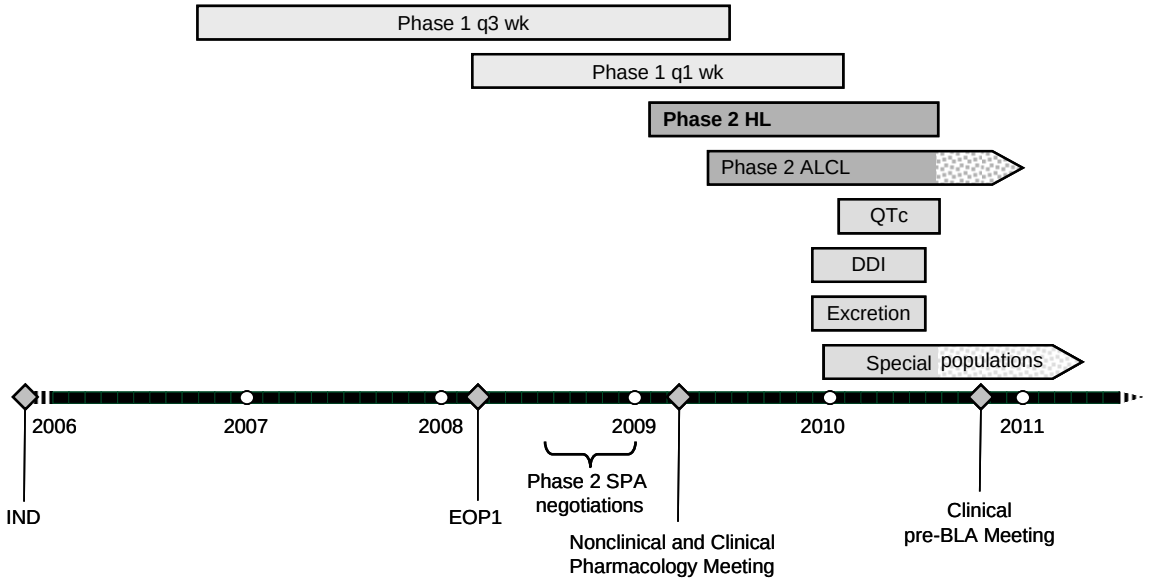
this evaluation is ongoing due to the rarity of patients with a CD30-positive malignancy who meet criteria for hepatic or renal insufficiency.

- A pre-BLA meeting was held on 18 November 2010 and FDA feedback was provided on the registrational strategy for brentuximab vedotin based on the efficacy and safety data obtained in the phase 2 clinical trial in relapsed or refractory HL (SG035-0003). There were no issues raised by FDA that precluded or advised against the planned BLA submission.

2 CLINICAL DEVELOPMENT PROGRAM FOR BRENTUXIMAB VEDOTIN SUPPORTING ORIGINAL BLA

Seattle Genetics, Inc. initiated clinical evaluation of brentuximab vedotin for patients with relapsed or refractory CD30-positive hematologic malignancies in 2006. The chronology of the clinical development program and the timing of key FDA interactions on the clinical and clinical pharmacology development are illustrated in Figure 1. Solid bars indicate clinical data contained in the BLA.

Figure 1: Overview of brentuximab vedotin clinical development program in support of relapsed or refractory HL



The brentuximab vedotin clinical program in support of the original BLA includes two phase 1 dose-escalation studies in patients with relapsed or refractory CD30-positive malignancies. The initial phase 1 dose-escalation study employed an every 3 week dosing schedule and identified the MTD as 1.8 mg/kg. The ORR in this study was 40% for all doses (0.1, 0.2, 0.4, 0.6, 0.8, 1.2, 1.8, 2.7, 3.6 mg/kg) and 52% for doses ≥1.2 mg/kg. The CR rate was 26% for all doses and 38% for doses ≥1.2 mg/kg. A second phase 1 study employed a weekly dosing schedule, which was not pursued by the sponsor. The ORR for all doses in the second study was 59% and the CR rate was 34%.

The pivotal phase 2 study in relapsed or refractory HL post-autologous SCT was an international, multicenter, single-arm study employing a dosing regimen of brentuximab vedotin 1.8 mg/kg every 3 weeks. Additionally, a phase 2 single-arm study in relapsed or refractory systemic ALCL provides supporting efficacy data. Both phase 2 trials employed ORR by an independent radiographic review facility as the primary endpoint. The program also includes two phase 1 clinical pharmacology studies, an intensive QT/QTc study and a drug-drug interaction/excretion study. Table 4 provides a summary of the clinical studies included in the BLA.

Table 4: Summary of clinical studies included in BLA

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration[a]	Primary Endpoint	Planned/ Treated/ Analyzed[b]	M:F Median age (Range)	Study Dates[c]/ CSR Status	Sites/ Location
SG035-0001 Phase 1	open-label, single-arm, dose-escalation	safety	CD30+ hematologic malignancies	0.1–3.6 mg/kg IV q3 wk NA	AEs; laboratory abnormalities	51/45/45	62%:38% 36 (20–87)	Nov 2006–Jul 2009/ Final	4/ US
SG035-0002[d] Phase 1	open-label, single-arm, dose-escalation	safety	CD30+ hematologic malignancies	0.4–1.4 mg/kg IV q1 wk 12 cycles	AEs; laboratory abnormalities	72/44/44	70%:30% 33 (12-82)	Mar 2008–Feb 2010/ Final	5/ US
SG035-0003 Phase 2	open-label, single-arm	efficacy and safety	HL	1.8 mg/kg IV q3 wk 16 cycles	ORR	100/102/102	47%:53% 31 (15-77)	Feb 2009–August 2010/ Final	25/ US, Canada, W. Europe
SG035-0004 Phase 2	open-label, single-arm	efficacy and safety	systemic ALCL	1.8 mg/kg IV q3 wk 16 cycles	ORR	55/58/58	57%:43% 52 (14-76)	Jun 2009–Aug 2010/ Interim	22/ US, Canada, W. Europe
SGN35-007 Phase 1	open-label, single-arm	clinical pharmacology	CD30+ hematologic malignancies	1.8 mg/kg IV q3 wk 16 cycles	Duration of ventricular repolarization	48/52/46	48%:52% 34.5 (19-76)	Feb 2010–July 2010/ Interim	9/ US, W. Europe
SGN35-008A Phase 1	open-label, nonrandomized, 3-arm, drug-drug interaction, excretion	clinical pharmacology	CD30+ hematologic malignancies	1.2 or 1.8 mg/kg IV q3 wk 2 cycles	PK parameters	36/56/45	59%:41% 33.5 (16-71)	Dec 2009–June 2010/ Final	7/ US

a Maximum treatment duration represented as treatment cycles (1 cycle = q3 wk, 1 dose/21-day cycle; or q1 wk, 3 doses/28-day cycle)
b Contributed to evaluation of the primary endpoint
c First patient visit to date of last assessment for BLA
d Designed as two-part dose escalation study of monotherapy followed by combination therapy (with gemcitabine); study was terminated prior to initiating combination therapy cohorts.

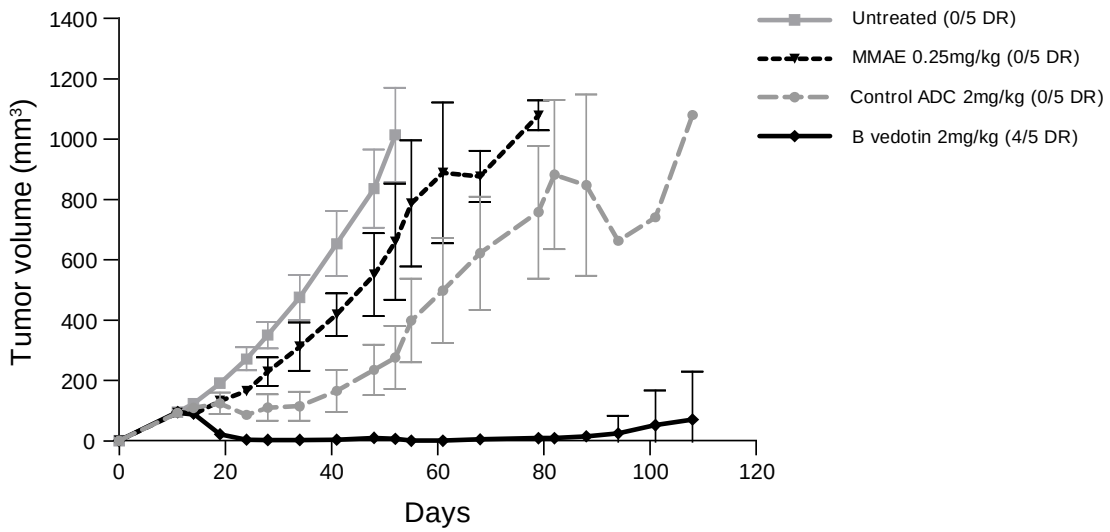
3 NONCLINICAL

In vivo, antitumor activity of brentuximab vedotin was demonstrated in mouse xenograft models using human HL and ALCL tumor cell lines. Importantly, studies using a control nonbinding ADC, the cAC10 antibody or MMAE alone, and/or an admixture of MMAE and cAC10, did not demonstrate the durable activity observed with the ADC brentuximab vedotin. Representative data are presented in the following sections (data on file, Seattle Genetics, Inc.); similar data have been published (Francisco 2003).

3.1 Hodgkin Lymphoma Models

Brentuximab vedotin demonstrated antitumor activity in xenograft models derived from human HL L540cy (Diehl 1981; Kapp 1994) and L428 (Schaadt 1979) tumor cell lines. Tumor growth was delayed when mice were treated with 1 mg/kg brentuximab vedotin every 4 days for a total of 4 doses (q4dx4) in the HL L428 subcutaneous tumor xenograft model (data not shown). Furthermore, treatment with brentuximab vedotin at 2 mg/kg q4dx3 and 3 mg/kg q4dx4 resulted in durable responses with no measurable tumor mass at the end of the study in the L428 (Figure 2) and L540cy (data not shown) models, respectively. In contrast, treatment in mice with non-binding control ADC did not result in any durable responses (Figure 2). Likewise, administration of MMAE to tumor bearing mice, at doses 5-fold higher than that delivered by brentuximab vedotin, induced minimal tumor growth delay and no complete or durable responses (Figure 2). These data show that targeted delivery of MMAE to CD30-positive tumors via brentuximab vedotin results in greater antitumor activity than administration of free MMAE alone.

Figure 2: Antitumor activity of brentuximab vedotin and controls in HL L428 tumor model

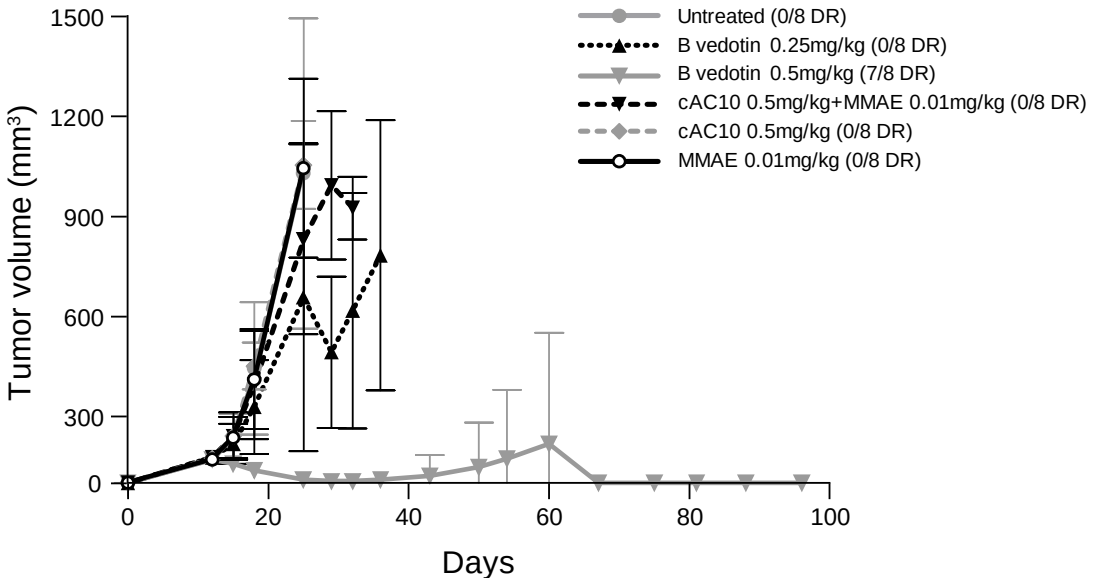


NSG mice were implanted subcutaneously with HL L428 cells in the right flank. When the tumor size for all mice averaged approximately 100 mm^3, dosing (every 4 days for 3 doses) was initiated. Groups of mice (5/group) were either untreated, or received brentuximab vedotin (B vedotin), non-binding control ADC or free MMAE. Points represent the mean tumor volume of surviving mice. Bars represent standard deviation. DR, durable response.

3.2 Anaplastic Large Cell Lymphoma Models

Dose-dependent delays in tumor growth were observed in the ALCL Karpas 299 (Fischer 1988) subcutaneous model treated with brentuximab vedotin every 4 days for a total of 4 doses (q4dx4). At a dose of 0.5 mg/kg brentuximab vedotin, 7 of 8 mice showed a durable response as defined by the absence of any palpable tumors at the termination of the experiment on Day 96. When administered separately, cAC10 or MMAE did not show significant tumor growth inhibition compared with the untreated mice. Additionally, no significant tumor growth inhibition was observed when an admixture of cAC10 and MMAE was administered, demonstrating that the ADC is more active than an admixture of the antibody and drug.

Figure 3: Antitumor activity of brentuximab vedotin and controls in ALCL Karpas 299 tumor model



SCID mice were implanted with Karpas 299 ALCL cells in the right flank. When the tumor size averaged approximately 100 mm3, dosing (q4dx4) was initiated. Groups of mice (8/group) were untreated, or received brentuximab vedotin (B vedotin), cAC10, a mixture of cAC10 and MMAE, or free MMAE. Points represent the mean tumor volume of surviving mice. Bars represent standard deviation. DR, durable response.

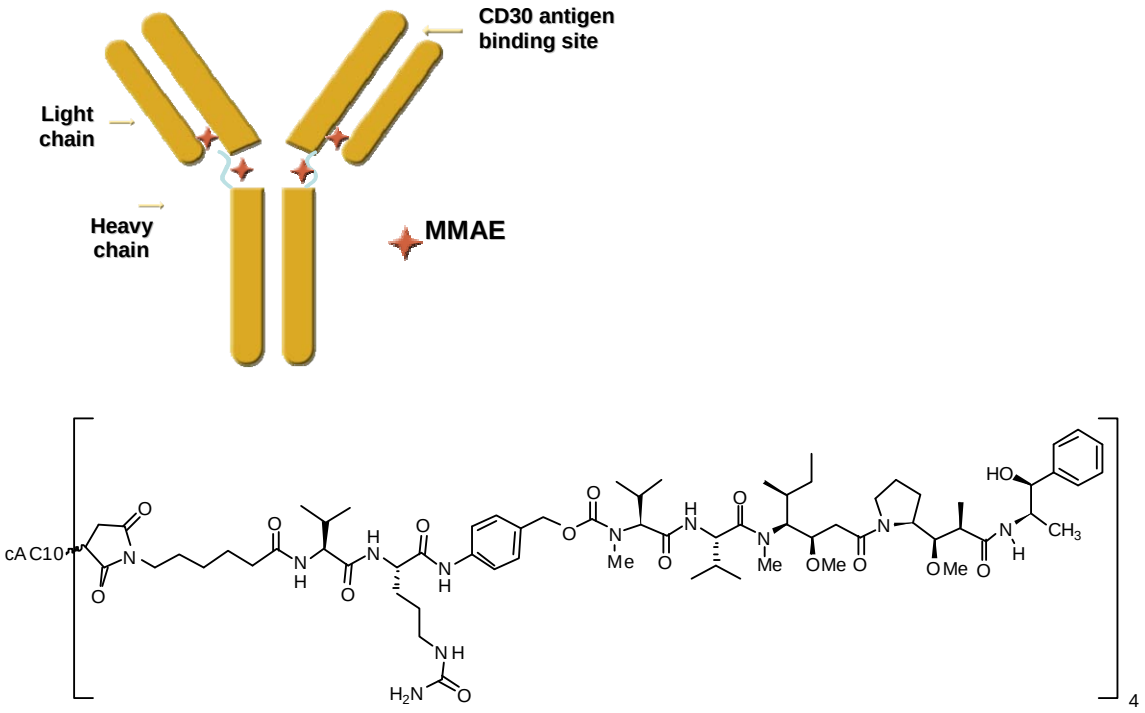
4 CLINICAL PHARMACOLOGY

4.1 Product Description

Brentuximab vedotin consists of 3 components: 1) the antibody cAC10, specific for human CD30, 2) the potent antimicrotubule agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10 (Figure 4). Brentuximab vedotin has a well-defined structure with an average of 4 drugs per antibody with consistent distribution of variants and isoforms. The combined drug and linker (SGD-1006) are synthetic materials produced by chemical processes. The chimeric antibody is produced by a Chinese hamster ovary cell-

culture process. The drug-linker and antibody are covalently attached in a conjugation step, and after purification by diafiltration, the formulated bulk drug substance is lyophilized to produce the drug product. There is no free MMAE in the drug product.

Figure 4: Structure of brentuximab vedotin



Brentuximab vedotin is formulated as a lyophilized cake or powder in 50 mg single-use vials. It is reconstituted with sterile water for injection and then diluted for intravenous (IV) infusion.

4.2 Pharmacokinetics

The pharmacokinetic (PK) characteristics of brentuximab vedotin have been assessed in a number of studies, all in patients with CD30-positive hematologic malignancies, including patients with HL and ALCL, using sensitive and validated analytical methods. The clinical pharmacology program adequately characterized the PK profile of 3 analytes using both traditional and population methods:

- ADC – brentuximab vedotin antibody-drug conjugate
- MMAE – monomethyl auristatin E (released small molecule)
- TAb – total antibody (ADC plus unconjugated cAC10 antibody)

Maximum concentrations of ADC were typically observed at the end of infusion.
A multiexponential decline in brentuximab vedotin serum concentrations was observed with a terminal half-life of approximately 4 days at the 1.8 mg/kg dose level. Exposures were approximately dose proportional. After multiple-dose administration of brentuximab

vedotin, steady-state was achieved by 21 days, consistent with the terminal half-life estimate. Minimal to no accumulation was observed with multiple doses at the every 3 week schedule.

The plasma pharmacokinetics of MMAE following an intravenous dose of brentuximab vedotin in patients with CD30-positive hematologic malignancies appeared to be formation limited. Maximum concentrations were typically observed 2 days postdose and MMAE declined with an apparent terminal half-life of approximately 4 days at the 1.8 mg/kg dose level. Exposures were approximately dose proportional. MMAE $AUC_{0\text{-}21d}$ and C_{max} decreased following multiple doses.

Total antibody exposures were higher than brentuximab vedotin ADC exposures while T_{max} was similar.

4.2.1 Effect of Intrinsic Factors on Pharmacokinetics

The effect of intrinsic factors was evaluated by a population PK approach using pooled data including patients with HL and ALCL as well as patients with other CD30-positive malignancies included in studies in Table 4 except SGN35-007. No clinically meaningful differences in brentuximab vedotin or MMAE population pharmacokinetics were found for gender, age, race, disease type (HL versus ALCL), renal function or hepatic function. Weight and body surface area were significant covariates and the recommended dose is weight based.

In an exploratory analysis of patients with low calculated creatinine clearance, brentuximab vedotin clearance appeared to be affected by severe renal impairment (calculated creatinine clearance <30 mL/min) while MMAE apparent clearance appeared to be affected by moderate (calculated creatinine clearance 30 to 50 mL/min) and severe renal impairment. Brentuximab vedotin should be used with caution in patients with a calculated creatinine clearance of less than 30 mL/min.

Antitherapeutic antibody titer by treatment cycle was a statistically significant covariate for brentuximab vedotin clearance, but the difference was small. Additional information is summarized in Section 4.2.3 below.

4.2.2 Drug-Drug Interactions

In vitro data suggested that MMAE, at concentrations more than 1000-fold higher than the clinical C_{max} achieved with brentuximab vedotin at 1.8 mg/kg, has the potential to be a quasi-irreversible time-dependent inhibitor of CYP3A4. Based on these findings, drug-drug interaction studies were conducted with brentuximab vedotin with a sensitive CYP3A4 substrate, a strong CYP3A4 inducer, and a strong CYP3A4 inhibitor. In the clinical study, brentuximab vedotin did not affect the PK of midazolam, a sensitive CYP3A4 substrate, suggesting that brentuximab vedotin and MMAE are neither inhibitors nor inducers of CYP3A4 at the clinical dose of 1.8 mg/kg. Based on these results, an interaction with CYP3A4 substrates at the clinical dose of 1.8 mg/kg brentuximab vedotin is highly unlikely in patients.

Clinical data from coadministration of brentuximab vedotin with rifampin, a CYP3A4 inducer, or ketoconazole, a strong CYP3A4 inhibitor, indicate that MMAE is a substrate of CYP3A4. Patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for adverse events because of the potential for modest increases in MMAE levels.

4.2.3 Population Pharmacokinetics

A base model and covariate analysis were performed on data from SG035-0001 and SG035-0002, then population and empirical Bayesian estimates (individual predictions) were generated for the two phase 2 studies (SG035-0003, SG035-0004), the drug-drug interaction study (SGN35-008A), and available data from the ongoing special populations study (SGN35-008B) using the developed population PK model. The predictions were evaluated for bias and the structural and covariate models were adjusted.

The PK of ADC was described by a linear three-compartment model with zero-order input and first-order elimination. The PK of MMAE was described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to a hypothetical target. Overall, the model fit the data well. Demographics (gender, age, race, ethnicity, body weight, body surface area), disease (HL, ALCL, other), organ function (creatinine clearance, ALT [alanine transaminase], AST [aspartate transaminase], bilirubin, serum albumin) and ATA (antitherapeutic antibodies) were evaluated as covariates in this model.

For ADC, body weight was a clinically and statistically important covariate in the population PK model. Other covariates did not result in a clinically meaningful change in the estimates from the model. Gender and ATA titer were statistically significant, but the point estimate of the effect on the model parameters was small.

As MMAE PK is dependent on ADC PK , the clinically meaningful covariates for ADC were incorporated in the MMAE modeling. Baseline albumin was a clinically significant covariate in the model, with higher baseline albumin concentrations correlating with increased clearance and volume of distribution for MMAE. Baseline albumin was statistically significant in the model; but the point estimate of the effect on the model parameters was small. No clinically meaningful difference was observed with other covariates including other markers of hepatic function.

4.3 Distribution, Metabolism and Elimination

Following an intravenous dose of brentuximab vedotin (1.2 to 2.7 mg/kg), the steady-state volume of distribution was approximately 6 to 10 L, indicating that brentuximab vedotin was primarily limited to the vascular space, consistent with other monoclonal antibody products. MMAE human plasma protein binding was moderate, ranging from 67.9% to 82.2%. MMAE was a substrate but not a strong inhibitor (IC_{50} >50 µM) of the P-gp efflux transporter. In vitro experiments with HL tumor cell lines suggest that MMAE can diffuse from viable cells regardless of whether a transporter protein is present likely due to the

inherent membrane permeability of MMAE. Furthermore the extracellular appearance of MMAE can be inhibited by the inhibition of lysosomal proteases suggesting that MMAE originated from intracellular processing of the ADC, followed by subsequent passive diffusion or active efflux of MMAE (Okeley 2010).

Intact MMAE was the primary species excreted in humans, suggesting a low propensity for metabolism based biotransformations. MMAE was excreted in both feces (72%) and urine (28%) in patients with CD30-positive hematologic malignancies, though mass balance was not achieved with approximately 23.5% of the equivalent amount of MMAE administered being recovered in excreta.

4.4 Pharmacodynamics and Mechanism of Action

4.4.1 Exposure-Response Analysis

An exploratory analysis was performed to determine the relationship between ADC and MMAE exposure and response based on the results from SG035-0001 (every 3 week dosing) and SG035-0002 (weekly for 3 of 4 weeks dosing). The overall tumor response to brentuximab vedotin, measured as either best percentage change in tumor size or as best response, was similar in the 2 studies.

The correlation between best tumor size percent change and measures of exposure from Cycle 1 of treatment (AUC and C_{max}) was estimated. For ADC, a correlation was observed between both AUC and C_{max} and the best tumor size percent change for both dose regimens. For MMAE, a negative correlation was observed for both AUC and C_{max} and best tumor size percent reduction, but only with the every 3 week dosing schedule. No correlation was observed between MMAE exposure and best tumor size percent change following weekly dosing, suggesting that MMAE is less likely to be correlated with tumor response. Taken together, these results suggest that tumor response is likely driven by ADC concentrations, consistent with the proposed mechanism of action.

4.4.2 Immunogenicity

Patients with HL and systemic ALCL in the phase 2 studies were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive and validated electrochemiluminescent immunoassay. Patients were categorized as being negative, transiently positive (1 to 2 positive samples) or persistently positive (>2 positive samples) based on their postbaseline ATA assessment. Patients categorized as persistently positive did not necessarily need to have a positive ATA sample at the end of treatment. ATA titers were generally low.

The majority of patients (95%) in the phase 2 studies were ATA negative at baseline. Most patients (62%) were negative at baseline and remained ATA negative throughout treatment, 27% became transiently positive for ATA, and 6% of patients developed persistently positive antibodies postbaseline. Of the persistently positive patients (including both baseline negative and baseline positive patients), 2 (1% of all patients in the phase 2 studies)

experienced adverse events consistent with infusion reactions that led to discontinuation of treatment.

Of 58 patients with ATA postbaseline, 18 (31%) were negative for the presence of neutralizing antibodies, 36 (62%) were positive for the presence of neutralizing antibodies, and 4 (7%) were of unknown status due to insufficient sample.

The presence of anti-brentuximab vedotin antibodies did not correlate with a substantial reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin. The ATA response was always directed against the antibody portion of the ADC and typically was detected for the first time in the pre-dose Cycle 2 sample.

5 CLINICAL EFFICACY

5.1 Implications of Study Design, Conduct, and Analysis

5.1.1 Study Population

The pivotal phase 2 HL trial (SG035-0003) population consisted of a homogeneous population of relatively young patients who had all experienced relapsed or refractory HL after high-dose chemotherapy and autologous SCT (Table 5). Disease diagnosis was 100% concordant between the investigator and central pathology review. The median age of 31 years and relatively even gender distribution was consistent with demographics reported from autologous SCT series in the literature (Schmitz 2002). Patients who had received an allogeneic SCT were excluded from enrollment.

Table 5: Patient demographics and baseline characteristics

	Study SG035-0003 (N=102)
Age (yr)	
Median	31.0
Min, Max	15, 77
Categorical, n (%)	
18-64	98 (96)
<18	1 (1)
>=65	3 (3)
Gender, n (%)	
Male	48 (47)
Female	54 (53)
Race, n (%)	
American Indian or Alaska Native	0
Asian	7 (7)
Black or African American	5 (5)
Native Hawaiian or Other Pacific Islander	0
White	89 (87)
Other	1 (1)
Ethnicity, n (%)	
Hispanic or Latino	12 (12)
Not Hispanic or Latino	90 (88)
Missing	0
ECOG performance status, n (%)	
0	42 (41)
1	60 (59)
2	0

Baseline disease characteristics and prior therapies for patients in the SG035-0003 study are presented in Table 6.

Table 6: Baseline disease characteristics and prior therapies

	Study SG035-0003 (N=102)
Time from initial diagnosis to first dose (months)	
Median	39.9
Min, Max	11.8, 219.7
Stage at initial diagnosis, n (%)	
Stage I	4 (4)
Stage II	47 (46)
Stage III	27 (26)
Stage IV	20 (20)
Unknown	4 (4)
Baseline B symptoms, n (%)	35 (34)
Baseline bone marrow lymphoma involvement, n (%)	8 (8)
Disease status relative to most recent prior therapy,[a] n (%)	
Relapse	59 (58)
Refractory	43 (42)
Subjects with primary refractory disease[b], n (%)	72 (71)
Prior cancer-related therapies	
Number of systemic chemotherapy regimens[c]	
Median	3.5
Min, Max	1, 13
Number of autologous stem cell transplants, n (%)	
0	0
1	91 (89)
2 or more	11 (11)
Radiotherapy, n (%)	67 (66)

a Relapse, best response of CR or PR to most recent prior therapy. Refractory, best response of SD or PD to most recent prior therapy.
b Primary refractory disease is defined as either a best response of CR not achieved with frontline therapy, or less than 3 months from last date of frontline therapy administration to date of progression.
c Includes chemotherapy given for stem cell mobilization

All patients were required to have histology confirmed CD30-positive relapsed or refractory HL by central review. To further ensure that enrolled patients had evidence of metabolically active, clinically important tumor, at least one of the following criteria were employed:

a) Histologically-documented CD30-positive HL from a biopsy obtained *at least 4 weeks subsequent to* the most recently delivered prior treatment with radiation, chemotherapy, biologics, immunotherapy and/or other investigational agents.

b) Interval tumor growth documented between two successive computed tomography (CT) evaluations with the second evaluation occurring at least 4 weeks after delivery of any radiation, chemotherapy, biologics, immunotherapy and/or other investigational agents.

c) Fluorodeoxyglucose (FDG)-avidity by positron emission tomography (PET) in a new tumor mass on CT that is unlikely to have an alternative explanation.

d) Recurrent FDG-avidity by PET in a previously identified FDG-avid tumor mass on CT that had become negative.

e) FDG-avid tumor mass by PET in conjunction with HL related symptoms (e.g., pruritus, B symptoms [fever, night sweats, or weight loss >10%]), after infectious causes have been excluded.

Meeting at least one of these criteria ensured that lymphoma was actively growing at the time of enrollment; 57% of patients met two or more criteria.

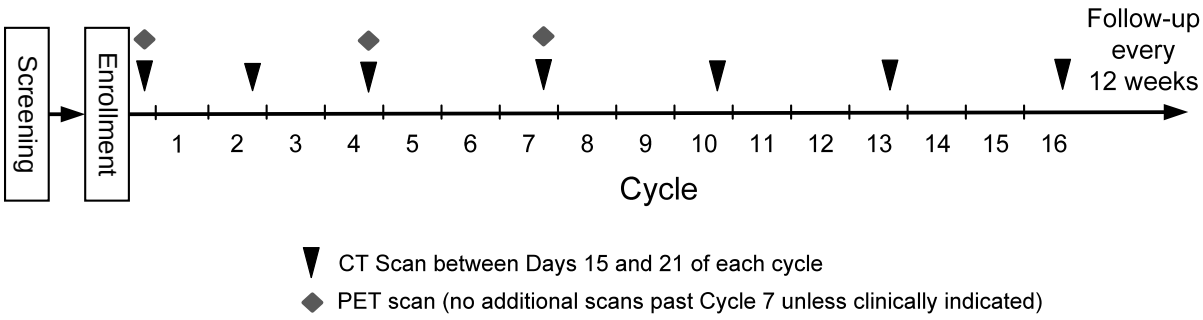
Study enrollment by country was as follows: United States, 86 patients; Canada, 8 patients; France, 5 patients; Italy, 3 patients.

5.1.2 Study Design

Single-Arm Study

Study SG035-0003, a pivotal study of patients with relapsed or refractory Hodgkin lymphoma, was a single-arm, open-label, multicenter clinical trial to evaluate the efficacy and safety of brentuximab vedotin as a single agent. The study was conducted under a SPA agreement. The primary objective of the study was to determine the antitumor efficacy of single-agent brentuximab vedotin as measured by the overall objective response rate in patients with relapsed or refractory HL following autologous stem cell transplant (SCT). Secondary objectives included the assessment of duration of tumor control (duration of response and progression-free survival), survival, safety and tolerability, and pharmacokinetics of brentuximab vedotin. Additional objectives were to assess disease-related symptoms. Brentuximab vedotin 1.8 mg/kg was administered on Day 1 of each 21-day cycle via IV infusion. Tumor response assessments were performed at Cycles 2, 4, 7, 10, 13, and 16. Patients who achieved stable disease (SD) or better as assessed by the investigator were allowed to receive additional treatment cycles up to a maximum of 16 cycles (Figure 5).

Figure 5: Study Design



Independent Determination of Clinical Responses

Clinical response assessments were made in accordance with the Revised Response Criteria for Malignant Lymphoma (Cheson 2007), which includes radiographic disease assessment by CT and/or PET scans and oncology review of clinical data. Patients were required to have FDG-avid disease by PET and measurable disease of at least 1.5 cm by spiral CT for study entry. Up to 6 of the largest dominant nodes or nodal masses were selected as index lesions for radiographic response assessments. If bone marrow was positive at baseline, a negative follow-up bone marrow was required for assessment of CR. A summary of disease response criteria is presented in Table 7. Refer to the Appendix for the complete manuscript.

Table 7: Summary of disease response criteria

Response	Nodal Lesions	Spleen, Liver	Bone Marrow
CR	Residual mass of any size permitted if PET-negative	Not palpable; nodules disappeared	Negative
PR	≥50% decrease in SPD of index lesions; one or more PET-positive at previously involved site	No increase in size; ≥50% decrease in SPD of nodules	NA
SD	Does not meet CR, PR, or PD criteria; no new sites of disease		NA
PD	Progression of existing non-index lesions, >50% increase in SPD of index lesions or appearance of new lesions >1.5 cm in any axis	>50% increase in SPD of nodules	New or recurrent involvement

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; SPD, sum of the products of the diameters of the index lesions

To manage the potential for bias or inconsistency in the application of the standardized criteria in the open-label, multicenter clinical trial, all images used to confirm disease status at study entry and to assess responses during the study were submitted for independent review by a third-party imaging core laboratory, the IRF. In addition, clinical data from the treating institutions were submitted to the independent facility to enable a third party oncologist to render an independent response determination representing a composite of radiographic and clinical data.

5.1.3 Endpoints

The primary endpoint used in the registrational HL study, ORR, defined as the sum of the complete and partial remission rates, has been established as an appropriate surrogate endpoint for accelerated or regular approval (McKee 2010). ORR is a direct measure of antitumor activity and is one of the surrogate endpoints recommended by the FDA for approval of anti-cancer drugs (FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007). Secondary efficacy endpoints were duration of response, CR rate, progression-free survival (PFS), and overall survival. Additional efficacy endpoints included B symptom resolution rate.

The adequacy of ORR as an endpoint for approval depends on the magnitude and duration, and the percentage of complete remissions, as well as the benefits of other available therapies. High response rates with a high percentage of CRs and with more durable responses may be persuasive evidence of clinical benefit.

5.1.4 Statistical Plan and Methodology

The primary efficacy analysis was conducted as planned and described in the study protocol and the statistical analysis plan that was approved under the SPA.

The primary efficacy hypothesis tested in study SG035-0003 was H_0: ORR for brentuximab vedotin (1.8 mg/kg) is <20% versus H_a: ORR for brentuximab vedotin (1.8 mg/kg) is ≥20%. An exact two-sided 95% confidence interval around the ORR was calculated using the *F* distribution method (Collett 1991). If the lower bound of the confidence interval around the ORR was greater than or equal to 20%, the primary efficacy objective was achieved. All patients who were enrolled in the study were included in the primary efficacy analyses. Patients who were enrolled but did not have their histology confirmed by central review were to have been considered non-responders.

Descriptive statistics (mean, median, standard deviation, minimum and maximum) are used to describe continuous efficacy and safety variables. Frequencies and percentages are used to describe categorical efficacy and safety variables.

The two-sided 95% exact confidence interval using the *F* distribution method given in Collett is calculated for the endpoints of CR rate and B symptom resolution rate.

Kaplan-Meier analyses are used for time-to-event endpoints of duration of response, PFS, and overall survival. The associated two-sided 95% CI for the estimated medians are computed using the method described in Brookmeyer and Crowley (Brookmeyer 1982).

A comparison of intrapatient PFS (prior therapy vs. current study) used a correlated survival analysis method (Lin 1989). PFS from most recent prior cancer-related therapy is defined as the time from the start date of that treatment to the date of progression following that treatment. If the progression date for the prior therapy was not available, PFS was censored on the date of informed consent for the brentuximab vedotin study (SG035-0003). This

comparison used the investigator assessment of response for brentuximab vedotin and the treating physician assessment of responses for the prior therapy.

5.1.5 Study Conduct

There were no protocol deviations in the registrational study that were considered to have impacted the study results. No exemptions were granted.

5.2 Efficacy

5.2.1 Key Efficacy Results

In the pivotal phase 2 study, 75% of patients had an objective response (complete or partial remission) with median duration of 6.7 months. Notably, 34% of patients achieved complete remission with a median duration of 20.5 months (Table 8). Response was rigorously assessed by an IRF according to the current international standards. Median time to objective response was 5.7 weeks, which corresponded with the first response assessment at approximately 6 weeks.

Table 8: Summary of key efficacy results

Efficacy endpoint	N = 102	
	Original BLA August 2010	Durability Update[a] March 2011
ORR (95% CI)	75% (64.9, 82.6)	75% (64.9, 82.6)
Median duration of response (95% CI)	6.7 months (3.6, 12.0)	6.7 months (3.6, 14.8)
CR (95% CI)	34% (25.2, 44.4)	34% (25.2, 44.4)
Median duration of response (95% CI)	not reached (8.8 months, NE)	20.5 months (10.8, NE)

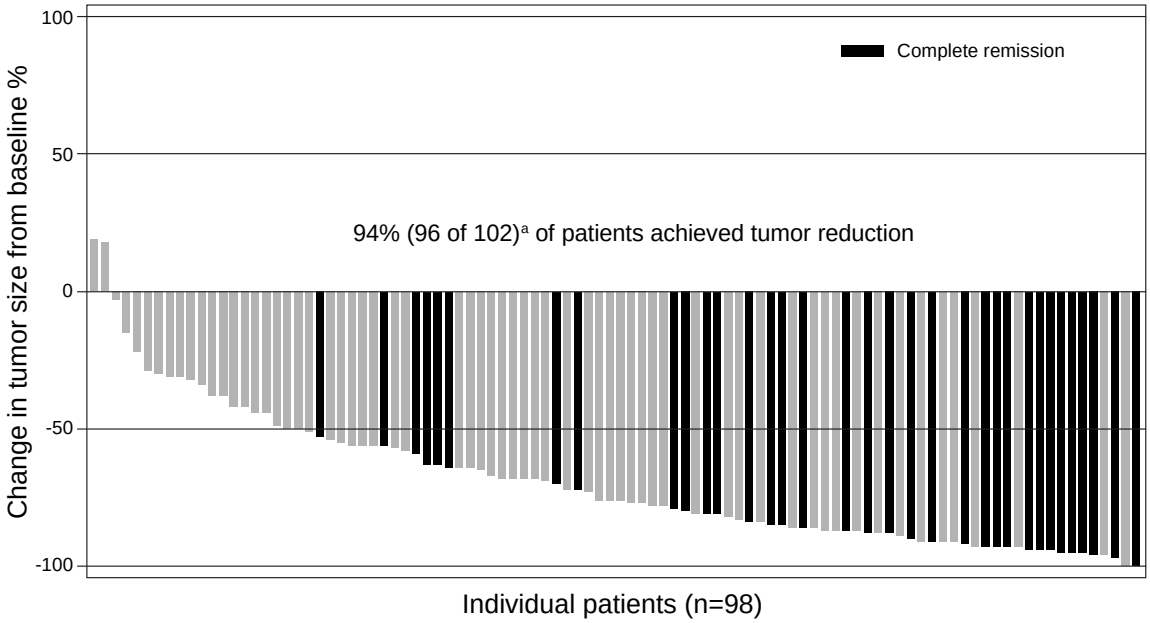
NE, not estimable

a Updated durability includes response duration through 04 March 2011; median observation time was 18.5 months.

The lower bound of the 95% confidence interval about the ORR was 64.9%, which is substantially greater than 20% as specified in the primary efficacy hypothesis. See Table 7 for a summary of disease response criteria.

Nearly all patients (94%) in the phase 2 study experienced some benefit as demonstrated by measurable reduction in tumor volume (Figure 6).

Figure 6: Maximum reduction in target lesion size



[a] 4 patients not included in analysis (3, no measurable lesions per IRF; 1, no post-baseline scans).

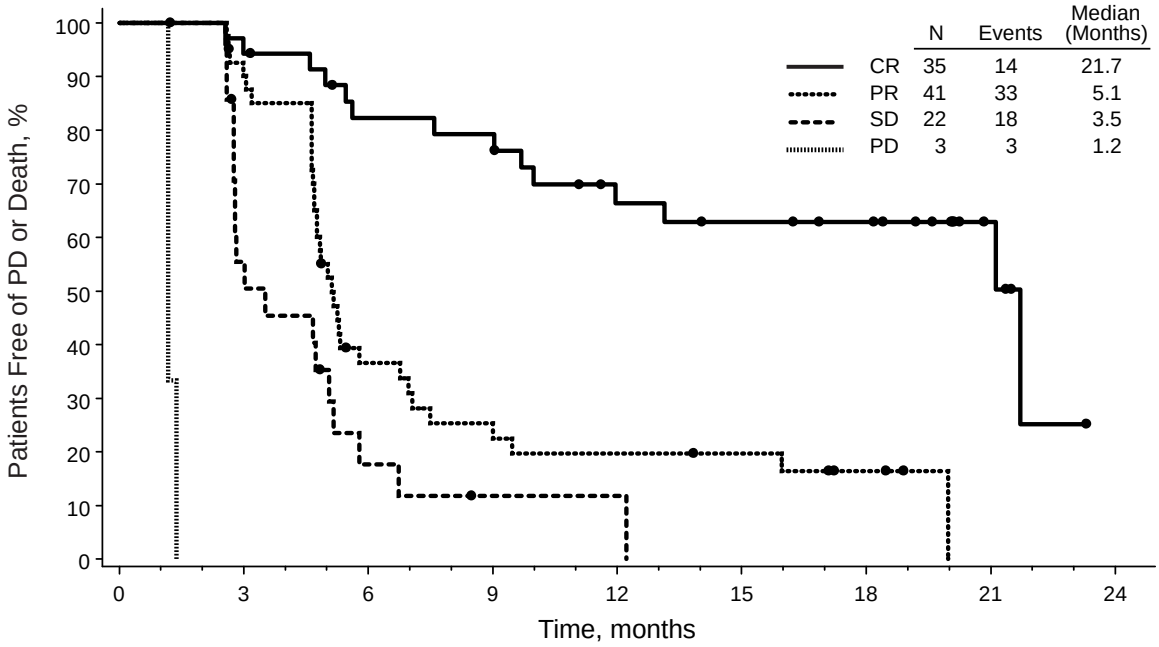
Based on March 2011 durability update
a 4 patients were not included in the analysis, 3 had no measureable lesions per IRF and 1 had no post-baseline scans

5.2.2 Progression-Free Survival

The median PFS in the pivotal HL trial was 5.6 months (95% CI; 5.0, 9.0) based on IRF assessment.

As would be expected, the subset of patients who had an objective response appeared to have a longer PFS. PFS is presented by best clinical response in Figure 7.

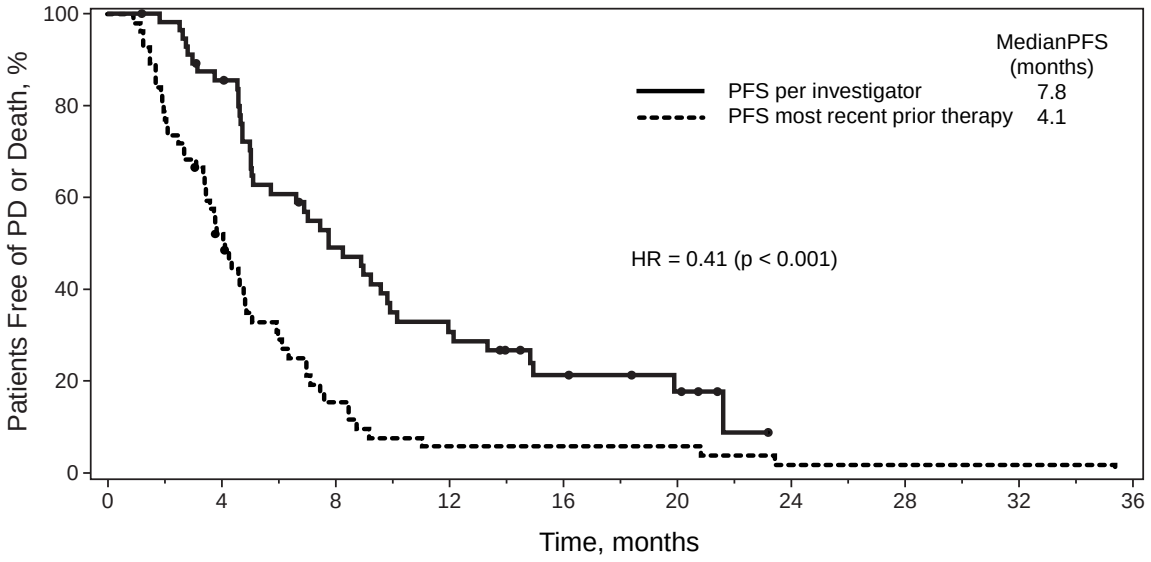
Figure 7: PFS with brentuximab vedotin by best clinical response



Symbols on the plot indicate censored patients. Based on March 2011 durability update.

The potential benefit of brentuximab vedotin versus other possible therapies available to patients with relapsed or refractory systemic HL was assessed by a correlated survival analysis comparing the PFS with brentuximab vedotin and PFS from the most recent post-autologous SCT systemic therapy prior to study enrollment with each patient serving as their own control. In the subset of patients with at least 1 post-autologous SCT systemic therapy (57 patients), PFS was significantly prolonged with brentuximab vedotin as compared with prior systemic therapy (7.8 versus 4.1 months; hazard ratio (HR), 0.41; P <0.001) (Figure 8).

Figure 8: Comparison of PFS with brentuximab vedotin versus PFS achieved with most recent post-autologous SCT therapy



Symbols on the plot indicate censored patients. Based on March 2011 durability update.

5.2.3 Symptom Resolution

In the pivotal HL trial, 77% of patients who had B symptoms at baseline had resolution of these symptoms during brentuximab vedotin treatment. Median time to resolution in these patients was 3.1 weeks (range, 0.4 to 11.9 weeks); see Table 9. Because fevers, night sweats, and weight loss that often characterize symptomatic HL can be disabling and affect a patient's quality of life, achieving resolution of these symptoms in a high proportion of patients represents clinical benefit.

Table 9: Symptom resolution summary

	HL (N = 102)
Postbaseline B symptoms resolution	77% (27 of 35 patients with symptoms at baseline)
Median time to resolution (range)	3.1 weeks (0.4 to 11.9)

5.2.4 Investigator Assessment of Response and Concordance with Independent Review

Analysis of efficacy parameters per investigator assessment supported the primary analyses by IRF assessment. At the time of the BLA data cut, the ORR per investigator was 72% (73 of 102 patients); the CR rate was 33% (34 of 102 patients), and 38% of patients (39 of 102) were assessed as achieving partial remission (PR). Assessment of objective response was concordant between IRF and investigator in 89 of 102 patients (87%). The Kappa coefficient was 0.6767, which suggests good concordance between the assessors.

Concordance between IRF and investigator assessment of best clinical response and durability remained high at the time of the durability update.

The median duration of objective response as assessed by the investigator was 47.3 weeks (95% CI: 30.7, not estimable), or approximately 11 months, versus 29.0 weeks (95% CI; 15.9, 52.1) per IRF, which is equivalent to 6.7 months. The most common reason for discordance in response duration was that IRF assessed patients as having PD prior to assessment of PD by investigator.

5.2.5 Additional Efficacy Results

Enabling Stem Cell Transplant

Allogeneic SCT represents an exploratory treatment approach employed with the intent to secure prolonged disease control in patients with chemorefractory lymphoma. Achievement of an objective response with brentuximab vedotin could enable subsequent SCT, which represents potentially curative therapy. In the phase 2 study in relapsed/refractory HL, 8 patients received allogeneic SCT subsequent to brentuximab vedotin treatment as of March 2011.

Efficacy in Subgroups

Analyses of efficacy by subgroups did not reveal any group of patients that failed to achieve clinically meaningful antitumor activity. The following subgroups were examined:

- Age (<65 years, ≥65 years)
- Gender
- Race
- Baseline tumor volume (≤5 cm^2, >5 cm^2)
- Baseline B symptoms (yes/no)
- Bone marrow involvement (yes/no)
- Number of treatments prior to autologous SCT (≤2 treatments, >2 treatments)
- Relapsed versus refractory disease status
- Primary refractory disease (yes/no)
- Baseline ATA status
- Development of ATA (yes/no)

ORR was consistent among all subgroups analyzed. Of note, relapsed versus refractory disease status did not appear to affect ORR. In the phase 2 HL study, 76% of relapsed and 72% of refractory patients achieved an objective response. Additionally, the demographics, baseline disease characteristics, and prior therapy data were compared between those patients who achieved CR per IRF compared to those without CR per IRF. A slightly higher BMI (body mass index) was observed in those who obtained CR (mean of 27.5 versus. 23.7kg/m^2). Tumor size as estimated by the sum of product dimensions (SPD) at baseline

per IRF was not meaningfully different between the two groups. Notably, CRs were observed both in patients with relatively low volume disease as well as some presenting with relatively high baseline SPD values (>60 cm^2).

The development of persistently positive antitherapeutic antibodies also did not appear to adversely affect clinical response to brentuximab vedotin as the ORR in this group was 86% (6 of 7 patients). In addition, the majority of patients (5 of 6) with a positive antitherapeutic antibody status at baseline achieved objective responses.

5.2.6 Efficacy in Patients Without Prior Autologous SCT

In the phase 1 dose-escalation studies, there were 20 patients with HL who met the criteria for study entry without prior autologous SCT. In general, these patients reflected the phase 1 transplant ineligible criteria as evidenced by a higher proportion of patients with the following characteristics: an Eastern Cooperative Oncology Group (ECOG) status of 1 or 2, refractory and primary refractory disease, bone marrow involvement, and advanced stage disease. These patients had a shorter median time since diagnosis; however, they had received the same number of median prior therapies indicating that they were more intensively pre-treated. Patient demographics and disease characteristics are summarized in Table 10 and Table 11, respectively.

Table 10: Patient demographics and baseline characteristics in HL patients without prior autologous SCT

	Studies SG035-0001, SG035-0002 (N=20)
Age (yr)	
Median	31.5
Min, Max	12, 87
Categorical, n (%)	
18-64	14 (70)
<18	2 (10)
>=65	4 (20)
Gender, n (%)	
Male	13 (65)
Female	7 (35)
Race, n (%)	
American Indian or Alaska Native	0
Asian	0
Black or African American	4 (20)
Native Hawaiian or Other Pacific Islander	0
White	16 (80)
Other	0
Ethnicity, n (%)	
Hispanic or Latino	2 (10)
Not Hispanic or Latino	14 (70)
Missing	4 (20)
ECOG performance status, n (%)	
0	10 (50)
1	6 (30)
2	4 (20)

Table 11: Baseline disease characteristics and prior therapies in HL patients without prior autologous SCT

	Studies SG035-0001, SG035-0002 (N=20)
Time from initial diagnosis to first dose (months)	
Median	27.4
Min, Max	6, 105
Stage at initial diagnosis, n (%)	
Stage I	0
Stage II	8 (40)
Stage III	5 (25)
Stage IV	7 (35)
Unknown	0
Baseline B symptoms, n (%)	7 (35)
Baseline bone marrow lymphoma involvement, n (%)	4 (20)
Disease status relative to most recent prior therapy, n (%)	
Relapse	3 (15)
Refractory	7 (35)
Subjects with primary refractory disease, n (%)	6 (30)
Prior cancer-related therapies	
Number of systemic chemotherapy regimens	
Median	3.0
Min, Max	1, 7
Number of autologous stem cell transplants, n (%)	
0	20 (100)
1	0
2 or more	0
Radiotherapy, n (%)	9 (45)

ORR in this population was 30% (95% CI: 11.9, 54.3) with a CR rate of 10% (95% CI: 1.2, 31.7). Only 1 of 6 responders had a qualifying event of disease progression or death at the time of study closure (disease progression at 2.7 weeks); therefore, median duration of response could not be estimated. Censored response duration in the 5 responders without an event are as follows: 29.6+, 34.1+, 46.4+, 50.1+, and 60.1+ weeks. Of these, the patients with a best response of CR are represented by the censored response durations of 46.4+ and 60.1+ weeks. These data suggest that clinical benefit with brentuximab vedotin is observed in relapsed or refractory HL in the pre-autologous SCT setting. Because a fraction of

patients with HL that have failed frontline therapy never achieve sufficient disease control to qualify for autologous SCT, demonstration of durable responses in these particularly high-risk patients provides evidence of direct clinical benefit that extends to this additional unmet need population.

5.3 Efficacy in Another CD30-Positive Hematologic Malignancy

In the phase 2 study in 58 patients with relapsed or refractory systemic ALCL, which had the same design as the pivotal phase 2 study in HL, 86% of ALCL patients achieved a complete or partial remission at the time of the analysis of the primary endpoint (ORR) based on the data cut for the BLA in August 2010 (Table 12). Median time to objective response was 5.9 weeks, which corresponded with the first response assessment at approximately 6 weeks. Median duration of response had not been reached at the time of the interim data cut for the BLA.

A durability update including a minimum of 6 months follow up since the first response for all patients was performed in January 2011. The durability update was limited to response duration, though it was noted that two best clinical responses of PR had evolved to CR. Median duration of objective response was estimated at 12.6 months and median duration of response in patients with a CR was 13.2 months (Table 12).

Table 12: Summary of key efficacy endpoints from a phase 2 study in systemic ALCL patients

Efficacy endpoint	N = 58	
	Original BLA[a] August 2010	Durability Update[b] January 2011
ORR (95% CI)	86% (74.6, 93.9)	86% (74.6, 93.9)
Median duration of response (95% CI)	not reached (8.3 months, NE)	12.6 months (5.7, NE)
CR (95% CI)	53% (39.9, 66.7)	57% (43.2, 69.8)
Median duration of response (95% CI)	not reached (8.3 months, NE)	13.2 months (10.8, NE)

NE, not estimable

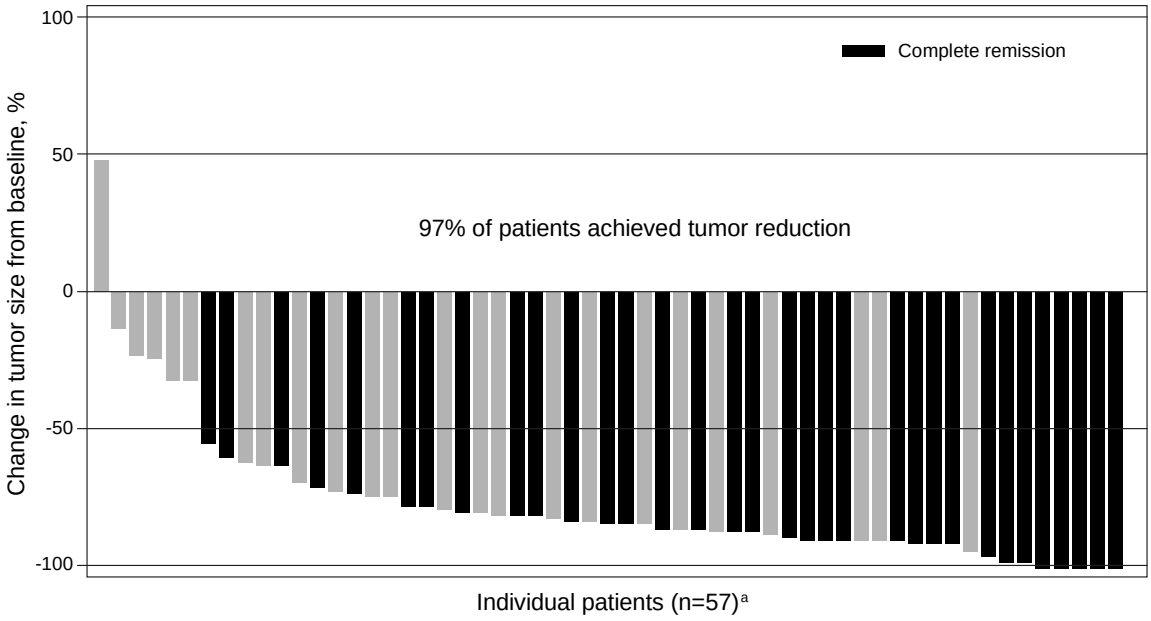
a Interim data through 11 August 2010 are included, the date the last patient was assessed for the primary endpoint. At the time of the data cut, 18 patients continued to receive treatment in the study.

b Interim data through 14 January 2011 are included; the durability update includes a minimum of 6 months follow up since the first response assessment for all patients; median observation time was 9.9 months.

The lower bound of the 95% confidence interval about the ORR was 74.6%, which is substantially greater than 20% as specified in the primary efficacy hypothesis.

Nearly all patients (97%) in the phase 2 systemic ALCL study experienced some benefit as demonstrated by reduction in tumor volume (Figure 9).

Figure 9: Maximum reduction in target lesion size in patients from a phase 2 study in systemic ALCL patients

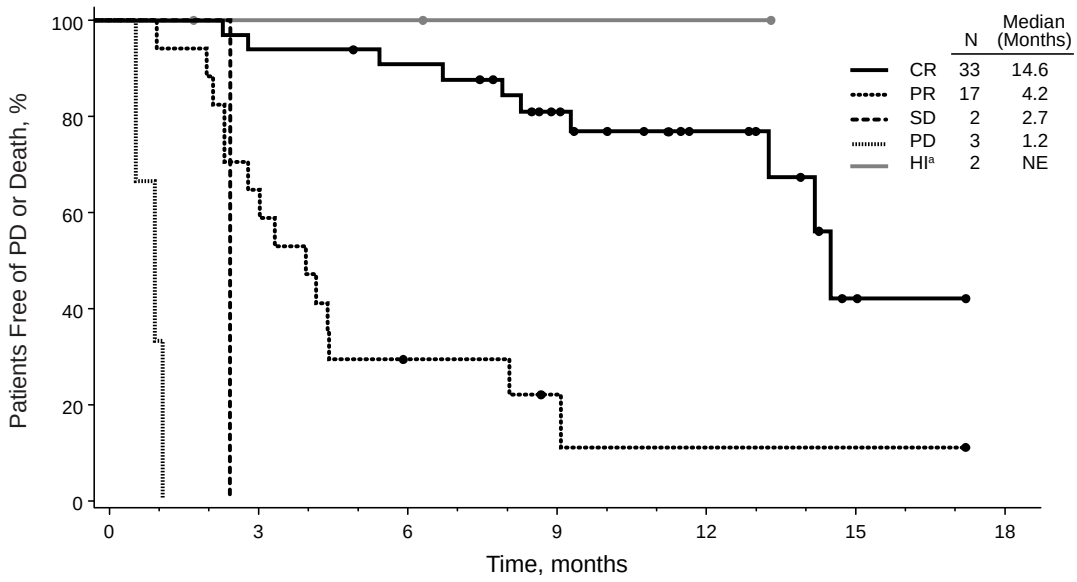


Based on January 2011 data cut for SG035-0004 study
a 57 of 58 patients with post-baseline CT assessments

Progression-Free Survival

Median PFS was not estimable at the August 2010 data cut. Median PFS at the time of the January 2011 data cut was 13.3 months (95% CI; 6.9, not estimable). As would be expected, the subset of patients who had an objective response appeared to have a longer PFS. PFS is presented by best clinical response in Figure 10.

Figure 10: PFS with brentuximab vedotin by best clinical response in a phase 2 study in systemic ALCL patients



Symbols on the plot indicate censored patients. Based on January 2011 data cut for SG035-0004 study.
HI, histology ineligible; NE, not estimable.
a Patients had confirmed CD30-positive disease.

5.4 Efficacy Conclusions

Key efficacy results from the phase 2 study of brentuximab vedotin 1.8 mg/kg administered every 3 weeks in patients with relapsed or refractory HL post autologous SCT are as follows:

- ORR of 75%, median response duration of 6.7 months
- CR rate of 34%, median response duration of 20.5 months
- PFS of 7.8 months versus PFS of 4.1 months with most recently delivered treatment as documented by investigator assessment (HR, 0.41; P <0.001)
- B symptom resolution in 77% patients with B symptoms at baseline
- 20 CR patients remained alive and free of progression at the time of last data cut

These results show that brentuximab vedotin induced durable remissions in patients with HL post-autologous SCT. Progression-free survival results comparing PFS with brentuximab vedotin to PFS from the most recent post-autologous SCT systemic therapy indicate that PFS is significantly prolonged with brentuximab vedotin. A substantial number of patients with B symptoms at baseline had symptoms resolve during treatment with brentuximab vedotin. In addition, results of the phase 2 pivotal study in relapsed or refractory HL were corroborated with the results of a phase 2 study in relapsed or refractory systemic ALCL patients in that a high ORR, high CR rate, and clinically meaningful response duration was

observed in two studies of CD30-positive hematologic malignancies. In the phase 1 patient population without prior autologous SCT, an ORR of 30% and a CR rate of 10% were observed. Most of these responses were durable with no disease progression by the time of study closure.

6 CLINICAL SAFETY

6.1 Safety Evaluation Plan

The safety of brentuximab vedotin has been evaluated in GLP-compliant nonclinical studies, including toxicology studies in rat and monkey.

The clinical safety program consisted of 6 clinical studies in patients with CD30-positive hematologic malignancies (see Table 4). Two phase 1 dose-escalation studies investigated different dose levels and schedules in patients with CD30-positive malignancies. Two phase 2 single-arm safety and efficacy studies were conducted in patients with relapsed or refractory HL or systemic ALCL. An independent data monitoring committee conducted ongoing reviews of safety data from the phase 2 studies. In addition, a phase 1 cardiac safety and a drug-drug interaction/excretion study were performed. Safety analyses are based on the August 2010 data cut.

6.2 Nonclinical Information Related to Safety

The primary treatment-related effect of repeat-dose brentuximab vedotin administration to rats and monkeys, myelotoxicity (bone marrow hypocellularity and lymphoid depletion), is consistent with pharmacologic disruption of microtubules caused by MMAE. Repeat-dose administration of MMAE caused qualitatively similar effects while no adverse effects were associated with the repeat-dose administration of cAC10 (the anti-CD30 antibody component of brentuximab vedotin). The no-observed-adverse-effect level for repeat-dose administration of brentuximab vedotin was 0.5 and 1 mg/kg in rat and monkey, respectively. The highest non-severely toxic dose for repeat-dose administration of brentuximab vedotin was 5 and 3 mg/kg in rat and monkey, respectively.

In both species, bone marrow (atrophy/hypocellularity), thymus (lymphoid depletion) and spleen (lymphoid depletion) were identified as treatment-related target organs. In rats only, testis (seminiferous tubular degeneration), liver (single cell hepatocellular necrosis and bile duct hyperplasia), intestine (single cell necrosis), pancreas (single cell necrosis) and lung (alveolar histiocytosis) were identified as target organs. Findings in intestine, pancreas and lung were observed only at a dose level of 15 mg/kg brentuximab vedotin in rat and not at dose levels of 10 mg/kg or below. Following a treatment-free recovery period of up to 6 weeks all findings were reversible, with the exception of those in testis. Testicular toxicity in rat was partially resolved following a 16-week off-treatment recovery phase. Consistent with the primary target organ histopathology findings (bone marrow hypocellularity and lymphoid depletion), decreases in peripheral blood cell counts, most notably neutrophils, were observed in animals. At systemic exposures similar to or slightly higher (2- to 4-fold)

than those in humans at the recommended dose of 1.8 mg/kg, mild decreases in neutrophil counts were observed in monkeys.

Brentuximab vedotin was negative for genotoxicity in the bacterial reverse mutation assay (Ames test) and the L5178Y $TK^{+/-}$ mouse lymphoma forward mutation assay; the 2 in vitro tests in the standard battery. The in vivo rat bone marrow micronucleus study revealed aneugenic rather than clastogenic micronuclear formation. Thus, these results were consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubular network) in cells.

Embryo-fetal development studies revealed that brentuximab vedotin resulted in embryo-fetal lethality and teratogenicity that was characterized by decreased fetal viability with increased early resorptions and post implantation loss. These effects on embryo-fetal development are also consistent with the pharmacologic disruption of microtubules caused by MMAE.

6.3 Extent of Exposure

Across the 6 studies summarized in the BLA, a total of 357 patients have received at least 1 dose of brentuximab vedotin (Table 13).

Table 13: Summary of patients exposed to brentuximab vedotin in all studies

Study No	Phase	Diagnosis	Dosage	N
SG035-0001	1	CD30+ hematologic malignancies	0.1–3.6 mg/kg IV q3 wk	45
SG035-0002	1	CD30+ hematologic malignancies	0.4–1.4 mg/kg IV q1 wk	44
SG035-0003	2	HL	1.8 mg/kg IV q3 wk	102
SG035-0004	2	systemic ALCL	1.8 mg/kg IV q3 wk	58
SGN35-007	1	CD30+ hematologic malignancies	1.8 mg/kg IV q3 wk	52
SGN35-008A	1	CD30+ hematologic malignancies	1.2 or 1.8 mg/kg IV q3 wk	56
Total				357

In the pivotal phase 2 studies of brentuximab vedotin administered at a dose of 1.8 mg/kg every 3 weeks, 102 patients with HL and 58 patients with systemic ALCL were exposed for a median duration of approximately 27 weeks (9 cycles) and 20 weeks (6 cycles), respectively. At the time of the data cut for the BLA submission, all patients in the SG035-0003 study (HL) had completed their end of treatment (EOT) visit while 31% of patients in the SG035-0004 study (systemic ALCL) had not yet reached their EOT visit.

Table 14: Summary of exposure in patients with HL

	Study		
	SG035-0003 (N=102)	SG035-0001 (N=42)	SG035-0002[a] (N=38)
Duration of treatment[b] (weeks)			
Mean (STD)	30.8 (14.3)	16.0 (11.6)	16.4 (9.6)
Median (Min, Max)	27.0 (3, 56)	12.1 (2, 52)	15.0 (3, 41)
Number of cycles per patient			
Mean (STD)	9.7 (4.4)	4.9 (3.4)	4.5 (2.7)
Median (Min, Max)	9.0 (1, 16)	4.0 (1, 16)	4.0 (1, 12)
Dose intensity (%)			
n	102	41	38
Mean (STD)	93.5 (7.9)	98.6 (7.6)	91.9 (12.2)
Median (Min, Max)	96.0 (69, 107)	100.0 (52, 105)	98.7 (56, 116)

a Drug administered on Days 1, 8, and 15 of 28 day cycles
b Duration of treatment is [(Last dose date +21) - First dose date]/7 for q3 week studies and is [(Last dose date +7) -First dose date]/7 for q1 week study. If death occurred less than 21 days (7 days for q1 week study) after the last study dose, duration of treatment is [date of death – first dose date +1].

Table 15: Summary of exposure in patients with ALCL

	Study		
	SG035-0004 (N=58)	SG035-0001 (N=2)	SG035-0002[a] (N=5)
Duration of treatment[b] (weeks)			
Mean (STD)	20.3 (10.4)	28.0 (27.0)	22.4 (16.3)
Median (Min, Max)	19.9 (3, 51)	28.0 (9, 47)	15.0 (11, 50)
Number of cycles per patient			
Mean (STD)	6.5 (3.2)	8.5 (7.8)	5.6 (3.8)
Median (Min, Max)	6.0 (1, 16)	8.5 (3, 14)	4.0 (3, 12)
Dose intensity (%)			
Mean (STD)	95.8 (10.2)	99.1 (1.8)	95.2 (4.7)
Median (Min, Max)	100.0 (47, 115)	99.1 (98, 100)	93.9 (89, 100)

a Drug administered on Days 1, 8, and 15 of 28 day cycles
b Duration of treatment is [(Last dose date +21) - First dose date]/7 for Q3 week studies and is [(Last dose date +7) – First dose date]/7 for Q1 week study. If death occurred less than 21 days (7 days for Q1 week study) after the last study dose, duration of treatment is [date of death – first dose date +1].

6.4 Adverse Events

Because of the nearly identical study designs, adverse events in the SG035-0003 and SG035-0004 studies were captured, analyzed, and reported similarly. These studies employed the dosing regimen proposed in the BLA, 1.8 mg/kg IV infusion given over 30 minutes once every 3 weeks. This enabled a consistent and meaningful pooling of the

safety data from two phase 2 studies to facilitate by-indication and overall safety observations. Unless noted, safety results are presented for this pooled population.

Adverse events were graded by investigators according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

6.4.1 Common Adverse Events

The most common treatment-emergent adverse events, occurring in ≥10% of either HL or systemic ALCL patients, in the phase 2 studies are summarized in Table 16. Treatment-emergent adverse events occurring in ≥20% of patients were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily Grade 1 or 2, with the exception of neutropenia, for which Grade 3 and Grade 4 events were reported for 13% and 7% of patients, respectively. Similar patterns and incidence rates of adverse events were observed for HL and systemic ALCL patients, with the exception of a higher incidence of upper respiratory tract infections in HL patients.

Table 16: Adverse events occurring in ≥10% of HL or systemic ALCL patients

	HL (N=102) n (%)			ALCL (N=58) n (%)			Total (N=160) n (%)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Peripheral sensory neuropathy	48 (47)	8 (8)	0	22 (38)	6 (10)	0	70 (44)	14 (9)	0
Fatigue	47 (46)	2 (2)	0	20 (34)	1 (2)	1 (2)	67 (42)	3 (2)	1 (1)
Nausea	43 (42)	0	0	22 (38)	1 (2)	0	65 (41)	1 (1)	0
Diarrhoea	37 (36)	1 (1)	0	17 (29)	2 (3)	0	54 (34)	3 (2)	0
Pyrexia	30 (29)	2 (2)	0	19 (33)	1 (2)	0	49 (31)	3 (2)	0
URTI	38 (37)	0	0	7 (12)	0	0	45 (28)	0	0
Neutropenia	22 (22)	14 (14)	6 (6)	12 (21)	7 (12)	5 (9)	34 (21)	21 (13)	11 (7)
Vomiting	22 (22)	0	0	10 (17)	2 (3)	0	32 (20)	2 (1)	0
Cough	21 (21)	0	0	10 (17)	0	0	31 (19)	0	0
Headache	19 (19)	0	0	9 (16)	1 (2)	0	28 (18)	1 (1)	0
Constipation	16 (16)	0	0	11 (19)	1 (2)	0	27 (17)	1 (1)	0
Pruritus	16 (16)	0	0	11 (19)	0	0	27 (17)	0	0
Myalgia	17 (17)	0	0	9 (16)	1 (2)	0	26 (16)	1 (1)	0
Rash	14 (14)	0	0	12 (21)	0	0	26 (16)	0	0
Arthralgia	19 (19)	0	0	5 (9)	0	0	24 (15)	0	0
Dyspnoea	13 (13)	1 (1)	0	10 (17)	1 (2)	0	23 (14)	2 (1)	0
Insomnia	14 (14)	0	0	9 (16)	0	0	23 (14)	0	0
Abdominal pain	17 (17)	1 (1)	1 (1)	5 (9)	1 (2)	0	22 (14)	2 (1)	1 (1)
Alopecia	13 (13)	0	0	8 (14)	0	0	21 (13)	0	0
Chills	13 (13)	0	0	7 (12)	0	0	20 (13)	0	0
Dizziness	11 (11)	0	0	9 (16)	0	0	20 (13)	0	0
Back pain	14 (14)	0	0	5 (9)	1 (2)	0	19 (12)	1 (1)	0
Decreased appetite	11 (11)	0	0	8 (14)	1 (2)	0	19 (12)	1 (1)	0
Lymphadenopathy	11 (11)	0	0	6 (10)	0	0	17 (11)	0	0
Night sweats	12 (12)	0	0	4 (7)	0	0	16 (10)	0	0
Pain in extremity	10 (10)	0	0	6 (10)	1 (2)	1 (2)	16 (10)	1 (1)	1 (1)
Thrombocytopenia	8 (8)	6 (6)	2 (2)	8 (14)	5 (9)	3 (5)	16 (10)	11 (7)	5 (3)
Anxiety	11 (11)	2 (2)	0	4 (7)	0	0	15 (9)	2 (1)	0
Muscle spasms	9 (9)	0	0	6 (10)	1 (2)	0	15 (9)	1 (1)	0
Peripheral motor neuropathy	12 (12)	1 (1)	0	3 (5)	2 (3)	0	15 (9)	3 (2)	0
Oropharyngeal pain	11 (11)	0	0	3 (5)	0	0	14 (9)	0	0
Pain	7 (7)	0	0	6 (10)	0	1 (2)	13 (8)	0	1 (1)
Weight decreased	6 (6)	0	0	7 (12)	2 (3)	0	13 (8)	2 (1)	0
Dry skin	4 (4)	0	0	6 (10)	0	0	10 (6)	0	0
Oedema peripheral	4 (4)	0	0	6 (10)	0	0	10 (6)	0	0

6.4.2 Adverse Events in Subpopulations

Adverse events in subpopulations were evaluated for the pooled phase 2 population of relapsed or refractory patients with HL or systemic ALCL. Males and females had similar adverse event profiles with respect to types, incidence, and severity of adverse events reported. Reaching conclusions regarding the effects of age and race was difficult due to the small number of patients who were younger than 18 years, 65 years or older, or nonwhite. Although almost all patients in the 3 age categories had at least one treatment-emergent adverse event, patients 65 years or older tended to have higher incidence of serious adverse events (SAEs). No discernible patterns emerged across system organ class or AEs indicative of an overall increased risk of older patients to treatment with brentuximab vedotin. The higher incidence of SAEs in older patients is likely due to comorbidities and/or the aggressive nature of T-cell lymphoma, as the majority of older patients had systemic ALCL. There were no trends for race observed in incidence of AEs.

The phase 2 studies enrolled patients in North America (140 patients in US and Canada) and Western Europe (20 patients in France, Belgium, the United Kingdom, and Italy). Adverse event profiles for patients in North America and Western Europe appeared similar; however, comparisons are inconclusive given the small number of patients enrolled in Western Europe.

6.4.3 Time to Onset of Adverse Events

In general, patients tended to develop common adverse events within the first 3 months of treatment (4 treatment cycles). Higher grades of peripheral neuropathy occurred in later treatment cycles, and upper respiratory tract infection was observed throughout treatment.

6.4.4 Discontinuations Due to Adverse Events

Patients in the phase 2 studies were allowed to remain on treatment until disease progression or unacceptable toxicity, up to a maximum of 16 treatment cycles. Overall, 19% of patients discontinued treatment due to adverse events, the most common of which was peripheral sensory neuropathy (6%). Peripheral motor neuropathy led to treatment discontinuation in 3 patients (2%).

6.4.5 Dose Modifications

Across both phase 2 studies, doses were reduced in 8% of patients for peripheral sensory neuropathy, which was the only adverse event that led to the dose reduction for more than 1 patient in either of the phase 2 studies. Adverse events that led to dose delays in the most patients were neutropenia (14%), peripheral sensory neuropathy (11%), and thrombocytopenia (4%). A total of 13 patients (8%) had an adverse event that led to interruption or early stoppage of the infusion.

Table 17: Adverse events leading to dose modifications in ≥2 HL or systemic ALCL patients

	HL SG035-0003 (N=102) n (%)	ALCL SG035-0004 (N=58) n (%)	Total (N=160) n (%)
Any dose modification	55 (54)	19 (33)	74 (46)
Any dose reduction[a]	11 (11)	5 (9)	16 (10)
Peripheral sensory neuropathy	10 (10)	2 (3)	12 (8)
Any dose delay[a]	48 (47)	18 (31)	66 (41)
Neutropenia	16 (16)	7 (12)	23 (14)
Peripheral sensory neuropathy	13 (13)	4 (7)	17 (11)
Thrombocytopenia	4 (4)	3 (5)	7 (4)
Alanine aminotransferase increased	2 (2)	0	2 (1)
Herpes zoster	2 (2)	0	2 (1)
Influenza	2 (2)	0	2 (1)
Lymphadenopathy	2 (2)	0	2 (1)
Pyelonephritis	2 (2)	0	2 (1)
URTI	2 (2)	0	2 (1)
Any dose adjustment due to an AE[b]	12 (12)	1 (2)	13 (8)
Any AE leading to an interruption of the infusion	11 (11)	1 (2)	12 (8)
Chills	4 (4)	0	4 (3)
Pruritus	4 (4)	0	4 (3)
Nausea	3 (3)	0	3 (2)
Dyspnoea	2 (2)	0	2 (1)
Flushing	2 (2)	0	2 (1)
Vomiting	2 (2)	0	2 (1)
Any AE leading to an early stoppage of the infusion	4 (4)	0	4 (3)
Throat tightness	2 (2)	0	2 (1)

Preferred terms are sorted by decreasing frequency.

a In accordance with the recommended dose modifications for treatment-associated toxicity in Section 5.2.5 of the study protocols.

b Includes dose interruptions (full dose received within 24 hours) and early stoppages (full dose not received within 24 hours) to the infusion.

In the phase 2 population with HL, most patients tolerated brentuximab vedotin treatment at 1.8 mg/kg throughout their respective treatment period. Doses of brentuximab vedotin were prospectively reduced to 1.2 mg/kg for adverse events in 11 patients. Of these, 10 of 11 patients received a dose reduction because of peripheral neuropathy; the other patient had a dose reduction for Grade 4 thrombocytopenia. For all 11 patients, the first dose reduction occurred after multiple cycles of treatment at the 1.8 mg/kg dose (minimum of 7 cycles). The greatest number of dose reductions occurred at Cycles 10 through 16. Overall, 5% of doses were reduced to 1.2 mg/kg for adverse events (54 of 985 doses).

6.4.6 Adverse Events of Special Importance

6.4.6.1 Peripheral Neuropathy

The severity of all peripheral neuropathy (PN) Standardised MedDRA Query (SMQ) adverse events was graded by investigators using the NCI CTCAE version 3.0, which was the current version at the time the study was conducted and analyzed. According to the grading criteria, neuropathy characterized by (for sensory) loss of deep tendon reflexes or paresthesia or (for motor) weakness on exam or testing that does not interfere with function is assigned Grade 1; neuropathy that interferes with function, but not activities of daily living is assigned Grade 2; neuropathy that interferes with activities of daily living is assigned Grade 3; and neuropathy that is disabling or fatal is assigned Grades 4 and 5, respectively.

In the phase 2 studies, 53% of patients experienced treatment-emergent adverse events within the PN SMQ. These events were primarily Grade 1 or 2. The most frequently occurring events were peripheral sensory neuropathy (44%), peripheral motor neuropathy (9%) and paresthesia (4%). Grade 3 peripheral neuropathy events occurred in 18 patients (11%). No Grade 4 events were reported. Peripheral motor neuropathy events were observed in 9% and Grade 3 motor events were reported in 2% of patients (Table 18).

Table 18: Treatment-emergent peripheral neuropathy (SMQ) adverse events

	HL (N =102) n (%)		ALCL (N = 58) n (%)		Total Ph 2 (N = 160) n (%)	
	Grade		Grade		Grade	
	Any	3	Any	3	Any	3
Any PN SMQ AE	56 (55)	11 (11)	28 (48)	7 (12)	84 (53)	18 (11)
Peripheral sensory neuropathy	48 (47)	8 (8)	22 (38)	6 (10)	70 (44)	14 (9)
Peripheral motor neuropathy	12 (12)	1 (1)	3 (5)	2 (3)	15 (9)	3 (2)
Paraesthesia	4 (4)	0	3 (5)	0	7 (4)	0
Demyelinating polyneuropathy	2 (2)	2 (2)	0	0	2 (1)	2 (1)
Hypoaesthesia	2 (2)	0	0	0	2 (1)	0
Muscular weakness	2 (2)	1 (1)	0	0	2 (1)	1 (1)
Neuralgia	0	0	2 (3)	0	2 (1)	0
Polyneuropathy	0	0	1 (2)	1 (2)	1 (1)	1 (1)
Burning sensation	0	0	1 (2)	0	1 (1)	0
Gait disturbance	1 (1)	0	0	0	1 (1)	0
Nerve conduction studies abnormal	1 (1)	0	0	0	1 (1)	0

SMQ = Standardized MedDRA query

For the phase 2 patients with at least 1 PN SMQ event, the median time to onset of any event was 12.4 weeks (range, 0.1 to 41.3). The median time to onset of the first Grade 2 PN SMQ event was 24.1 weeks (range, 0.1 to 51.9), and the median time to onset of the first Grade 3 PN SMQ event was 32.8 weeks (range, 6.0 to 57.1).

As previously presented, median number of cycles for patients in the phase 2 study in HL was 9 cycles and for patients in the phase 2 study in systemic ALCL was 6 cycles at the time

of the safety analyses. The first onset of peripheral neuropathy of any grade appeared to be incrementally higher as the number of cycles increased (Table 19). A trend of increased incidence of first onset Grade 3 peripheral neuropathy in later cycles (Cycles 9 through 16) was apparent.

Table 19: First onset of treatment-emergent peripheral neuropathy (SMQ) by cycle

	Cycle 1-4 (N=160) n_1/n_2 (%)	Cycle 5-8 (N=126) n_1/n_2 (%)	Cycle 9-12 (N=69) n_1/n_2 (%)	Cycle 13-16 (N=35) n_1/n_2 (%)
Onset of treatment-emergent PN SMQ	40/160 (25)	31/98 (32)	10/33 (30)	3/8 (38)
Onset of Grade 3 treatment-emergent PN SMQ	2/160 (1)	2/126 (2)	8/69 (12)	6/34 (18)

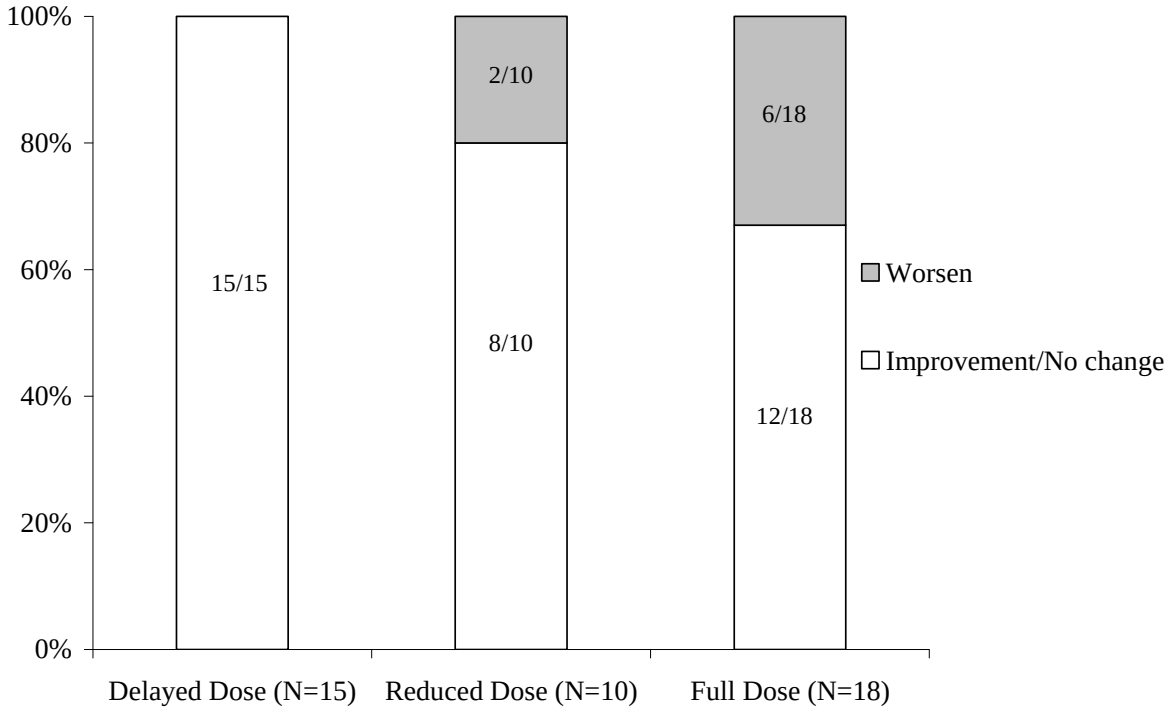
For 'Cycle X-Y' column, N is number of patients who received at least X cycle(s) treatment.
n_1 is the number of subjects who had the first onset of an event during the specified cycles (from Cycle X to Cycle Y, inclusive)
n_2 is the number of subjects at risk at the beginning of Cycle X, (i.e., the number of subjects who received at least X cycles of treatment and had not developed the event prior to the beginning of Cycle X).
No Grade 4 or Grade 5 PN SMQ AEs were reported.

Collectively, the data support peripheral neuropathy, in particular Grade 3 peripheral neuropathy, as an effect of cumulative exposure to brentuximab vedotin.

Protocol-specified dose modifications were recommended for ≥ Grade 2 treatment-associated peripheral neuropathy in the phase 2 studies, entailing withholding the dose until resolution to Grade 1 or baseline for the first occurrence. For the second occurrence of Grade 2 neuropathy, the dose was to be reduced to 1.2 mg/kg following resolution to Grade 1 or baseline. Treatment discontinuation was recommended for Grade 3 or higher neuropathy.

Despite these protocol recommendations, 18 patients received at least 1 full dose (1.8 mg/kg) of brentuximab vedotin concurrent with at least 1 treatment emergent Grade 2 PN SMQ event. Of these 18 patients, 6 patients (33%) had worsening neuropathy defined as subsequent Grade 3 neuropathy and/or the development of motor neuropathy (Figure 11). In contrast, only 2 of 10 patients (20%) who had dose reduction after experiencing a Grade 2 PN SMQ event and none of the 15 patients with dose delay concurrent with a Grade 2 PN SMQ event had worsening subsequent to or during the dose modification. These data suggest that the protocol recommendations for dose delay in the event of Grade 2 or higher neuropathy were appropriate and effective in preventing worsening of symptoms.

Figure 11: Outcome for patients who received delayed, reduced, or full dose with a Grade 2 peripheral neuropathy (SMQ) event



Overall, 15% of patients had dose modifications for PN SMQ events of any grade. Dose delays for PN SMQ events of any grade occurred in 20 patients (13%) and dose reductions for PN SMQ events occurred in 12 patients (8%). Treatment discontinuations for PN SMQ events of any grade occurred in 14 patients (9%) in the phase 2 studies.

Neuropathy was generally reversible. Median time from onset to resolution or improvement of peripheral neuropathy events was 6.6 weeks (range, 0.3 to 54.4 weeks). At the EOT visit, approximately 30 days after the last dose, 16 of the 84 patients (19%) with treatment-emergent peripheral neuropathy had resolution of all symptoms. Of the remaining 68 patients with ongoing peripheral neuropathy symptoms at EOT, 43% had ongoing Grade 1, 25% had ongoing Grade 2, and 13% had ongoing Grade 3 symptoms (Table 20).

Table 20: Resolution and/or improvement of treatment-emergent peripheral neuropathy (SMQ)

	HL (N =56) n (%)	ALCL (N = 28) n (%)	Total Ph 2 (N = 84) n (%)
Status at end of treatment			
Patients with resolution of all PN SMQ events[a], n (%)	13 (23)	3 (11)	16 (19)
Patients with ongoing PN SMQ events, n (%)	43 (77)	25 (89)	68 (81)
Grade 1	23 (41)	13 (46)	36 (43)
Grade 2	13 (23)	8 (29)	21 (25)
Grade 3	7 (13)	4 (14)	11 (13)
Length of follow-up after end of treatment (weeks)			
Patients with ongoing PN SMQ events, n	43	25	68
Median	11.86	7.57	10.21
Min, max	0.1, 38.0	0.1, 31.4	0.1, 38.0
Status at last follow-up			
Patients with resolution of all PN SMQ events[a]	20 (36)	6 (21)	26 (31)
Patients with resolution of some PN SMQ events[a]	1 (2)	3 (11)	4 (5)
Patients with improvement of any PN SMQ event[b]	17 (30)	5 (18)	22 (26)
Patients with no improvement or resolution of any PN SMQ event[a,b]	18 (32)	14 (50)	32 (38)
Patients with ongoing PN SMQ events at last follow-up	36 (64)	22 (79)	58 (69)
Grade 1	21 (38)	11 (39)	32 (38)
Grade 2	13 (23)	7 (25)	20 (24)
Grade 3	2 (4)	4 (14)	6 (7)

N = number of patients with treatment-emergent peripheral neuropathy (SMQ).
No Grade 4 or Grade 5 PN SMQ AEs were reported.
a Resolution is defined as event status of resolved/recovered or resolved/recovered with sequelae; or (for pre-existing events) a return to baseline or lower severity as of the latest assessment.
b Improvement is defined as decrease by at least one grade from worst grade as of the latest assessment.

The median duration from EOT until last follow-up was approximately 10 weeks. At the time of last follow up, 31% of patients had resolution of all events and 31% had resolution of some events or improvement of at least 1 grade level. A total of 32 patients (38% of 84 patients with treatment-emergent peripheral neuropathy) did not have resolution or improvement in any peripheral neuropathy symptom.

At EOT, Grade 3 peripheral neuropathy was ongoing for 11 of the 18 patients for whom maximum severity Grade 3 neuropathy was reported. Patients showed continued improvement or resolution between EOT and last follow-up; Grade 3 peripheral neuropathy was ongoing for 6 patients at last follow-up representing 7% of patients who experienced any peripheral neuropathy and approximately 4% of all patients in the phase 2 studies. Taken together, the majority of patients with Grade 3 peripheral neuropathy in the phase 2 studies (12/18 or 67%) had improvement or resolution as of last follow-up.

The incidence and severity of neuropathy, as well as the nature of the events (sensory more common than motor events and distal to proximal pattern of development), is similar to that observed with microtubule inhibitors such as paclitaxel and docetaxel. Also consistent with the clinical experience with microtubule inhibitors was the observation that neuropathy appeared to be a cumulative effect. Onset of motor neuropathy was later than non-motor events, suggesting that in most cases motor neuropathy occurs with higher cumulative exposure. There was not a clear pattern suggesting autonomic neuropathy.

Across the phase 2 studies, 53% of patients experienced peripheral neuropathy. The majority of events were Grade 1 to 2; however, 11% of patients experienced a Grade 3 event. Dose delay and reduction appeared to mitigate worsening of neuropathy. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at the 1.2 mg/kg dose level. There were no occurrences of Grade 4 peripheral neuropathy; discontinuation of brentuximab vedotin is recommended for Grade 4 events.

6.4.6.2 Neutropenia

In the phase 2 studies, neutrophils were measured as a part of the hematology evaluations (CBC with differential) that were performed at baseline, within 24 hours prior to each dose, and at the EOT. Additional unscheduled neutrophil measurements could be performed by central or local laboratories; however, only central laboratory results were entered in the clinical database. Per protocol, all abnormal neutrophil values considered by the investigator to be clinically significant were to be recorded as AEs.

Consistent with the nonclinical toxicology results, neutropenia was a relatively common treatment-emergent adverse event, with an incidence of 21% in the phase 2 studies. Grade 3 and Grade 4 neutropenia occurred in 13% and 7% of patients, respectively.

The first onset of neutropenia (any grade) occurred within the first 4 cycles of treatment for most patients (28/34), suggesting that neutropenia is not cumulative. Neutropenia ≥Grade 3 tended to develop after a median of 2 doses and last a median of approximately 1 week. Of 11 patients (7%) with Grade 4 neutropenia, 3 had neutropenia that lasted ≥7 days.

No AEs of febrile neutropenia were reported in the phase 2 studies and medical review of patients with Grade 3 or 4 neutropenia and concurrent fever found no cases consistent with the definition of febrile neutropenia (Aapro 2011). In the 32 patients with Grade 3 (21 patients) or 4 (11 patients) neutropenia, concurrent fever (preferred term pyrexia) was reported in 2 patients.

No treatment discontinuations for neutropenia were reported in the phase 2 studies.

Neutropenia appeared to be well managed with the protocol-specified recommendations for hematologic toxicity (i.e., dose delay, growth factor support). The median duration of Grade 3 or Grade 4 neutropenia was limited (1 week) and only 3 patients had Grade 4 neutropenia that lasted ≥7 days. Temporally associated infections occurred in 39% of patients with neutropenia (9% [14 of 160] patients overall). The majority of infections were

Grade 1 or Grade 2. The relative dose intensity in the phase 2 studies was >90%, indicating that the dose withholdings for neutropenia had a minimal impact on overall brentuximab vedotin dosing.

6.4.6.3 Infections

Infections were observed in 58% of patients in the phase 2 studies. The majority of infections were Grade 1 or Grade 2, and occurred with an incidence comparable to that reported in similar populations. No patient discontinued treatment due to infection and infection led to dose delay in only 10% of patients. The most frequent infection was Grade 1 or Grade 2 upper respiratory tract infection (URTI), which was more frequent in HL relative to systemic ALCL patients, but importantly, the incidence of pneumonia was lower than that reported in the literature for comparable populations. Grade 3/4 infections occurred in <10% of patients, and no Grade 5 infections were reported. Viral infections and fungal infections were observed more frequently in the HL population than the systemic ALCL population. Three patients experienced ≥Grade 3 events and the overall incidence of the viral and fungal infections observed in the HL study population was similar to that reported from historical studies of the general population of patients with HL. While serious infections were reported in 10% of patients, no specific pattern of serious infections could be discerned, the majority were not considered by the investigator to be related brentuximab vedotin, and none led to treatment discontinuation.

6.4.6.4 Infusion-Related Reactions

Adverse events that were considered by the investigator to represent possible infusion-related reactions (IRRs) occurred in 11% of patients in the phase 2 studies. A similar rate was observed in the phase 1 studies. Nearly all events were mild to moderate in severity and most occurred in the first 2 treatment cycles. The most common preferred terms reported as IRRs in the phase 2 studies were chills (4%), nausea (3%), dyspnea and pruritus (3% each), and cough (2%).

Assessment of IRRs was evaluated in patients based on ATA. Patients were categorized as being negative, transiently positive (1 to 2 positive samples) or persistently positive (>2 positive samples) based on their postbaseline ATA assessment. Patients categorized as persistently positive did not necessarily need to have a positive ATA sample at the end of treatment. A higher incidence of IRRs was observed in patients with persistently positive ATA (3/10, 30%) relative to transiently positive (5/42, 12%) and never positive (7/96, 7%) patients. Two patients in the phase 2 studies discontinued treatment because of IRRs or adverse events of IRRs; both patients were categorized as persistently positive for antitherapeutic antibodies. Two cases of anaphylaxis occurred, both in phase 1 studies. One event resulted in treatment discontinuation; the other patient continued treatment with IRR prophylaxis and a longer infusion time.

Infusion interruption for IRR treatment led to the successful completion of the dose in most cases, and continued treatment with brentuximab vedotin (with or without IRR prophylaxis according to the clinical judgment of the investigator) was typically possible. The routine

use of steroid premedication was discouraged in clinical studies with brentuximab vedotin, as was IRR prophylaxis in the absence of an IRR.

The data support brentuximab vedotin administration by appropriately trained personnel without routine prophylaxis. If IRR symptoms develop, prophylaxis should be considered for future doses.

6.4.6.5 Stevens-Johnson Syndrome

One patient with HL had a serious adverse event of Stevens-Johnson syndrome. A 37-year-old male developed a pruritic, maculopapular rash approximately 2 weeks after receiving his second dose of brentuximab vedotin. One day after the rash started he was seen in the clinic. The rash was maculopapular, generalized throughout the body including the mouth and throat. He was prescribed cephalexin, valacyclovir, oral prednisone, topical nystastin/triamcinolone cream, alprazolam, and zolpidem tartrate. The next day the patient went to the emergency room where he was admitted to the Burn Unit for possible Stevens-Johnson syndrome. A skin biopsy showed extensive epidermal necrosis involving mostly the suprabasal epidermis. Although laboratory results showed elevated white blood cells and absolute neutrophil count, the patient was afebrile and denied systemic symptoms of infection, including fever, chills, or night sweats. Treatment recommendations included tigecycline and intravenous acyclovir. The patient's condition improved; duration of hospitalization was 5 days. The event was considered resolved in less than 1 month. The investigator reported that it was difficult to determine which medications (if any) had caused the rash; both brentuximab vedotin and naproxen had been started within the month prior to the event. The patient discontinued study treatment because of the event.

6.4.6.6 Tumor Lysis Syndrome

One patient with systemic ALCL had treatment-related Grade 3 tumor lysis syndrome. A 42-year-old male patient developed symptoms of hyperpyrexia, hypoxia, crepitations, and wheezing on the first day of treatment with brentuximab vedotin. The patient was admitted to the hospital where laboratory results were consistent with tumor lysis syndrome. Treatment for tumor lysis syndrome included intravenous fluids, rasburicase, oxygen, and nebulizers. The event was considered resolved 5 days after onset. The patient was administered prophylactic allopurinol for hyperuricemia prior to the start of Cycle 2 and ultimately based on response to therapy received 8 cycles of brentuximab vedotin with no additional events of tumor lysis syndrome.

6.4.7 Effects of Dose and Regimen

In a phase 1 dose-escalation study of brentuximab vedotin administered every 3 weeks (SG035-0001), treatment was generally well tolerated up to 1.8 mg/kg, the dose determined to be the maximum tolerated dose based on protocol-defined dose-limiting toxicities. Events of peripheral neuropathy and neutropenia generally occurred less frequently, were less severe, and resulted in fewer treatment modifications in patients receiving 1.8 mg/kg compared with those receiving 2.7 mg/kg. Additionally, no accumulation was observed at

1.8 mg/kg and slight accumulation was observed at 2.7 mg/kg. A single patient was treated at 3.6 mg/kg and experienced Grade 5 (fatal) febrile neutropenia and septic shock (presumed, all cultures negative for microbial findings) and died 14 days after receiving the dose.

A second phase 1 study (SG035-0002) employed a more frequent dosing schedule. In this study, brentuximab vedotin was administered weekly 3 out of 4 weeks. At this schedule, the maximum tolerated dose was determined to be 1.2 mg/kg based on dose-limiting toxicities as defined by the protocol. Moderate accumulation was observed for brentuximab vedotin and MMAE with the weekly dosing regimen.

6.5 Deaths and Other Serious Adverse Events

There were 6 deaths in the phase 2 studies that occurred within 30 days of the last dose of brentuximab vedotin. These deaths all occurred in systemic ALCL patients and were considered unrelated to treatment and were attributable to ALCL recurrent (3 patients), acute myocardial infarction and acute renal failure (1 patient), respiratory failure (1 patient), and sudden death (1 patient). During the follow-up period (more than 30 days after the last dose of brentuximab vedotin), 19 patients died; a Grade 5 adverse event was recorded for 1 of these patients (Hodgkin's disease recurrent). Of the 25 deaths total in the phase 2 studies, 18 were considered by the investigator to be related to the disease under study.

In the phase 1 dose-escalation studies, 2 patients died within 30 days of the last dose of brentuximab vedotin: 1 patient died from febrile neutropenia and septic shock (Study SG035-0001) and 1 patient died from pneumonia influenzal (Study SG035-0002). During the follow-up period in the phase 1 dose-escalation studies, there were 14 patient deaths (SG035-0001, 7 patients; SG035-0002, 7 patients).

In the phase 1 study assessing cardiac ventricular repolarization (SGN35-007), no patients died within Cycle 1 (data cut for BLA because the primary study endpoint was met, treatment up to 16 cycles was allowed for patients with responses). In the phase 1 clinical pharmacology study (Study SGN5-008A), 1 patient with a history of allogeneic stem cell transplant died after receiving 1 dose of brentuximab vedotin from intracranial hemorrhage, CMV infection, and pancytopenia, all of which were considered by the investigator to be related to treatment.

In the phase 2 studies, 31% of patients had a serious adverse event (SAE), 28% had an SAE of Grade 3 or higher, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAE preferred terms (2%) were abdominal pain, disease progression (recurrent ALCL), pulmonary embolism, and septic shock. A higher proportion of systemic ALCL patients experienced SAEs, including deaths within 30 days of last dose, relative to HL patients, possibly due to the older age and more aggressive nature of the malignancy in this patient population.

Table 21: Serious adverse events occurring in ≥2 HL or systemic ALCL patients

	HL SG035-0003 (N=102) n (%)			ALCL SG035-0004 (N=58) n (%)			Total (N=160) n (%)		
	Any	Grade ≥3	Rel	Any	Grade ≥3	Rel	Any	Grade ≥3	Rel
Any SAE	25 (25)	24 (24)	14 (14)	24 (41)	20 (34)	10 (17)	49 (31)	44 (28)	24 (15)
Abdominal pain	2 (2)	2 (2)	1 (1)	1 (2)	0	0	3 (2)	2 (1)	1 (1)
ALCL recurrent	0	0	0	3 (5)	3 (5)	0	3 (2)	3 (2)	0
Pulmonary embolism	2 (2)	2 (2)	1 (1)	1(2)	1 (2)	1 (2)	3 (2)	3 (2)	2 (1)
Septic shock	1 (1)	1 (1)	0	2 (3)	1 (2)	0	3 (2)	2 (1)	0
Arrhythmia supraventricular	0	0	0	2 (3)	1 (2)	0	2 (1)	1 (1)	0
Demyelinating polyneuropathy	2 (2)	2 (2)	2 (2)	0	0	0	2 (1)	2 (1)	2 (1)
Pain in extremity	0	0	0	2 (3)	2 (3)	0	2 (1)	2 (1)	0
Pneumonitis	2 (2)	2 (2)	1 (1)	0	0	0	2 (1)	2 (1)	1 (1)
Pneumothorax	2 (2)	1 (1)	0	0	0	0	2 (1)	1 (1)	0
Pyelonephritis	2 (2)	2 (2)	0	0	0	0	2 (1)	2 (1)	0
Pyrexia	2 (2)	2 (2)	2 (2)	0	0	0	2 (1)	2 (1)	2 (1)
Urinary tract infection	0	0	0	2 (3)	2 (3)	2 (3)	2 (1)	2 (1)	2 (1)

Preferred terms are sorted by descending frequency of the Total "Any" column.
Rel, related as assessed by the investigator

6.6 Laboratory Evaluations and Other Safety Evaluations

6.6.1 Laboratory Abnormalities

Clinically significant laboratory abnormalities were to be reported as adverse events per the study protocols. Central laboratory data were collected only pre-dose for each treatment cycle in the phase 2 studies. Few patients overall had postbaseline worsening to Grade 3 or higher in clinical laboratory values. The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥ Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%); see Table 22. Only 1 patient in the phase 2 studies had Grade 3 ALT and AST.

Table 22: Incidence of ≥ Grade 3 laboratory abnormalities in phase 2

	HL (N=102)		ALCL (N=58)		Total (N=160)	
Lab Abnormality[a]	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
			Hematology			
Hemoglobin (low)	4	1	0	0	3	1
Leukocytes (low)	6	0	4	0	5	0
Lymphocytes (low)	9	1	12	2	10	1
Neutrophils (low)	12	0	11	0	11	0
Platelets (low)	6	0	5	0	6	0
			Biochemistry			
ALT (high)	1	0	0	0	1	0
Albumin (low)	1	0	0	0	1	0
AST (high)	0	0	2	0	1	0
Calcium (low)	1	0	0	2	1	1
Glucose[b] (high)	6	0	6	0	6	0
Potassium (low)	2	0	0	0	1	0
Sodium (low)	0	0	2	0	1	0
Sodium (high)	1	0	0	0	1	0
Urate (high)	0	1	0	4	0	2

a New or worsening postbaseline
b Non-fasting

Of note, while 54% of patients had new or worsening low neutrophils predose at one or more treatment cycles, 21% of patients had clinically significant treatment-emergent neutropenia reported as an adverse event at any time during treatment. There were no occurrences of Grade 4 low neutrophils predose, however 7% of patients had Grade 4 neutropenia during treatment as reflected by adverse event reports (see Section 6.4.6.2).

In the phase 1 dose-escalation study assessing brentuximab vedotin administered every 3 weeks, laboratory assessments for hematology parameters were performed pretreatment on Day 1, and posttreatment on Day 1, Day 2, Day 4, Day 8, and Day 15. Baseline to post-baseline grade changes (<3 to ≥3) for absolute neutrophil count (ANC) were observed for 7 patients (16%); no patients had Grade ≥3 ANC at baseline. Of patients who had post-baseline shifts to Grade ≥3 ANC, 4 were in the 2.7 mg/kg cohort, 2 were in the 1.8 mg/kg cohort, and 1 was in the 3.6 mg/kg cohort. ANC nadir was generally observed at Day 8 with prompt recovery by Day 21. Given this, an every 3 week dosing schedule is appropriate.

6.6.2 Immunogenicity

Trends toward higher incidences of adverse events in patients with persistently positive ATA (>2 positive samples) relative to patients with transiently positive (1 to 2 positive samples) or negative ATA were not apparent, except for a higher incidence of IRRs in patients with

persistently positive ATA (30%) relative to transiently positive (12%) and never positive (7%) patients. ATA titers were generally low. There were 10 patients (6%) in the two phase 2 studies who developed persistently positive antibodies postbaseline; 2 of these patients (1% of all patients in phase 2 studies) experienced adverse events consistent with infusion reactions that led to discontinuation of treatment. Although there were higher rates of IRRs in patients with persistently positive ATA relative to patients who were transiently positive or never positive for ATA, the reactions were generally Grade 1 or 2 adverse events and no cases of anaphylaxis associated with ATA were observed.

6.6.3 Cardiac Ventricular Repolarization

A multicenter study was conducted to evaluate the effect of brentuximab vedotin on the duration of cardiac ventricular repolarization. Intensive electrocardiogram monitoring was conducted using an ambulatory 12-lead Holter monitor during the first 4 days of Cycle 1. No clinically significant prolongation in the duration of ventricular repolarization as measured by Fridericia's corrected QT interval (QTcF) in patients treated with brentuximab vedotin was observed. The QTcF change (increase) from baseline was <10 ms at all evaluated timepoints. There was no significant relationship between plasma MMAE concentrations and changes in QTcF from baseline to Cycle 1 Days 1, 2, 3, or 4. These results are consistent with the hERG assay results in which the IC_{50} of MMAE on the hERG K^+ channel was estimated to be greater than 100 μM, over 14,000-fold higher than the MMAE C_{max} associated with the 1.8 mg/kg dose of brentuximab vedotin, and also with the results from the safety pharmacology study in cynomolgus monkeys that showed no evidence for QT prolongation.

6.7 Safety in Special Populations

A clinical study to evaluate the effects of renal impairment and hepatic impairment on brentuximab vedotin and MMAE pharmacokinetics is ongoing. Results of population pharmacokinetic analyses and an exploratory analysis are presented in Section 4.2.

6.8 Safety Conclusions

Treatment-emergent adverse events occurring in ≥20% of patients in phase 2 were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily mild to moderate in severity. Treatment-emergent peripheral neuropathy occurred in 53% patients. It was predominantly sensory in nature and had an onset and severity pattern consistent with a cumulative effect. Dose delay and reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. At the time of last follow up, 31% of patients had resolution of all peripheral neuropathy events and 31% had resolution of some events or improvement of at least 1 grade level. Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively; however, it was typically of short duration and well managed by brief dose delays with growth factor support in some cases. IRRs occurred in 11% of patients and were typically managed by dose interruptions.

IRR prophylaxis in subsequent treatment cycles was instituted at the discretion of the investigator.

7 ONGOING CLINICAL STUDIES AND FUTURE DEVELOPMENT PLANS

Ongoing clinical studies are presented in Table 23.

Table 23: Summary of additional ongoing clinical studies

Study No. Phase	Design	Study Objective	Diagnosis	Dosage (b-v) Frequency Duration[a]	Primary Endpoint	Planned	Age	Study Dates[b]
SGN35-005 Phase 3	randomized, double-blind, 2-arm, placebo-controlled	efficacy and safety	HL (high risk post ASCT)	1.8 mg/kg or placebo IV q3 wk 16 cycles	progression-free survival	322	≥18	Apr 2010/ enrolling
SGN35-006 Phase 2	open-label, nonrandomized, 2-arm, retreatment	safety and efficacy	CD30+ hematologic malignancies	1.2 or 1.8 mg/kg IV q3 wk NA	AEs; laboratory abnormalities; ORR	125	≥12	July 2009/ enrolling
SGN35-008B Phase 1	open-label, nonrandomized, hepatic or renal impairment	clinical pharmacology	CD30+ hematologic malignancies	1.2 mg/kg IV q3 wk 2 cycles	PK parameters	12	≥18	Jan 2010/ enrolling
SGN35-009 Phase 1	open-label, single-arm, dose-escalation with ABVD	safety	HL (treatment-naïve)	0.6, 0.9, or 1.2 mg/kg IV q2 wk 6 cycles	AEs; laboratory abnormalities	40	≥18, ≤60	Jan 2010/ enrolling
SGN35-011 Phase 1	open-label, nonrandomized, 3-arm, with CHOP	safety	ALCL (treatment-naïve)	0.8, 1.2, or 1.8 mg/kg IV q3 wk 16 cycles	AEs; laboratory abnormalities	58	≥18	Feb 2011/ enrolling
SGN35-010 Expanded Access Program[c]	open-label, treatment option	safety and expanded access	HL ALCL	1.8 mg/kg IV q3 wk NA	AEs		≥6	Sep 2010/ enrolling

a Maximum treatment duration represented as treatment cycles (1 cycle = q3 wk, 1 dose/21-day cycle; or q2 wk, 2 doses/28-day cycle).
b First visit of first enrolled patient.
c SGN35-010 also provides the option of treatment with brentuximab vedotin for patients in Study SGN35-005 who received placebo and experienced HL progression; accordingly, patient enrollment information pertinent to maintaining the sponsor treatment blind in Study SGN35-005 is not presented.

Brief descriptions of ongoing efficacy and safety studies are provided in the following paragraphs.

SGN35-005: A Phase 3 Study of Brentuximab Vedotin in Patients at High-Risk of Residual HL Following Autologous Stem Cell Transplant (AETHERA). The antitumor activity and safety of brentuximab vedotin will be assessed in patients at high-risk of residual HL post autologous SCT. Brentuximab vedotin 1.8 mg/kg or placebo will be administered intravenously every 3 weeks. The safety and pharmacokinetics of brentuximab vedotin, tolerability, progression-free survival, and overall survival will also be assessed in this study. Patients who achieve stable disease or better are permitted to receive a maximum of 16 cycles.

SGN35-006: A Phase 2 Study of Retreatment with Brentuximab Vedotin. The safety and efficacy of retreatment with brentuximab vedotin will be evaluated. Patients with CD30-positive malignancies who have previously participated in a brentuximab vedotin trial, achieved an objective response, discontinued brentuximab vedotin treatment, and subsequently experienced a relapse of disease, or patients who completed treatment in a qualifying prior brentuximab vedotin trial without unacceptable toxicity, and experienced clinical benefit as assessed by the Investigator are eligible for this study. Brentuximab vedotin will be administered intravenously at 1.2 or 1.8 mg/kg every 3 weeks.

SGN35-008B: A Phase 1 Study of Pharmacokinetics in CD30-Positive Hematologic Malignancies for Patients with Hepatic or Renal Impairment. The pharmacokinetics of brentuximab vedotin will be evaluated in patients with hepatic impairment (Arm A-hep) or renal impairment (Arm B-ren). Brentuximab vedotin 1.2 mg/kg will be administered intravenously every 3 weeks for 2 cycles. For each treatment cycle, pharmacokinetic samples will be drawn at multiple timepoints on Day 1, daily through Day 5, then twice weekly through 3 weeks.

SGN35-009: A Phase 1 Study of Brentuximab Vedotin Combined with Multi-Agent Chemotherapy in HL. The safety and tolerability of brentuximab vedotin in combination with ABVD or AVD as front-line therapy will be assessed in patients with HL. Brentuximab vedotin 0.6, 0.9, or 1.2 mg/kg will be administered intravenously in combination with standard doses of ABVD or AVD on Days 1 and 15 of each 28-day cycle. The safety and pharmacokinetics of brentuximab vedotin will be assessed in this study. Patients will receive a maximum of 6 cycles of treatment.

SGN35-011: A Phase 1 Study of Brentuximab Vedotin in Sequence and Combined with Multi-Agent Chemotherapy in Front-Line ALCL. The safety and tolerability of brentuximab vedotin in sequence and in combination with multi-agent chemotherapy as front-line therapy will be assessed in patients with systemic ALCL. This phase 1, open-label, multicenter study is designed to evaluate safety of brentuximab vedotin when administered before, during, and after multi-agent chemotherapy in treatment-naïve patients with systemic ALCL. The safety and pharmacokinetics of brentuximab vedotin will be assessed in this study. Patients will receive up to 16 cycles of treatment.

SGN35-010: An Expanded Access Treatment-Option Study of Brentuximab Vedotin in Relapsed or Refractory HL and ALCL. Patients who have previously participated in the placebo arm of Study SGN35-005 who experienced progression of HL are eligible for this study. Additionally, in the US only, patients with relapsed or refractory HL, including patients who did not participate in study SGN35-005, and patients with relapsed or refractory ALCL are also eligible for this study. Brentuximab vedotin will be administered IV at 1.8 mg/kg every 3 weeks. The safety and tolerability of brentuximab vedotin will be evaluated.

Additional studies in CD30-positive malignancies are planned including cutaneous T-cell lymphoma (CTCL), other non-Hodgkin lymphoma (excluding ALCL), and solid tumors.

8 BENEFIT-RISK ASSESSMENT

8.1 Rationale for the Proposed Indication and Usage

HL that recurs after high-dose, multiple-agent chemotherapy and/or autologous SCT is notoriously difficult to eradicate. There is no clear standard of care and median survival has been reported to be as short as 12 months in a patient population that is relatively young (median age in pivotal study, 31 years). These factors amount to a pronounced unmet need.

Brentuximab vedotin 1.8 mg/kg administered intravenously every 3 weeks is the recommended dose for treatment of patients with relapsed or refractory Hodgkin lymphoma. Per protocol, Hodgkin lymphoma patients were treated with brentuximab vedotin until disease progression or unacceptable toxicity, to a maximum of 16 cycles or approximately 1 year of therapy. The median and mean number of cycles delivered was 9 and 10, respectively, and 18% of patients successfully completed all 16 doses of planned treatment. Among patients in whom treatment was discontinued, the most common reason was lymphoma progression.

The primary endpoint of the pivotal study in Hodgkin lymphoma was ORR based on all enrolled patients. Key efficacy results demonstrating robust efficacy in the pivotal study are as follows:

- ORR of 75%
- Median response duration of 6.7 months
- CR rate of 34%, manifested by no evidence of lymphoma by clinical, laboratory, or radiographic measures
- Median duration of response in patients with CR of 20.5 months
- Tumor volume reduction in 94% of patients

- Progression-free survival with brentuximab vedotin was nearly twice that of the most recently delivered treatment as documented by investigator assessment (7.8 versus 4.1 months; HR, 0.41; P <0.001).
- Among patients who had B symptoms at baseline, 77% had resolution of these symptoms during brentuximab vedotin treatment.
- Assessment of objective response was concordant between IRF and investigator in 89 of 102 patients (87%). The Kappa coefficient was 0.6767, which suggests good concordance between the assessors.
- Clinical benefit was observed in the transplant ineligible patients in phase 1 studies (ORR 30%, CR rate 10%).
- Results of a phase 2 study in systemic ALCL patients with the same design and dosing regimen corroborated results observed in the pivotal study in HL; therefore, high ORR, high CR rate, and clinically meaningful response duration was observed in two studies of CD30-positive lymphomas.

The primary efficacy endpoint was analyzed for subgroups of age, gender, race, baseline tumor volume, relapsed versus refractory disease status, primary refractory disease, and postbaseline antitherapeutic antibody development. There were no clinically meaningful differences in these populations.

Safety findings demonstrated an acceptable safety profile. Adverse events in the phase 2 studies are summarized as follows:

- Treatment-emergent AEs occurring in ≥20% of patients were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%).
- Notable dose modifications were dose reductions for peripheral sensory neuropathy (8% patients) and dose delays for neutropenia (14%) and peripheral sensory neuropathy (11%).
- Treatment-emergent AEs of peripheral neuropathy occurring in >1% of patients were sensory neuropathy (44%), peripheral motor neuropathy (9%) and paresthesia (4%).
- Median time to onset of any treatment-emergent adverse event of peripheral neuropathy was 12.4 weeks, to the first Grade 2 event was 24.1 weeks, and to the first Grade 3 event was 32.8 weeks. In a by-cycle analysis, the first onset of any grade peripheral neuropathy appeared incrementally higher as the number of cycles increased.

- Median time from onset to resolution or improvement of peripheral neuropathy events was 6.6 weeks. At the time of the BLA submission, when the median duration from the end of treatment visit to last follow up was approximately 10 weeks, 31% of patients had resolution of all peripheral neuropathy events and 31% had resolution of some events or improvement of at least 1 grade level. Continued improvement was observed for patients with Grade 3 (the highest grade observed in phase 2 studies) between the end of treatment visit (11 patients with Grade 3) and the last follow up (6 patients with Grade 3).

- Neutropenia was a relatively common treatment-emergent adverse event, with an incidence of 21%. Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively.

- First onset of neutropenia of any grade occurred within the first 4 cycles of treatment for >80% patients who developed neutropenia, suggesting that neutropenia is not cumulative. Neutropenia ≥ Grade 3 tended to develop after a median of 2 doses and last a median of approximately 1 week. Of the 11 patients with Grade 4 neutropenia, 3 had neutropenia that lasted ≥7 days.

- Infusion-related reactions occurred in 11% of patients and were typically managed by dose interruptions for IRR treatment. In most cases, the dose was subsequently completed. IRR prophylaxis in later treatment cycles was instituted at the discretion of the investigator. In phase 1 studies, 2 patients had serious events of anaphylaxis with the Cycle 2 dose. A higher incidence of IRRs occurred in patients who were persistently positive (>2 positive samples) for ATA.

Adverse events were evaluated for age, race, sex, and geographic subgroups. There were no notable differences in these subgroups.

In the phase 1 dose-escalation study assessing brentuximab vedotin administered every 3 weeks, laboratory assessments for hematology parameters were performed at multiple timepoints before and after each dose; therefore providing a robust hematology profile. Baseline to post-baseline grade changes (<3 to ≥3) for absolute neutrophil count were observed for 7 patients (16%); 4 were in the 2.7 mg/kg cohort, 2 were in 1.8 mg/kg, and 1 was in 3.6 mg/kg. ANC nadir was generally observed at Day 8 with prompt recovery by Day 21. Given this, an every 3 week dosing schedule is appropriate.

In a multicenter study, intense electrocardiogram monitoring was conducted to assess the effect of brentuximab vedotin on the duration of cardiac ventricular repolarization. No clinically significant prolongation in the duration of ventricular repolarization as measured by QTcF was observed in patients treated with brentuximab vedotin. The mean QTcF change (increase) from baseline was <10 ms at all evaluated timepoints.

8.2 Benefit-Risk Analysis

The BLA supports the use of brentuximab vedotin for the treatment of relapsed or refractory Hodgkin lymphoma. The high rate of objective responses (ORR, 75%) and complete remissions (CR rate, 34%) as assessed by independent review facility and the associated durability of these remissions (objective response, 6.7 months; CR, 20.5 months), in addition to disease symptom resolution and a manageable safety profile, represents clinical benefit in this population. The PFS achieved with brentuximab vedotin was significantly superior to that of the most recent prior therapy. In a disease paradigm with no clear standard of care, and where diminishing responses are largely expected with subsequent lines of therapy, this finding supports the clinical benefit of brentuximab vedotin in the population.

At the recommended dose and schedule, the most common adverse events were peripheral sensory neuropathy, fatigue, nausea, diarrhea, pyrexia, upper respiratory tract infection, neutropenia, and vomiting. These events were primarily mild to moderate in severity. The most notable adverse event associated with brentuximab vedotin was peripheral neuropathy, which tended to increase in severity with longer duration of therapy, consistent with what is observed with antimicrotubule agents. This toxicity was managed by dose delay and reduction to 1.2 mg/kg.

Treatments were successfully delivered in an outpatient setting and toxicity was both predictable and typically manageable by employing dose modifications. Clinical benefit is established by the high overall response and complete remission rates as observed by independent review facility and the associated durability of these remissions, in addition to disease symptom resolution in the context of an acceptable safety profile. Taken in aggregate, the relatively high proportion of durable complete remissions observed in the context of manageable adverse events justifies approval for the indication of relapsed or refractory Hodgkin lymphoma.

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10 APPENDIX: REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA