1 SYNOPSIS

Sponsor Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA	**Name of Finished Product** Brentuximab vedotin (SGN-35; ADCETRIS) **Name of Active Ingredient** Brentuximab vedotin

Study Title

Treatment with SGN-35 in patients with CD30-positive hematologic malignancies who have previously participated in an SGN-35 study

Phase

2

Study Center(s)

Multicenter

Publication(s) Based on the Study

Bartlett N, Grove LE, Kennedy DA, Sievers EL, Forero-Torres A (2010). Objective responses with brentuximab vedotin (SGN-35) retreatment in CD30-positive hematologic malignancies. ASCO Meeting Abstracts; Abstract 8062.

Bartlett N, Grove LE, Kennedy DA, Sievers EL, Forero-Torres A (2010). Objective responses with SGN-35 retreatment in CD30-positive hematologic malignancies: a case series. ISHL Meeting Abstracts; Abstract 113.

Forero-Torres A, Brice P, Chen R, Fanale M, Gopal AK, Matous J, Rosenblatt JD, Grove LE, Bartlett NL (2012). Retreatment with brentuximab vedotin in CD30-positive hematologic malignancies: A phase 2 study. EHA Meeting Abstract; Abstract 1166.

Bartlett N, Brice P, Chen RW, Fanale MA, Gopal AK, Matous J, Rosenblatt JD, Grove LE, Forero-Torres A (2012). Retreatment with brentuximab vedotin in CD30-positive hematologic malignancies: A phase II study. ASCO Meeting Abstract; Abstract 8027.

Study Period

Approximately 3 years and 8 months

Date first patient treated: 23-Jul-2009

Date of last patient last assessment: 11-Mar-2013

Study Objectives

Primary:

- To assess the safety of treatment with brentuximab vedotin
- To estimate the antitumor response of retreatment with brentuximab vedotin

Secondary:

- To assess duration of tumor control, including duration of response and progression-free survival (PFS) of retreatment with brentuximab vedotin
- To assess overall survival (OS)
- To assess the incidence of antitherapeutic antibodies (ATA)

Methodology

This was a multicenter, open-label study to determine the safety and efficacy of treatment with brentuximab vedotin in the following two study arms: retreatment (CD30-positive hematologic malignancies) and extension treatment (CD30-positive hematologic malignancies and non-hematologic malignancies).

Patients were administered either 1.2 or 1.8 mg/kg brentuximab vedotin intravenously (IV) over approximately 30 minutes once per 21-day cycle. Safety of retreatment with brentuximab vedotin was monitored throughout the trial via laboratory values and adverse event (AE) collection. Measures of antitumor activity were assessed by the investigator at intervals according to institutional standards. Plasma and serum samples for brentuximab vedotin concentration and immunogenicity evaluation were obtained prior to administration of brentuximab vedotin in Cycles 1 and 2, and at the end of treatment (EOT) visit.

Patients had an EOT assessment within 30 days of receiving the final dose of brentuximab vedotin retreatment. Long-term follow-up contact, including survival and disease status, was conducted in a minimum of 3-month intervals from the EOT assessment until either patient death or study closure. A Safety Monitoring Committee (SMC) monitored the interim safety and efficacy data periodically.

Number of Patients

Planned: It was anticipated that approximately 125 patients would be enrolled across both treatment arms of the study. This number was based on an estimate of the number of patients who would be eligible to participate and an approximation of attrition.

Analyzed: The number of patients analyzed includes a total of 32 unique retreatment patients; these 32 unique patients had a total of 35 retreatment experiences (3 patients were re-enrolled and retreated using a different patient identifier). The number of patients analyzed also includes a total of the 78 patients treated on the extension arm.

Diagnosis and Primary Criteria for Inclusion

Retreatment patients were included in the study if they had previously experienced complete remission (CR) or partial remission (PR) with known brentuximab vedotin treatment in a previous brentuximab vedotin study and had disease progression or relapse after treatment discontinuation. CD30 expression was evaluated prior to retreatment if obtaining a sample did not present patient risk, and a baseline computed tomography (CT) scan within 4 weeks prior to study start was planned. Patients with adequate hematologic, kidney, and liver function and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 were included. Patients with congestive heart failure, known cerebral/meningeal disease, including a history of progressive multifocal leukoencephalopathy (PML), or any active viral, bacterial, or fungal infection requiring treatment with antimicrobial therapy within 2 weeks prior to the first study dose were excluded. Patients who had received an allogeneic hematopoietic stem cell transplant may have been retreated, provided the transplant was >100 days prior to the first dose of brentuximab vedotin and patients did not have acute or chronic graft-versus-host-disease (GvHD). These patients were tested for detectable levels of cytomegalovirus (CMV) by polymerase chain reaction (PCR) at baseline; prior PCR positivity that was successfully treated was acceptable provided the baseline PCR result was negative prior to the first dose of study drug.

Extension patients must have completed treatment in a qualifying prior SGN-35 study without unacceptable toxicity, and experienced clinical benefit as assessed by the investigator. Patients who withdrew consent in any prior SGN-35 study or were unable to receive their first infusion of SGN-35 on Study SGN35-006 between 21–28 days of the last dose on the prior study were excluded. Patients were also excluded if they were receiving therapy with other systemic antineoplastic (with the exception of corticosteroids) or investigational agents. Extension patients who had received an allogeneic hematopoietic stem cell transplant must have been tested for detectable levels of CMV by PCR at

baseline; if a patient had detectable levels of CMV, permission to enter the study had to be granted by the Medical Monitor.

Test Product, Dose, Mode of Administration, Batch Number

Brentuximab vedotin, 1.2 or 1.8 mg/kg, every 21 days, administered IV over approximately 30 minutes. Batch numbers for the retreatment arm patients are SDD001, SDD002, FCR002, FKL001, FKL002, FKL003, FKL004, FKL005, SER004, SER005, SER006, FJX007, FTL001, and FAB001. Batch numbers for the extension arm patients were SDD001, SDD002, FKL001, FKL002, FKL003, FKL004, FKL005, and FCR002.

Duration of Treatment

No maximum duration of therapy was specified in the protocol; patients may have continued receiving treatment until disease progression, unacceptable toxicity, or study closure occurred.

Reference Product, Dose, Mode of Administration, Batch Number

Not applicable.

Duration of Treatment

Not applicable.

Criteria for Evaluation

Efficacy:

Treatment response was assessed by the investigator and based on objective response criteria according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Scanning frequency was based upon institutional standard of care.

Pharmacokinetics/Pharmacodynamics:

Samples for serum and plasma brentuximab vedotin concentration were analyzed using a validated enzyme-linked immunosorbent assay (ELISA), and a validated electrochemiluminescence (ECL) assay was used to detect anti-brentuximab vedotin antibodies.

Safety:

Assessments of safety included the incidence of AEs and changes in laboratory values. Adverse events were graded using the National Cancer Institute (NCI) Common Toxicity Criteria, Version 3.0. Additional monitoring for signs of potential opportunistic infections, including CMV, was conducted in patients who were post-allogeneic transplant and/or human immunodeficiency virus (HIV)-positive.

Statistical Methods

Summaries of patient disposition, demographics, disease characteristics, assessments of physical condition and functioning, and dosing of study drug are provided. Descriptive statistics were employed in the analysis of all safety and laboratory observations. The overall response rate and its two-sided 95% exact confidence interval (CI) were calculated. The CR rate and its two-sided 95% exact CI were calculated. Duration of response, PFS, and OS were estimated using Kaplan-Meier methodology. The median duration of response, PFS, OS, and their two-sided 95% CI were calculated.

An interim analysis was performed on the first 25 unique patients enrolled in the retreatment arm who had data collected as of 10-Apr-2012. Database lock for this interim analysis was performed on 30-Aug-2012 and an interim CSR is dated 30-Nov-2012.

RESULTS SUMMARY

Patient Disposition

There were 78 patients in the extension treatment arm and 32 patients in the retreatment arm who received brentuximab vedotin. Two patients were treated in the extension arm first and then were re-enrolled in the retreatment arm. There were also 3 patients who were retreated twice on the study, for a total of 35 patients with retreatment experiences.

Efficacy Results

Efficacy was summarized for all 35 retreatment experiences. In the retreatment arm, 1 patient did not have any post-baseline assessments and was not included in any summaries (N=34). The ORR was 68% [95% CI (49.5, 82.6)]. The estimated median duration of OR was 9.2 months and the range of response duration was 0+ to 28+ months. The estimated median PFS was 9.9 months and the range was 1.2 to 29.2+ months. The estimated median OS had not yet been reached and the range was 2.2 to 40.7+ months. A total of 8 patients had died before the end of the study.

In the extension treatment arm (N=78), the estimated median OS had not yet been reached and the range was 2+ to 36+ months. A total of 27 patients (35%) had died before the end of the study.

Safety Results

Safety was summarized for the 32 patients who were retreated and 78 patients who had extension treatment.

In the retreatment arm, treatment-emergent AEs (TEAEs) occurred in 97% of patients. Events occurring in ≥20% of patients were peripheral sensory neuropathy (56%); nausea (41%); diarrhea and fatigue (38% each); headache and peripheral motor neuropathy (28% each); arthralgia, dyspnea, and pyrexia (25% each); and anemia (22%). Related AEs occurred in 84% of patients. Half of the patients (50%) experienced at least one TEAE that was Grade 3 or higher. Nine patients (28%) experienced at least one AE that met the criteria for serious. Post-baseline abnormal laboratory values ≥Grade 3 occurred in 12 patients (38%). Nine patients (27%) tested positive for ATA against brentuximab vedotin at baseline and an additional 3 patients who tested negative at baseline developed ATA against brentuximab vedotin postbaseline. Infusion reactions occurred in 6 patients. Of these 6 patients with infusion reactions, 5 patients tested positive for ATA at any visit.

In the extension treatment arm, TEAEs occurred in 96% of patients. Events occurring in ≥20% of patients were peripheral sensory neuropathy (48%), upper respiratory tract infection (33%), fatigue (32%), pyrexia (27%), nausea (25%), cough (21%), and diarrhea (20%). Related AEs occurred in 90% of patients. Nearly half of the patients (49%) experienced at least one TEAE that was Grade 3 or higher. Sixteen patients (21%) experienced at least one AE that met the criteria for serious. Post-baseline abnormal laboratory values ≥Grade 3 occurred in 29 patients (37%). Fifteen patients (19%) tested positive for ATA at any postbaseline visit. Infusion reactions occurred in 10 patients. Of these 10 patients with infusion reactions, 5 patients tested positive for ATA at any visit.

In the retreatment arm, 1 patient died within 30 days of the last dose of brentuximab vedotin due to disease-related respiratory failure. Eight patients died during the follow-up period: 4 patient deaths were disease related, 3 were not disease related, and 1 was due to an unknown etiology. Nine patients (28%) discontinued retreatment because of an AE.

In the extension treatment arm, there were no deaths within 30 days of the last dose of brentuximab vedotin. Twenty-seven patients died more than 30 days after the last dose of brentuximab vedotin: 19 patient deaths were disease related, 4 were not disease related, and 4 were due to an unknown etiology. Thirteen patients (17%) discontinued extension treatment because of an AE.