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ORIGINAL REPORT

Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma: Results of a Phase II Study

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ABSTRACT

Purpose
Systemic anaplastic large-cell lymphoma (ALCL) is an aggressive subtype of T-cell lymphoma characterized by the uniform expression of CD30. The antibody-drug conjugate brentuximab vedotin delivers the potent antimicrotubule agent monomethylauristatin E to CD30-positive malignant cells. A phase II multicenter trial was conducted to evaluate the efficacy and safety of brentuximab vedotin in patients with relapsed or refractory systemic ALCL.

Patients and Methods
Patients with systemic ALCL and recurrent disease after at least one prior therapy received brentuximab vedotin 1.8 mg/kg intravenously every 3 weeks over 30 minutes as an outpatient infusion. The primary end point of the study was overall objective response rate as assessed by independent central review.

Results
Of 58 patients treated in the study, 50 patients (86%) achieved an objective response, 33 patients (57%) achieved a complete remission (CR), and 17 patients (29%) achieved a partial remission. The median durations of overall response and CR were 12.6 and 13.2 months, respectively. Grade 3 or 4 adverse events in ≥ 10% of patients were neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (12%).

Conclusion
Brentuximab vedotin induced objective responses in the majority of patients and CRs in more than half of patients with recurrent systemic ALCL. Targeted therapy with this CD30-directed antibody-drug conjugate may be an effective treatment for relapsed or refractory systemic ALCL and warrants further studies in front-line therapy.

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INTRODUCTION

Systemic anaplastic large-cell lymphoma (ALCL) is an aggressive subtype of T-cell lymphoma representing approximately 2% to 3% of all lymphoid neoplasms.[1,2] On the basis of the expression of the anaplastic lymphoma kinase (ALK) protein, ALCL can be further classified as ALK-positive or ALK-negative ALCL.[3] With the exception of low-intermediate–risk ALK-positive patients, patients with ALCL have a poor prognosis when treated with conventional anthracycline-based front-line chemotherapy. Approximately 40% to 65% of patients with ALCL develop recurrent disease after front-line therapy.[3] At relapse, the disease is historically resistant to conventional multiagent chemotherapy regimens, and there is no established standard of care. High-dose therapy and autologous hematopoietic stem-cell transplantation (SCT) may result in long-term remission in 30% to 40% of patients,[4-6] but the benefit is limited to patients with chemotherapy-sensitive disease[7,8] and patients without advanced age or comorbidities. ALCL is characterized by the uniform expression of CD30, making this surface antigen an attractive target for immunotherapeutic approaches.[9] Earlier phase I and II clinical trials with first-generation anti-CD30 antibodies showed an excellent safety profile but only modest clinical activity. Objective responses were observed in 17% of patients with ALCL who were treated with the chimeric anti-CD30 antibody SGN-30.[10]

Antibody-drug conjugates (ADCs) enable the delivery of a cytotoxic drug to the target malignant cell. Brentuximab vedotin (SGN-35) is an ADC comprising an anti-CD30 antibody conjugated by a protease-cleavable linker to the potent antimicrotubule agent, monomethylauristatin E (MMAE). Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment, releasing MMAE via proteolytic cleavage.[11] Binding of MMAE to tubulin disrupts the microtubule network, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.[12] When brentuximab vedotin was tested in preclinical models of ALCL, improved activity relative to the unconjugated antibody SGN-30 was observed.[12] The initial phase I clinical trial of brentuximab vedotin was conducted in patients with CD30-positive lymphomas and showed a response rate of 38%, including 11 complete remissions (CRs); the two patients with ALCL enrolled onto the study both achieved CRs.[13] A multicenter clinical trial was conducted to further investigate the activity and safety of brentuximab vedotin in patients with recurrent ALCL.

PATIENTS AND METHODS

Study Design

This was a multinational, open-label, phase II study that was conducted at 22 centers in the United States, Canada, and Europe (ClinicalTrials.gov identifier NCT00866047). Patient recruitment occurred from June 2009 through May 2010. Data analyzed included at least 6 months of follow-up after the first restage for all patients (last data collected January 14, 2011). The study was approved by the institutional review board at each study site, and written informed consent was obtained from all patients before any study-specific procedures, per the Declaration of Helsinki. The study was sponsored by Seattle Genetics, Bothell, WA.

Patients

Patients had a diagnosis of relapsed or refractory systemic ALCL after treatment failure of at least one prior therapy with curative intent, the most common being a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone. CD30-positive disease and histology were documented by central pathology review. Patients had measurable disease (> 1.5 cm) by computed tomography (CT) and fluorodeoxyglucose-avid disease by positron emission tomography (PET). Age ≥ 12 years and an Eastern Cooperative Oncology Group performance status[14] of 0 or 1 were required. Patients could not be pregnant and could not previously have received an allogeneic SCT. Additional inclusion criteria were absolute neutrophil count more than 1,000/μL, platelet count more than 50,000/μL, serum creatinine $\leq 1.5\times$ the upper limit of normal, and ALT and AST $\leq 2.5\times$ the upper limit of normal.

Study Treatment and Assessments

Brentuximab vedotin 1.8 mg/kg was administered intravenously once every 3 weeks over 30 minutes on an outpatient basis for up to 16 total doses. At baseline, assessment of disease-related signs and symptoms, a physical examination, bone marrow biopsy, and radiographic studies, including CT of the neck, chest, abdomen, and pelvis and PET scan, were performed. Both investigators and an independent review facility (CoreLab Partners, Princeton, NJ; formerly known as RadPharm) performed response assessments according to the Revised Response Criteria for Malignant Lymphoma[15] using clinical and imaging assessments. Response was assessed by CT scans at cycles 2, 4, 7, 10, 13, and 16 and PET scans at cycles 4 and 7. Survival and disease status information were collected every 12 weeks after discontinuing treatment until either patient death or study closure. A CT scan was also obtained every 12 weeks until documentation of progression for patients who discontinued study treatment with stable disease or better.

Safety was monitored with the recording of adverse events and physical examination findings, vital signs, and routine hematology and serum chemistries. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 13.0, and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). The ongoing safety of the patients and overall study conduct were evaluated by an independent data monitoring committee at specified time points in the study.

Statistical Analysis

The primary end point of the study was the objective response rate (ORR) per independent review. Duration of response and CR rate per independent review were analyzed as secondary end points, as were progression-free survival (PFS) per independent review and overall survival (OS).[15] According to the study definition of PFS and response duration, patients were censored in the analyses if another treatment was administered before documentation of progression, with the exception of subsequent SCT as the first therapy after discontinuing brentuximab vedotin. Incidence and severity of adverse events were also defined as secondary end points.

The ORR and its two-sided 95% exact CI were calculated. Median duration of response, PFS, and OS, along with two-sided 95% CIs, were estimated using the Kaplan-Meier method.

Per the protocol, assessment of efficacy by the study investigators was collected as an exploratory analysis, and a κ coefficient was calculated to determine the concordance in objective response and best response assessments between the investigator and independent review.

Kaplan-Meier analysis was conducted for PFS, including post-hoc analyses of patients by best clinical response and in patients with CR by subsequent transplantation. A prespecified comparison of intrapatient PFS (PFS achieved with the most recent prior systemic therapy v PFS per investigator with brentuximab vedotin) was also conducted. For this comparison of prior PFS with the PFS with brentuximab vedotin, a correlated survival analysis was performed using the methodology of Lin and Wei.[16]

RESULTS

Patients

Table 1 lists the baseline characteristics of all 58 patients who were enrolled onto the study. In general, the demographics reflect the characteristics of patients with systemic ALCL. The median age was 52 years (range, 14 to 76 years), and 57% were male. Seventy-two percent of patients had ALK-negative disease. Relative to their most recent therapy, 50% of patients experienced relapse, and 50% were considered refractory; 62% of patients were primary refractory to front-line treatment (definitions in Table 1), and 22% had not achieved an objective response to any prior therapy. The median number of prior chemotherapy regimens excluding autologous SCT was two (range, one to six regimens); 26% of patients experienced treatment failure with an autologous SCT before study enrollment. The most recent therapy before study enrollment was autologous SCT or multiagent chemotherapy for 91% of patients. At the time of the data analysis, 49 patients had discontinued treatment with brentuximab vedotin.

Efficacy

The ORR per independent review was 86% (95% CI, 74.6% to 93.9%); 57% of patients achieved CR (95% CI, 43.2% to 69.8%), and 29% achieved partial remission (Table 2). Tumor reductions were observed in 97% of patients (Fig 1). The median time to objective response was 5.9 weeks (range, 4.3 to 14 weeks), and the median time to CR was 11.9 weeks (range, 5.1 to 50.3 weeks); these medians approximate the timing of the first postbaseline CT assessment and the first postbaseline PET, respectively.

The median duration of objective response was 12.6 months (95% CI, 5.7 months to not estimable [NE]) per independent review.

Table 1. Demographic and Baseline Disease Characteristics

Characteristic	No. of Patients (N = 58)	%
Age, years		
Median	52	
Range	14-76	
Sex		
Male	33	57
Female	25	43
Race		
Asian	1	2
Black or African American	7	12
White	48	83
Other	2	3
ECOG performance status*		
0	19	33
1	38	66
2†	1	2
Pathologic diagnosis by central assessment		
Systemic anaplastic large-cell lymphoma	56	97
Other‡	2	3
Anaplastic lymphoma kinase status		
Negative	42	72
Positive	16	28
Malignant cutaneous lesions at baseline	15	26
Baseline "B" symptoms	17	29
Bone marrow involvement	8	14
Primary refractory to front-line treatment§	36	62
Disease status relative to most recent treatment		
Refractory‖	29	50
Relapsed¶	29	50
Patients who had not achieved a response to any prior treatment	13	22
No. of prior chemotherapy regimens		
Median	2	
Range	1-6	
Prior radiation	26	45
Prior autologous SCT	15	26

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SCT, stem-cell transplantation.
*ECOG performance status defined as follows: 0, able to perform daily activities with no restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; and 2, ambulatory and capable of self-care but unable to carry out work activities.
†ECOG status of 2 was prohibited per protocol; patient was enrolled in violation.
‡Determined by local pathology to have systemic anaplastic large-cell lymphoma but not confirmed on central review. Patients were scored as nonresponders per protocol.
§No complete remission or relapse within 3 months of front-line therapy.
‖Best response of partial remission, stable disease, or progressive disease if a patient had only one prior therapy, or a best response of stable disease or progressive disease to the most recent therapy if a patient had more than one prior therapy.
¶Best response of complete remission if a patient had only one prior therapy, or a best response of complete or partial remission to most recent therapy if a patient had more than one prior therapy.

Table 2. Key Response Results per Independent Review

Measure	Response (N = 58)	95% CI
Objective response rate, %	86	74.6 to 93.9
CR rate*	57	43.2 to 69.8
Partial remission rate	29	
Stable disease, %	3	
Progressive disease, %	5	
Histologically ineligible, %†	3	
Not evaluable, %	2	
Median duration of objective response, months	12.6	5.7 to NE
Median duration of response in patients with CR, months	13.2	10.8 to NE
Median progression-free survival, months	13.3	6.9 to NE
Median overall survival, months	Not reached	14.6 to NE

Abbreviations: CR, complete remission; NE, not estimable.
*All patients with CR had evidence of a postbaseline fluorodeoxyglucose-negative positron emission tomography scan, with the exception of one patient who achieved complete resolution of disease by computed tomography scan at a time point when positron emission tomography scans were not required per protocol.
†Patients who did not confirm a diagnosis of anaplastic large-cell lymphoma by central pathology assessment; patients were scored as nonresponders in the analysis (n = 2).

The median duration of response for patients who achieved a CR was 13.2 months (95% CI, 10.8 months to NE). When analyzed by subgroups of patients who had subsequent SCT, the duration of response did not seem to differ. For the 22 patients who achieved a CR and did not have a subsequent SCT, the median duration of response was 12.6 months, compared with a median of 13.2 months for the six patients who had a subsequent allogeneic SCT in CR and a median that was not reached for the five patients who had a subsequent autologous SCT in CR. The median time from last dose of brentuximab vedotin to the initiation of SCT was 25 days.

The estimated median PFS time per independent review was 13.3 months (95% CI, 6.9 months to NE; Fig 2); in the subset of patients who achieved a CR, the median PFS was 14.6 months (Appendix Fig A1, online only). Per investigator assessment, the median PFS with brentuximab vedotin was 14.3 months (95% CI, 9.1 months to NE), compared with a median PFS of 5.9 months (95% CI, 3.9 to 8.3 months) after the most recent prior therapy, including autologous SCT. Using a correlated survival analysis for this prespecified comparison, the hazard ratio was 0.48, indicating that PFS was significantly prolonged with brentuximab vedotin compared with the most recent prior therapy (P .001).

At the time of the analysis, 18 patients had died, and the median OS had not yet been reached (Fig 2). The estimated 12-month survival rate was 70%.

Among patients with ALK-negative disease (n = 42), the ORR was 88%, and the CR rate was 52%. These response rates were comparable to those among patients with ALK-positive disease

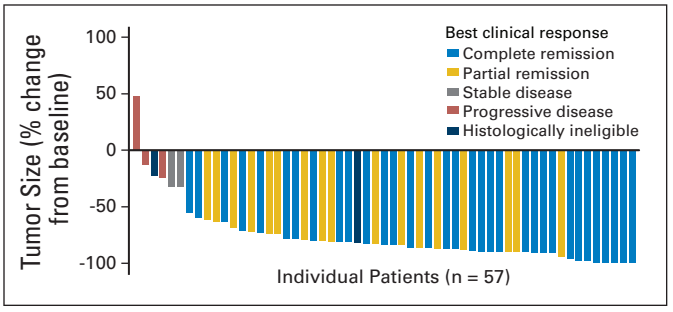

Fig 1. Maximum tumor reduction in individual patients (n = 57) by independent review. Reduction in tumor volume was observed in 97% of patients. One patient did not have a postbaseline assessment.

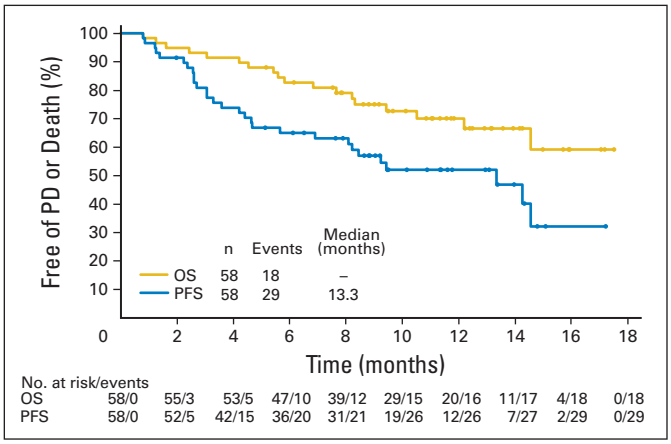

Fig 2. Median overall survival (OS) was not reached at the time of the analysis; 18 patients had died. Median progression-free survival (PFS) among all patients was 13.3 months by independent review. At the time of the analysis, 29 patients had either experienced progressive disease (PD) or died.

Table 3. Most Common Adverse Events (> 10%)

Adverse Event*	All Grades (N = 58) No. of Patients	%	Grade 3 (N = 58) No. of Patients	%	Grade 4 (N = 58) No. of Patients	%
Peripheral sensory neuropathy	24	41	7	12	0	0
Nausea	23	40	1	2	0	0
Fatigue	22	38	2	3	1	2
Pyrexia	20	34	1	2	0	0
Diarrhea	17	29	2	3	0	0
Rash	14	24	0	0	0	0
Constipation	13	22	1	2	0	0
Neutropenia	12	21	7	12	5	9
Headache	11	19	1	2	0	0
Pruritus	11	19	0	0	0	0
Cough	10	17	0	0	0	0
Dyspnea	10	17	1	2	0	0
Upper respiratory tract infection	10	17	0	0	0	0
Vomiting	10	17	2	3	0	0
Decreased appetite	9	16	1	2	0	0
Dizziness	9	16	0	0	0	0
Insomnia	9	16	0	0	0	0
Myalgia	9	16	1	2	0	0
Alopecia	8	14	0	0	0	0
Chills	8	14	0	0	0	0
Muscle spasms	8	14	1	2	0	0
Thrombocytopenia	8	14	5	9	3	5
Weight decreased	8	14	2	3	0	0
Edema peripheral	7	12	0	0	0	0
Pain in extremity	7	12	1	2	1	2

*Terms according to Medical Dictionary for Regulatory Activities, Version 13.0.

(n = 16), who had an ORR of 81% and a CR rate of 69%. Median PFS and duration of response were not different between patients with ALK-negative disease and patients with ALK-positive disease. In addition to ALK status, efficacy was analyzed among other subgroups of patients, including subgroups based on the following variables: disease status relative to most recent therapy (relapsed or refractory), primary refractory status, number of prior therapies (one $v >$ one therapy), prior autologous SCT, bone marrow involvement, sex, age ($<$ 18, 18 to 64, and $\geq$ 65 years), and baseline Eastern Cooperative Oncology Group status. All subgroups of patients analyzed achieved clinically meaningful antitumor activity, and no subgroup of patients was determined to be more likely to achieve a CR (Appendix Figs A2 and A3, online only).

Additional measures of activity were evaluated in the study. Of 17 patients who had "B" symptoms at baseline, 14 patients (82%) experienced resolution of all B symptoms after initiation of brentuximab vedotin. Complete resolution of all malignant cutaneous lesions occurred in 14 (93%) of 15 patients who had cutaneous lesions at baseline.

The investigator assessment of response supported the efficacy analyses by independent review. As assessed by the investigator, the ORR was 83% (95% CI, 70.6% to 91.4%), and the CR rate was 60% (95% CI, 46.6% to 73%). Best clinical response was concordant in 46 (79%) of 58 patients with a κ coefficient (statistical measure of agreement between two observations) of 0.65, suggesting good concordance between the assessors.

Safety

All patients enrolled onto this study received at least one dose of brentuximab vedotin. The median number of cycles was seven (range, one to 16 cycles); among patients with an objective response, the median number of cycles was eight (range, one to 16 cycles).

The most common ($\geq$ 20%) treatment-emergent adverse events of any grade, regardless of relationship to brentuximab vedotin, were peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhea (29%), rash (24%), constipation (22%), and neutropenia (21%; Table 3). Adverse events of grade 3 or higher were experienced by 60% of patients. Among events of grade 3 or higher severity that occurred in the study, the most common were neutropenia (21%), thrombocytopenia (14%), peripheral sensory neuropathy (12%), and anemia (7%).

Tumor lysis syndrome was observed in one patient after receiving the first dose of brentuximab vedotin. The patient recovered with supportive care measures, continued to receive study treatment, and achieved a CR (Fig 3). After the first dose of therapy, four patients experienced palpable, painful enlargement of affected nodes with overlying erythema (adverse event term of tumor flare), which subsequently regressed radiographically. In these patients, the tumor flare was felt to reflect an inflammatory process, not disease progression.

Six deaths occurred within 30 days of the last administration of brentuximab vedotin; none of these deaths were attributed to study drug. Four of the deaths were attributed to disease recurrence, one patient had an acute myocardial infarction and acute renal failure leading to death, and another patient experienced sudden death related to an obstruction of the patient's tracheal prosthesis.

Adverse events led to treatment discontinuation in 14 patients (24%); the only adverse event that resulted in treatment discontinuation in more than one patient was peripheral sensory neuropathy (six patients). Doses of brentuximab vedotin were delayed because of adverse events in 40% of patients; however, only 10% of doses were delayed overall. The most common events leading to dose delays were peripheral sensory neuropathy (14%) and neutropenia (12%). Doses of brentuximab vedotin were prospectively reduced from 1.8 to 1.2 mg/kg in seven patients; the most common

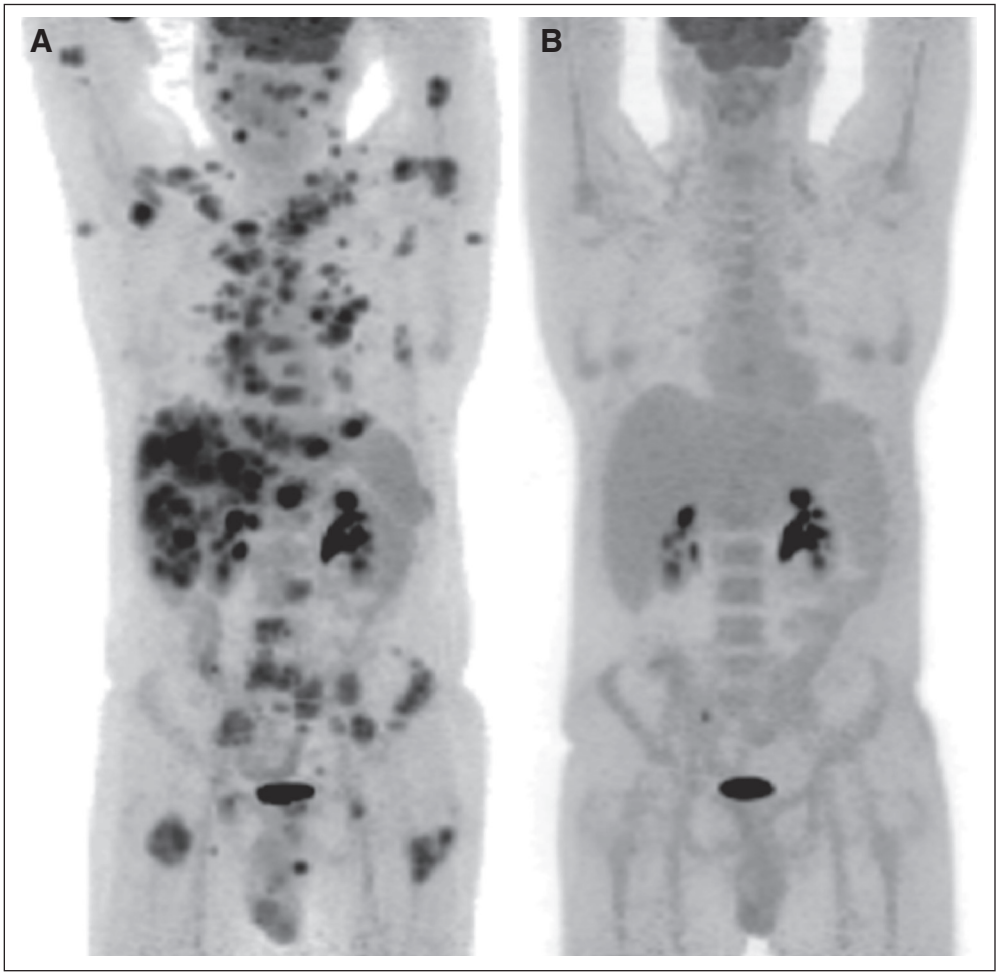

Fig 3. (A) Baseline scans of 42-year-old male with anaplastic lymphoma kinase–positive disease. (B) Complete remission was achieved in this patient after four cycles of treatment with brentuximab vedotin. Prior therapies administered were cyclophosphamide, doxorubicin, vincristine, and prednisone; doxorubicin, cyclophosphamide, etoposide, vincristine, and bleomycin; and an autologous stem-cell transplantation (SCT). The patient experienced tumor lysis syndrome after the first dose of brentuximab vedotin; after he recovered from this event, seven additional doses of brentuximab vedotin were administered in the study (eight total doses). The patient received an allogeneic SCT after discontinuing treatment with brentuximab vedotin; 9 months after the last dose in the study, the patient remained in remission.

adverse event leading to dose reduction was peripheral sensory neuropathy (four patients). Two of the patients with dose reductions eventually discontinued treatment in the study as a result of peripheral sensory neuropathy.

Thirty-one patients (53%) experienced peripheral neuropathy events (as identified by Standardized MedDRA Query) of any grade; event terms were peripheral sensory neuropathy (41%), paresthesia (7%), neuralgia (5%), peripheral motor neuropathy (5%), burning sensation (2%), and polyneuropathy (2%). Fourteen percent of patients had grade 3 peripheral neuropathy events, primarily sensory, and there were no grade 4 events. The median time to onset of peripheral neuropathy events was 13.3 weeks for any grade events, 16.9 weeks for grade 2 events, and 28.4 weeks for grade 3 events. Resolution or some improvement in neuropathy was observed in 81% of patients (25 of 31 patients). Complete resolution of all events was achieved in 48% of patients (15 of 31 patients). The median time to improvement or resolution was 9.9 weeks (range, 0.3 to 32.9 weeks). No baseline factors were identified to be associated with increased incidence of peripheral neuropathy on study.

DISCUSSION

In the largest prospective trial reported in patients with recurrent systemic ALCL, a majority of patients responded to treatment with brentuximab vedotin. Objective responses were observed in 86% of patients, and importantly, more than half of patients achieved a CR. Responses generally occurred within 6 weeks of treatment initiation (first postbaseline disease assessment); the median duration of response was greater than 1 year (12.6 months). Furthermore, 97% of patients achieved tumor reduction, and the majority had resolution of disease-related signs and symptoms whenever these were present at baseline. These improvements were independent of ALK status or number of prior therapies, suggesting that responses observed with brentuximab vedotin are not limited to a specific subgroup of patients. Despite the high percentage of patients with refractory disease, 70% of patients were alive 1 year after the initiation of treatment, with the median duration of survival not yet reached.

Historically, patients with recurrent ALCL have experienced poor outcomes. Pralatrexate, an antifolate agent, and romidepsin, a histone deacetylase inhibitor, have received accelerated approvals from the US Food and Drug Administration for treatment of relapsed or refractory peripheral T-cell lymphoma (including ALCL). In phase II studies that supported pralatrexate and romidepsin approvals, both agents demonstrated ORRs of less than 30%, with less than 15% of patients achieving CR.[17,18] In the subset of patients with systemic ALCL, six of 17 patients achieved an objective response with pralatrexate.[18] With romidepsin, the proportions of patients who achieved

objective responses were similar for the subset of patients with ALCL and the overall study population.[19]

Although conventional chemotherapy approaches are not curative, there is some evidence that autologous and allogeneic SCT may offer the opportunity for long-term benefit for patients with chemotherapy-sensitive recurrent ALCL.[20-22] However, the utility of SCT is generally limited by the inability of standard salvage therapies to deliver a high rate of CRs. After achieving remission with brentuximab vedotin in this study, 16 patients received an autologous or allogeneic SCT with the intent of securing a long-term remission. At the time of this analysis, response durations among patients who achieved a CR were similar, regardless of subsequent transplantation. When a sensitivity analysis of PFS was conducted censoring patients at the time of transplantation, the median PFS was equivalent to the PFS calculated using the prespecified analysis (13.3 months), indicating that the analyses performed in the study were robust (Appendix Fig A4, online only).

Overall, outpatient treatment with brentuximab vedotin was well tolerated, with adverse events similar to those reported in the initial phase I study.[13] The most common adverse events in the study were generally constitutional in nature, with the exception of peripheral sensory neuropathy. Peripheral neuropathy is a known class effect of agents with an antimicrotubule mechanism of action[23,24]; the patients on trial may have been predisposed to peripheral neuropathy after exposure to multiple prior chemotherapy regimens. Dose delays and dose reductions to 1.2 mg/kg were used to manage adverse events, including events of peripheral neuropathy, and allow continued treatment in some patients. Although 53% of patients experienced some form of peripheral neuropathy, in the majority of patients, it was sensory in nature and grade 1 or 2 in severity. Subsequent resolution or improvement was observed in 81% of patients.

Brentuximab vedotin is a rationally designed, targeted therapy for the treatment of a specific cancer. The study results validate a CD30-targeted approach in a disease with uniform antigen expression. The CR rate (57%) and acceptable safety profile achieved in this study demonstrate that brentuximab vedotin could be valuable as a potential treatment strategy for aggressive, CD30-positive, T-cell lymphomas. Clinical evaluation of brentuximab vedotin in newly diagnosed patients with ALCL and other CD30-expressing lymphomas is warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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