A Phase I Weekly Dosing Study of Brentuximab Vedotin in Patients with Relapsed/Refractory CD30-Positive Hematologic Malignancies

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Abstract

Purpose: The antibody–drug conjugate (ADC) brentuximab vedotin comprises a CD30-directed antibody covalently attached to the potent antimicrotubule agent monomethyl auristatin E (MMAE) via a protease-cleavable linker. This study explored the safety, maximum-tolerated dose (MTD), and activity of weekly dosing of brentuximab vedotin in patients with relapsed or refractory CD30-positive hematologic malignancies.

Experimental Design: In this phase I dose-escalation study, brentuximab vedotin was administered intravenously on Days 1, 8, and 15, of each 28-day cycle at doses ranging from 0.4 to 1.4 mg/kg. Forty-four patients were enrolled: 38 with Hodgkin lymphoma, five with systemic anaplastic large cell lymphoma, and one with peripheral T-cell lymphoma not otherwise specified. Doses were escalated in increments of 0.2 mg/kg until dose-limiting toxicity (DLT) was observed. Patients were monitored for antitherapeutic antibodies and pharmacokinetic parameters. Antitumor assessments were carried out every two cycles.

Results: The MTD was 1.2 mg/kg. The most common adverse events were peripheral sensory neuropathy, fatigue, nausea, diarrhea, arthralgia, and pyrexia; and the majority of events were mild to moderate in severity. Tumor regression occurred in 85% of patients and the overall objective response rate was 59% (n = 24), with 34% (n = 14) complete remissions. The median duration of response was not reached at a median follow-up of 45 weeks on study.

Conclusions: Weekly administration of brentuximab vedotin resulted in tumor regression and durable remissions in patients with CD30-positive malignancies. This ADC was associated with manageable toxicity, including peripheral neuropathy. Further study in CD30-positive malignancies is warranted.

Introduction

Hodgkin lymphoma is characterized by the presence of the malignant Hodgkin Reed-Sternberg cell, where CD30 expression is a hallmark of the pathologic diagnosis (1–3). Advances in front-line treatment for Hodgkin lymphoma have improved outcomes over the past 20 years; however, approximately 30% to 40% of patients with advanced Hodgkin lymphoma are refractory to initial therapy or will relapse (4). Current management of these patients includes the use of second-line chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (ASCT; refs. 5, 6). Nevertheless, approximately 50% of patients with Hodgkin lymphoma relapse after ASCT (7, 8). Survival for these predominantly young adult patients is often limited, with a 5-year OS rate of approximately 32% (9). Those who relapse within 3 months following ASCT have a worse prognosis, with a median survival of less than 8 months (10).

Single agent chemotherapy has shown only moderate benefit for these patients with relapsed or refractory Hodgkin lymphoma (11–13). Combination regimens of conventional chemotherapy have resulted in higher overall response rates (ORR) than single agent therapies but, in general, confer substantial toxicities in the post-ASCT population (14). Reduced intensity conditioning allogeneic stem cell transplantation (RIC–alloSCT) has also been...
CD30 is a member of the tumor necrosis receptor superfamily and its restricted expression is shared by classical Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL). Treatment of these CD30-expressing lymphomas with unconjugated anti-CD30 monoclonal antibodies has shown in vivo antitumor activity, though modest clinical activity. For this reason, brentuximab vedotin, an antibody–drug conjugate (ADC) linking the antimitotubule agent monomethyl auristatin E to a CD30 monoclonal antibody, was developed. This phase I trial was conducted to assess weekly dosing with brentuximab vedotin in patients with relapsed or refractory CD30-positive malignancies. Promising responses were observed with tumor regression in 85%, overall response rate of 59%, and a complete remission rate of 34%. Toxicities were manageable. These outcomes are of particular significance for this patient population given the unmet need for therapeutic options and the potential of ADC technology to selectively ablate cancer cells based upon their restricted antigen expression.

Translational Relevance

CD30 is a member of the tumor necrosis receptor superfamily and its restricted expression is shared by classical Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL). Treatment of these CD30-expressing lymphomas with unconjugated anti-CD30 monoclonal antibodies has shown in vivo antitumor activity, though modest clinical activity. For this reason, brentuximab vedotin, an antibody–drug conjugate (ADC) linking the antimitotubule agent monomethyl auristatin E to a CD30 monoclonal antibody, was developed. This phase I trial was conducted to assess weekly dosing with brentuximab vedotin in patients with relapsed or refractory CD30-positive malignancies. Promising responses were observed with tumor regression in 85%, overall response rate of 59%, and a complete remission rate of 34%. Toxicities were manageable. These outcomes are of particular significance for this patient population given the unmet need for therapeutic options and the potential of ADC technology to selectively ablate cancer cells based upon their restricted antigen expression.

investigated and although decreased toxicities were observed compared with conventional alloSCT, chronic GVHD occurs in 73% of these patients and 55% still progress within 2 years (15, 16).

Systemic anaplastic large cell lymphoma (ALCL) is an aggressive subtype of mature T-cell lymphomas, characterized by the uniform expression of the cell surface antigen CD30 (17). Patients diagnosed with systemic ALCL can be stratified by the expression of anaplastic lymphoma kinase (ALK). ALK-positive status has been viewed as conferring a more favorable prognosis. However, a recent consortium review showed that a subset of ALK-positive patients with ALCL with high-risk features have a 5-year failure-free survival (FFS) rate of only 25% to 60% with front-line chemotherapy, similar to the 5-year FFS for ALK-negative patients (18). Patients with relapsed and refractory ALCL have few therapeutic options and can be considered for RIC-alloSCT (19). Pralatrexate is the only Food and Drug Administration approved treatment for relapsed peripheral T-cell lymphomas, including ALCL, and induces an ORR of 29%, with a complete remission rate (CR) of 11% and a median progression-free survival (PFS) of only 3.5 months (20).

The identification of the Ki-1 monoclonal antibody in 1982 led to high interest in expression of CD30 on Hodgkin lymphoma cells and, in 1985, ALCL was described as a new type of CD30-positive non–Hodgkin lymphoma. CD30 was further defined as being a member of the tumor necrosis factor family and its restricted expression on normal cells made it an attractive target for antibody-directed therapy. Although unconjugated CD30 monoclonal antibodies showed in vivo antitumor activity, clinical activity was modest (21, 22).

The antibody–drug conjugate (ADC) brentuximab vedotin (Seattle Genetics) was developed to increase antitumor activity by linking a potent antimitotubule agent, monomethyl auristatin E (MMAE), to the CD30 monoclonal antibody cAC10 via a protease-cleavable linker (23). This ADC binds to CD30, is rapidly internalized in the cell, and then traffics to the lysosomal compartment where the dipeptide linker is cleaved (24). Once released, binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell-cycle arrest, and results in apoptotic death of the tumor cell. After promising preclinical activity was observed with brentuximab vedotin (24–26), a phase I dose-escalation study was conducted in patients with relapsed or refractory CD30-positive lymphomas. The maximum-tolerated dose (MTD) was 1.8 mg/kg administered every 3 weeks with an ORR of 50% and CR rate of 27% observed at the MTD. Median duration of response was 9.7 months and adverse events were manageable and included fatigue, diarrhea, neutropenia, and peripheral neuropathy (27).

The phase I trial, reported herein, was conducted to test the hypothesis that more frequent administration of brentuximab vedotin on a weekly schedule would improve on-target CD30 antitumor activity without increasing off-target toxicity. The primary objective of this study was to determine the MTD and safety profile of brentuximab vedotin delivered weekly. Secondary objectives were to determine pharmacokinetic parameters for the ADC, MMAE, and total antibody, as well as to evaluate immunogenicity, and assess antitumor response.

Materials and Methods

This single-arm, open-label, dose-escalation study was conducted at 5 study centers in the United States in accordance with good clinical practice guidelines and the ethical principles based in the Declaration of Helsinki. Approval for study procedures was obtained from the Institutional Review Boards of each study site, and all patients provided written informed consent upon study enrollment.

Eligibility

Eligible patients were 12 or more years of age and had relapsed or refractory, histologically confirmed CD30-positive hematologic malignancies with bi-dimensional measurable disease of at least 1.5 cm by radiographic evaluation. Patients with Hodgkin lymphoma had received systemic chemotherapy as induction therapy for advanced-stage disease or salvage therapy after initial radiotherapy for early-stage disease and had previously undergone ASCT unless they were ineligible for or had declined treatment. Patients with other CD30-positive malignancies had previously failed or were refractory to front-line chemotherapy. Patients were excluded if they had a current diagnosis of primary cutaneous ALCL; however, patients who had transformed to systemic ALCL were eligible. Furthermore,
patients with a history of alloSCT or prior treatment with any anti-CD30 antibody were also ineligible.

**Treatment and dose-escalation**

Brentuximab vedotin was administered intravenously on Days 1, 8, and 15 of each 28-day cycle. The starting dose of brentuximab vedotin (0.4 mg/kg) was selected on the basis of preliminary data from a phase 1 dose-escalation study, which evaluated an every 3-week schedule (27). Doses were escalated in increments of 0.2 mg/kg until dose-limiting toxicity (DLT) or a maximum dose of 1.8 mg/kg was reached.

As specified in the protocol, patients were monitored for treatment-related DLTs occurring during cycle 1. Dose-limiting toxicities were defined as grade III or greater nonhematologic adverse events, including laboratory abnormalities that did not resolve to grade 1 or baseline within 14 days; or grade IV hematologic events that did not improve to grade III or less within 14 days. Febrile neutropenia requiring hospitalization or intravenous antibiotics and grade III infusion reactions that did not resolve to grade 1 or baseline within 24 hours were also considered to be DLTs.

At least 3 patients were enrolled in each cohort. If no DLTs were identified by the Safety Monitoring Committee, escalation to the next dose level was permitted. If 1 of the first 3 patients experienced a DLT, the cohort was to be expanded to 6 patients. If 2 or more DLTs were observed, the MTD was formally exceeded and the preceding dose level was declared the MTD. Cohort expansions to 12 patients total were permitted at or below the MTD.

**Study assessments**

Safety monitoring included the ongoing assessment of adverse events and DLTs. Adverse events were summarized using the Medical Dictionary for Regulatory Activities and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Clinical laboratory testing, collection of vital signs, physical examination, and evaluation of performance status were carried out on days 1, 8, and 15 of each cycle.

Immunogenicity to brentuximab vedotin was assessed before each day 1 dose using a validated electrochemiluminescence assay. Blood samples were collected for pharmacokinetic analyses on days 1, 2, 4, 8, 15, and 22 of cycle 1 and then on days 1, 8, 15, 16, 18, and 22 of each subsequent cycle of therapy. Serum concentrations of ADC and total antibody were measured using a validated ELISA and plasma concentrations of MMAE were measured with high-performance liquid chromatography with tandem-mass spectrometry. Pharmacokinetic parameters were estimated by noncompartmental analysis (WinNonlin).

Tumor assessments by radiographic evaluation (computed tomography and or positron emission tomography; CT and or PET) were carried out at the end of every 2 cycles. Repeat bone marrow aspirate and biopsy were carried out to confirm CR in patients with bone marrow involvement at baseline. B-symptom assessments (weight loss, fever, and night sweats) were also carried out. Response to treatment was characterized by the investigator as a CR, partial remission (PR), stable disease (SD), or progressive disease (PD) per the Revised Response Criteria for Malignant Lymphoma (28). As per the Cheson 2007 criteria, CR could be declared with or without a PET scan. Patients who experienced clinical benefit with acceptable safety were eligible to receive up to a maximum of 12 cycles of treatment.

An exploratory analysis to assess potential relationships between individual cytokine and chemokine concentrations with brentuximab vedotin dose level and with clinical outcomes was carried out. The set of cytokines and chemokines evaluated were interleukin-6 (IL-6), IL-1 receptor antagonist (IL-1ra), thymus and activation-regulated chemokine (TARC), TNF-α, and soluble CD30.

<table>
<thead>
<tr>
<th>Table 1. Baseline patient characteristics</th>
<th>Total (N = 44)</th>
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<tbody>
<tr>
<td>Age, y</td>
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</tr>
<tr>
<td>Median</td>
<td>33.0</td>
</tr>
<tr>
<td>Range</td>
<td>12–82</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>31 (70)</td>
</tr>
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<td>ECOG performance status, n (%)</td>
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<tr>
<td>0</td>
<td>27 (61)</td>
</tr>
<tr>
<td>1</td>
<td>12 (27)</td>
</tr>
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<td>2</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Disease diagnosis, n (%)</td>
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</tr>
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<td>Hodgkin lymphoma</td>
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<tr>
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<td>ALK-1 positive</td>
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<td>ALK-1 negative</td>
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</tr>
<tr>
<td>PTCL-NOS</td>
<td>1 (2)</td>
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<td>Stage of initial disease diagnosis, n (%)</td>
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</tr>
<tr>
<td>Stage I</td>
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<td>Stage II</td>
<td>18 (41)</td>
</tr>
<tr>
<td>Stage III</td>
<td>14 (32)</td>
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<td>Stage IV</td>
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</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
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<tr>
<td>Disease status relative to most recent prior therapy</td>
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</tr>
<tr>
<td>Relapsed #</td>
<td>24 (55)</td>
</tr>
<tr>
<td>Refractory</td>
<td>20 (45)</td>
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<td>Baseline B-symptoms (fever, night sweats, and weight loss)</td>
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<td>Baseline bone marrow involvement</td>
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<td>Number of prior cancer-related systemic therapies</td>
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</tr>
<tr>
<td>Median</td>
<td>3.0</td>
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<tr>
<td>Range</td>
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<td>Prior radiation therapy</td>
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<td>Prior ASCT, n (%)</td>
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<td>30 (68)</td>
</tr>
<tr>
<td>No</td>
<td>14 (32)</td>
</tr>
</tbody>
</table>

*Relapsed disease defined as achieving a CR or PR with the most recent prior therapy.
Statistical analysis

All analyses of data from this study were descriptive and calculations of confidence intervals were 2-sided.

The data reported herein were collected from the first patient visit on March 27, 2008, to the last patient visit on February 25, 2010. Patients were evaluable for safety if they received any amount of brentuximab vedotin. The population for pharmacokinetic analysis comprised all treated patients with adequate analyte concentration measurements from blood samples. Patients were included in the population evaluated for efficacy if they received at least 2 cycles of brentuximab vedotin or progressed at any time after the first treatment.

Results

Patients

Forty-four patients with a median age of 33 (range: 12–82) were treated in this study, including 38 diagnosed with Hodgkin lymphoma, 5 with systemic ALCL (1 ALK-positive and 4 ALK-negative), and one with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS; Table 1). Patients had received a median of 3 prior chemotherapy regimens (range: 1–8), and 30 patients (68%) had undergone prior ASCT. Twenty-four (55%) patients were enrolled with relapsed disease and 20 (45%) were characterized as having treatment-refractory disease relative to their most recent prior treatment. The median time from initial pathologic diagnosis to the first dose of brentuximab vedotin was 32.4 months.

MTD

Patients were enrolled into 6 dosing cohorts, ranging from 0.4 to 1.4 mg/kg. After one patient in the 1.0 mg/kg cohort experienced a DLT (diarrhea), this cohort was expanded to 6 patients and no additional DLTs were observed. No patient in the 1.2 mg/kg cohort experienced a DLT. After one patient in the 1.4 mg/kg cohort experienced a DLT (hyperglycemia), this cohort was expanded to 6 patients. After a second patient experienced a DLT (diarrhea), this cohort was determined to have exceeded the MTD and dose-escalation was stopped. On the basis of these findings, the MTD was defined as 1.2 mg/kg and this cohort was expanded to 12 patients. A second DLT (vomiting) was noted in the 1 mg/kg cohort after this cohort was expanded to 12 patients; however, this did not exceed the specified MTD (>1 of 3 of patients experiencing DLT).

Safety profile

Across all dose levels, the median number of treatment cycles was 4 (range: 1–12) and the median dose intensity was 0.970 mg/kg (range: 0.56–1.16 mg/kg). Routine premedications to prevent infusion reactions were not required per protocol. Mild to moderate (grade I/II) acute infusion reactions were recorded for 6 (14%) patients. All 6 patients recovered from their reactions and received subsequent cycles of treatment with premedications per institution standards, which were delivered without incident for all but 1 patient, who experienced a second reaction. This patient was subsequently discontinued from the study on

Table 2. Common adverse events

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>0.4 (n = 4)</th>
<th>0.6 (n = 4)</th>
<th>0.8 (n = 6)</th>
<th>1.0 (n = 12)</th>
<th>1.2 (n = 12)</th>
<th>1.4 (n = 6)</th>
<th>Total (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral sensory neuropathy</td>
<td></td>
<td></td>
<td></td>
<td>5 (83)</td>
<td>7 (58)</td>
<td>9 (75)</td>
<td>29 (66)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>4 (67)</td>
<td>5 (42)</td>
<td>8 (67)</td>
<td>4 (67)</td>
<td>23 (52)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (25)</td>
<td>0</td>
<td>3 (50)</td>
<td>7 (58)</td>
<td>6 (50)</td>
<td>5 (83)</td>
<td>22 (50)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (25)</td>
<td>0</td>
<td>2 (33)</td>
<td>4 (33)</td>
<td>6 (50)</td>
<td>1 (17)</td>
<td>14 (32)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>2 (33)</td>
<td>2 (17)</td>
<td>3 (25)</td>
<td>1 (17)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>1 (25)</td>
<td>1 (17)</td>
<td>2 (17)</td>
<td>5 (42)</td>
<td>2 (33)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>5 (42)</td>
<td>2 (17)</td>
<td>2 (33)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (8)</td>
<td>5 (42)</td>
<td>3 (50)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>1 (25)</td>
<td>1 (17)</td>
<td>2 (17)</td>
<td>4 (33)</td>
<td>2 (33)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>2 (33)</td>
<td>2 (17)</td>
<td>2 (17)</td>
<td>0</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Rash pruritic</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (8)</td>
<td>4 (33)</td>
<td>2 (33)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (25)</td>
<td>0</td>
<td>1 (17)</td>
<td>3 (25)</td>
<td>3 (25)</td>
<td>0</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (25)</td>
<td>0</td>
<td>0</td>
<td>3 (25)</td>
<td>1 (8)</td>
<td>2 (33)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
<td>2 (33)</td>
<td>4 (33)</td>
<td>0</td>
<td>1 (17)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>2 (50)</td>
<td>0</td>
<td>1 (17)</td>
<td>3 (25)</td>
<td>0</td>
<td>1 (17)</td>
<td>7 (16)</td>
</tr>
</tbody>
</table>

NOTE: All values are represented as n (%). Adverse events occurring in at least 15% of patients.
day 21 for an adverse event of chills. None of the infusion reactions was characterized as serious.

The most common adverse events were peripheral sensory neuropathy (29 patients; 66%), fatigue (23 patients; 52%), nausea (22 patients; 50%), diarrhea (14 patients; 32%), arthralgia (12 patients; 27%), pyrexia (11 patients; 25%), and decreased appetite, myalgia, and upper respiratory tract infection (10 patients; 23% each; Table 2). The majority of these events were grade I or II in severity. Grade III adverse events that occurred in 2 or more patients were peripheral sensory neuropathy (6 patients; 14%); anemia (4 patients; 9%); neutropenia, and peripheral motor neuropathy (3 patients; 7% each); and hyperglycemia, diarrhea, and vomiting (2 patients; 5% each). Three patients experienced a single grade IV adverse event: hyperglycemia, low potassium and magnesium, and neutropenia. Thirteen patients (30%) had an adverse event that led to treatment discontinuation. Events occurring in more than 1 patient included peripheral sensory neuropathy (6 patients; 14%) and peripheral motor neuropathy (2 patients; 5%).

Overall, 32 patients (73%) and at least half of patients at each dose level experienced 1 or more events of peripheral sensory neuropathy (6 patients; 14%) and peripheral motor neuropathy (2 patients; 5%).

Of the 3 patients who experienced grade III motor neuropathies, each had improvement of symptoms at a median onset time of 25.9 weeks and the median time to improvement was 21.6 weeks. Three of these patients experienced both sensory and motor neuropathies, and 3 experienced peripheral sensory neuropathy alone. Of the 3 patients who experienced grade III motor neuropathies, each had improvement of symptoms at follow-up though 1 patient continued to display weakness in his hands. Overall, 8 patients discontinued treatment because of peripheral neuropathy symptoms (6 for peripheral sensory neuropathy and 2 for peripheral motor neuropathy); of these, 5 had improved at a median follow-up of 31.3 weeks (range: 0–48).

A total of 8 patients (18%) died during the study. None of these deaths was deemed to be treatment related. One death occurred within 28 days of the last dose of study drug, and was attributed to pneumonia secondary to influenza (presumed H1N1). At the time of this report, no patients remain on treatment or are being followed for survival.

### Immunogenicity and pharmacokinetics

Of 39 patients who were negative for antitherapeutic antibodies (ATA) at baseline, 27 remained negative for ATA throughout the study and 2 patients developed persistently positive ATA, defined as a positive titer at more than 2 time points post-baseline. Both of these patients experienced infusion reactions and the brentuximab vedotin exposures for one patient were markedly reduced.

Peak brentuximab vedotin blood concentrations typically occurred at the end of infusion and declined in a biexponential manner, whereas peak MMAE concentrations occurred approximately 1 to 3 days following each infusion. Increases in both brentuximab vedotin and MMAE exposures were approximately dose proportional (Supplementary Fig. S1).

Following multiple doses of brentuximab vedotin, accumulation was moderate with cycle 3:cycle 1 AUC\(_{0–7d}\) (area under the curve from 0 to 7 days) accumulation ratios of 1.72 and 1.28 at the 1.0 and 1.2 mg/kg dose levels, respectively. Accumulation of MMAE was more modest; cycle 3:cycle 1 AUC\(_{0–7d}\) accumulation ratios were 1.09 and 1.17 at 1.0 mg/kg and 1.2 mg/kg, respectively (Supplementary Table S1).

### Antitumor response

A total of 41 of 44 patients were evaluable for antitumor response. Three patients were excluded from the efficacy evaluable population because they did not receive at least 2 cycles of brentuximab vedotin and did not have documented progression of disease at the time of treatment discontinuation. Responses by dose level and overall are provided in Table 4. The ORR was 59% (n = 24), with 34% (n = 14)
CR. For patients treated at the MTD (1.2 mg/kg), the ORR was 58% (7 of 12 patients) and of these, 3 (25%) achieved a CR. Of the 7 patients who had B-symptoms at baseline, 6 patients (86%) had resolution of these symptoms. Supplementary Table S2 presents antitumor response rates by disease diagnosis. The ORR for patients diagnosed with Hodgkin lymphoma was 54%. Among the 5 patients diagnosed with ALCL, the CR rate was 80%; one patient with ALCL who received treatment at the lowest dose, 0.4 mg/kg, achieved SD. The patient who was enrolled with a disease diagnosis of PTCL-NOS had a best clinical response of PR. The median time to objective response was 8.1 weeks (range: 7.1–23.3), which corresponded with the first post-baseline disease assessment. The median durations of ORR and CR as determined by Kaplan–Meier analyses were not met because of the high number of censored events (Supplementary Fig. S2). The median follow-up on study for all patients was 45.1 weeks (range: 6–91).

Reductions in tumor size were observed for 35 (85%) of evaluable patients (Fig. 1). The Kaplan–Meier estimated median overall PFS was 28.7 weeks (range: 7.3–83.6+). Figure 2 provides a Kaplan–Meier estimate of PFS by dose cohort grouping of low doses (<0.8 mg/kg) and high doses (≥0.8 mg/kg). The median OS was not reached.

**Correlative analyses**

All 44 treated patients were included in an exploratory analysis of biomarkers and clinical outcomes. Post-baseline reductions in cytokine and chemokine concentrations were observed in the majority of patients; however, no relationships between brentuximab vedotin dose levels and cytokine and chemokine concentrations were identified. In patients with increased post-baseline cytokine and chemokine concentrations, there were no clear associations with dose level or best clinical response observed with treatment. Concentrations of IL-6 greater than 30 pg/mL at baseline were associated with disease progression. All other relationships were not significant in this exploratory analysis. There were no significant relationships between cytokine and chemokine concentrations and tumor size or clinical outcome. Likewise, there was no correlation between soluble CD30 and tumor size and clinical outcome. Higher levels of soluble CD30 were not associated with progression of disease.

**Discussion**

The primary objectives of this phase I study were the determination of the MTD and the evaluation of treatment safety. The MTD was established as 1.2 mg/kg administered weekly for 3 weeks of a 4-week cycle. Most adverse events were mild or moderate in intensity and were managed with supportive care. Peripheral neuropathy events were the most clinically meaningful toxicity. Peripheral neuropathy was observed in more than half of treated patients, was primarily sensory in nature, and was generally mild to
moderate in severity. A small number of patients developed grade III neuropathy, which tended to arise later in treatment and in some instances included both sensory and motor symptoms.

Weekly dosing with brentuximab vedotin induced tumor regression in the majority of patients. Prompt objective responses were observed in more than half of patients across all dose levels. The median duration of response was not reached at a median follow-up of 45 weeks.

The antitumor activity observed in this phase I study was similar to that in the earlier phase I trial with brentuximab vedotin, where drug was administered once every 3 weeks (27). The CR rate observed at higher dose cohorts for patients with Hodgkin lymphoma and ALCL suggests a weekly dosing strategy may be useful for short-term remission induction. These results may support the hypothesis that more frequent administration could improve on-target CD30 antitumor activity, but further study is needed to understand if this approach is advantageous to less frequent administration. In contrast, a higher rate of peripheral neuropathy was observed with weekly treatment of brentuximab vedotin versus treatment delivered every 3 weeks (27): the median time to onset of neuropathy-related events was shorter and a higher incidence of grade III events was observed with weekly dosing. While a weekly schedule of brentuximab vedotin could be explored as a remission induction strategy, the onset and severity of peripheral neuropathy events would prohibit long-term therapy.

MMAE, the cytotoxic agent of brentuximab vedotin, is a potent antimitotubule agent and the peripheral neuropathy observed in this study is an expected class effect of antimitotubule drugs (29, 30). In addition, patients enrolled in this study had been exposed to multiple prior chemotherapy regimens, including the potential conditioning regimens associated with prior ASCTs, potentially predisposing many to the development of peripheral neuropathy. In all, 14% of patients had preexisting peripheral neuropathy at the time of enrollment.

In conclusion, brentuximab vedotin administered weekly resulted in an overall tumor response that was similar to every 3-week dosing, with the suggestion of a higher CR rate, but a greater incidence of peripheral neuropathy. Given these findings, future studies could explore the use of weekly dosing to rapidly induce response, followed by every 3-week dosing to further consolidate response and minimize toxicity. This type of approach might be beneficial for a patient with Hodgkin lymphoma or ALCL who presents with bulky and symptomatic disease. Current trials are evaluating the incorporation of brentuximab vedotin into front-line treatments for Hodgkin lymphoma and ALCL, and for the prevention of progression following ASCT in Hodgkin lymphoma patients. In addition, these data warrant the exploration of brentuximab vedotin in combination with salvage chemotherapies and in the treatment of other CD30-positive lymphomas.

Disclosure of Potential Conflicts of Interest


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with Relapsed/Refractory CD30-Positive Hematologic Malignancies

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