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Title:

Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma

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CLINICAL TRIALS AND OBSERVATIONS

Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma

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Key Points

- A total of 47% of patients who achieved CR on brentuximab vedotin remain progression-free after being followed a median of 53 months.
- Younger age, less functional impairment, and lower disease burden at baseline were associated with CR and prognostic for longer survival.

We present response and survival outcomes of a pivotal phase 2 trial of the antibody-drug conjugate brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma following autologous stem cell transplant (N = 102) after a median observation period of approximately 3 years. Median overall survival and progression-free survival were estimated at 40.5 months and 9.3 months, respectively. Improved outcomes were observed in patients who achieved a complete remission (CR) on brentuximab vedotin, with estimated 3-year overall survival and progression-free survival rates of 73% (95% confidence interval [CI]: 57%, 88%) and 58% (95% CI: 41%, 76%), respectively, in this group (medians not reached). Of the 34 patients who obtained CR, 16 (47%) remain progression-free after a median of 53.3 months (range, 29.0 to 56.2 months) of observation; 12 patients remain progression-free without a consolidative allogeneic stem cell transplant. Younger age, good performance status, and lower disease burden at baseline were characteristic of patients who achieved a CR and were favorable prognostic factors for overall survival. These results suggest that a significant proportion of patients who respond to brentuximab vedotin can achieve prolonged disease control. The trial was registered at www.clinicaltrials.gov as #NCT00848926. (*Blood*. 2015;125(8):1236-1243)

Introduction

The standard of care for patients with relapsed or refractory Hodgkin lymphoma (HL) is salvage chemotherapy followed by autologous stem cell transplant (auto-SCT) in responding patients, which is curative in approximately half of those who undergo the procedure. The ability to achieve and maintain a complete remission (CR) prior to transplant has emerged as a factor important for a favorable progression-free and overall survival (OS) after transplant.^{1,2}

Unfortunately, approximately 50% of patients will experience relapse or progression after auto-SCT. For this population, outcomes have historically been poor, with median OS rates from time of relapse ranging from 10.5 months to 27.6 months.^{3,4} Although reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT) can induce long-term progression-free survival (PFS), and in some cases secondary cure, in a subset of patients who relapse following auto-SCT, its use is associated with high rates of progression and nonrelapse mortality.⁵

Brentuximab vedotin (ADCETRIS) is composed of an anti-CD30 antibody conjugated by a protease cleavable linker to monomethyl

aurostatin E, a microtubule-disrupting agent. In a pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory HL after auto-SCT, 75% of patients achieved an objective response (95% confidence interval [CI]: 64.9%, 82.6%) and 34% of patients achieved CR (95% CI: 25.2%, 44.4%) per independent central review.⁶ The most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. Herein, we present response durability and survival in this trial population after a median follow-up period of approximately 3 years. Factors associated with durable remissions and favorable survival are explored.

Methods

Patient eligibility

Eligible patients were aged 12 years or older with relapsed or refractory HL after auto-SCT. Histologic confirmation of CD30-positive Hodgkin Reed-Sternberg

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Table 1. Patient demographics and characteristics at enrollment

	All patients (N = 102)
Median time from initial HL diagnosis to first dose in months (range)	39.9 (12-220)
Stage at initial diagnosis, n (%)	
Stage I/II	51 (50)
Stage III	27 (26)
Stage IV	20 (20)
Unknown	4 (4)
ECOG performance status, n (%)	
Grade 0	42 (41)
Grade 1	60 (59)
Patients with primary refractory disease,* n (%)	72 (71)
Disease status relative to most recent prior therapy,† n (%)	
Relapse	59 (58)
Refractory	43 (42)
Median number of prior cancer-related systemic therapy regimens‡ (range)	3.5 (1-13)
Median PFS for most recent regimen in months (95% CI)	6.1 (4.4, 7.2)
Number of prior auto-SCTs, n (%)	
1	91 (89)
2	11 (11)
Median time from most recent auto-SCT to relapse after auto-SCT in months (range)	6.7 (0-131)

*Absence of CR or relapse within 3 months of front-line therapy.

†Relapse indicates the best response of CR or PR to most recent prior therapy, whereas refractory indicates the best response of stable or progressive disease to most recent prior therapy.

‡Includes chemotherapy given for stem cell mobilization.

cells by central pathology review was required, as well as fluorodeoxyglucose-avid disease by positron emission tomography (PET) and measurable disease of at least 1.5 cm by computed tomography (CT). Patients who had received a prior allo-SCT were ineligible. Additional eligibility criteria are reported by Younes et al.⁶

Study design and treatment

A complete description of this open-label, phase 2, single-arm study has been previously reported.⁶ Briefly, this clinical trial was conducted at 25 centers within the United States, Canada, and Europe and was approved by each investigational site's institutional review board or ethics committee. Patients were recruited between February and August 2009, and all patients provided written informed consent.

Patients received brentuximab vedotin 1.8 mg/kg IV once every 3 weeks over 30 minutes on an outpatient basis for up to 16 infusions.

Study assessments

Clinical response was determined both by investigators and by an independent central review facility (Bioclinica, formerly known as CoreLab Partners and RadPharm; Princeton, NJ) according to the Revised Response Criteria for Malignant Lymphoma.⁷ Patients were assessed for response by CT at cycles 2, 4, 7, 10, 13, and 16 and by PET at cycles 4 and 7.

During the long-term follow-up period, all patients were followed for survival every 3 months during years 1 to 2, every 6 months during years 3 to 5, and annually thereafter. Patients who discontinued study treatment for any reason other than progressive disease or initiation of new anticancer therapy were also assessed on this schedule for radiographic progression. In October 2013, the protocol was amended to require a CT scan only if progression was suspected clinically. At the time of the amendment, 18 patients were still being assessed for progression; these patients had been in long-term follow-up for a median of over 30 months.

Investigators were also asked to record whether patients had initiated new cancer-related therapy during the long-term follow-up period. Although

investigators were asked to specify the type of therapy (eg, systemic chemotherapy vs allogeneic stem cell transplant), details of the therapy (eg, type of conditioning regimen for a transplant) were not prospectively collected.

An independent data monitoring committee assessed the safety of study participants during the trial and monitored the overall study conduct.

Statistical analysis

Data were analyzed by representatives of Seattle Genetics, Inc., and all authors had access to the primary clinical trial data.

The primary end point of the trial was objective response rate (ORR) per the independent review facility (IRF). Secondary end points included duration of response by IRF, CR rate by IRF, PFS by IRF, OS, and the incidence and severity of adverse events. These end points have been previously described and reported.⁶

The current paper, based on a March 2014 data cutoff, represents a median of approximately 3 years of observation time for all patients. In this paper, we present long-term OS results as well as investigator assessments of response duration and PFS, which were both prespecified additional analyses in the study's statistical analysis plan. Response duration was calculated from the first objective tumor response (CR or partial remission [PR]) to the first documentation of progression or to death, and PFS was calculated from the start of study treatment to the first documentation of progression or to death. For these analyses, patients were censored at their last assessment (radiologic or clinical) that documented the absence of progressive disease if they were given another treatment before documentation of progression, with the exception of stem cell transplant as the first therapy after discontinuing brentuximab vedotin ("consolidative allo-SCT").

OS was calculated from start of study treatment to the date of death due to any cause and was censored at the last date the patient was known to be alive. As a post hoc analysis, the Cox proportional hazard model with forward selection was used to assess the effect of multiple variables on OS.⁸ Significant variables at $P = .05$ in the univariate analyses were incorporated into the multivariate analyses. The hazard ratio with its 95% confidence interval and 2-sided P values are presented for the final selected factors.

An intrapatient PFS comparison (PFS achieved with the most recent prior systemic therapy before or after auto-SCT vs PFS per investigator with brentuximab vedotin) was performed as a prespecified exploratory analysis. Post hoc subgroup analyses of PFS and OS were performed for best response and for patients who achieved CR per the investigator and then either did or did not undergo allo-SCT.

Results

Patient demographics and characteristics prior to enrollment have been previously summarized.⁶ Briefly, 102 patients (53% female, 47% male)

Table 2. Duration of response per the investigator following treatment with brentuximab vedotin

	All patients (N = 102)
Objective response according to the investigator, n (%)	
CR, n (%)	73 (72)
PR, n (%)	34 (33)
	39 (38)
Duration of response for patients with CR, months	
Median	NE
95% CI	20.5, NE
Duration of objective response, months	
Median	11.2
95% CI	7.7, 18.7

Duration of response is calculated from the earliest occurrence of either CR or PR.

NE, not estimable.

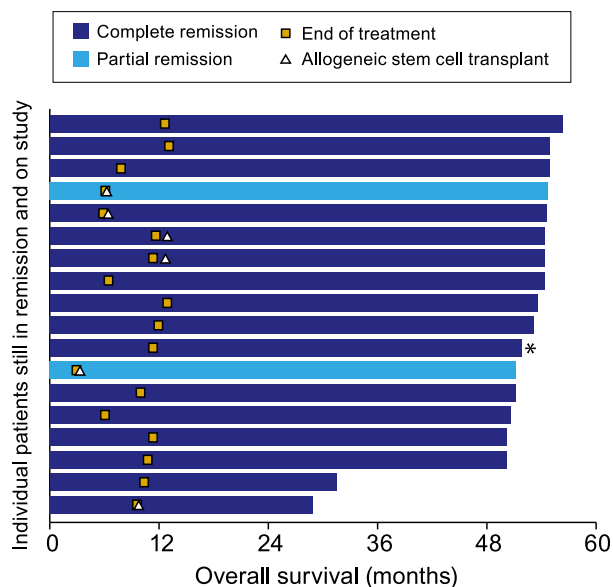


Figure 1. Patients who remain in remission per the investigator following treatment with brentuximab vedotin. Includes patients who remain in remission according to the investigator, are still on study being followed for survival, and have not started new anticancer therapy ($n = 18$). Patients are shaded according to their best response on treatment with brentuximab vedotin. Six patients received an allogeneic stem cell transplant shortly after completing treatment with brentuximab vedotin. The 2 patients with a PR to brentuximab vedotin achieved a CR following transplant. Subsequent to end of treatment, 1 patient (indicated by an asterisk) received continued treatment with brentuximab vedotin as part of a separate treatment extension protocol.

with a median age of 31 years (range, 15-77 years) were enrolled. The majority of enrolled patients were white (87%). Patients were heavily pretreated, and all had received at least 1 auto-SCT. The median time to relapse following the most recent auto-SCT was 6.7 months (range, 0-131 months; Table 1).

By investigator assessment, the ORR to brentuximab vedotin was 72% (33% CR, 38% PR), which was nearly identical to the ORR per IRF that was previously reported.⁶ Median time to the first objective response per investigator was 5.7 weeks, or approximately the time of the first response assessment (CT) after the cycle 2 infusion. Median time to CR per investigator was 12.2 weeks, or approximately the time of the second response assessment (CT/PET) after the cycle 4 infusion.

After discontinuing treatment with brentuximab vedotin, patients could receive additional therapies at the discretion of the investigator. No specific salvage therapy was recommended per protocol; subsequent therapies were heterogeneous and included both single- and multiagent regimens. Eight patients received a consolidative allo-SCT (6 received the consolidative allo-SCT in CR and 2 received the consolidative allo-SCT in PR).

Long-term follow-up

Duration of response. Enrolled patients ($N = 102$) have been followed for a median of almost 3 years (median, 33.3 months; range, 1.8 to 57.3 months) from their first dose of brentuximab vedotin. The estimated median duration of response in the 73 patients who achieved at least a PR on treatment was 11.2 months (95% CI: 7.7, 18.7; Table 2). The median duration of response for the 34 patients who achieved a CR per the investigator has not been reached (95% CI: 20.5 months, —).

As of last follow-up, a total of 18 patients, or 25% of patients with an objective response to brentuximab vedotin, are still on study and in remission without the start of new therapy, other than a consolidative allo-SCT (Figure 1). The 18 patients have been followed for a median

of 53.3 months (range, 29.0 to 56.2 months) from their first dose of brentuximab vedotin. Sixteen of the 18 patients who are still in remission achieved a CR on brentuximab vedotin, which represents 47% (16/34) of all patients with an investigator assessment of CR.

Six of the 18 patients who remain in remission received a consolidative allo-SCT, including 4 of 6 patients who went to allo-SCT in CR and the 2 patients who went to allo-SCT in PR. The proportion of patients with a best response of CR who remain in remission without a consolidative allo-SCT is 43% (12/28); the median observation time in this group is 52.5 months (range, 31.5 to 56.2). The 2 patients who went to allo-SCT in PR subsequently converted to CR.

Table 3. Characterization of patients who remain in remission per the investigator following treatment with brentuximab vedotin

	In remission* (n = 18)	All other responders† (n = 55)	Nonresponders (n = 29)
Demographics and baseline disease characteristics			
Median age in years (range)	26.5 (15-63)	32.0 (18-69)	35.0 (18-77)
Female, n (%)	12 (67)	31 (56)	11 (38)
ECOG performance status, n (%)			
Grade 0	10 (56)	22 (40)	10 (34)
Grade 1	8 (44)	33 (60)	19 (66)
Relapsed relative to most recent therapy,‡ n (%)	14 (78)	29 (53)	16 (55)
Primary refractory disease,§ n (%)	13 (72)	36 (65)	23 (79)
Stage, n (%)			
Stage I/II	14 (78)	27 (49)	10 (34)
Stage III	3 (17)	14 (25)	10 (34)
Stage IV	1 (6)	11 (20)	8 (28)
Median time in months from initial diagnosis to first dose (range)	36.5 (12-99)	46.1 (14-219)	38.1 (12-114)
Median time in months from last auto-SCT to relapse prior to b-v (range)	7.8 (1-63)	6.4 (1-131)	6.5 (0-53)
Median SPD (cm ²) per investigator (range)	16.1 (2-55)	24.5 (2-276)	29.1 (3-157)
Exposure			
Median duration of treatment in weeks (range)	43.6 (13-56)	30.1 (9-54)	20.9 (3-52)
Median number of cycles (range)	13.5 (4-16)	10 (3-16)	7 (1-16)
Median % relative dose intensity (range)	94.5 (73-103)	96.0 (69-107)	98.7 (79-102)
Adverse events, n (%)			
Serious adverse event	3 (17)	11 (20)	11 (38)
Adverse event discontinuation	5 (28)	9 (16)	6 (21)
≥Grade 3 adverse event	11 (61)	28 (51)	17 (59)
Peripheral neuropathy (standardized MedDRA query)	13 (72)	28 (51)	15 (52)

b-v, brentuximab vedotin.

*Patients with a best response of CR ($n = 16$) or PR ($n = 2$) on treatment who are still on study and in remission without the start of new anticancer therapy, other than allogeneic stem cell transplant. The 2 patients with a PR to brentuximab vedotin achieved CR subsequent to transplant.

†Patients with a best response of CR or PR on treatment who experienced progressive disease, initiated new therapy, or discontinued from the study for reasons including death, lost to follow-up, withdrawal of consent, and investigator decision.

‡Best response of CR or PR to most recent prior therapy.

§No CR or relapse within 3 months of front-line therapy.

Table 4. Demographics and baseline characteristics of patients with a best response of CR per the investigator by current status

	CR and in remission* (n = 16)	All other CR† (n = 18)
Median age in years (range)	26.5 (15-63)	38.5 (21-51)
Female, n (%)	10 (63)	13 (72)
ECOG performance status, n (%)		
Grade 0	9 (56)	9 (50)
Grade 1	7 (44)	9 (50)
Relapsed relative to most recent therapy,‡ n (%)	12 (75)	11 (61)
Primary refractory disease,§ n (%)	12 (75)	12 (67)
Stage, n (%)		
Stage I/II	12 (75)	12 (67)
Stage III	3 (19)	2 (11)
Stage IV	1 (6)	3 (17)
Median time in months from initial diagnosis to first dose (range)	36.5 (16-99)	45.8 (14-185)
Median time in months from last auto-SCT to relapse prior to b-v (range)	8.4 (1-63)	8.9 (2-31)
Median SPD (cm ²) per investigator (range)	16.1 (2-55)	17.3 (3-116)

b-v, brentuximab vedotin.

*Patients with a best response of CR on treatment who are still on study and in remission without the start of new anticancer therapy, other than allogeneic stem cell transplant.

†Patients with a best response of CR on treatment who either: experienced progressive disease, initiated new therapy, or discontinued from the study for reasons including death, lost to follow-up, withdrawal of consent, and investigator decision.

‡Best response of CR or PR to most recent prior therapy.

§No CR or relapse within 3 months of front-line therapy.

In an effort to identify characteristics associated with long-term remission, the 18 patients were compared with patients who had a CR or PR to brentuximab vedotin but who had subsequently progressed, started new therapy, or came off study (“all other responders”); as well as with patients who did not have at least a PR to brentuximab vedotin (“nonresponders”) (Table 3). Relative to other patients, those in remission tended to be female, younger, diagnosed with HL for a shorter period prior to receiving treatment with brentuximab vedotin, and have relapsed rather than refractory disease to the most recent prior therapy, a more favorable Eastern Cooperative Oncology Group (ECOG) performance score, and a smaller disease burden (ie, lower-stage disease and lower median sum of the products of diameters

[SPD]) prior to enrollment. Relative to other patients, those still in remission also received more cycles of brentuximab vedotin, which is not unexpected given the protocol requirement that patients with progressive disease discontinue treatment. Notably, patients still in remission were comparable to other patients with respect to the incidence and severity of AEs, suggesting that their longer treatment duration relative to the other patients was not directly attributable to a lesser AE burden.

The demographics and baseline disease characteristics of the 16 patients who achieved CR on brentuximab vedotin and who remain in remission were compared with those of the other 18 patients who achieved CR but who subsequently progressed, started new therapy, or came off study (Table 4). Although patients with CR who remain in remission were younger and had been diagnosed with HL for a shorter period of time relative to other patients with a best response of CR, the 2 groups were generally comparable across variables.

OS and PFS. After a median follow-up period of approximately 3 years for all enrolled patients, 47% of patients (48/102) were alive. The estimated median OS was 40.5 months (95% CI: 28.7, —; Figure 2). Patients who achieved a CR had a longer OS compared with those without a CR (CR: median not reached [95% CI: 48.1 months, —], PR: 39.4 months [95% CI: 22.9, —], and stable disease [SD]: 18.3 months [95% CI: 12.6, 36.8]). The estimated 3-year OS for the 34 patients with a CR to brentuximab vedotin was 73% (95% CI: 57%, 88%). The estimated 3-year OS was 80% (95% CI: 45%, 100%) for the subgroup of 6 patients with a CR who received a consolidative allo-SCT and 71% (95% CI: 54%, 88%) for the subgroup of 28 patients with a CR who did not receive a consolidative allo-SCT (Kaplan-Meier curves are shown in supplemental Figure 1, available on the *Blood* Web site).

Univariate analyses were conducted to explore potential associations between patient characteristics and OS. Five characteristics emerged as significant prognostic factors in univariate analyses: age, number of systemic chemotherapy regimens prior to treatment with brentuximab vedotin, baseline ECOG performance status score, baseline SPD, and baseline serum concentration of soluble CD30 (Table 5). Multivariate analyses revealed age, baseline ECOG status, and baseline SPD as significant independent prognostic factors for OS (Table 6).

The updated estimated median PFS per the investigator for all patients was 9.3 months (95% CI: 7.1, 12.2; Figure 3), which was approximately 3 months longer than the median PFS of 6.1 months (95% CI: 4.4, 7.2; Table 1) that was observed on the patients’ last systemic therapy prior to brentuximab vedotin. For approximately 64%

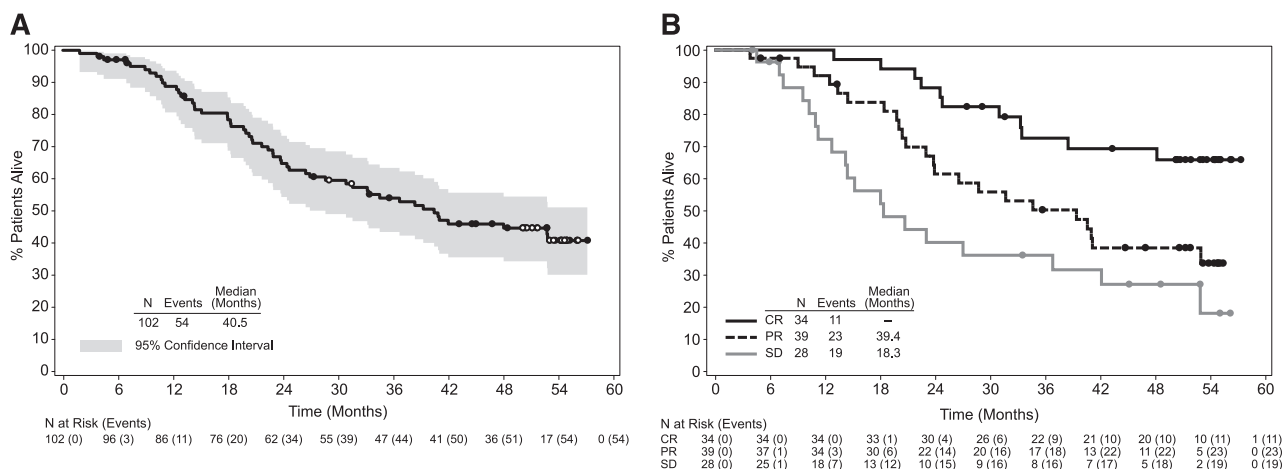


Figure 2. OS following treatment with brentuximab vedotin. OS was analyzed using Kaplan-Meier methodology and is shown overall (A) and by best response (B). All censored patients are indicated by dots on the Kaplan-Meier curve. Patients still on study and in remission without the start of new therapy are indicated by open dots on the Kaplan-Meier curve in panel A.

Table 5. Patient characteristics and OS (univariate analysis)

Characteristics	No. of patients (N = 102)	Hazard ratio	95% CI	P
Age*	—	1.33†	1.07, 1.65	.010
Gender				.505
Female‡	54			
Male	48	1.20	0.70, 2.05	
Total number of prior systemic therapy regimens*	—	1.12	1.01, 1.24	.026
Best response achieved with most recent regimen				.537
Objective response‡	47			
Stable disease	23	0.86	0.43, 1.71	
Progressive disease	26	1.34	0.7, 2.58	
Unknown/other	6	0.55	0.13, 2.31	
Any prior cancer-related radiotherapy				.975
Yes‡	67			
No	35	1.01	0.58, 1.76	
Time from initial diagnosis to first dose (months)*	—	1.00	0.99, 1.00	.406
Time since diagnosis (months)/ total no. of systemic therapies*	—	1.02	0.99, 1.06	.233
Time from last auto-SCT to relapse prior to b-v (months)*	—	1.00	0.98, 1.01	.694
PFS from prior cancer therapy (months)*	—	0.99	0.97, 1.01	.455
Stage at initial diagnosis,§ n (%)				.094
Stage I/II‡	51			
Stage III	27	1.64	0.84, 3.19	
Stage IV	20	2.04	1.04, 4.01	
Baseline ECOG performance status				.004
Grade 0‡	42			
Grade 1	60	2.37	1.32, 4.26	
Baseline electrocardiogram				.423
Normal‡	60			
Abnormal	42	1.25	0.73, 2.14	
Baseline SPD per investigator (cm ²)*	—	1.04	1.00, 1.08	.033
Baseline soluble CD30 (ng/mL)*	—	1.00	1.00, 1.00	.025
Primary refractory status				.931
No‡	30			
Yes	72	0.97	0.55, 1.73	
Disease status relative to most recent prior therapy				.089
Refractory‡	43			
Relapse	59	0.63	0.37, 1.07	
Baseline B symptoms				.662
No‡	67			
Yes	35	1.13	0.65, 1.97	

Significant factors in the univariate analysis are indicated in italic font.

b-v, brentuximab vedotin.

*Continuous variable.

†Hazard ratio applies to 10-year increments.

‡Reference level for the hazard ratio.

§Stage was unknown for 4 patients.

||Hazard ratio applies to 10-cm² increments.

(65/102) of enrolled patients, the PFS on brentuximab vedotin was longer than that reached on their last prior therapy (Figure 4). Most progression events occurred early and in patients who did not achieve CR: 78% (54/69) of all events occurred within the first year of observation and 87% (47/54) of events during the first year occurred in patients with PR or SD. A total of 16 patients have been followed longer than the last event that occurred at 36.4 months after the first dose of brentuximab vedotin; 15 of these patients (13 with a best response of

CR and 2 with a best response of PR) have been followed for at least 50 months without progression. The median PFS for patients who achieved CR has not been reached (95% CI: 21.7 months, —), which is in contrast to a median PFS of 5.8 months (95% CI: 3.8, 8.1) to the last prior therapy for the same group of patients. Thirty-one of the 34 patients (91%) with a best response of CR to brentuximab vedotin had a longer PFS on brentuximab vedotin than their last prior therapy. Three-year PFS was estimated at 58% (95% CI: 41%, 76%) for the 34 patients with a CR to brentuximab vedotin (Figure 3). The estimated 3-year PFS was 80% (95% CI: 45%, 100%) for the subgroup of 6 patients with a CR who received a consolidative allo-SCT and 53% (95% CI: 34%, 73%) for the subgroup of 28 patients with a CR who did not receive a consolidative allo-SCT (Kaplan-Meier curves available in supplemental Figure 1).

Discussion

Durable remissions and favorable long-term survival are observed in patients with relapsed/refractory HL who received treatment with brentuximab vedotin. Eighteen patients, 25% of patients with an objective response to brentuximab vedotin, remain on study and in remission without the start of new therapy, other than consolidative allo-SCT, after having been followed for a median of 53.3 months from their first dose. Ongoing remissions of more than 4 years are particularly noteworthy for a single agent in patients who had relapsed or progressed after both combination therapy and auto-SCT. Fifteen of the 18 patients have been followed for more than 4 years, or more than a year after the last progression event, which suggests that brentuximab vedotin may be curative in a fraction of patients. Of course, a decade or more of follow-up may be required before the curative potential of brentuximab vedotin in the multiply relapsed/refractory setting can be confirmed. Although relapses are usually clinically symptomatic and patient-reported signs and symptoms appear reliable in the detection of lymphoma progression,⁹⁻¹⁵ it is possible that progression based on CT assessment alone and in lieu of clinical symptoms may have been declared for some patients if the requirement for routine CT scanning had been maintained.

The median OS was estimated at 40.5 months after a median follow-up of approximately 3 years for all enrolled patients. A median OS of approximately 3.5 years compares favorably to the historical survival duration range of 10.5 to 27.6 months that has been reported for patients with HL who relapse/progress after auto-SCT.^{3,4} The median OS is particularly noteworthy given that patients in the present study, who have relapsed/progressed a median of only 6.7 months from their auto-SCT, represent a particularly vulnerable population. Shorter survival durations have been reported for patients who relapse within a year of transplant relative to patients who relapse later.^{3,16} Of course, given the potential for bias in comparisons to historical data, the ability of brentuximab vedotin to prolong survival in patients with relapsed/refractory HL requires confirmation in a randomized clinical trial.

Table 6. Patient characteristics and OS (multivariate analysis)

Characteristics	Hazard ratio	95% CI	P
Age*	1.33	1.05, 1.69	.016
Baseline ECOG performance status			.019
Grade 0‡			
Grade 1	2.05	1.13, 3.73	
Baseline SPD per investigator (cm ²)‡	1.06	1.01, 1.10	.009

*Continuous variable; hazard ratio applies to 10-year increments.

†Reference level for the hazard ratio.

‡Continuous variable; hazard ratio applies to 10-cm² increments.

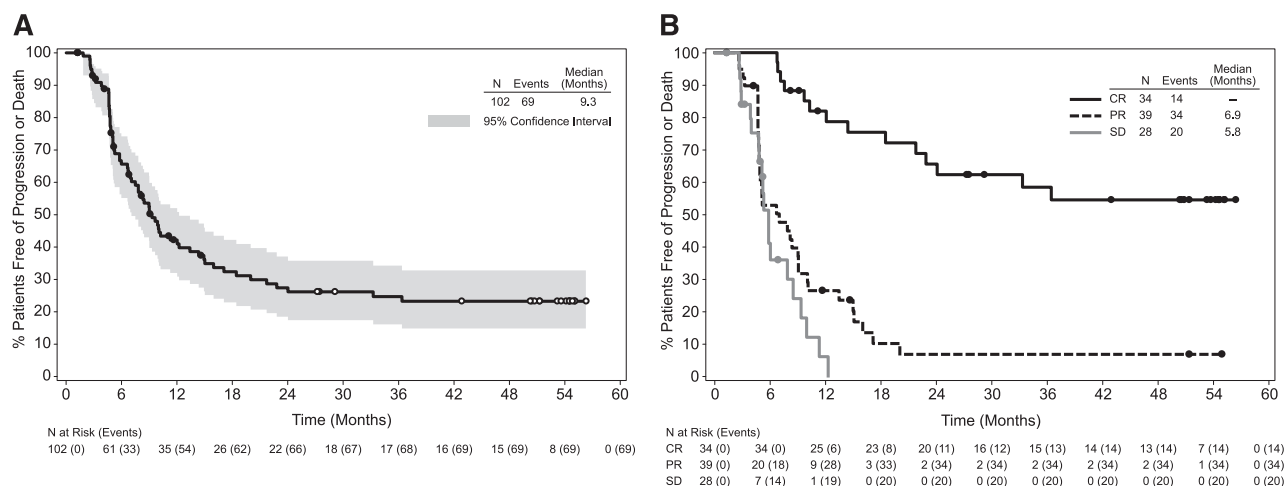


Figure 3. PFS following treatment with brentuximab vedotin. PFS was analyzed using Kaplan-Meier methodology and is shown overall (A) and by best response (B). All censored patients are indicated by dots on the Kaplan-Meier curve. Patients still on study and in remission without the start of new therapy are indicated by open dots on the Kaplan-Meier curve in panel A. One patient was not evaluable for response and is excluded from panel B.

Patients' median PFS on brentuximab vedotin was longer than the median PFS on their most recent prior therapy by more than 3 months (brentuximab vedotin: 9.3 months; most recent prior therapy: 6.1 months). Although shorter PFS durations could be expected to accompany subsequent therapies for patients with multiply relapsed disease, the majority of patients (64%) demonstrated a longer PFS on brentuximab vedotin compared with their most recent prior systemic therapy. Initiation of posttreatment anticancer therapy that included allo-SCT, additional cycles of brentuximab vedotin, as well as additional single-and combination chemotherapy regimens likely contributed to the prolonged survival that was observed relative to the PFS.

Attainment of a CR appeared critical for prolonged disease control. Sixteen of the 18 patients still in remission achieved CR on brentuximab vedotin, representing a long-term remission rate of 47% for patients with CR. The estimated medians for response duration, PFS, and OS have not been reached for patients who achieved CR. The vast majority of progressions occurred within the first year of observation and in patients with PR or SD. Acknowledging that patients must have had relapsed/refractory disease after their last prior therapy in order to enroll in this study, it is notable that patients who attained a CR on brentuximab vedotin did not enjoy longer disease control on their last prior therapy relative to other patients. Patients with a CR on

brentuximab vedotin had a median PFS of 5.8 months on their last prior therapy, which was comparable to the median PFS on prior therapy for all patients (6.1 months).

In addition to the majority having had attained a CR on brentuximab vedotin, the 18 patients who are still in remission after extended follow-up tended to be young females with a performance status score of "0" and smaller disease burden who had relapsed disease to their most recent prior therapy and less elapsed time since their HL diagnosis. These characteristics were also representative of the general ability to achieve a CR on brentuximab vedotin, with younger age and shorter elapsed times since diagnosis being even more pronounced in the subgroup of patients with CR who remain in remission. When baseline characteristics were explored across the total enrolled patient population for their association with OS, not surprisingly, younger age, a baseline ECOG performance status score of "0", and smaller baseline index lesion size emerged as significant favorable independent prognostic factors. The associations between lower age, improved baseline functioning, and lower disease burden with improved survival could suggest that lymphoma may best be treated with brentuximab vedotin in the minimal residual disease state, rather than waiting until frank relapse. Alternatively, these associations could simply reflect a cohort of younger, less impaired patients starting treatment with

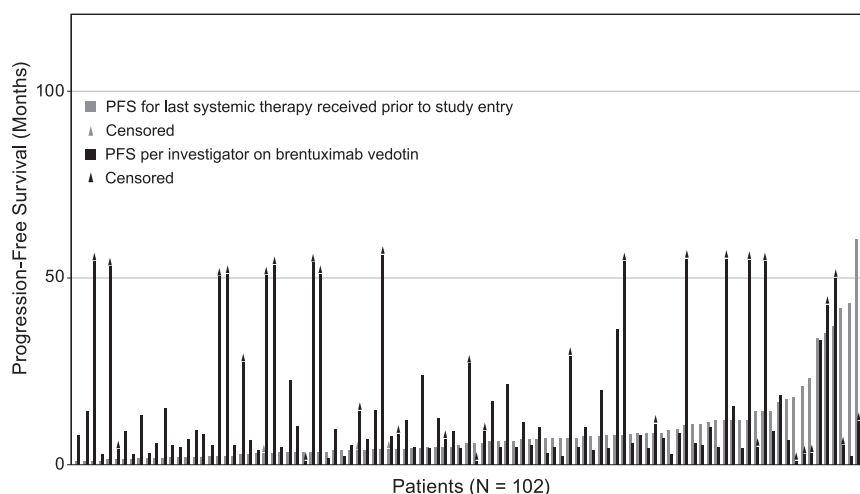


Figure 4. PFS relative to most recent prior therapy. Includes all enrolled patients (N = 102). PFS was analyzed using Kaplan-Meier methodology and was calculated for each patient's last systemic therapy received prior to study (gray bar) and on brentuximab vedotin (black). Triangles at the end of bars indicate censored patients. Patients are sorted left to right on the x-axis according to the duration of PFS on their last systemic therapy. Sixty-five patients (64%) had longer PFS on brentuximab vedotin than their last prior therapy.

brentuximab vedotin earlier in their disease course relative to other patients. Results from a phase 3 randomized, double-blind, placebo-controlled study evaluating the potential of brentuximab vedotin to prevent relapse post–auto-SCT in patients at high risk of lymphoma progression (AETHERA trial, ClinicalTrials.gov #NCT01100502) will help determine the benefit of treatment with brentuximab vedotin earlier in the disease course of HL.

Allografting select patients with HL has been used to improve clinical outcomes,^{5,17-27} and recent case series have started to explore brentuximab vedotin as a potential “bridge” to allo-SCT.²⁸⁻³² Eight patients (6 in CR and 2 in PR) in the present study received an allo-SCT as their first treatment after discontinuing brentuximab vedotin. Four of 6 patients who received an allo-SCT in CR remain progression-free, with the 3-year PFS rate estimated at 80% for this small population. This rate compares favorably to 3-year PFS rates of 22%²⁴ to 25%²⁰ that have been reported for patients with relapsed/refractory HL who undergo allo-SCT and is consistent with the higher PFS rates of 50% to 62% (4 years) reported for subsets of patients who enter allo-SCT in CR or with minimal residual disease.^{5,18} The proportion of patients remaining in remission was slightly higher in the subgroup of patients who achieved a CR on brentuximab vedotin and received a consolidative allo-SCT (4 of 6, or 67%) relative to patients who achieved a CR on treatment and who did not undergo transplant (43%). However, the number of patients who received an allo-SCT was small, and additional studies are required to determine whether allo-SCT is the best management approach for patients who achieve remission on brentuximab vedotin. Whether consolidative allo-SCT has a role in improving outcomes for patients who achieve a best response of PR to brentuximab vedotin is worthy of further exploration in light of the observation that both patients in the current study who received an allo-SCT in PR converted to CR and remain in remission.

Brentuximab vedotin can induce durable remissions in a subset of heavily pretreated patients with HL who had relapsed post–auto-SCT, and the OS compares favorably to historical data. The single-arm design is a limitation of the study. Results from the AETHERA trial will provide PFS estimates for brentuximab vedotin relative to best supportive care in patients at risk of relapse after auto-SCT. A randomized phase 3 study is also being conducted to evaluate brentuximab vedotin in combination with AVD (doxorubicin, vinblastine, and dacarbazine) vs ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for front-line treatment of HL (Echelon-1 trial, ClinicalTrials.gov #NCT01712490). Together, these phase 3 studies will help evaluate the role of brentuximab vedotin alone and in combination with standard chemotherapy in earlier phases of HL.

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Authorship

Contribution: A.K.G., R.C., E.K.L., X.C., and E.L.S. contributed to the analysis and interpretation of data and wrote the manuscript; A.K.G., R.C., S.E.S., S.M.A., J.D.R., K.J.S., J.M.C., A.E., and A.Y. contributed to the acquisition of the data; S.E.S., S.M.A., J.D.R., K.J.S., J.M.C., A.E., and A.Y. critically reviewed the manuscript; and all authors contributed to the concept and design of the study and approved the final version of the manuscript.

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