CLINICAL TRIALS AND OBSERVATIONS

Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

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Key Points

- A total of 38% of patients who achieved CR (13 of 34) on brentuximab vedotin have remained in remission for >5 years and may be cured.
- Nine of the 13 patients (9% of all enrolled patients) have remained in long-term remission without a consolidative allogeneic transplant.

Presented here are the 5-year end-of-study results from the pivotal phase 2 trial of brentuximab vedotin in patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL) after failed hematopoietic autologous stem cell transplantation. At 5 years, the overall patient population (N = 102) had an estimated overall survival (OS) rate of 41% (95% confidence interval [CI]: 31-51) and progression-free survival (PFS) rate of 22% (95% CI: 13-31). Patients who achieved a complete response (CR) to brentuximab vedotin (N = 34) had estimated OS and PFS rates of 64% (95% CI: 48-80%) and 52% (95% CI: 34-69%), respectively. The median OS and PFS were not reached in CR patients, with 13 patients (38% of all CR patients) remaining in follow-up and in remission at study closure. Of the 13 patients, 4 received consolidative hematopoietic allogeneic stem cell transplant, and 9 (9% of all enrolled patients) remain in sustained CR without receiving any further anticancer therapy after treatment with brentuximab vedotin. Of the patients who experienced treatment-emergent peripheral neuropathy, 88% experienced either resolution (73%) or improvement (14%) in symptoms. These 5-year follow-up data demonstrate that a subset of patients with R/R HL who obtained CR with single-agent brentuximab

vedotin achieved long-term disease control and may potentially be cured. The trial was registered at www.clinicaltrials.gov as #NCT00848926. (*Blood*. 2016;128(12):1562-1566)

Introduction

Brentuximab vedotin (ADCETRIS; Aptuit [Glasgow] Ltd., Glasgow, United Kingdom) is an anti-CD30 antibody conjugated by a protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E (MMAE). Targeted delivery of MMAE to CD30-expressing tumor cells is the primary mechanism of action. Additional mechanisms of tumor cell killing that may contribute to the clinical activity of brentuximab vedotin include antibody-dependent cellular phagocytosis, immunogenic cell death, and the bystander effect.

We previously reported the primary results for the pivotal trial of brentuximab vedotin in 102 patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL) after failed autologous stem cell transplantation (auto-SCT), with a complete response (CR) rate of 34% (95% confidence interval [CI]: 25.2-44.4) and objective response rate of 75% (95% CI: 64.9-82.6) per independent review. Brentuximab vedotin received

accelerated US Food and Drug Administration (FDA) approval for patients with R/R HL after auto-SCT or failure of ≥ 2 prior therapies.

In the pre-brentuximab vedotin era, options were limited and outcomes were poor for HL patients who relapsed or progressed after auto-SCT, with median overall survival (OS) ranging from 10.5 to 27.6 months. ^{8,9} Reduced intensity conditioning (RIC) allogeneic SCT (allo-SCT) strategies have been studied, but toxicity is high and relapses are common, with 2- to 3-year nonrelapse mortality and median progression-free survival (PFS) ranging from 13% to 23% and 20% to 30%, respectively, ¹⁰⁻¹³ and a 5-year OS of 28%. ¹³

Previous reports from the pivotal phase 2 trial of brentuximab vedotin demonstrated both significant efficacy and 3-year disease control in heavily pretreated R/R HL patients.^{7,14} Herein, we present the final end-of study results per investigator assessment.

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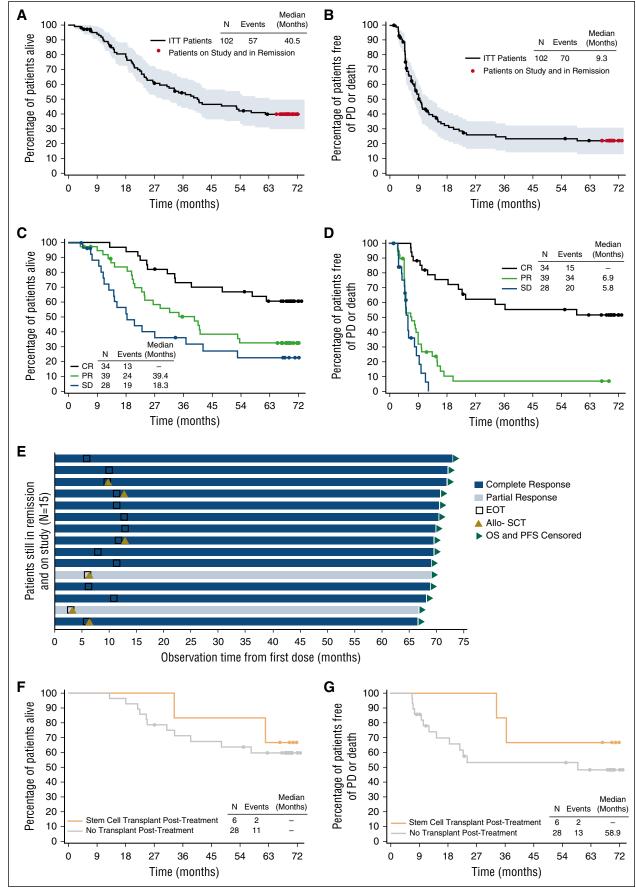


Figure 1.

Study design

Complete descriptions of the study design and statistical analyses have been reported. Patients received 1.8 mg/kg brentuximab vedotin via outpatient intravenous infusion over 30 minutes, once every 3 weeks, for up to 16 cycles. Clinical response was determined by independent central review and by investigators using the Revised Response Criteria for Malignant Lymphoma. Response duration was calculated from the first objective tumor response (CR or partial response [PR]) to tumor progression or death due to any cause, and PFS was calculated from the start of treatment to tumor progression or death. Patients were censored at their last radiologic or clinical assessment that documented the absence of progressive disease. OS was calculated from the start of study treatment to date of death due to any cause and was censored at the last date the patient was known to be alive.

To capture all peripheral neuropathy (PN) events, an analysis was performed using the standard Medical Dictionary for Regulatory Activities. Grade of severity was determined per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Prior to study initiation, the protocol, informed consent form, and any advertisements for patient recruitment were approved by each site's institutional review board or independent ethics committee.

Results and discussion

At the time of study closure, which occurred \sim 5 years from the last patient's end of treatment visit, 15 patients remained on study and in remission without the start of new therapy other than consolidative allo-SCT. These 15 patients had a median observation time of 69.5 months (range, 66.5-72.9 months). The median observation time for all enrolled patients (N = 102) from first dose was 35.1 months (range, 1.8-72.9 months). The median OS and PFS were 40.5 (95% CI: 28.7-61.9) and 9.3 months (95% CI: 7.1-12.2), respectively (Figure 1A-B), and the estimated 5-year OS and PFS rates were 41% (95% CI: 31-51) and 22% (95% CI: 13-31), respectively.

Of the 102 enrolled patients, 77 (75%) received \geq 1 anticancer therapy following brentuximab vedotin. Forty-four of the 77 patients received multiagent therapy, 42 received single-agent therapy, and 22 underwent stem cell transplant, 8 of whom received consolidative allo-SCT. Excluding consolidative allo-SCT, the median number of subsequent treatments received was 3 (range, 1-10). Thirteen of the 77 received brentuximab vedotin retreatment (10 as single-agent and 3 in a multiagent regimen), and 6 patients received treatment with a programmed death 1 pathway inhibitor (5 as single agent and 1 in a combination therapy), as summarized in supplemental Table 1, available on the *Blood* Web site. Brentuximab vedotin retreatment results, including a second response in 60% (30% CR) of HL patients with median response duration of 9.2 months, have been described previously. 16

Per investigator, 34 of the 102 enrolled patients (33%) achieved a CR on the study, and improved outcomes were observed for this group. The median response duration was not reached in this subset (95% CI: 20.5, nonestimable [range, 2 to 71.6+]), the estimated 5-year OS rate was 64% (95% CI: 48-80), and PFS was 52% (95% CI: 34-69) (Figure 1C-D). Of the 15 patients in remission at study closure, 13 had achieved CR (having received a median 14 cycles of brentuximab

vedotin) and 2 achieved a PR (median, 6.5 cycles) as their best response. The 2 PR patients converted to CR after allo-SCT (Figure 1E). Relative to their most recent prior therapy, 12 of these patients had relapsed, and 3 had refractory disease. Nine patients had primary refractory disease defined as failure to achieve CR or relapse within 3 months of frontline therapy.

Of the 13 CR patients that remained in follow-up and in remission, 4 patients underwent a consolidative allo-SCT, and 9 (26% of all CR patients) received no further cancer treatment after brentuximab vedotin. Characterization of these 9 patients with sustained remission and the patients who achieved CR but subsequently relapsed without having received a consolidative allo-SCT are provided in Table 1. Patients with sustained CR tended to be younger and with more extranodal disease relative to patients who did not achieve CR, and had a shorter interval from both initial diagnosis and most recent relapse to initiation of treatment with brentuximab vedotin. ¹⁴ By-patient demographics and disease characteristics for these 9 patients are provided in supplemental Table 2.

Of the 34 CR patients, there were 6 total that underwent a consolidative allo-SCT as their next therapy subsequent to brentuximab vedotin. The estimated 5-year PFS and OS rates are 67% (95% CI: 29-100) and 83% (95% CI: 54-100) for these 6 patients, and 48% (95% CI: 28-68) and 60% (95% CI: 41-78) for the other 28 nontransplant CR patients (Figure 1F-G), respectively. As there were only 6 patients that underwent consolidative allo-SCT on this study, further studies are needed to define which patients may benefit from this therapy. Among the 6, 2 patients died and 4 remained in CR at study closure. Of the 28 patients who did not receive consolidative allo-SCT, 14 were known to have relapsed lymphoma, 10 remained in remission (1 of whom received consolidative radiation which was considered a new treatment), and 4 came off study prior to closure due to other reasons.

PN is the most common adverse effect associated with accumulated exposure to brentuximab vedotin. Patients on the pivotal trial who experienced PN symptoms were followed for improvement and/or resolution until ~ 3 years into long-term follow-up. Of the 56 patients (55% of enrolled patients) who experienced PN, 49 (88%) experienced resolution or improvement, with 41 (73%) reporting complete resolution and 8 (14%) reporting some improvement at last assessment. Of the 15 patients with ongoing neuropathy at last follow-up, 11 patients had grade 1 severity and 4 patients had grade 2. Overall, patients experienced resolution or improvement of symptoms from 1 week to >1 year after onset. Of the 15 patients in remission at study closure, 10 experienced PN, with 9 experiencing complete resolution. Larger experiences with brentuximab vedotin have been described in recent reports and support PN and neutropenia as the most common adverse effects associated with this therapy. 17,18

In these final results, we report that 9% (9 of 102) of the enrolled study population has achieved long-term remission exceeding 5 years in response to single-agent brentuximab vedotin without any additional therapy. Given that the historical outcomes are poor for HL patients who relapse after auto-SCT, these results provide a new perspective on prognosis for this patient population in the brentuximab vedotin era. For patients who achieve CR in response to brentuximab vedotin, the notion that RIC allo-SCT is the only option for long-term disease control is challenged. These results show that CR patients have a 5-year OS of

Table 1. Characterization of patients with a best response of CR (N = 34) following treatment with single-agent brentuximab vedoting

	CR no PD no EOS and no New treatment (N = 9)	CR with PD or death due to disease (N = 14)	All other CR (N = 11)
Age in years			
Median	27.0	41.0	28.0
Range	15, 63	21, 51	20, 54
95% CI for median	20.6, 45.0	32.4, 44.2	23.8, 37.5
Sex			
Male, n (%)	5 (56)	4 (29)	2 (18)
95% CI for male percentage	21.2, 86.3	8.4, 58.1	2.3, 51.8
Female, n (%)	4 (44)	10 (71)	9 (82)
95% CI for male percentage	13.7, 78.8	41.9, 91.6	48.2, 97.7
ECOG performance status	,	,	,
Grade 0, n (%)	5 (56)	8 (57)	5 (45)
95% CI for ECOG 0 percentage	21.2, 86.3	28.9, 82.3	16.7, 76.6
Grade 1, n (%)	4 (44)	6 (43)	6 (55)
95% CI for ECOG 1 percentage	13.7, 78.8	17.7, 71.1	23.4, 83.3
Disease status relative to most recent prior	16.7, 76.5	17.7, 7 1.1	20.1, 00.0
therapy*			
* *	6 (67)	8 (57)	0 (82)
Relapse, n (%)	6 (67) 29.9, 92.5	8 (57) 28.9, 82.3	9 (82) 48.2, 97.7
95% CI for relapse percentage			,
Refractory, n (%)	3 (33) 7.5, 70.1	6 (43) 17.7, 71.1	2 (18) 2.3, 51.8
95% CI for refractory percentage			
Primary refractory disease, n (%)†	6 (67)	9 (64)	9 (82)
95% CI for percentage	54.1, 100.0	66.4, 100.0	66.4, 100.0
Stage	7 (70)	2 (2.1)	0 (70)
Stage I/II, n (%)	7 (78)	9 (64)	8 (73)
95% for I/II percentage	40.0, 97.2	35.1, 87.2	39.0, 94.0
Stage III	1 (11)	2 (14)	2 (18)
95% CI for III percentage	0.3, 48.2	1.8, 42.8	2.3, 51.8
Stage IV	1 (11)	2 (14)	1 (9)
95% CI for IV percentage	0.3, 48.2	1.8, 42.8	0.2, 41.3
Median time in months from initial diagnosis to	−37.5 (-98.7, −16.4)	-45.8 (-184.7, -14.4)	-29.7 (-134.6, -21.0)
first dose (range)			
95% CI	-67.9, -27.3	-90.5, -35.3	-66.7, -21.3
Median time in months from most recent	−1.3 (- 5.6, −1.1)	-3.0 (-4.0, -0.9)	-2.3 (-8.5, -0.7)
relapse to first dose (range)‡			
95% CI	-4.9, -0.3	-3.7, -1.7	-6.2, -1.4
Median SPD (cm²) per investigator (range)	11.3 (2.0, 55.2)	18.4 (2.5, 59.0)	16.7 (4.0, 116.1)
95% CI	4.4, 41.2	13.3, 33.8	4.5, 46.3
Extranodal status, n (%)§			
No	4 (44)	9 (64)	5 (45)
95% for No percentage	13.7, 78.8	35.1, 87.2	16.7, 76.6
Yes	5 (56)	5 (36)	6 (55)
95% for Yes percentage	21.2, 86.3	12.8, 64.9	23.4, 83.3
Number of prior cancer-related systemic			
therapy regimens¶			
Median	4.0	3.5	2.0
Range	2, 7	2, 13	1, 9
95% for median	2.3, 4.8	2.9, 6.4	1.7, 4.8
Visit of earliest best response	,	,	,
Cycle 2, n (%)	2 (22)	1 (7)	1 (9)
95% CI for C2 percentage	2.8, 60.0	0.2, 33.9	0.2, 41.3
Cycle 4, n (%)	3 (33)	8 (57)	7 (64)
95% CI for C4 percentage	7.5, 70.1	28.9, 82.3	30.8, 89.1
Cycle 7, n (%)	1 (11)	4 (29)	2 (18)
95% CI for C7 percentage	0.3, 48.2	8.4, 58.1	2.3, 51.8
Cycle 10, n (%)	2 (22)	1 (7)	1 (9)
95% CI for C10 percentage	2.8, 60.0	0.2, 33.9	0.2, 41.3
Cycle 16, n (%)	1 (11)	_	_
95% CI for C16 percentage	0.3, 48.2	_	_

The categories of CR no PD no EOS No new treatment and Known PD per INV or death due to disease exclude patients with consolidative stem cell transplant. Patients with consolidative stem cell transplant are included in the All other CR column. ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; SPD, sum of the products of diameters.

^{*}Relapse = best response of CR or PR to most recent prior therapy; Refractory = best response of SD or PD to most recent prior therapy.

[†]No CR or relapse within 3 months of frontline therapy.

[‡]For those with relapsed disease status to most recent prior therapy.

[§]Extranodal lesions identified by the investigator as either index or non-index lesions at the baseline assessment.

[¶]Includes chemotherapy given for stem cell mobilization.

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64% and PFS of 52%, with the majority not undergoing allo-SCT (28 vs 6), and 9 of 28 experiencing durable remissions in the absence of allo-SCT. Furthermore, the reported toxicities were manageable, with the most common toxicity of PN demonstrating a high rate of resolution. Encouragingly, the rate continues to increase over time, with 88% of patients demonstrating complete resolution or improvement at 5 years vs 80% at last report.⁷

In summary, these end-of-study survival outcomes and freedom-from-progression results demonstrate that, among patients with R/R HL, a substantial fraction of patients who obtained CR with single-agent brentuximab vedotin have achieved long-term disease control and may potentially be cured.

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Authorship

Contribution: R.C., A.K.G., E.K.L., D.H., and A.F. contributed to the analysis and interpretation of the data and wrote the manuscript; R.C., A.K.G., 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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