Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background High-dose therapy followed by autologous stem-cell transplantation is standard of care for patients with relapsed or primary refractory Hodgkin's lymphoma. Roughly 50% of patients might be cured after autologous stem-cell transplantation; however, most patients with unfavourable risk factors progress after transplantation. We aimed to assess whether brentuximab vedotin improves progression-free survival when given as early consolidation after autologous stem-cell transplantation.

Methods We did this randomised, double-blind, placebo-controlled, phase 3 trial at 78 sites in North America and Europe. Patients with unfavourable-risk relapsed or primary refractory classic Hodgkin's lymphoma who had undergone autologous stem-cell transplantation were randomly assigned, by fixed-block randomisation with a computer-generated random number sequence, to receive 16 cycles of 1·8 mg/kg brentuximab vedotin or placebo intravenously every 3 weeks, starting 30–45 days after transplantation. Randomisation was stratified by best clinical response after completion of salvage chemotherapy (complete response *vs* partial response *vs* stable disease) and primary refractory Hodgkin's lymphoma versus relapsed disease less than 12 months after completion of frontline therapy versus relapse 12 months or more after treatment completion. Patients and study investigators were masked to treatment assignment. The primary endpoint was progression-free survival by independent review, defined as the time from randomisation to the first documentation of tumour progression or death. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01100502.

Findings Between April 6, 2010, and Sept 21, 2012, we randomly assigned 329 patients to the brentuximab vedotin group (n=165) or the placebo group (n=164). Progression-free survival by independent review was significantly improved in patients in the brentuximab vedotin group compared with those in the placebo group (hazard ratio [HR] 0·57, 95% CI 0·40–0·81; p=0·0013). Median progression-free survival by independent review was 42·9 months (95% CI 30·4–42·9) for patients in the brentuximab vedotin group compared with 24·1 months (11·5–not estimable) for those in the placebo group. We recorded consistent benefit (HR <1) of brentuximab vedotin consolidation across subgroups. The most frequent adverse events in the brentuximab vedotin group were peripheral sensory neuropathy (94 [56%] of 167 patients *vs* 25 [16%] of 160 patients in the placebo group) and neutropenia (58 [35%] *vs* 19 [12%] patients). At time of analysis, 28 (17%) of 167 patients had died in the brentuximab vedotin group compared with 25 (16%) of 160 patients in the placebo group.

Interpretation Early consolidation with brentuximab vedotin after autologous stem-cell transplantation improved progression-free survival in patients with Hodgkin's lymphoma with risk factors for relapse or progression after transplantation. This treatment provides an important therapeutic option for patients undergoing autologous stem-cell transplantation.

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Introduction

High-dose therapy followed by autologous stem-cell transplantation is standard of care for patients with relapsed or primary refractory Hodgkin's lymphoma. Two randomised trials[1,2] showed a significant improvement in progression-free survival after autologous stem-cell transplantation and several large studies[3–8] have shown that this procedure can provide a cure in roughly 50% of patients. Risk factors have been extensively studied to identify patients most likely to benefit from autologous stem-cell transplantation. Factors consistently reported to be associated with poor prognosis include primary

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refractory Hodgkin's lymphoma, an initial remission duration of less than 1 year, and presence of extranodal or advanced-stage disease at time of relapse.[3,4,6–14] Two important risk factors before autologous stem-cell transplantation are lack of chemosensitivity to pre-autologous stem-cell transplantation salvage chemotherapy, and residual disease at the time of high-dose therapy, defined by CT or PET.[3,4,6,9,15]

Various treatment strategies to improve outcomes after autologous stem-cell transplantation have been investigated, including PET-adapted approaches,[9] intensification of the conditioning regimen,[11] radiation before or after transplantation,[16] tandem transplantation,[17,18] and consolidation therapy after transplantation.[19,20] Investigators of previous studies of consolidation therapy have been challenged by the difficulty of delivery of effective and well-tolerated therapy early after autologous stem-cell transplantation, when there might be the greatest therapeutic effect.

Brentuximab vedotin consists of an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E. Brentuximab vedotin showed substantial efficacy, including an objective response rate of 75% and a complete remission rate of 34%, in a pivotal phase 2 study[21] of patients with CD30-positive Hodgkin's lymphoma in whom high-dose therapy and autologous stem-cell transplantation had been ineffective; longer-term follow-up showed a median overall survival of 40·5 months (95% CI 28·7–not estimable).[22] As a targeted therapy with a low frequency of severe haematologic toxic effects, brentuximab vedotin might provide a unique opportunity to deliver pre-emptive therapy after autologous stem-cell transplantation. We did the AETHERA study to investigate whether brentuximab vedotin improves progression-free survival in patients with relapsed or primary refractory Hodgkin's lymphoma when given as early consolidation after autologous stem-cell transplantation.

See Online for appendix

Methods

Study design and patients

We did this randomised, double-blind, placebo-controlled, phase 3 trial at 78 sites in North America and Europe. We included patients (aged ≥18 years) with histologically confirmed classical Hodgkin's lymphoma who had undergone high-dose therapy and autologous stem-cell transplantation before randomisation. Eligible patients had at least one of the following risk factors for progression after autologous stem-cell transplantation: primary refractory Hodgkin's lymphoma (failure to achieve complete remission, as determined by investigator), relapsed Hodgkin's lymphoma with an initial remission duration of less than 12 months, or extranodal involvement at the start of pre-transplantation salvage chemotherapy. Furthermore, patients had to have had complete remission, partial remission, or stable disease after pre-transplantation salvage chemotherapy, and adequate liver, kidney, and bone marrow function on the basis of haematology and chemistry laboratory results. We excluded patients who had previously received brentuximab vedotin. Patients who had undergone more than one previous autologous stem-cell transplantation were allowed to participate.

Patients provided written informed consent in accordance with the Declaration of Helsinki and the study was approved by the institutional review board at each study site.

Randomisation and masking

Participants were randomly assigned (1:1), via fixed-block randomisation with computer-generated random numbers, to receive either 1·8 mg/kg intravenous brentuximab vedotin or placebo. Randomisation was stratified by best clinical response after completion of salvage chemotherapy, in accordance with 2007 international consensus criteria[23] (complete response *vs* partial response *vs* stable disease) and primary refractory Hodgkin's lymphoma versus relapsed disease less than 12 months after completion of frontline therapy versus relapse 12 months or more after treatment completion. Patients and study investigators were masked to treatment assignment.

Procedures

Administration of brentuximab vedotin or placebo was done over 30 min on day 1 of each 21 day cycle once every 3 weeks for up to 16 cycles. This dosing regimen was safe and effective in a pivotal phase 2 study[21] of brentuximab vedotin in patients with relapsed or refractory Hodgkin's lymphoma in whom autologous stem-cell transplantation had been ineffective. Infection prophylaxis for herpes simplex virus, varicella-zoster virus, and *Pneumocystis jiroveci* after autologous stem-cell transplantation were to be followed as per standard international guidelines, and we allowed growth factor and blood product support.[24] Dose modifications were also allowed (appendix). If patients met radiographical criteria for progressive disease, as determined by the investigator, treatment assignment could be revealed and patients in the placebo group were given the opportunity to receive brentuximab vedotin, when not available commercially, as part of a separate study (ClinicalTrials.gov, number NCT0 1196208).

We assessed disease progression in accordance with the Revised Response Criteria for Malignant Lymphoma[23] and did CT scans at baseline and at months 3, 6, 9, 12, 18, and 24 after first dose. Scans after 24 months were done at the discretion of the investigator. Although PET scans could be done, we used only CT-scan criteria for determination of radiographical progression. An independent review facility assessed CT scans and biopsy results (if available) to assess disease progression; however, investigator assessment of progression was used for all treatment decisions and administration of new therapy. After 24 months, patients were followed up for survival and

disease status (if available), every 6 months until study closure. Safety assessments included the recording of adverse events, including serious adverse events, concomitant drugs, physical examination findings, and laboratory tests. We graded the severity of adverse events with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4). Safety was monitored by an independent data monitoring committee.

Outcomes

The primary endpoint was progression-free survival by independent review, defined as the time from randomisation to the first documentation of tumour progression or death. Secondary endpoints were overall survival and safety.

Statistical analysis

Patients without progression by independent review, but with disease progression by investigator assessment, were censored at the time of the last radiographical assessment before receipt of subsequent therapy. The protocol did not include regular radiographical assessments after 24 months, although radiographical assessments could be done at the discretion of the investigator. Progression-free survival by investigator assessment was a prespecified sensitivity analysis. Patients without documented progression were censored at the time of the last radiographical assessment or physical exam without known progression before receipt of subsequent therapy. Unlike the primary analysis, this sensitivity analysis included regularly scheduled clinical lymphoma assessments after 24 months (appendix). We did an additional prespecified sensitivity analysis with censoring rules defined in the European Medicines Agency's (EMA) scientific guideline, which disregards missed visits or initiation of new anticancer treatment for censoring. We did a prespecified interim analysis of overall survival at the time of primary analysis of progression-free survival. Final analysis of overall survival was planned at study closure, roughly 6 years after the first patient started study treatment.

We used the Kaplan-Meier method to analyse both progression-free and overall survival, with p values calculated based on the log-rank test stratified for the randomisation stratification factors, and hazard ratios (HRs) estimated based on stratified Cox regression models. Efficacy analysis was on an intention-to-treat basis while the safety analysis set consisted of patients who received at least one dose of study drug, irrespective of allocated treatment.

An event-based analysis (202 events) was originally planned for the primary efficacy analysis to detect an HR of 0·667 with the log-rank test, with 80% power and an overall one-sided α level of 0·025. After all patients had been enrolled, an analysis of masked, pooled progression-free survival data showed that 202 events were unlikely to be recorded in the study. Historical data for patients with Hodgkin's lymphompa after autologous stem-cell transplantation shows that most events happen within the first 24 months after transplantation.[4,25] For this reason, we amended the protocol to do the primary efficacy analysis upon completion of all scheduled radiographical assessments. One prespecified interim analysis for futility was done by an independent statistical reporting group when 50% of the originally planned progression-free survival events (ie, 101 events) had been recorded. With the target HR of 0·667 and 101 observed progression-free survival events, the boundary at the futility analysis expressed as a p value was 0·2879.

This trial is registered with Clinicaltrials.gov, number NCT01100502.

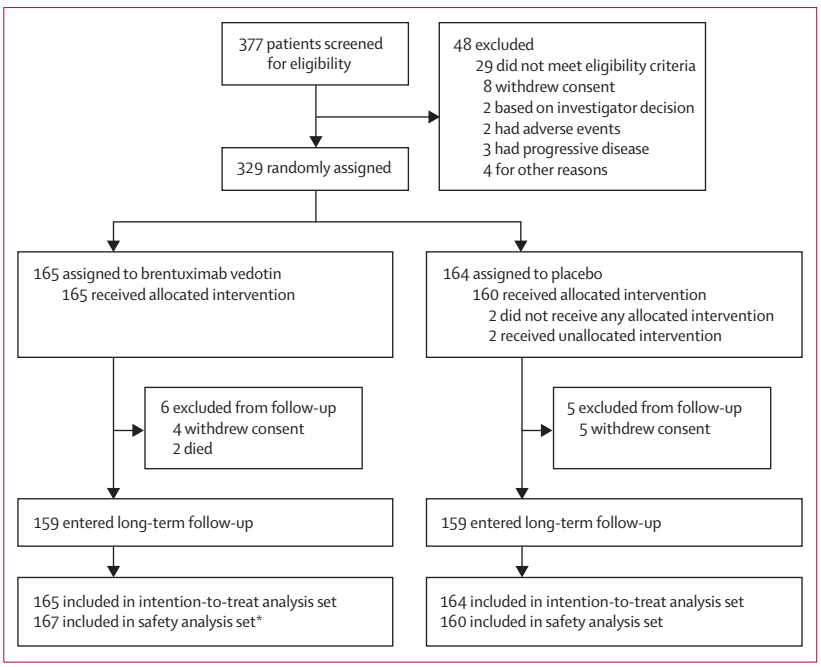

***Figure 1*: Trial profile**

*Two patients allocated to the placebo group received a dose of brentuximab vedotin.

Role of the funding source

The sponsors of the study had a role in study design, data analysis, data interpretation, and writing of the report; the investigators collected the data and the sponsor verified its accuracy. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between April 6, 2010, and Sept 21, 2012, we randomly assigned 329 patients to either the brentuximab vedotin group (n=165) or the placebo group (n=164; figure 1). All patients had discontinued treatment as of July 25, 2013, and the data cutoff for the primary efficacy analysis was Aug 18, 2014. A higher proportion of female patients and black patients were assigned to the brentuximab vedotin

group; otherwise, baseline characteristics were generally similar between treatment groups (table 1). A high proportion of patients had primary refractory Hodgkin's lymphoma or had relapsed less than 12 months from the completion of frontline therapy (table 1). At the time of salvage therapy, a third of all patients had extranodal disease and roughly a quarter had B symptoms (table 1). Before high-dose therapy, best responses to salvage therapy were complete remission in 123 (37%) patients, partial remission in 113 (34%) patients, and stable disease in 93 (28%) patients; 149 (45%) received at least two salvage regimens (table 1). All patients had discontinued treatment at the time of data cutoff for the primary analysis, and 251 patients remained in long-term follow-up (122 [74%] patients in the brentuximab vedotin group and 129 [79%] patients in the placebo group). Reasons for treatment discontinuation were completion of 16 cycles of therapy (78 [47%] patients given brentuximab vedotin and 81 [49%] patients given placebo), progressive disease (24 [15%] and 69 [42%] patients, respectively), adverse events (54 [33%] and ten [6%] patients, respectively), and patient decision (nine [5%] and four [2%] patients, respectively). The most common adverse events leading to discontinuation of brentuximab vedotin were peripheral sensory and motor neuropathies (data not shown).

	Brentuximab vedotin group (n=165)	Placebo group (n=164)
Age (years)	33 (18–71)	32 (18–76)
Sex		
Male	76 (46%)	97 (59%)
Female	89 (54%)	67 (41%)
Race		
Asian	2 (1%)	3 (2%)
Black or African American	10 (6%)	2 (1%)
White	153 (93%)	156 (95%)
Other	0	3 (2%)
ECOG performance status		
0	87 (53%)	97 (59%)
1	77 (47%)	67 (41%)
2	1 (1%)	0
Centrally confirmed Hodgkin's lymphoma	159 (96%)	156 (95%)
Number of previous cancer-related systemic salvage therapies		
1	94 (57%)	86 (52%)
≥2	71 (43%)	78 (48%)
>1 previous ASCT	5 (3%)	10 (6%)
Time from ASCT to first dose (days)	41 (28–49)	41 (30–51)
Frontline therapy		
ABVD	119 (72%)	129 (79%)
BEACOPP	26 (16%)	20 (12%)
Other	20 (12%)	15 (9%)
Stem-cell transplantation conditioning regimen		
BEAM	106 (64%)	96 (59%)
CBV	13 (8%)	22 (13%)
Other	46 (28%)	46 (28%)
Any radiation	11 (7%)	10 (6%)
Hodgkin's lymphoma status after frontline therapy		
Refractory	99 (60%)	97 (59%)
Relapse <12 months	53 (32%)	54 (33%)
Relapse ≥12 months	13 (8%)	13 (8%)
Best response to salvage therapy after ASCT		
Complete remission	61 (37%)	62 (38%)
Partial remission	57 (35%)	56 (34%)
Stable disease	47 (28%)	46 (28%)
Pre-ASCT PET status		
Fluorodeoxyglucose positive	64 (39%)	51 (31%)
Fluorodeoxyglucose negative	56 (34%)	57 (35%)
Unknown	45 (27%)	56 (34%)
Extranodal involvement at pre-ASCT relapse	54 (33%)	53 (32%)
B symptoms after frontline therapy	47 (28%)	40 (24%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. ASCT=autologous stem-cell transplantation. ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine. BEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone. BEAM=carmustine, etoposide, cytarabine, melphalan. CBV=cyclophosphamide, carmustine, etoposide.

Table 1: **Baseline characteristics**

After a median observation time of 30 months (range 0–50 months), the primary endpoint of progression-free survival by independent review was significantly improved in patients in the brentuximab vedotin group, with a stratified HR of 0·57 (95% CI 0·40–0·81; p=0·0013; figure 2), which is equivalent to a 43% reduction in the hazard rate for progression-free survival. The median progression-free survival in the brentuximab vedotin group was 42·9 months (95% CI 30·4–42·9) compared with 24·1 months (11·5–not estimable) in the placebo group. The estimated 2-year rate of progression-free survival by independent review was 63% (95% CI 55–70) in the brentuximab vedotin group and 51% (95% CI 43–59) in the placebo group (figure 2). Progression-free survival by investigator assessment was also improved for patients in the brentuximab vedotin group (figure 2). The estimated 2-year rate of progression-free survival by investigator assessment was 65% (95% CI 57–72) in the brentuximab vedotin group versus 45% (95% CI 37–52) in the placebo group (figure 2). With EMA guidelines, the stratified HR was 0·55 (95% CI 0·39–0·77). Prespecified subgroup analysis of progression-free survival by independent review showed consistent benefit (HR<1) in the brentuximab vedotin group across subgroups (figure 3). The appendix presents Kaplan-Meier plots for progression-free survival by response to frontline therapy (eligibility criteria).

The concordance between independent review and investigator assessment of progression was 87% (147 [89%] of 165 patients in the brentuximab vedotin group and 139 [85%] of 164 patients in the placebo group). More progression events were recorded in the investigator assessment (figure 2); 21 (13%) patients in the placebo group and six (4%) patients in the brentuximab vedotin group were censored from the analysis of progression-free

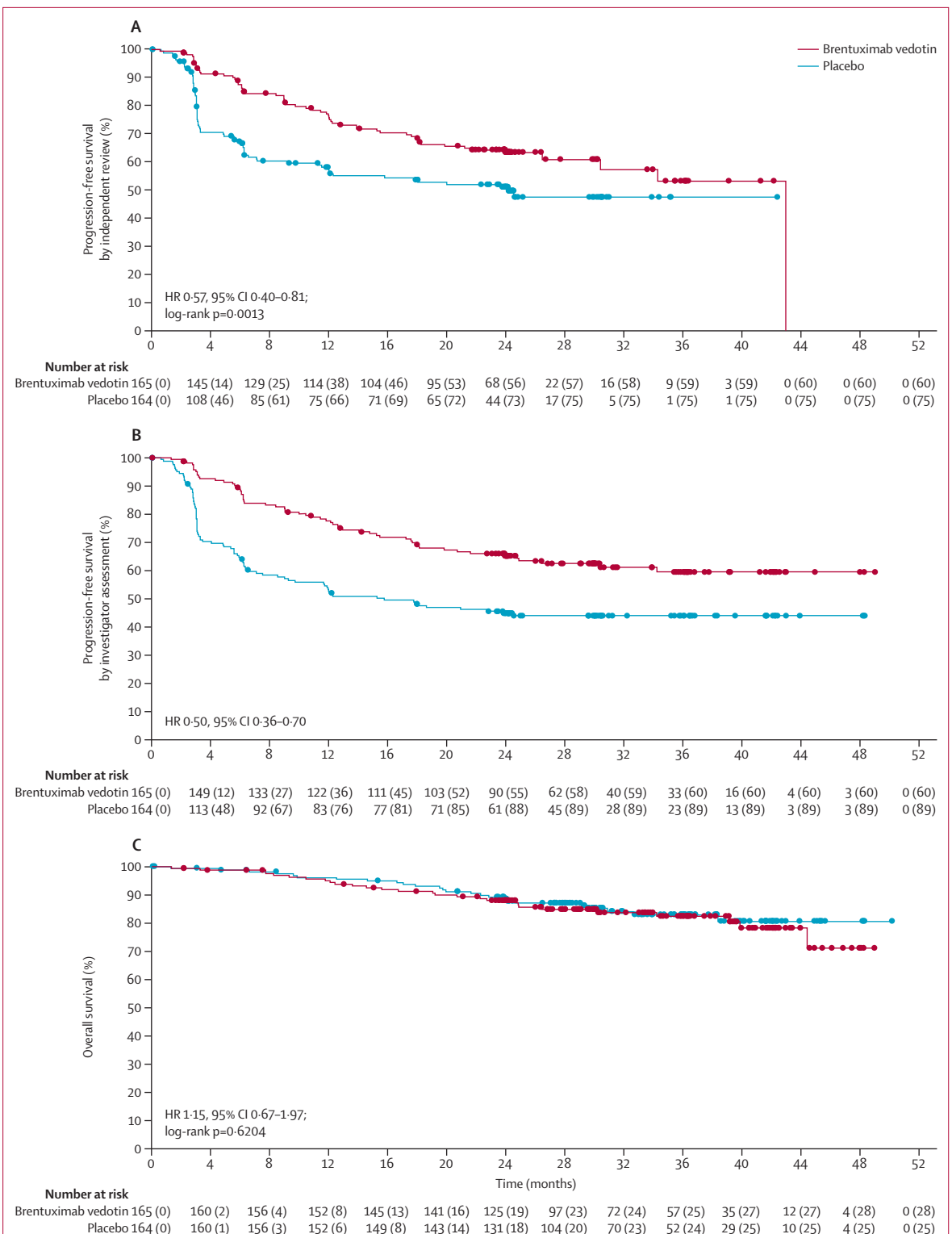

Figure 2: **Progression-free and overall survival analyses**
Kaplan-Meier plots showing the primary endpoint of progression-free survival by independent review (A), progression-free survival by investigator assessment (B), and interim analysis of overall survival (C). Filled circles show censored patients. No p value was calculated for the analysis in panel B.

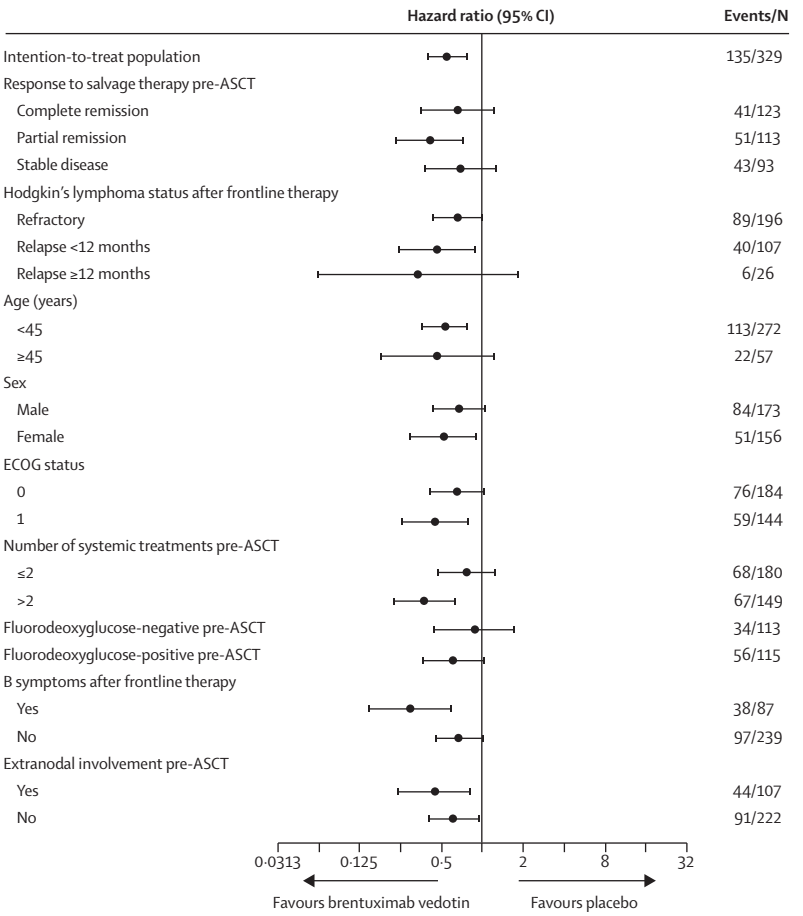

***Figure 3*: Subgroup analysis of progression-free survival by independent review**
ASCT=autologous stem-cell transplantation. ECOG=Eastern Cooperative Oncology Group.

	N	Progression-free survival by independent review	Overall survival
≥1	329	0·57 (0·40–0·81)	1·15 (0·67–1·97)
≥2	280	0·49 (0·34–0·71)	0·94 (0·53–1·67)
≥3	166	0·43 (0·27–0·68)	0·92 (0·45–1·88)

Data are hazard ratio (95% CI), unless otherwise indicated. Risk factors were primary refractory Hodgkin's lymphoma or relapse less than 12 months from completion of frontline therapy, partial response or stable disease as best response to most recent salvage therapy, extranodal disease at pre-autologous stem-cell transplantation relapse, B symptoms at pre-autologous stem-cell transplantation relapse, or two or more previous salvage therapies

***Table 2*: Hazard ratios for progression-free and overall survival by number of risk factors**

survival by independent review because of investigator determination of disease progression and initiation of subsequent therapies without independent-review-assessed progression. These occurrences were regarded as events for the analysis of progression-free survival by investigator review. Most patients who had not yet progressed were censored from the progression-free survival by independent review analysis at 24 months—the time of the last study-mandated radiographical assessment.

Interim analysis of overall survival showed no significant difference between treatment groups (figure 2). Importantly, 72 (85%) of 85 patients in the placebo group who received subsequent treatments after progression received brentuximab vedotin outside of the study. Furthermore, allogeneic stem-cell transplantation was more common in patients in the placebo group than in those in the brentuximab vedotin group (n=23 *vs* n=12; appendix). In a post-hoc analysis, patients grouped by increasing numbers of risk factors had progressively more improvement in progression-free survival when given brentuximab vedotin consolidation than when given placebo (table 2). A similar pattern was shown for overall survival, with a decreasing HR for overall survival in patients with more than one risk factor (table 2).

The safety analysis set consisted of 167 patients who received brentuximab vedotin and 160 patients given placebo (figure 1). Patients in both treatment groups received a median of 15 cycles (range one to 16) once every 3 weeks. We recorded dose reductions because of adverse events in 53 (32%) patients in the brentuximab vedotin group versus four (3%) patients in the placebo group. Adverse events led to a delay in dosing for 186 (9%) of 2004 doses in patients receiving brentuximab vedotin and for 56 (3%) of 1756 doses in those receiving placebo.

Table 3 summarises treatment-emergent adverse events and serious adverse events are shown in the appendix. The most common treatment-emergent adverse event in the brentuximab vedotin group was peripheral sensory neuropathy (table 3). A standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ)-based analysis showed treatment-emergent peripheral neuropathy in 112 (67%) patients in the brentuximab vedotin group and 31 (19%) patients in the placebo group. Most peripheral neuropathy events in the brentuximab vedotin group were sensory in type and grade 1–2 in severity (table 3); we recorded grade 3 events in 22 (13%) patients and there were no grade 4 events. The median time to onset of peripheral neuropathy events in the brentuximab vedotin group was 13·7 weeks (range 0·1–47·4). Peripheral neuropathy led to discontinuation of brentuximab vedotin treatment in 38 (23%) patients and required dose modification (dose reduction or delay) in 51 (31%) patients. Of the 51 patients with peripheral neuropathy requiring dose modifications, 13 (25%) discontinued treatment because of peripheral neuropathy and 29 (57%) completed all 16 cycles of treatment. For patients completing fewer than 16 cycles of treatment, the median number of cycles for patients in the brentuximab vedotin group was 10·5 cycles (range two to 15). 95 (85%) of 112 patients in the brentuximab vedotin group had resolution or improvement of treatment-emergent neuropathy symptoms, with a median time to resolution of 23·4 weeks (range 0·1–138). Neutropenia was more

	Brentuximab vedotin group (n=167)		Placebo group (n=160)	
	Any grade	≥Grade 3*	Any grade	≥Grade 3
Any event	163 (98%)	93 (56%)	142 (89%)	51 (32%)
Peripheral sensory neuropathy	94 (56%)	17 (10%)	25 (16%)	2 (1%)
Neutropenia	58 (35%)	49 (29%)	19 (12%)	16 (10%)
Upper respiratory tract infection	44 (26%)	0	37 (23%)	2 (1%)
Fatigue	40 (24%)	3 (2%)	29 (18%)	4 (3%)
Peripheral motor neuropathy	38 (23%)	10 (6%)	3 (2%)	1 (1%)
Nausea	36 (22%)	5 (3%)	12 (8%)	0
Cough	35 (21%)	0	26 (16%)	0
Diarrhoea	33 (20%)	3 (2%)	16 (10%)	1 (1%)
Pyrexia	31 (19%)	3 (2%)	25 (16%)	0
Weight decreased	32 (19%)	1 (1%)	9 (6%)	0
Arthralgia	30 (18%)	1 (1%)	15 (9%)	0
Vomiting	27 (16%)	4 (2%)	11 (7%)	0
Abdominal pain	23 (14%)	3 (2%)	5 (3%)	0
Constipation	21 (13%)	4 (2%)	5 (3%)	0
Dyspnoea	21 (13%)	0	10 (6%)	1 (1%)
Decreased appetite	20 (12%)	1 (1%)	9 (6%)	0
Pruritus	20 (12%)	1 (1%)	12 (8%)	0
Headache	19 (11%)	3 (2%)	13 (8%)	1 (1%)
Muscle spasms	18 (11%)	0 (0%)	9 (6%)	0
Myalgia	18 (11%)	1 (1%)	6 (4%)	0
Chills	17 (10%)	0	8 (5%)	0
Paraesthesia	16 (10%)	3 (2%)	2 (1%)	0

Data are n (%). *Inclusive of all treatment-emergent adverse events of grade 3 or higher severity with an incidence of 5% or more in the brentuximab vedotin group.

Table 3: **Treatment-emergent adverse events with an incidence of 10% or more in the brentuximab vedotin group, in the safety analysis set**

frequent in patients in the brentuximab vedotin group than in those in the placebo group (table 3). We recorded grade 3 or higher neutropenia in 49 (29%) patients in the brentuximab vedotin group (table 3); only one (1%) patient in that group had febrile neutropenia. Neutropenia resulted in dose delays in 36 (22%) patients in the brentuximab vedotin group, but did not require dose reductions or treatment discontinuation. 42 (25%) patients in the brentuximab vedotin group and 17 (11%) patients in the placebo group received growth factor support. Severe infections (grade 3 or higher) were reported in 11 (7%) patients in the brentuximab vedotin group and nine (6%) patients in the placebo group.

Overall, 13 (4%) of 327 patients had treatment-emergent pulmonary toxic effects (SMQ analysis): eight (5%) in the brentuximab vedotin group and five (3%) in the placebo group. The appendix provides a summary of deaths in the study. One patient in the brentuximab vedotin group died within 30 days of treatment from treatment-related acute respiratory distress syndrome [ARDS] associated with pneumonitis and another patient in that group died at day 40 from ARDS after an episode of treatment-related acute pancreatitis, which had resolved at the time of death (appendix). At the time of analysis, 53 (16%) patients had died: 28 (17%) in the brentuximab vedotin group and 25 (16%) in the placebo group (appendix). The proportion of patients who died from disease-related illness was similar in both treatment groups (18 [11%] deaths in the brentuximab vedotin group and 17 [11%] deaths in the placebo group; appendix).

Discussion

Our findings show that consolidative treatment with brentuximab vedotin provided a statistically and clinically significant improvement in progression-free survival by independent review and by investigator assessment, compared with placebo. By independent review, the estimated proportion of patients who were alive and progression free at 24 months was 63% with brentuximab vedotin versus 51% with placebo; by investigator assessment, the estimated 24 month proportions were 65% and 45%, respectively. We recorded only four progression-free survival events after the 24 month assessment period, encompassing 108 patient-years of follow-up.

Previous studies[4,25] have shown that relapse or progression after autologous stem-cell transplantation generally happens early: 71% of progression events take place within 1 year of transplant and 90% take place within 2 years. This finding is supportive of the possibility that many of the patients who were progression free at 24 months might be cured, but further survival follow-up is necessary. In addition to the sustained clinical benefit of brentuximab vedotin consolidation in our study, more patients needed subsequent antitumour therapies in the placebo group than in the brentuximab vedotin group, including nearly twice as many allogeneic stem-cell transplantations.

Concordance between investigator determined and independent review assessments of progression was high and the apparent differences between the progression-free survival curves were mainly due to two types of censoring in the independent review analysis: (1) patients considered to have progressed by investigator assessment, but not by independent review, were typically censored at the time they received subsequent antitumour therapy, and (2) only a few patients had CT scans submitted for independent review after 24 months, resulting in most non-progressed patients being censored in the independent review analysis at 24 months. A small number of events in the few patients who did have scans submitted after 24 months resulted in a disproportionate effect on the progression-free survival curve for independent review. In the investigator analysis of progression-free survival, all lymphoma assessments to analyse clinical progression are included, providing additional information about patient status, particularly for asymptomatic patients more than 2 years from autologous stem-cell transplantation.

Panel: Research in context

Systematic review

High-dose therapy and autologous stem-cell transplantation is the standard of care for patients in whom frontline therapy for Hodgkin's lymphoma has been ineffective and who are regarded as transplant eligible on the basis of disease status and ability to tolerate the treatment. This treatment is based on findings from two studies[1,2] in which patients were randomly assigned to either a standard-dose chemotherapy regimen or to high-dose therapy and autologous stem-cell transplantation. Both studies showed a decreased rate of disease progression and a pattern for improved overall survival. Additionally, several large studies[3-5] have established that high-dose therapy and autologous stem-cell transplantation can provide a cure for roughly 50% of patients who are eligible for the procedure. Risk factors that have been repeatedly associated with strong prognostic value in identification of patients who might benefit from additional therapy after autologous stem-cell transplantation include a history of Hodgkin's lymphoma refractory to frontline therapy or a short time to first relapse, presence of extranodal disease before transplantation, absence of chemoresponsiveness to salvage therapy before transplantation, and presence of residual disease at the time of transplantation.[3-7,10,13,30,31] More recently, Fluorodeoxyglucose-PET assessment of disease status before autologous stem-cell transplantation has been shown to be of substantial prognostic value.[32,33] No previous completed randomised trials of maintenance or consolidation therapy after autologous stem-cell transplantation have been reported.[19,20] Indeed, before the AETHERA study, no randomised study has shown a reduced rate of relapse or progression after autologous stem-cell transplantation, and no drugs are approved in this setting. The standard of care for this patient population is observation with best supportive care until disease progression or relapse.

Interpretation

With modern supportive care, mortality related to autologous stem-cell transplantation is low in patients with Hodgkin's lymphoma and the long-term progression-free survival rate is roughly 50%. Unfortunately, outcomes have improved only marginally in the past 15 years, which probably indicates optimisation of frontline therapy, leaving mainly patients with unfavourable risk factors still needing high-dose therapy and autologous stem-cell transplantation. This is the first randomised study of consolidation or maintenance therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma. Our findings show that early consolidation with brentuximab vedotin significantly improved progression-free survival in patients with Hodgkin's lymphoma with risk factors for relapse or progression post-transplant, and provide an important therapeutic option for patients after undergoing autologous stem-cell transplantation.

We noted a consistent progression-free survival benefit with brentuximab vedotin across prespecified subgroups, including in primary refractory patients and patients who relapsed less than 12 months after frontline therapy. The benefit seemed to be diminished in patients who were PET-negative before autologous stem-cell transplantation; however interpretation is restricted because PET scans were not mandated in the protocol and no objective criteria were needed for interpretation of the scans. About two-thirds of patients had a PET scan before autologous stem-cell transplantation. Patients who are PET negative before autologous stem-cell transplantation and have extranodal disease have intermediate outcomes.[9] Further analysis of these risk factors could better elucidate a population of patients most likely to benefit from early brentuximab vedotin consolidation.

In the short follow-up time in the present study, we expected that the interim analysis of overall survival would not show a difference between the treatment groups in view of the small number of events and because the analysis was confounded by the high crossover rate of patients in the placebo group. In most regions, brentuximab vedotin was not commercially available with reimbursement during the study. Brentuximab vedotin treatment was provided only to patients in the placebo group after progression on a separate study. As a result, 85% of patients in the placebo group received brentuximab vedotin after progression versus only 18% of those in the brentuximab vedotin group. More determinations of progression in the brentuximab vedotin group took place after patients had discontinued therapy, and data are now available to show that retreatment with brentuximab vedotin can be beneficial in relapsed or refractory populations.[26]

Compared with historical survival data for high-risk patients with Hodgkin's lymphoma undergoing autologous stem-cell transplantation, the 3-year rate of overall survival exceeding 80% in this study is remarkable and might show the clinical benefit of brentuximab vedotin, both as consolidation therapy and as rescue therapy.[3–5] Patients who have progressed after autologous stem-cell transplantation are living with chronic Hodgkin's lymphoma and most will die from their disease or from complications of therapy; however these patients are benefitting from the availability of novel drugs, including brentuximab vedotin. Additional survival benefit might be recorded with use of reduced-intensity allogeneic stem-cell transplantation and with new drugs such as histone deacetylase or checkpoint inhibitors.[27,28] Long-term follow-up data in relapsed or refractory patients with Hodgkin's lymphoma show a median overall survival of 40·5 months (95% CI 28·7–not estimable) with brentuximab vedotin treatment.[29] Consequently, a survival benefit in the brentuximab vedotin group might be shown, but longer follow-up will be necessary and is mandated in the study. Early brentuximab vedotin consolidation resulted in a reduced number of progression events and more patients might be cured with consolidation therapy. Clearly, reduced numbers of patients will need subsequent toxic therapy for active disease including allogeneic stem-cell transplantation. Although preliminary, a post-hoc analysis showed a pattern suggestive of a decrease in the HR for overall survival with brentuximab vedotin consolidation in patients with more than one risk factor for progression.

Brentuximab vedotin treatment seemed to be generally well tolerated and the safety profile was consistent with findings from previous studies. Nearly half of patients in the brentuximab vedotin group completed all 16 cycles of therapy. Peripheral neuropathy was the most common adverse event, with most patients showing resolution or improvement of symptoms at the time of analysis. Of note, a third of patients in the brentuximab vedotin

group discontinued therapy because of toxic effects, mostly neuropathies. Neutropenia was manageable with growth factors or dose delays. Importantly, brentuximab vedotin had a favourable tolerability profile early after autologous stem-cell transplantation, with no increase in serious infections, suggesting that brentuximab vedotin therapy could be initiated early after autologous stem-cell transplantation, when tumour burden is lowest and consolidation might provide the most effect.

Our study has some limitations. Since the start of this trial, changes have taken place in the standard treatment of patients with Hodgkin's lymphoma. Fluorodeoxyglucose-PET scanning was not routinely done for stratification or disease assessment, and it is possible that PET scanning done before autologous stem-cell transplantation could have more accurately classified patient responses to salvage chemotherapy. Additionally, brentuximab vedotin has now received approval in more than 40 countries for use in patients with relapsed or refractory Hodgkin's lymphoma after autologous stem-cell transplantation and is also used in many patients before this procedure. We did not include patients who had received previous brentuximab vedotin treatment in our study; however, retreatment data suggest that patients who previously responded to brentuximab vedotin are likely to respond again.[26] Another limitation of this study is that the crossover of patients in the placebo group to brentuximab vedotin confounds the survival analysis and, at this early interim analysis, whether the progression-free survival benefit recorded with brentuximab vedotin consolidation will translate into an eventual survival benefit is unknown. Consequently, whether early brentuximab vedotin consolidation can provide a better survival benefit than brentuximab vedotin treatment after progression cannot yet be answered. Furthermore, although we made every effort to mask study investigators to treatment assignment, the higher incidence of peripheral neuropathy in the brentuximab vedotin group than in the placebo group might have introduced some bias to the investigator assessment of progression.

In conclusion, delivery of brentuximab vedotin as consolidation therapy was generally well tolerated immediately after autologous stem-cell transplantation and provided a sustained progression-free survival benefit for patients with Hodgkin's lymphoma with risk factors for relapse or progression after autologous stem-cell transplantation (panel). Consolidation therapy with brentuximab vedotin might increase the possibility of cure or potentially avoid exposure to subsequent toxic therapies, and seems to be effective in this young cancer population with high unmet need.

Contributors

CHM, AN, TM, EA, JH, MHA, AIC, PS, AMG, ACa, DO, VB, JS, and JW contributed to data collection, data interpretation, and writing and approval of the manuscript. CHM, JS, AS, DH, ELS, ACh, EKL, and NNH contributed to study design. DH, ELS, ACh, EKL, and NNH contributed to data interpretation, data analysis, and writing and approval of this manuscript. All authors agree to be accountable for all aspects of this work.

Declaration of interests

CHM, AN, TM, EA, JH, MHA, AIC, PS, AMG, ACa, DO, VB, JS, and JW received research funding from Seattle Genetics. CHM, PS, and VB acted as consultants for Seattle Genetics. PS, JS, JH, and MHA received honoraria from Seattle Genetics. AMG has received honoraria from Takeda Pharmaceuticals International. AIC, VB, and PS have served on an advisory board for Seattle Genetics. JS has participated in a speakers' bureau for Seattle Genetics. JW has participated in lectures and an advisory board for Takeda Pharmaceuticals International. EKL, ELS, and NNH are employees of and have equity interest in Seattle Genetics. DH and ACh are employees of and have equity interest in Takeda Pharmaceuticals International. ELS has a patent issued related to the present study.

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