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Prospective study of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma patients who are not suitable for stem cell transplant or multi-agent chemotherapy

Jan Walewski,[1] Andrzej Hellmann,[2] Noppadol Siritanaratkul,[3] Guner Hayri Ozsan,[4] Muhit Ozcan,[5] Suporn Chuncharunee,[6] Ai Sim Goh,[7] Wojciech Jurczak,[8] Jan Koren,[9] Ewa Paszkiewicz-Kozik,[1] Bingxia Wang,[10] Shalini Singh,[10] Dirk Huebner,[10] Andreas Engert[11] and Bastian von Tresckow[11]

[1]Department of Lymphoid Malignancy, Maria Sklodowska-Curie Institute – Oncology Centre, Warszawa, [2]Department of Haematology, Medical University of Gdańsk, Gdańsk, Poland, [3]Department of Medicine, Siriraj Hospital, Bangkok, Thailand, [4]Department of Haematology, Dokuz Eylul University, Izmir, [5]Department of Haematology, Ankara University School of Medicine, Ankara, Turkey, [6]Oncology Centre, Ramathibodi Hospital, Mahidol University, Bangkok,Thailand, [7]Department of Medicine, Hospital Pulau Pinang, Pulau Pinang, Malaysia, [8]Department of Haematology, Jagiellonian University, Kraków, Poland, [9]Department of Haematology, Charles University, Prague, Czech Republic, [10]Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA and [11]Department of Internal Medicine, University Hospital Cologne, Cologne, Germany

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Correspondence: Jan Walewski, Department of Lymphoid Malignancy, Maria Sklodowska-Curie Institute – Oncology Centre, 5 W.K. Roentgen Street, Warszawa 02-781, Poland.
E-mail: jan.walewski@coi.pl

Summary

Some patients with relapsed/refractory Hodgkin lymphoma (HL) are not considered suitable for stem cell transplant (SCT) and have a poor prognosis. This phase IV study (NCT01990534) evaluated brentuximab vedotin (1·8 mg/kg intravenously once every 3 weeks) in 60 patients (aged ≥18 years) with CD30-positive relapsed/refractory HL, a history of ≥1 prior systemic chemotherapy regimen, who were considered unsuitable for SCT/multi-agent chemotherapy. Primary endpoint was overall response rate (ORR) per independent review facility (IRF). Secondary endpoints included duration of response (DOR), progression-free survival (PFS) per IRF, overall survival (OS), proportion proceeding to SCT and safety. The ORR was 50%, with 12% CR; 47% proceeded to SCT. Median DOR was 4·6 months and median duration of CR was 6·1 months. After a median follow-up of 6·9 and 16·6 months, median PFS and OS were 4·8 months (95% confidence interval, 3·0–5·3) and not reached, respectively; estimated OS rate was 86% at 12 months. Most common adverse events (≥10%) were peripheral neuropathy (35%), pyrexia (18%), diarrhoea and neutropenia (each 10%). Brentuximab vedotin showed notable activity with a safety profile consistent with known toxicities, and may act as a bridge to SCT, enabling high-risk patients who achieve suboptimal response to frontline/salvage chemotherapy/radiotherapy to receive potentially curative SCT.

Keywords: Hodgkin lymphoma, relapsed/refractory, novel anti-tumour agents, brentuximab vedotin, phase IV.

Hodgkin lymphoma (HL) is an uncommon B cell malignancy accounting for ~11% of all lymphomas, with an annual incidence in the United States and European Union (EU) of 2·66 and 2·2 per 100 000, respectively (Ansell, 2015; Ferlay *et al*, 2015; Howlader *et al*, 2016). Currently, >80% of newly diagnosed HL patients are likely to be cured with multi-agent chemotherapy with/without radiotherapy; however, 5–10% of patients do not respond to frontline therapy and ~10–30% of patients may relapse after achieving a complete response (CR) (Ansell, 2015). Standard treatment for

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relapsed/refractory HL patients is high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) (Eichenauer *et al*, 2014); however, disease recurrence occurs in more than half of these patients, usually within the first year (Crump, 2008). A number of patients are not considered suitable candidates for ASCT due to chemorefractory disease, advanced age, comorbidities or personal preference. These patients have an extremely poor prognosis, and the disease is often considered incurable (Forero-Torres *et al*, 2012; Mocikova *et al*, 2014).

Brentuximab vedotin is an antibody-drug conjugate directed against CD30, a cell surface antigen expressed on malignant HL Reed–Sternberg cells. It is composed of the anti-CD30 monoclonal antibody cAC10 conjugated to the microtubule disrupting agent monomethyl auristatin E via a protease-cleavable linker (Wahl *et al*, 2002; Francisco *et al*, 2003). Limited data are available on the efficacy/safety of brentuximab vedotin in transplant-naïve relapsed/refractory HL patients. Brentuximab vedotin received accelerated approval by the US Food and Drug Administration (FDA) for the treatment of classical HL patients who have relapsed after ASCT or after ≥2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and subsequently in classical HL patients at high risk of relapse/progression post-ASCT (http://www.seattlegenetics.com/application/files/1915/2157/0234/adcetris_USPI.pdf). The European Medicines Agency provided conditional approval for the treatment of adult patients with relapsed/refractory CD30-expressing HL following ASCT or following failure of ≥2 prior therapies where ASCT or multi-agent chemotherapy is not a treatment option, and, subsequently, in CD30-positive HL at increased risk of relapse/progression following ASCT (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002455/WC500135055.pdf).

Initial approval was based on data from the pivotal, phase II, single-arm, SG035-0003 trial (NCT00848926) of brentuximab vedotin in 102 patients with relapsed/refractory HL post-ASCT. The overall response rate (ORR) was 75% [95% confidence interval (CI), 64·9–82·6%], with a 34% (95% CI, 25·2–44·4%) CR rate per independent review facility (IRF) assessment. Median progression-free survival (PFS) was 5·6 (95% CI, 5·0–9·0) months, and median duration of response (DOR) for those in CR was 20·5 months (95% CI, 10·8 months–not estimable). Grade ≥3 treatment-emergent adverse events (TEAEs) that occurred in ≥5% of patients were neutropenia (20%), peripheral sensory neuropathy (8%), thrombocytopenia (8%) and anaemia (6%) (Younes *et al*, 2012). After a 5-year follow-up period, the median overall survival (OS) was 40·5 (95% CI, 28·7–61·9) months, and the median PFS was 9·3 (95% CI, 7·1–12·2) months (Chen *et al*, 2016).

Despite limited data on the efficacy/safety of brentuximab vedotin in transplant-naïve relapsed/refractory HL patients, the observed efficacy results represent meaningful activity of brentuximab vedotin in this patient population. A retrospective analysis of 41 relapsed/refractory HL patients who had not received a prior ASCT, and received brentuximab vedotin in phase I dose-escalation and clinical pharmacology studies ($N = 15$) (Younes *et al*, 2010; Fanale *et al*, 2012; Han *et al*, 2013) and in a named patient programme (NPP) ($N = 26$) (Gibb *et al*, 2013; Sasse *et al*, 2013), demonstrated an ORR of 54% and a CR rate of 22% per investigator (INV) assessment after a median of five cycles of brentuximab vedotin (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002455/WC500135055.pdf.

This phase IV, single-arm, multicentre study is the first prospective study to evaluate the efficacy/safety of single-agent brentuximab vedotin in CD30-positive relapsed/refractory HL patients who were not considered suitable for SCT or multi-agent chemotherapy due to the resistant course of their disease and was designed to fulfill a post-authorisation measure that accompanied the conditional marketing authorisation of brentuximab vedotin in the EU.

Methods

Patients

Eligible patients (≥18 years) had histologically confirmed CD30-positive relapsed/refractory classical HL, a history of ≥1 prior systemic chemotherapy regimen, and were considered unsuitable for SCT/multi-agent chemotherapy at the time of study entry. Patients were not considered eligible for SCT/multi-agent chemotherapy according to one of the following criteria: progressive disease (PD) during frontline multi-agent chemotherapy, PD within 90 days of CR or unconfirmed CR after treatment with multi-agent frontline chemotherapy and/or radiotherapy, or relapse after ≥2 prior chemotherapy regimens (including pre-SCT salvage treatments). Other eligibility criteria included: Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, measurable disease (≥1·5 cm) by computed tomography (CT) scan, and adequate haematological/hepatic/renal function. Patients who had received previous brentuximab vedotin therapy, or undergone an ASCT/allogenic SCT, were excluded. Institutional review boards at all sites approved the study, which was conducted in accordance with International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent.

Study design

This phase IV, single-arm, global, multicentre study (NCT01990534) was conducted at 18 sites in seven countries: Czech Republic, Germany, Malaysia, Poland, Spain, Thailand and Turkey. This study was conducted as part of a post-authorisation requirement in the European Union; a sample size of 60 patients was determined to enable estimation of the activity of brentuximab vedotin (ORR) in this setting

with reasonably narrow 95% CIs. Patients received brentuximab vedotin 1·8 mg/kg intravenously, once every 3 weeks, for up to 16 cycles, or until PD/unacceptable toxicity. Actual dose to be administered was determined on the basis of the patient's weight, but capped at 100 kg. Patients with a CR, partial response (PR) or stable disease (SD) received a minimum of eight cycles. Patients with an objective response (CR or PR) and who became suitable for a SCT could discontinue receiving brentuximab vedotin after four cycles and proceed to SCT.

The primary endpoint was ORR by IRF assessment. Key secondary endpoints were DOR, PFS by IRF assessment, OS, proportion of patients proceeding to SCT following brentuximab vedotin, and safety. Other secondary endpoints included CR rate, and duration of CR. Tertiary/exploratory endpoints were time to response (CR or PR), time to best response, time to CR, time to progression, and B symptom resolution rate.

Assessments

Tumour response was assessed by CT scans of chest, neck, abdomen and pelvis at baseline and at cycles 2, 4, 7, 10, 13 and 16, and positron-emission tomography (PET) scans at baseline and cycles 4 and 7. Response rates were determined both by an IRF and INV according to the International Working Group Revised Response Criteria for Malignant Lymphoma (Cheson *et al*, 2007). Post-treatment follow-up for PFS and OS was performed every 3 months until 18 months after end of treatment. OS assessment continued thereafter every 6 months until death/study closure. Safety was assessed throughout until 30 days after last dose. TEAEs were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) and tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (https://www.meddra.org/). Peripheral neuropathy was evaluated using Standardized MedDRA Queries (SMQ; broad search); preferred terms included peripheral sensory neuropathy, peripheral neuropathy, polyneuropathy, paresthesia and autonomic neuropathy.

Statistical analysis

Statistical analyses were primarily descriptive. No formal statistical hypothesis testing was performed. For the primary endpoint of ORR per IRF, two-sided 95% exact CI were calculated, and exploratory subgroup analyses were performed by sex, race, weight (≤100 kg vs. >100 kg), number of prior regimens (1 vs. >1), baseline ECOG PS score and baseline B symptoms (present vs. absent). Time-to-event endpoints were estimated using Kaplan–Meier methodology. For the primary analysis of PFS, an event was defined as PD or death; the date of PD was based on the time of the first documentation of PD regardless of violations, discontinuation of study treatment, or initiation of subsequent anticancer therapy. A prespecified comparison of PFS from the most recent treatment prior to study entry *versus* PFS per INV with brentuximab vedotin was performed using a correlated analysis, with Kaplan–Meier methodology used to assess PFS distribution on prior therapy. The Cox proportional hazards model was used to estimate the hazard ratio (HR) and its 95% CIs; the *P*-value was calculated based on Sandwich variance estimate.

The intent-to-treat (ITT) population included all patients enrolled and was used for all efficacy analyses. The per-protocol population included all patients who received at least one brentuximab vedotin dose, had measurable disease at baseline and had no major protocol deviations, and was used for analysis of the primary efficacy endpoint. The safety population included all patients who received at least one brentuximab vedotin dose, and was used for patient demographics, extent of exposure and all safety analyses.

Results

Patients

Sixty patients were enrolled between March 2014 and March 2015. Patient and disease characteristics at baseline are summarised in Table I and were considered representative of patients with relapsed/refractory HL unsuitable for SCT/multi-agent chemotherapy. The majority of patients were male (60%) and had stage III/IV disease (57%). The median age was 32 (range, 18–75) years, with 55 (92%) patients aged <65 years. However, despite this, all patients were considered unsuitable for SCT/multi-agent chemotherapy, as defined by study eligibility criteria. Nineteen patients (32%) were ineligible as a result of PD during front-line multi-agent chemotherapy, 11 patients (18%) were ineligible due to PD within 90 days of CR or unconfirmed CR after treatment with multi-agent frontline chemotherapy and/or radiotherapy and 30 patients (50%) were ineligible due to relapse after ≥2 prior chemotherapy regimens. Patients had received a median of two prior therapies (range, 1–7 regimens); 42% had received prior radiation therapy and 15% had received a prior surgical procedure related to treatment for HL. Sixty-seven percent of patients were refractory (PD as best response) to their last prior therapy. Common prior therapies included ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) in 56 patients, ICE (ifosfamide, carboplatin and etoposide) in 26 patients and DHAP (dexamethasone, cytarabine and cisplatin) in 13 patients.

All 60 patients have discontinued treatment; reasons for treatment discontinuation were PD (55%), initiation of SCT (15%), completion of 16 cycles of therapy per protocol (13%), TEAE, symptomatic deterioration, patient withdrawal (each 5%) and protocol violation (2%). Of the 41 patients who developed PD post-brentuximab vedotin treatment (at any time point), 18 patients received subsequent chemotherapy plus SCT, and four patients received

Table I. Summary of study population demographics and baseline disease characteristics.

Characteristics	Brentuximab vedotin ($N = 60$)
Median age, years (range)	32 (18–75)
Male, *n* (%)	36 (60)
Age, *n* (%)	
<65 years	55 (92)
≥65 years	5 (8)
Race, *n* (%)	
White	42 (70)
Asian	18 (30)
Ann Arbor stage at initial diagnosis, *n* (%)	
I	3 (5)
II	21 (35)
III	16 (27)
IV	18 (30)
Other	2 (3)
ECOG PS, *n* (%)	
0	27 (45)
1	33 (55)
B symptoms, *n* (%)	22 (37)
Extranodal involvement, *n* (%)	22 (37)
Bone marrow involvement, *n* (%)	4 (7)
Prior radiation, *n* (%)	25 (42)
Median number of prior therapies, *n* (range)	2 (1–7)
Best response to last prior therapy, *n* (%)	
CR	6 (10)
PR	9 (15)
SD	4 (7)
PD	40 (67)
Unknown	1 (2)
Median time from initial diagnosis to first dose of brentuximab vedotin, months (range)	15·9 (0–312)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PR, partial response; SD, stable disease.

subsequent chemotherapy plus SCT plus radiotherapy. Thirty-six patients remain in post-treatment follow-up.

Efficacy

Table II summarises the key response data. The ORR in the ITT population was 50% (95% CI, 37–63%) per IRF; 12% achieved a CR (95% CI, 5–23%). Overall, tumour reductions were observed in 91% of response-evaluable patients (Fig 1). The ORR in the per-protocol population ($N = 58$) was 52% (95% CI, 38–65%); two patients were excluded from the per-protocol population due to major protocol deviations, one due to having received prior ASCT, and one because the inclusion criteria pertaining to clinical laboratory values was not met at the time of the first brentuximab vedotin dose. Assessment of objective response by INV assessment was 48% (95% CI, 35–62%) in the ITT population and correlated well with the efficacy analysis by IRF; 15% of patients achieved a CR (95% CI, 7–27%). Anti-tumour activity was consistent across all prespecified subgroups (Table III).

For patients who achieved an objective response, the median time to response was 6·0 (range, 5–39) weeks, and the median time to CR was 12 (range, 6–60) weeks. The median DOR was 4·6 (95% CI, 3·4–7·9) months, and the median duration of CR was 6·1 months (95% CI, 2·1–not evaluable). The median TTP was 5·1 months for the ITT population by INV assessment.

After a median follow-up of 6·9 months, 39 PFS events were observed in the ITT population, and the median PFS was 4·8 (95% CI, 3·0–5·3) months (Fig 2A). All patients had received prior systemic therapy at the time of study entry, and a prespecified analysis was performed comparing PFS from the most recent treatment prior to study entry with PFS following brentuximab vedotin treatment. The median PFS obtained with the most recent treatment prior to study entry was 4·1 months compared with a median PFS of 5·0 months for brentuximab vedotin. The hazard ratio was 0·66 (95% CI, 0·45–0·98; $P = 0·037$) indicating a 34% improvement in PFS over prior therapy for patients who received brentuximab vedotin. After a median follow-up of 16·6 months, 12 deaths were reported for the ITT population, the estimated OS rate was 86% (95% CI, 74·0–93·4%) at 12 months, and the median OS was not reached (Fig 2B).

Proportion of patients who received SCT after brentuximab vedotin

Figure S1 summarises patients who did and did not receive SCT in the course of the study. Of the 60 patients who were considered not suitable for SCT/multi-agent chemotherapy at the time of study entry, 28 (47%) went on to receive SCT after receiving a median of seven (range, 4–16) cycles of brentuximab vedotin. Ten of the 28 patients discontinued study treatment to receive SCT immediately post-brentuximab vedotin treatment, including one patient who completed the maximum number of brentuximab vedotin cycles and proceeded straight to conditioning therapy for SCT. The remaining 18 patients discontinued study treatment due to other reasons [PD ($n = 15$), completed maximum number of cycles per protocol, adverse event (AE), and symptomatic deterioration ($n = 1$ each)] before eventually receiving SCT. Six of the 28 patients (21%) had received one prior therapy and a median of six (range, 4–16) cycles of brentuximab vedotin. The remaining 22 patients (79%) had received more than one prior therapy and a median of seven (range, 4–16) cycles of brentuximab vedotin.

Safety

All enrolled patients received at least one brentuximab vedotin dose and were included in the safety population. The median number of cycles received was seven (range, 1–16)

Table II. Summary of key response results in the ITT population.

Response	Brentuximab vedotin (N = 60)	
	Per IRF	Per INV
ORR (CR + PR), *n* (%) (95% CI)	30 (50) (37–63)	29 (48) (35–62)
Best clinical response, *n* (%) (95% CI)		
CR	7 (12) (5–23)	9 (15) (7–27)
PR	23 (38) (26–52)	20 (33) (22–47)
SD	18 (30) (19–43)	25 (42) (29–55)
PD	8 (13) (6–25)	2 (3) (<1–12)
NE	4 (7) (2–16)	4 (7) (2–16)
Median DOR, months (95% CI)	4·6 (3·4–7·9)	5·3 (3·6–NE)
Median duration of CR, months (95% CI)	6·1 (2·1–NE)	7·6 (2·1–NE)
Median duration of PR, months (95% CI)	3·7 (2·4–7·9)	3·8 (3·5–6·4)
Median time to response, weeks (range)		
Time to response (CR + PR)	6·0 (5–39)	6·1 (5–53)
Time to best response	11·2 (5–60)	11·8 (5–53)
Time to CR	12 (6–60)	12·1 (11–29)
Time to PR	6·0 (5–39)	9·1 (5–53)

CI, confidence interval; CR, complete response; DOR, duration of response; INV, investigator; IRF, independent review facility; ITT, intent-to-treat; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

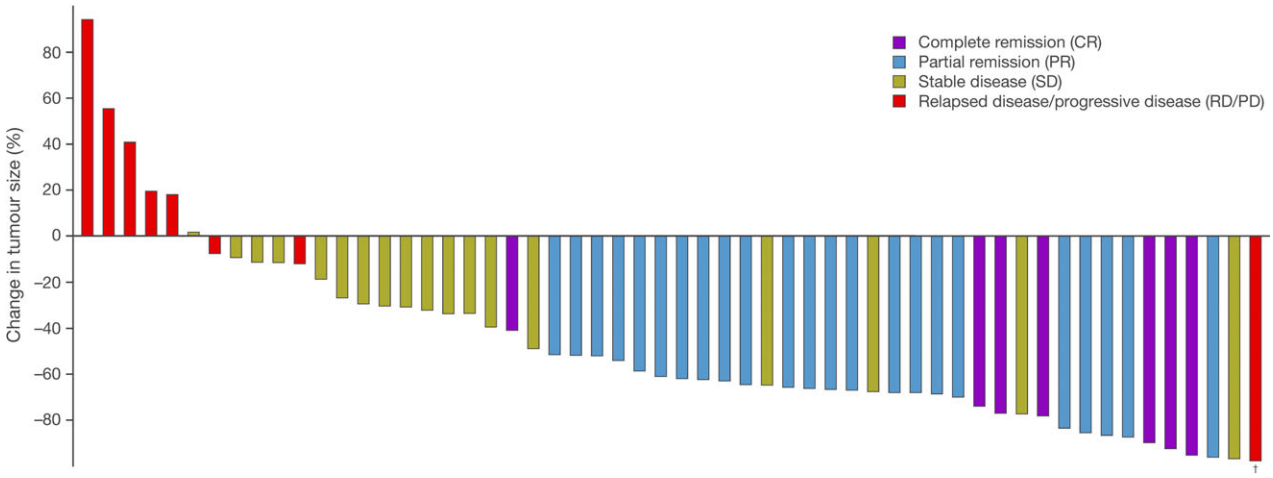

Fig 1. Maximum percentage change in tumour size in patients with post-baseline assessments* (n = 56). *Bar colour refers to best response per independent review facility assessment. †New lesion reported at cycle 2, day 21; progressive disease according to the International Working Group Revised Response Criteria for Malignant Lymphoma (Cheson *et al*, 2007).

cycles and 8 (13%) patients completed the maximum 16 cycles. The median relative dose-intensity of brentuximab vedotin was 100% (range, 66·8–108%). Table IV summarises the safety profile of single-agent brentuximab vedotin. A total of 52 (87%), 21 (35%) and 11 (18%) patients experienced any TEAEs, grade ≥3 TEAEs and serious AEs, respectively. The most common TEAEs (≥10%) were peripheral neuropathy (SMQ; 35%), pyrexia (18%), diarrhoea and neutropenia (10% each). The most common grade ≥3 TEAEs (≥2 patients) were anaemia, neutropenia (n = 3 each), back pain and pyrexia (n = 2 each). Three patients (5%) discontinued study treatment due to treatment-related TEAEs of peripheral neuropathy, polyneuropathy and septic shock (n = 1 each). There was one on-study death due to septic shock within 30 days of the last dose, which was considered treatment-related.

Resolution of peripheral neuropathy

Twenty-one patients (35%) experienced peripheral neuropathy (SMQ) (grade 1, 22%; grade 2, 10%; grade 3, 3%); symptoms were considered treatment-related in 19 patients (32%). The median time to onset of any event was 9·4 (range, 0·6–39·1) weeks. At the end of treatment/time of last follow-up, 12/21 (57%) patients experienced complete resolution of peripheral neuropathy (SMQ) symptoms while nine

Table III. Subgroup analysis of ORR by IRF in the ITT population.

Characteristic	ORR per IRF (CR + PR), *n*/*N* (%)	95% CI
Sex		
Male	16/36 (44)	28–62
Female	14/24 (58)	37–78
Race		
White	19/42 (45)	30–61
Asian	11/18 (61)	36–83
Weight (kg)		
≤100	29/55 (53)	39–66
>100	1/5 (20)	<1–72
Prior regimen		
1	5/11 (45)	17–77
>1	25/49 (51)	36–66
ECOG PS		
0	14/27 (52)	32–71
1	16/33 (48)	31–66
B symptoms at baseline		
Present	7/22 (32)	14–55
Absent	23/38 (61)	43–76

CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRF, independent review facility; ITT, intent-to-treat; ORR, overall response rate; PR, partial response.

(43%) had no resolution or improvement of symptoms (grade 1, 24%; grade 2, 14%; grade 3, 5%).

B symptom resolution rate

Of the 22 patients (37%) with B symptoms at baseline, 91% (95% CI, 71–99%) experienced resolution of all B symptoms at a median time of 3·1 (range, 3·0–6·1) weeks from initiation of brentuximab vedotin.

Discussion

This phase IV, single-arm, multicentre study was the first prospective study to evaluate the efficacy/safety of single-agent brentuximab vedotin in CD30-positive relapsed/refractory HL patients who were not considered suitable for SCT/multi-agent chemotherapy due to the resistant course of their disease. Treatment with brentuximab vedotin resulted in an objective response of 50% in this difficult-to-treat population, where the prognosis is extremely poor and the disease is often considered incurable. The ORR, although lower than that seen in the pivotal phase II study of brentuximab vedotin for patients with relapsed/refractory HL post-ASCT (50% vs. 75%), is notable for a single-agent therapy in patients considered unsuitable for SCT, with a history of at least one prior systemic chemotherapy regimen, and with limited treatment options. The median PFS per IRF obtained with brentuximab vedotin was 4·8 months, and PFS estimates by INV assessment compared favourably with PFS estimates from the most recent treatment before study entry. Brentuximab vedotin was well tolerated in this patient population, with a safety profile consistent with known toxicities; serious AEs were rare, and there was a low incidence of grade ≥3 TEAEs. These results continue to support the favourable benefit-to-risk profile for brentuximab vedotin in patients with relapsed/refractory HL.

These data add to the previously limited body of evidence available on the use of brentuximab vedotin in transplant-naïve relapsed/refractory HL patients. Forero-Torres *et al* (2012) reported an ORR of 30% (CR rate of 10%) in a retrospective analysis of 20 transplant-naïve relapsed/refractory HL patients who were not candidates for ASCT (mainly due to chemorefractory disease) in two phase I studies of brentuximab vedotin. Three of the six responders subsequently received ASCT (Forero-Torres *et al*, 2012). A retrospective study by Sasse *et al* (2013) of 14 relapsed/refractory HL patients who had not received high-dose chemotherapy (HDCT) and ASCT due to reasons including refractory disease and comorbidity reported an ORR of 71% (CR rate of 36%) following treatment with brentuximab vedotin in a NPP. Five (36%) patients proceeded to HDCT and SCT. Similarly, Gibb *et al* (2013) reported that 12 relapsed/refractory HL patients who had not received a previous ASCT and were treated with brentuximab vedotin in a separate NPP conducted at a single UK centre, achieved an ORR of 58% (Gibb *et al* 2013). A recent study by Zinzani *et al* (2015) demonstrated that brentuximab vedotin normalised PET status (Deauville score ≤2) in 9/30 (30%) relapsed/refractory HL patients unsuitable for ASCT due to persistence of the disease following salvage therapy, all of whom proceeded to ASCT. Although these studies were limited to a small number of patients and report different brentuximab vedotin doses/schedules, which may account for the wide range of results reported, they all support the use of brentuximab vedotin in the transplant-naïve relapsed/refractory HL setting. The findings from this study, which reports data for a much larger cohort of patients, are consistent with these previous studies, as well as recent real-world, retrospective studies of brentuximab vedotin in transplant-naïve relapsed/refractory HL patients conducted in the UK (ORR of 56%; Eyre *et al*, 2017) and the UK/Germany (ORR of 74·3%, Bröckelmann *et al*, 2016). This study is the first prospective study to confirm the effectiveness of brentuximab vedotin in relapsed/refractory transplant-naïve HL, and further demonstrates that the anti-tumour activity of brentuximab vedotin is not limited to those patients who receive the drug post-ASCT.

Notably, nearly half of the patients (47%) who were considered not suitable for SCT/multi-agent chemotherapy at the time of study entry proceeded to SCT; 17% (10/60) of patients received SCT immediately following successful brentuximab vedotin treatment, suggesting that brentuximab vedotin may act as a bridge to SCT, enabling a higher proportion of HL patients who achieve a suboptimal response to multi-agent frontline/salvage chemotherapy/radiotherapy and

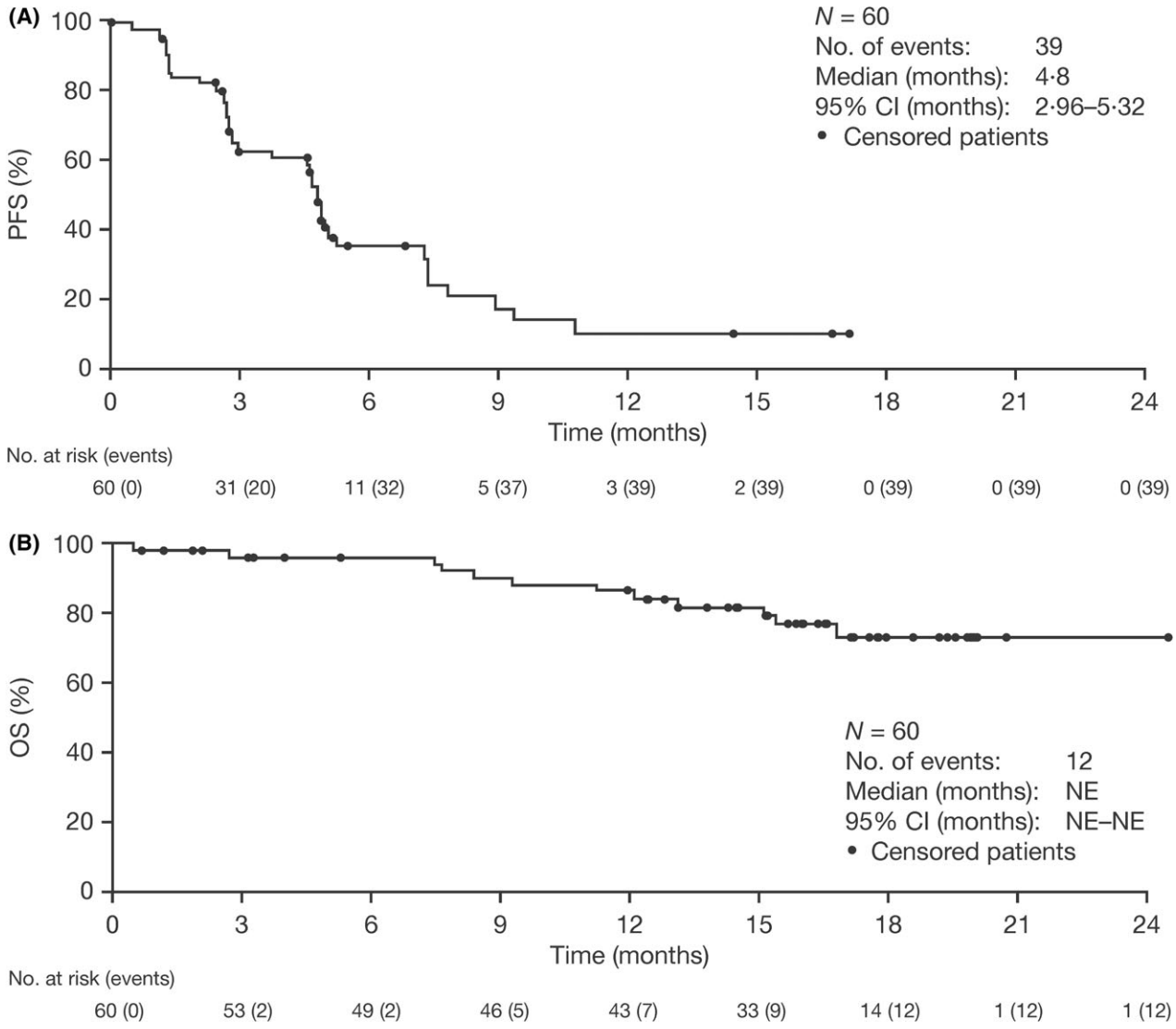

Fig 2. PFS by (A) independent review facility and (B) OS in the intent-to-treat population. CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.

have limited subsequent palliative treatment options, to receive potentially curative SCT. In this context, as has been demonstrated previously in NPPs (Gibb *et al*, 2013; Sasse *et al*, 2013), brentuximab vedotin may constitute an effective salvage therapy for high-risk patients. It is important to note that the range of treatments evaluated in this setting has expanded since the present study was conducted, including studies of brentuximab vedotin plus multi-agent chemotherapy. However, at the time of this study, these patients were not considered suitable for SCT and/or the standard multi-agent chemotherapy salvage therapies available. The use of brentuximab vedotin, with or without multi-agent chemotherapy, to proceed to transplant is important in the context of the findings from Sibon *et al* (2016), who reported substantial 'cure' rates (10-year freedom from second failure and OS rates of 41% and 47%, respectively, in the poor-risk group) using a double autoSCT approach.

Results of the use of brentuximab vedotin in combination with conventional chemotherapy are also promising in this poor-risk population of relapsed/refractory HL. A study assessing the efficacy of brentuximab vedotin in combination with bendamustine reported a CR rate of 74% (64% and 84% for refractory and relapsed patients, respectively) and an ORR of 93% (LaCasce *et al*, 2015), while brentuximab vedotin in combination with ICE produced ORR and CR rates of 94% and 88%, respectively (Cassaday *et al*, 2016). Treatment with a combination of brentuximab vedotin and ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) in patients with primary chemorefractory disease who were candidates for HDT and ASCT resulted in a pre-transplant CR rate of 70% (Garcia-Sanz *et al*, 2016). These results suggest that brentuximab vedotin plus chemotherapy may represent a good option for progressing patients to transplant.

Table IV. Overview of safety profile of single-agent brentuximab vedotin.

AE profile	Brentuximab vedotin ($N = 60$), *n* (%)
Any TEAE	52 (87)
Drug-related TEAE	41 (68)
Grade ≥3 TEAE	21 (35)
Drug-related grade ≥3 TEAE	11 (18)
SAE*	11 (18)
Drug-related SAE	3 (5)
TEAE resulting in drug modification	15 (25)
TEAE resulting in drug discontinuation	3 (5)
Infusion-related TEAE	4 (7)
On-study death	1 (2)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

*SAEs reported for one patient each: anaphylactic reaction, anxiety, bronchitis, cerebrovascular accident, dengue fever, device-related sepsis, general physical health deterioration, Hodgkin lymphoma, pleural effusion, pneumonia, septic shock, serum sickness-like reaction, tachycardia, urinary tract infection, vena cava thrombosis, viral infection, vomiting.

Furthermore, these results should be considered in the context of programmed death-1 (PD-1, also termed PDCD1) inhibitors, which have been developed following the discovery that PD-ligand expression was upregulated on Hodgkin Reed-Sternberg cells (Yamamoto *et al*, 2008). Nivolumab was approved by the FDA in 2016 for the treatment of patients with HL that had relapsed or progressed after autologous SCT and post-transplantation brentuximab vedotin on the basis of two single-arm open-label studies (Ansell *et al*, 2015a; Younes *et al*, 2016). The phase I, dose-escalation study of nivolumab in patients with heavily treated relapsed/refractory HL reported an ORR of 87% (CR 17%, PR 70%) (Ansell *et al*, 2015a), with median PFS not reached at 101 weeks (Ansell *et al*, 2015b). An ORR of 66% was then reported in the phase II CheckMate 205 study of nivolumab in patients with relapsed/refractory HL following failure of both ASCT and brentuximab vedotin (Younes *et al*, 2016). The efficacy of brentuximab vedotin in combination with nivolumab is also encouraging in patients with relapsed/refractory HL, with an ORR of 89% and CR rate of 50% (Diefenbach *et al*, 2017). These preliminary data suggest that brentuximab vedotin and PD-1 inhibition could be effective in enabling patients to receive transplant. Pembrolizumab, a second PD-1 inhibitor (approved by the FDA in 2017 for patients with HL who are refractory or have relapsed after three or more lines of therapy, based on the KEYNOTE-087 trial), resulted in similar response rates (ORRs 64–74%) in patients with relapsed/refractory HL regardless of prior ASCT and brentuximab vedotin treatment status in an open-label phase II study (Chen *et al*, 2017). Safety profiles for PD-1 inhibitors are also encouraging, with particularly low rates of grade ≥3 AEs when using pembrolizumab (Younes *et al*, 2016; Chen *et al*, 2017). Despite promising results, however, until the evidence builds for these newer agents or head-to-head studies indicate otherwise, brentuximab vedotin is likely to be used, consistent with its approved indications, in earlier lines of therapy than PD-1 inhibitors.

Safety findings in the present study were consistent with the known safety profile of brentuximab vedotin in the monotherapy setting (Younes *et al*, 2012). In general, brentuximab vedotin was well tolerated and toxicities were typically grade 1/2. Peripheral neuropathy, a known toxicity with brentuximab vedotin, was observed in 35% of patients but continued to improve over time; 57% of patients experienced complete resolution of all peripheral neuropathy symptoms at the end of treatment/time of last follow-up. The toxicity profile of brentuximab vedotin does not overlap with most multi-agent chemotherapy regimens. Thus, our results suggest that brentuximab vedotin may be used to overcome chemorefractory disease in relapsed/refractory HL patients and may enable these patients to proceed to SCT without the significant haematological toxicity that is associated with other salvage chemotherapy regimens, such as gemcitabine, vinorelbine and pegylated liposomal doxorubicin and gemcitabine, carboplatin and dexamethasone (Bartlett *et al*, 2007; Gopal *et al*, 2010).

In conclusion, single-agent brentuximab vedotin demonstrated notable activity and a favourable safety profile in relapsed/refractory HL patients who were considered not suitable for SCT/multi-agent chemotherapy at the time of enrolment into the study and had limited alternative treatment options. These results continue to support the favourable benefit-to-risk profile for brentuximab vedotin in relapsed/refractory HL patients and suggest brentuximab vedotin may act as a bridge to SCT in HL patients achieving a suboptimal response to multi-agent frontline/salvage chemotherapy/radiotherapy.

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Author contributions

Conception and design: Shalini Singh, Dirk Huebner, Andreas Engert. Collection and assembly of data: Andrzej

Hellmann, Noppadol Siritanaratkul, Guner Hayri Ozsan, Muhit Ozcan, Suporn Chuncharunee, Ai Sim Goh, Wojciech Jurczak, Jan Koren, Shalini Singh, Andreas Engert, Bastian von Tresckow. Data analysis and interpretation: Jan Walewski, Andrzej Hellmann, Wojciech Jurczak, Ewa Paszkiewicz-Kozik, Bingxia Wang, Shalini Singh, Andreas Engert, Bastian von Tresckow. Manuscript writing, review and/or revision of the manuscript: All authors.

Conflict of interest

JW reports honoraria from Roche, Millennium Pharmaceuticals, Inc., Celgene, Servier, Gilead Sciences, and Janssen-Cilag; consulting or advisory role with Roche, Millennium Pharmaceuticals, Inc., Janssen-Cilag, and Celgene; research funding from Roche, Mundipharma, Celgene, Genentech, Seattle Genetics, Inc., GlaxoSmithKline/Novartis, Gilead Sciences, Bayer/Onyx, Pfizer, Boehringer Ingelheim and Celltrion; travel expenses from Roche, Millennium Pharmaceuticals, Inc. and Gilead Sciences. AH reports travel, accommodation, expenses from Novartis, Bristol-Myers Squibb and Servier. NS reports research funding from Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. GHO reports honoraria from Roche, Novartis and Janssen; consulting or advisory role with Celgene and Alexion; research funding from Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and MSD Pharmaceuticals. MO reports honoraria from Janssen, Bristol-Myers Squibb, and Roche; consulting or advisory role with Janssen; research funding from Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Janssen, Novartis, Bayer, and Roche; and travel, accommodation, expenses from Novartis, Roche, Bristol-Myers Squibb, Millennium Pharmaceuticals, Inc., Sanofi and Gilead Sciences. SC reports research funding from Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. ASG declares no conflict of interest. WJ reports consulting or advisory role from AbbVie, Janssen, Roche, Sandoz-Novartis and Millennium Pharmaceuticals, Inc.; speakers' bureau from Roche and Mundipharma; and research funding from AbbVie, Janssen, Roche, Sandoz-Novartis, Gilead Sciences, Pfizer and Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. JK declares no conflict of interest. EPK reports honoraria from Roche and travel, accommodation, expenses from Roche, Sandoz-Novartis and Sanofi. BW reports employment from Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. SS reports employment from Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. DH reports employment from Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and stock ownership from Takeda Pharmaceutical Company Limited. AE reports honoraria and consulting/advisory role from Millennium Pharmaceuticals, Inc., Affimed, Novartis and Bristol-Myers Squibb; research funding from Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Affimed, and Bristol-Myers Squibb. BvT reports honoraria from Novartis, Millennium Pharmaceuticals, Inc., Takeda GmbH, Amgen, and Celgene; consulting or advisory role with Novartis, MSD Pharmaceuticals, Millennium Pharmaceuticals, Inc., and Takeda Pharmaceuticals International, Inc.; research funding from Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Novartis, and MSD Pharmaceuticals; and travel, accommodation, expenses from Millennium Pharmaceuticals, Inc., Takeda GmbH, Novartis and Bristol-Myers Squibb.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Proportion of patients receiving SCT after treatment with brentuximab vedotin.

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