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As an extended half-life recombinant FVIII, Esperoct®offers a simple way to reach higher trough FVIII activity levels compared to standard half-life treatments.**[1,4-9]

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In adults and adolescents (12 years and over)[†] with severe haemophilia A, Esperoct® demonstrated:

A simple, fixed dose:[††1,4]
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Mean trough FVIII activity levels of 3%

Low ABR:[1,4]
Median total ABR[‡§] of 1.18

*40°C storage for up to 3 months before reconstitution[1] **Esperoct® is licenced for the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency). The safety and efficacy of Esperoct in previously untreated patients have not yet been established.[1]

This Novo Nordisk advertisement is intended for UK Healthcare Professionals

Prescribing Information

Esperoct®▼ powder and solvent for solution for injection Turoctocog alfa pegol Esperoct 500 IU Esperoct 1000 IU Esperoct 1500 IU Esperoct 2000 IU Esperoct 3000 IU **Indication:** Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency) **Posology and administration:** The dose, dosing interval and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding, on the targeted factor VIII activity level and the patient's clinical condition. On demand treatment and treatment of bleeding episodes: Required dose IU = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL). *Mild haemorrhage:* early haemarthrosis, mild muscle bleeding or mild oral bleeding. Factor VIII level required (IU/dL or % of normal): 20-40. Frequency of doses: 12-24, until the bleeding is resolved. *Moderate haemorrhage:* More extensive haemarthrosis, muscle bleeding, haematoma. Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses: 12-24, until the bleeding is resolved. *Severe or life-threatening haemorrhages:* Factor VIII level required (IU/dL or % of normal) – 60-100. Frequency of doses: 8-24, until the threat is resolved Perioperative management: *Minor surgery Including tooth extraction.* Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses (hours): within one hour before surgery; repeat after 24 hours if necessary. Duration of therapy: single dose or repeat injection every 24 hours for at least 1 day until healing is achieved. *Major surgery.* Factor VIII level required (IU/dL or % of normal): 80-100 (pre- and post-operative). Frequency of doses (hours): Within one hour before surgery to achieve factor VIII activity within the target range. Repeat every 8 to 24 hours to maintain factor VIII activity within the target range. Repeat injection every 8 to 24 hours as necessary until adequate wound healing is achieved. Consider continuing therapy for another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL). Prophylaxis: The recommended dose is 50 IU of Esperoct per kg body weight every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency. Paediatric population: The dose in adolescents (12 years and above) is the same as for adults. In children below 12 years long-term safety has not been established. Method of administration: Intravenous injection (over approximately 2 minutes) after reconstitution of the powder with 4 mL supplied solvent (sodium chloride 9 mg/mL (0.9%) solution for injection). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, or to hamster protein. **Special warnings and precautions for use:** Name and the batch number of the administered product should be clearly recorded to improve traceability. Hypersensitivity: Allergic-type hypersensitivity reactions are possible due to traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to immediately discontinue the use of the medicinal product and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented. Inhibitors: The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII pro-coagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon. The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors. Patients treated with coagulation factor VIII products should be monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Cardiovascular events: In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk. Catheter-related complications: If a central venous access device (CVAD) is required, the risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered. Paediatric population: Listed warnings and precautions apply both to adults and adolescents (12-18 years). Excipient-related considerations: Product contains 30.5 mg sodium per reconstituted vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2.0 g sodium for an adult. **Fertility, pregnancy and lactation:** Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated. **Undesirable effects:** Adverse events in clinical trials which could be considered **serious** include: (≥1/10): Rash, erythema, pruritis, injection site reactions (<1/10,000): Factor VIII inhibition, hypersensitivity The Summary of Product Characteristics should be consulted in relation to other adverse reactions. **MA numbers and Basic NHS Price:** Esperoct 500 IU EU/1/19/1374/001 £425 Esperoct 1000 IU EU/1/19/1374/002 £850 Esperoct 1500 IU EU/1/19/1374/003 £1,275 Esperoct 2000 IU EU/1/19/1374/004 £1,700 Esperoct 3000 IU EU/1/19/1374/005 £2,550 **Legal category:** POM. 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ABR, annualised bleed rate; EHL, extended half-life; FVIII, factor VIII; rFVIII, recombinant factor VIII; SHL, standard half-life

[†]Previously treated patients, 12 years and above.[1] [††] Prophylaxis: The recommended dose is 50 IU of Esperoct per kg body weight every 4 days. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency.[1] [§]Total ABR includes all bleeds: spontaneous, traumatic and joint bleeds[4]

References: 1. Esperoct® Summary of Product Characteristics. **2.** Adynovi® Summary of Product Characteristics. **3.** Elocta® Summary of Product Characteristics. **4.** Giangrande P et al. Thromb Haemost 2017; 117:252–261. **5.** Tiede A et al. J Thromb Haemost 2013; 11:670–678. **6.** Advate® Summary of Product Characteristics. **7.** NovoEight® Summary of Product Characteristics. **8.** Nuwiq® Summary of Product Characteristics. **9.** Refacto AF® Summary of Product Characteristics.

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bjh research paper

Results of a UK National Cancer Research Institute Phase II study of brentuximab vedotin using a response-adapted design in the first-line treatment of patients with classical Hodgkin lymphoma unsuitable for chemotherapy due to age, frailty or comorbidity (BREVITY)

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Abstract

Standard treatment for classical Hodgkin lymphoma (cHL) is poorly tolerated in older patients and results disappointing. We assessed safety and efficacy of brentuximab vedotin (BV), in previously untreated patients with cHL unfit for standard treatment due to age, frailty or comorbidity. The primary outcome was complete metabolic response (CMR) by positron emission tomography/computed tomography after four BV cycles (PET4). The secondary outcomes included progression-free survival (PFS), overall survival (OS), and toxicity. In all, 35 patients with a median age of 77 years and median total Cumulative Illness Rating Scale for Geriatrics (CIRS-G) score of 6 were evaluable for toxicity and 31 for response. A median of four cycles were given (range one–16). In all, 14 patients required dose reduction due to toxicity and 11 patients stopped treatment due to adverse events (AEs). A total of 716 AEs were reported, of which 626 (88%) were Grade 1/2 and 27 (77%) patients had at least one AE Grade ≥3. At PET4, CMR was 25·8% [95% confidence interval (CI) 13·7–42.2%] and objective response rate 83·9% (95% CI 63·7–90·8%). Median PFS was 7·3 months (95% CI 5·2–9·0), and OS 19·5 months. Our results suggest that BV monotherapy is tolerable but suboptimal in the front-line therapy of elderly or comorbid patients with cHL. Combining BV with other agents may be more effective.

Trial Registration: Clinicaltrials.gov identifier: NCT02567851.

Keywords: brentuximab Vedotin, elderly, Hodgkin lymphoma.

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Approximately 2100 people are diagnosed with classical Hodgkin lymphoma (cHL) in the UK each year. There are two peaks in the age-specific incidence; one in young adults aged 20–24 years and another in older people aged 75–79 years who form 13% of new diagnoses.[1] HL in younger people is treated with front-line chemotherapy usually ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) with or without consolidation radiotherapy. According to stage and other risk factors the 3-year progression-free survival (PFS) varies between 67% and 95%.[2,3] However, outcomes are significantly worse for people aged >60 years. One study reported a 5-year PFS of 46% and 58% for advanced and early stages respectively, with age ≥70 years and inability to perform the activities of daily living (ADL) being associated with the worst outcomes.[4] In another series, 23% of patients with HL aged >65 years died of complications related to ABVD.[5]

It is hypothesised that older individuals have a worse outcome due to more aggressive histology or differences in fundamental disease biology. In addition, standard chemotherapy is often poorly tolerated leading to dose reductions/delays and reduced dose intensity. Moreover co-existing heart disease, lung disease or general frailty may render it too dangerous in the opinion of the treating physician to use standard chemotherapy such as ABVD or BEACOPP, both of which contain agents known to be specifically toxic to the heart (doxorubicin) or lungs (bleomycin). Consequently, better tolerated but less effective therapies are employed.

Brentuximab vedotin (BV) is a CD30 targeted antibody-drug conjugate (ADC) composed of the anti-CD30 monoclonal antibody cAC10 and a potent anti-microtubule drug, monomethyl auristatin E (MMAE). cAC10 binds to the CD30 antigen, which has very low expression on normal cells, but is consistently expressed on Hodgkin Reed–Sternberg cells. Phase I[6] and II[7] data in the relapsed/refractory HL population suggest that BV is highly effective with a very manageable toxicity profile and no known cardiac or pulmonary toxicity when given as a single agent. These characteristics open up the possibility of using the drug to treat patients with newly diagnosed HL where standard doxorubicin and bleomycin containing chemotherapy is considered inappropriate because of co-morbidity or frailty.

Levels of soluble CD30 (sCD30) present in the serum of newly diagnosed patients with HL treated with ABVD (or similar),[8] and relapsed patients with HL treated with BV,[9] have been shown to be prognostic, with lower baseline levels associated with better outcomes. Similar findings have been reported for thymus and activation-regulated chemokine (TARC, also known as CCL17) in newly diagnosed patients treated with chemoradiotherapy,[10] and relapsed patients treated with BV, chemotherapy and haemopoietic stem cell transplant.[11]

In BREVITY, we aimed to test BV monotherapy in a population of patients with previously untreated cHL who were elderly, frail or had significant comorbidities at any age and for whom conventional chemotherapy was not considered a safe option by their treating physician. Clinical outcomes were correlated with baseline prognostic and comorbidity indices, and serial fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) responses.

Patients and methods

Patients

Patients were recruited at 13 UK haemato-oncology centres. Previously untreated patients with stages II (with B symptoms and/or mediastinal bulk), III and IV cHL were eligible if considered unfit for standard chemotherapy. This was assessed by the treating investigator, but had to include at least one of the following factors:

- Impaired cardiac function defined either by an ejection fraction of <50% assessed by echocardiogram or nuclear medicine [multigated acquisition (MUGA)] scan.
- Left ventricular ejection fraction of ≥50% measured by echocardiography or MUGA, but in the presence of significant comorbidities or cardiac risk factors such as diabetes mellitus, hypertension, peripheral vascular disease, ischaemic heart disease, previous myocardial infarction, obesity, stroke or transient ischaemic attacks (TIA) that make anthracycline-containing chemotherapy inadvisable as determined by the investigator.
- Heart failure clinically determined by the presence of New York Heart Association (NYHA) heart failure grade II and III due to a cause other than HL.
- Impaired respiratory function with carbon monoxide diffusion capacity (DLCO) and/or forced vital capacity/forced expiratory volume in 1 s (FVC/FEV1) ratio <75% of predicted due to a cause other than HL.
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) score 1–3 in patients aged ≥60 years.

Further details are provided in the Online *Supplement*.

Study design, end-points and treatment schedule

BREVITY is a Phase II, single-arm, adaptive-response study to investigate the level of activity and tolerability of BV as a single agent. The primary outcome was complete metabolic response (CMR) after four cycles of BV defined as a Deauville Score of 1, 2 or 3 by ^{18}F-FDG-PET/CT scan,[12] from which the CMR rate (CMRR) was calculated. Secondary outcomes included overall response (OR) as per the Lugano Classification,[13] defined as complete plus partial metabolic response (CMR + PMR) after two and four cycles of BV (PET2, PET4), from which the OR rate (ORR) was calculated. The PET2 results were blinded to the investigators to prevent early discontinuation in cases of pseudoprogression or other indeterminate responses. All scans were performed

on approved PET-CT scanners with quality assurance co-ordinated by the UK PET Core Laboratory at St Thomas' Hospital, London, UK.[14] Survival outcomes included PFS, overall survival (OS) and the correlation between PET4 and survival. Tolerability of BV was defined in terms of absence of toxicities related to BV quantified by the Common Terminology Criteria for Adverse Events (CTCAE) version 4 criteria, as well as dose intensity defined as the total dose delivered to each patient as a proportion of the planned protocol dose.

BV was administered at an initial dose of 1·8 mg/kg every 3 weeks as a 30-min outpatient intravenous (IV) infusion. The IV contrast-enhanced CT scans were performed at baseline and following cycles four, eight, 12, 16 or at study exit. Patients in response at PET 4 could continue with treatment providing no evidence of progressive disease was seen at any of these time points. Details of the treatment schedules, permitted dose reductions, assessments, study end-points and molecular methods are reported in the Online *Supplement*.

Follow-up and statistical analysis

Patients were followed-up for up to 3 years from day 1 of cycle one. A Simons two-stage minimax design determined 30 evaluable patients were required, with alpha at 20% and power at 90%. Registered patients subsequently found to have been ineligible at baseline or not starting treatment were to be replaced, although would still contribute toxicity data. Stage 1 recruited 20 eligible patients. Initially an unacceptable CMRR (p0) was set at 40%, below which BV would not be recommended for further investigation. Following agreement amongst the investigators that patients in PMR were deriving significant clinical benefit from BV monotherapy the protocol was amended in October 2014 to allow them to continue on BV. Recruitment into the study was much faster than expected. At the point where stage 1 recruitment was completed there were seven outstanding responses awaited from which three CMR responses would be required to reach the eight required overall to continue to stage 2. The Trial Steering Committee (TSC) reviewed all available data and concluded that as patients were deriving significant clinical benefit without excessive toxicities that recruitment should continue to the second stage without a pause to await the seven outstanding responses. An acceptable response rate (p1) was set at 60%, above which BV would definitely be worthy of further investigation. Response rates were calculated and reported as proportions, and a 95% confidence interval (CI) was constructed using Wilson's estimates due to its increased accuracy with small sample sizes. Time-to-event outcomes were analysed using the Kaplan–Meier method and the median, 12 and 24 month estimates are reported. Correlation of response at PET4 with PFS was conducted using a Cox regression model. Planned dose intensity per cycle was calculated for each patient using the protocol specified dose per kg and 21-day cycle length. Average dose intensity administered per patient was calculated using the actual dose given and the actual cycle length (accounting for delays). The relative dose intensity is defined as the actual dose intensity as a proportion of the planned dose intensity.

Results

Patients

Recruitment to BREVITY completed ahead of the planned accrual date, with a total of 38 patients recruited between 14 February 2014 and 20 October 2015, with a median follow-up of 3 years. Three patients did not receive BV (two ineligible, one failed to start treatment). Of the 35 patients who received BV a further four patients were found to be ineligible upon subsequent review. Following agreement from the TSC, these seven patients were replaced, although it was agreed that every patient who received BV would be evaluated for toxicity. In total 31 patients were eligible and hence evaluable for efficacy (Figure S1). All patients were followed-up. Baseline characteristics are summarised in Table I, including the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) data.

Treatment and tolerability

In all, 35 patients received 238 cycles of BV in total, with a median [interquartile range (IQR); range] number of cycles of 4 [IQR 2,7; 1–16]. Fourteen patients required dose modification due to toxicity [median (IQR; range) number of cycles of 1 (1,2·5; 1–5)] and 10 (29%) patients permanently stopped treatment due to unacceptable toxicity, eight with peripheral sensory neuropathy. The median (range) dose intensity was 100% (57–132%).

The 35 patients reported a total of 716 adverse events [AEs; median (IQR; range) 13 (6,25; 1–94), of which the majority (88%) were CTCAE Grade 1 or 2. Only two patients reported no AEs related to BV. In all, 31 evaluable patients reported a total of 246 events related to BV [median (IQR; range) 5 (3,8; 1–20)]; 84% of these were Grade 1 or 2. In all, 18 patients had at least one related AE of Grade $\geq$3 and 14 serious AEs (SAEs) were reported, 27 of which were deemed to be related to BV. Three SAEs were fatal and of these two were unrelated to BV and one (sepsis) was considered related. Figure 1 shows all adverse events experienced by at least 10% of patients, according to relationship to BV.

Response

A total of 31 patients were deemed evaluable for the primary end-point and 25·8% (95% CI 13·7–43·2%) achieved CMR after four cycles. This was lower than the 40% required by the initial trial design to indicate sufficient activity of BV in this patient population to warrant further investigation. Despite the low CMR rate, the ORR (CMR + PMR) at PET4 was 83·9% (95% CI 63·7–90·8%). In addition to the PET

Table I. Baseline characteristics of the patients

Characteristic	Treated patients $N = 35$	Evaluable patients $N = 31$
Age, years, median (IQR)	77 (72, 82)	77 (69, 82)
Sex, *n* (%)		
Male	22 (63)	20 (65)
Female	13 (37)	11 (35)
Disease stage, *n* (%)		
2	7 (20)	6 (19)
3	12 (34)	9 (29)
4	16 (46)	16 (52)
ECOG PS, *n* (%)		
0	1 (3)	1 (3)
1	17 (49)	16 (52)
2	11 (31)	9 (29)
3	5 (14)	5 (16)
4	1 (3)	
B symptoms, *n* (%)	25 (71)	23 (75)
Bulky disease, *n* (%)	4 (11)	3 (10)
Extra-nodal disease, *n* (%)	20 (57)	18 (58)
Reason standard chemotherapy is unsuitable, *n* (%)		
LVEF reduced with associated comorbidities or cardiac risk factors	4 (11)	4 (13)
Impaired respiratory function	1 (3)	1 (3)
ECOG PS 1, 2 or 3 and aged >60 years (ECOG)	10 (28)	9 (30)
LVEF and ECOG PS	9 (26)	7 (23)
LVEF, impaired respiratory function and ECOG PS	1 (3)	1 (3)
Impaired respiratory function and ECOG PS	5 (14)	4 (13)
LVEF and impaired respiratory function	1 (3)	1 (3)
Impaired cardiac function, LVEF and ECOG PS	1 (3)	1 (3)
Impaired cardiac function, impaired respiratory function and ECOG PS	1 (3)	1 (3)
Impaired cardiac function and ECOG PS	2 (6)	2 (6)
Cumulative illness rating scale for geriatrics		
Total number of categories endorsed (max. 14)		
Median (IQR)	3 (2, 5)	3 (2, 5)
Total score (max. 56)		
Median (IQR)	5 (4, 7)	6 (4, 7)
Severity index (worst 4)		
Median (IQR)	2 (1, 2)	2 (2, 2)
Number of categories at level 3 severity		
Number patients	7 all with 1 level 3	7 all with 1 level 3
Number of categories at level 4 severity		
Number patients	0	0
Most endorsed sites		
Heart	20	18
Endocrine/Metabolic and breast	19	16
Vascular	16	13

scan after four cycles, 25 patients had a PET scan after two cycles and seven had a PET after 16 cycles. The ORR after two cycles was 80·6% (95% CI 63·7–90·8%). A breakdown of responses is shown in Table II.

A total of 24 patients underwent both PET2 and PET4 scans; of these, response for 20 patients did not change between the two scans (six CMR, 14 PMR) and one patient improved their response from PMR to CMR.

Two patients with PMR at PET4 were reported to have CMR at PET2, when this result was unblinded. Both patients were deemed to have achieved PMR for the purposes of the primary end-point of the study by the TSC. Both patients' scans showed subtle changes between PET2 and PET4, and they both underwent unequivocal clinico-radiological progression at 7·3 and 8·8 months respectively.

Progression-free survival and overall survival. To date 28 of 31 evaluable patients have progressed. Of three patients who were progression free at the end of the trial, one patient withdrew after 6·7 months and the other two were followed

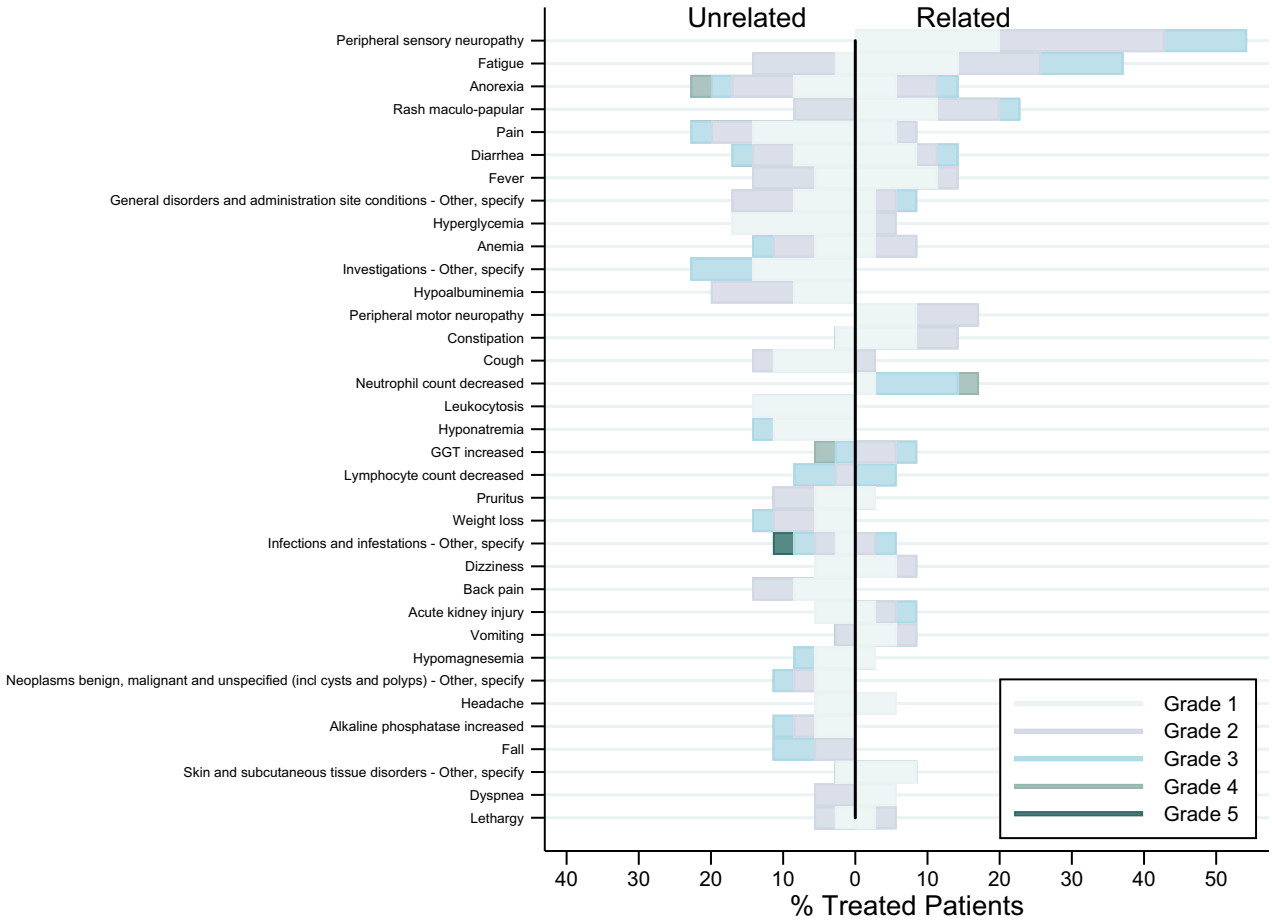

Fig 1. Adverse events (AEs) reported by ≥10% of patients, split by whether the AE was considered related or unrelated to brentuximab vedotin. [Colour figure can be viewed at wileyonlinelibrary.com]

up for a minimum of 29 months. The median PFS time was 7·3 months (95% CI 5·2–9·0). At 12 and 24 months, 13·7% (95% CI 4·3–28·4) and 6·9% (95% CI 1·2–19·6) of patients were progression free (Fig 2). The median OS was 19·5 months (95% CI 12·6–not reached). Survival estimates at 12 and 24 months were 73·4% (95% CI 53·7–85·7) and 42·0% (95% CI 24·1–58·8) respectively.

Kaplan–Meier curves exploring the relationship between response and both PFS and OS are shown in Fig 3. This analysis is exploratory due to the small numbers of patients, and the survival estimates are biased upwards as only those patients who reached the assessment points could be included.

sCD30 and TARC

An exploratory analysis of sCD30 and TARC was performed on serum from 10 patients. The TARC and CD30 results were obtained for all 37 samples analysed; for eight samples the CD30 assay fell below the level of detection. Baseline levels of CD30 and TARC varied dramatically between patients; mean (range) baseline CD30 and TARC levels were 347·4 (30·3–1720·9) pg/ml and 45 064 (391·4–181 681) pg/ml respectively. All 10 patients in this analysis had CMR or PMR at PET4, and tended to show an increase in CD30 levels from baseline measurements. An initial decrease in TARC between baseline and cycle three was observed for nine of the 10 patients; these analyses are presented graphically in Fig 4.

Discussion

In BREVITY, BV monotherapy produced a high ORR and modest CMR rate consistent with published data in the relapse setting;[7] however, the success criterion for the primary outcome was not achieved. Toxicity was common and mainly mild to moderate in severity; the mean dose intensity approaching 90% indicates that this is a tolerable therapy that can be delivered in the outpatient setting.

The PFS and OS were short; published studies of chemotherapy resulted in higher PFS and OS rates, but the BREVITY population specifically included patients deemed unsuitable for chemotherapy.[4,5] Indeed, the BREVITY-like (age >70 years and loss of ADL) subset of patients reported

Table II. Response determined using PET scans after two and four cycles of brentuximab vedotin for evaluable patients

Response outcome	Number evaluable	Number achieved	% (95% CI)
Primary outcome			
PET4: CMR	31	8	25·8 (13·7, 43·2)
Objective response rate			
PET2: CMR + PMR	27	25	80·6 (63·7, 90·8)
PET4: CMR + PMR	31	26	83·9 (67·4, 92·9)

Response at PET2	Response at PET4	Number of patients
PMR	PMR	14
CMR	CMR	6
CMR	PMR	2
Not done	PMR	2
PMR	CMR	1
PMR	PMD	1
Not done	CMR	1
Not done	PMD	1
Not done – treatment discontinued	Death	1
Not done – treatment discontinued	Not done – treatment discontinued	1
PMR	Not done – treatment discontinued	1

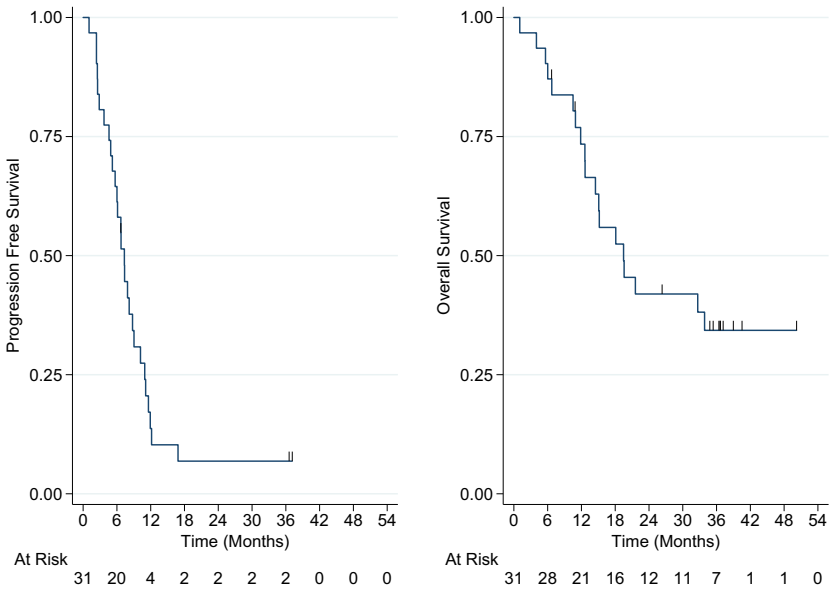

Fig 2. Kaplan–Meier progression-free (PFS) and overall survival (OS) curves. [Colour figure can be viewed at wileyonlinelibrary.com]

by Evens *et al.*[4] had a 2-year PFS/OS of only 13% and none were alive at 5 years. The PET responses with BV monotherapy appeared to be associated with duration of PFS. Scans timed after cycles two and four demonstrated similar findings.

Biomarker analysis of sCD30 and TARC was limited, but corroborated previously reported decreases in TARC levels following initial treatment[15] and at PET2.[16] Previously, TARC levels have been shown to remain high in non-responsive patients[15]; the initially high levels measured in the present study may be linked to the poor survival outcomes of these patients. Similarly, sCD30 tended to increase during treatment, and elevated levels of sCD30 have been linked with poor outcomes and disease relapse.[17] Exploratory proteomic analysis is underway and will be reported separately.

Other researchers have conducted similar studies with BV in elderly/unfit patients with HL, both as monotherapy[18] and in combination with the cytotoxic agents bendamustine[19] or dacarbazine.[20] Ferero-Torres *et al.*[18] treated 27 patients with HL with BV monotherapy. The median age was 78 years and 67% were impaired in at least one ADL. The ORR was 92%, with 73% achieving complete remission. However, similar to

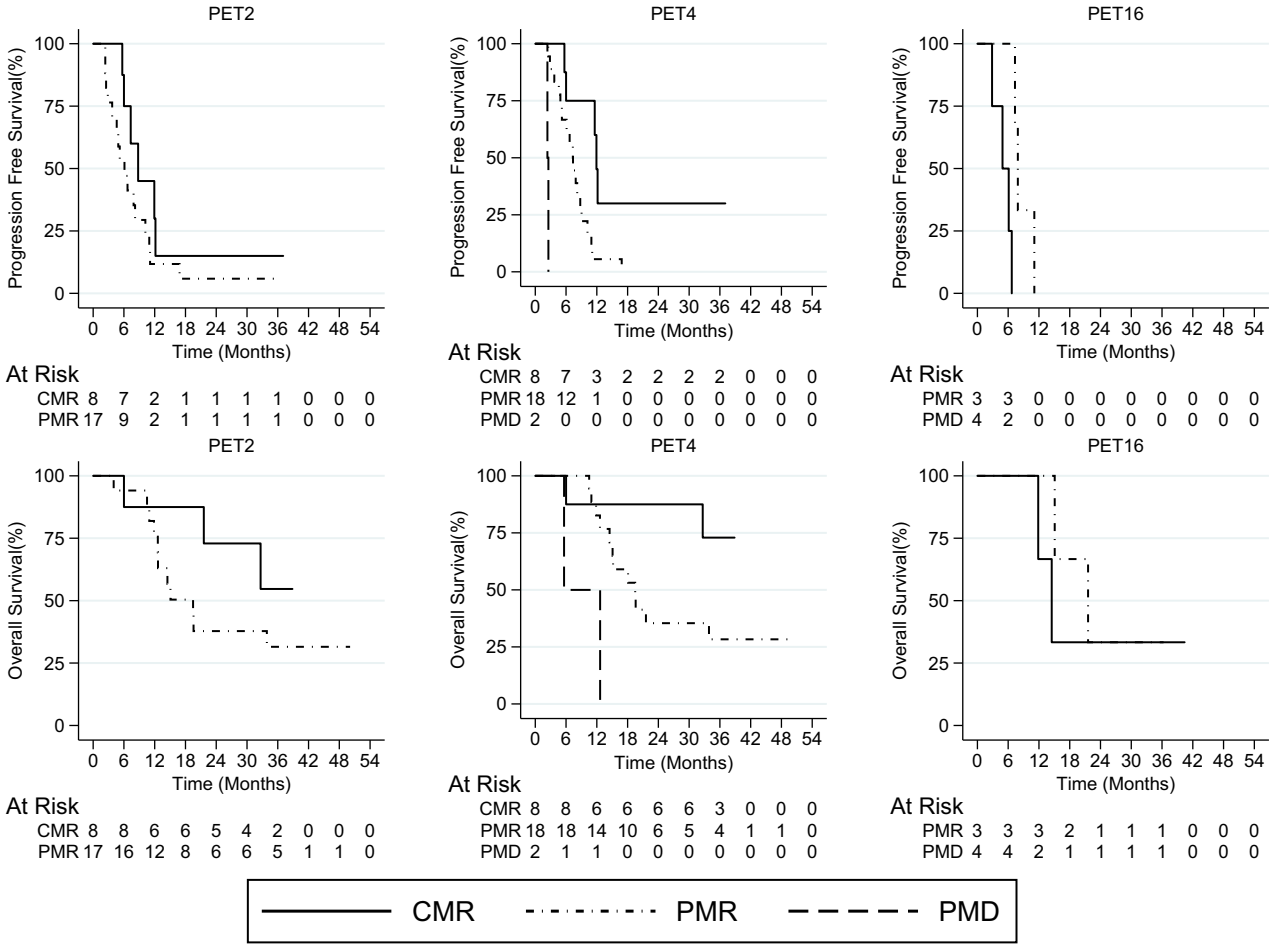

Fig 3. Kaplan–Meier curves showing progression-free (PFS) and overall survival (OS) split by whether patients achieved complete metabolic response (CMR) or partial metabolic response (PMR) at PET4. PMD, progressive metabolic disease. [Colour figure can be viewed at wileyonline library.com]

BREVITY, responses were not durable with a median (range) PFS of only 10·5 (2·6–22·3) months. Gallamini *et al.*[19] published data for 22 patients treated in an ongoing study with BV 1·2 mg/kg on day 1 and bendamustine 90 mg/kg on days 1 and 2. In all, 15 patients completed the full treatment course; 12 (80%) were in CMR. After a mean (range) follow-up of 271 (135–445) days, 10/15 (67%) were still in continuous CR. Friedberg *et al.*[20] reported a similar combination to be too toxic, albeit with BV dosed at 1·8 mg/kg, with a SAE incidence of 65% and two deaths on study, leading to the discontinuation of the bendamustine arm. The BV plus dacarbazine arm is ongoing with data reported for 22 patients. The ORR was 100% and CMR 62%, the median (range) PFS was 17·9 (4·2–29) months and the median OS was not reached (range, 14·8–29 months).

The results of BREVITY and similar studies suggest that BV monotherapy is suboptimal in the front-line therapy setting for elderly and/or comorbid patients with cHL. Although disappointing, outcomes are not dissimilar to those reported for chemotherapy in similar populations of elderly or frail patients with HL, suggesting that HL in this demographic remains a challenging disease. Nevertheless, whilst BV monotherapy failed to have a substantial impact on outcomes for these patients, treatment was tolerable and it may be feasible to combine BV with cytotoxic chemotherapy or other novel agents to achieve better results. Results of BV-chemotherapy combination studies look promising, and BV has also been combined with the immune checkpoint inhibitor nivolumab in the relapsed/refractory setting with encouraging early results.[21,22]

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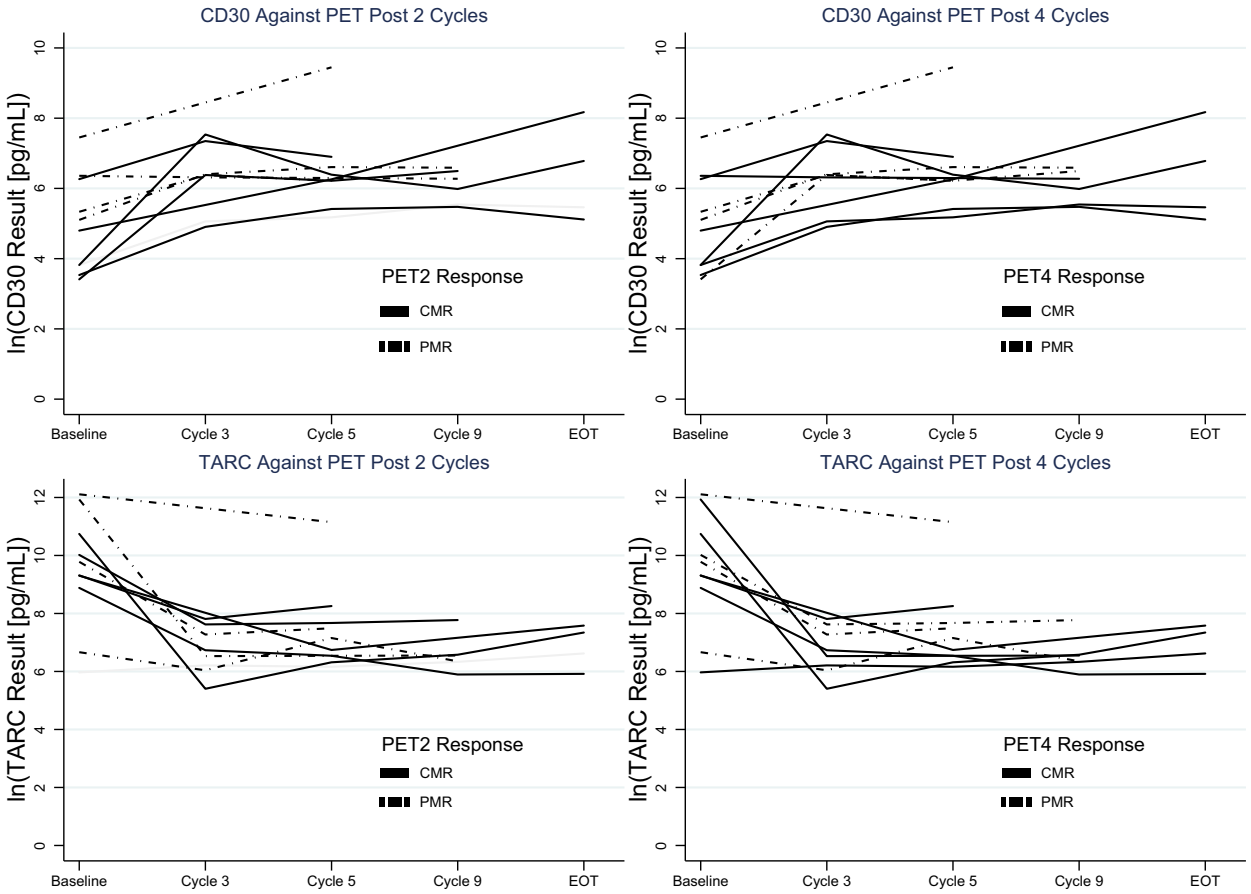

Fig 4. Logarithmic CD30 and thymus and activation-regulated chemokine (TARC) levels over time from baseline split by response at PET2 and PET4. CMR, complete metabolic response; PMR, partial metabolic response. [Colour figure can be viewed at wileyonlinelibrary.com]

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Conflict of interest

Dr Adam Gibb has received honoraria, speaker's bureau fees and educational support from Takeda. Professor Sally Barrington has received speaker's bureau fees from Takeda. Professor Andrew J. Davies has received honoraria, research support, and travel funding from Takeda, and is a member of the Takeda Advisory Board. Professor John Radford has received honoraria, financial support for accomodation and travel, speaker's bureau fees and research funding from Takeda.

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Supporting Information

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

Fig S1. Consort diagram showing participant flow in BREVITY.

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