Title Page

Results of a multicentre UK-wide retrospective study evaluating the efficacy of brentuximab vedotin in relapsed, refractory classical Hodgkin lymphoma in the pre-transplant naive setting.

T.A. Eyre[1], B. Phillips[2], K.M. Linton[3], S. Kassam[4], A. Gibb[3], S. Allibone[3], K. Peggs[2], C. Burton[5], G. Stewart[5], R. LeDieu[6], C. Booth[6], W.L. Osborne[7], F. Miall[8], D.W. Eyre[9], K. Ardeshna[2], & G. P. Collins[1].

1. Department of Haematology, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, OX3 7LE

2. Department of Haematology, University College London Hospitals NHS Foundation Trust, London, NW1 2BU

3. Department of Medical Oncology, The Christie Hospital NHS Trust, Wimslow Road, Manchester, M20 4BX, UK.

4. Department of Haematology, Kings College London Hospitals NHS Foundation Trust Denmark Hill, London SE5 9RS

5. Department of Haematology, Leeds Teaching Hospital NHS Trust, Beckett Street, Leeds, West Yorkshire, LS9 7TF

6. Department of Haematology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE

7. Department of Haematology, Newcastle upon Tyne NHS Foundation Trust, NE7 7DN

8. Department of Haematology University Hospitals of Leicester NHS Trust, Infirmary Square, Leicester LE1 5WW

9. Nuffield Department of Medicine, University of Oxford, Oxford, UK

*Author responsible for correspondence. Toby A. Eyre, Department of Haematology, Cancer and Haematology Centre, Oxford University Hospitals NHS Trust, OX3 7LE. Email: toby.eyre@ouh.nhs.uk

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Abstract

Relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) is associated with a relatively poor outcome once patients become resistant to traditional chemotherapy and new approaches are needed. Brentuximab vedotin (BV) is a novel anti-CD30 monoclonal antibody conjugated to the antimicrotubule cytotoxic monomethyl auristatin-E (MMAE). BV has been licenced and routinely used in patients who relapse after autologous stem cell transplant (SCT) since 2012. BV is also licensed in patients who have received two prior lines of therapy and who are not suitable for ASCT. There are very limited data on the efficacy of both the efficacy of BV in this setting; in particular the ability of the agent to enable suitability for autologous or allogenic SCT by inducing or deepening remissions. We performed a UK-wide retrospective multi-centre study of 99 SCT-naïve R/R cHL patients who received BV to assess the success of incorporating this agent pre-SCT. All had previously received two or more prior chemotherapy lines given with curative intent. Patients had all received prior salvage with the initial aim to proceed to potential curative SCT but were not deemed suitable due to failure of the treatment to induce deep and durable remissions. The median age of the cohort treated was 32 years (range 13-70 years) with an equal gender distribution. The majority had nodular sclerosis subtype and presented with good performance status and advanced stage disease. From the point of initial BV treatment, the median progression-free survival (PFS) was 5.65 months (95% confidence interval (CI) 4.41 - 12.20 months) and the median overall survival (OS) was 37.15 months (95% CI 18.28 months - not reached (NR)). The overall response rate to BV was 56% (complete metabolic response/complete response/complete response unconfirmed (CMR/CR/CRu) 29% plus partial metabolic response/partial response (PMR/PR) 27%). The median duration of response on those entering a CR was superior to that of a PR, consistent with previous reports. Multivariate Cox regression revealed that patients with improved performance status and haemoglobin at first relapse had an improved PFS from the start of BV. We demonstrate that BV has activity and is a non-toxic option in a cohort of high risk, predominantly refractory cHL, although the PFS of 5.65 months demonstrates that further work is required to improve outcomes in this high risk patient population.

Background and introduction

Classical Hodgkin lymphoma (cHL) is typically a highly chemosensitive and curable B-cell malignancy, with approximately 2000 new annual cases per year in the UK (Smith *et al.*, 2015). Newly diagnosed cHL are often managed according to whether the patient has early favourable, early unfavourable and late stage disease (Follows et al., 2014). Early stage disease is typically treated with combined modality therapy, most often with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and radiotherapy (RT). There is currently a lack of international consensus regarding the optimal first line treatment for advanced stage cHL. ABVD is favoured in the UK, some parts of continental Europe, Australia and the USA, whereas in Germany and other parts of Europe, $BEACOPP_{ESCALATED}$ (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisolone, procarbazine) is standard. Bleomycin is now frequently discontinued in patients who are interim PET negative after two cycles of ABVD in advanced stage disease (Johnson et al., 2016). Patients that are refractory to or who relapse after front line therapy are uncommon but represent a significant challenge and those patients that subsequently relapse or are refractory to first line salvage represent a clear area of need where the optimum therapeutic approach remains unknown.

Brentuximab Vedotin (BV) is a novel anti-CD30 monoclonal antibody conjugated to the antimicrotubule cytotoxic monomethyl auristatin-E (MMAE). BV is licenced in patients who relapse after autologous stem cell transplant. BV has been used routinely in this setting as a standard of care since 2012. BV is also licensed in patients who have received two prior lines of therapy for whom autologous stem cell transplantation ASCT or multi-agent chemotherapy is deemed to be not a treatment option. Data generated from the Memorial Sloan Kettering group have demonstrated that patients who do not achieve a negative functional imaging scan have a low event free survival following subsequent ASCT (Moskowitz, Blood 2010). For this reason, many clinicians would regard a patient as not suitable for autologous stem cell transplantation if they have failed to reach a complete metabolic remission after salvage therapy. Further salvage treatment is then typically given as a means of inducing or deepening responses thus enabling SCT (autologous or, some cases, allogeneic) to go ahead in some patients. Within the UK over recent years, patients deemed at high risk of ASCT-failure (typically positive PET scan after standard salvage chemotherapy) have often undergone treatment following a response-adjusted transplantation algorithm. T cell deplete (alemtuzumab conditioning) allogenic stem cell transplantation as a consolidation strategy has been used in those deemed at high risk of ASCT-failure following the publication of outcomes following this approach (Thomson et al, 2013). The 3-year PFS of 68% and 'current' PFS post-donor lymphocyte infusion of 80% of a large retrospective series was encouraging and led to the PAIRED trial which is yet to report. Given this impressive long term disease control with relatively minimal toxicity this approach has been adopted by several centres and as such, the data presented includes the relevant patients in our BV cohort.

There is very limited data on the efficacy of BV prior to planned stem cell transplantation in terms of survival rates and ability to enable stem cell transplant to occur. Table 1 highlights the limited experience from small case series of up to 30 SCT-naïve patients that have been published. Overall response rates (ORR) vary from 30% to 71% in patients relapsed or refractory to first line salvage therapy (Forero-Torres et al., 2012; Gibb et

al., 2013; Onishi et al., 2015; Sasse et al., 2013; Zinzani et al., 2015). Overall response to BV when assessed at first relapse, before administration of conventional salvage chemotherapy, was 68% (CR 35%; PR 33%) in a phase II trial of 37 patients (Chen et al., 2015).

Based on this relative paucity of data we therefore sought to assess the activity of BV monotherapy in patients fit, but not suitable, for stem cell transplantation, the ability of BV to enable SCT to occur, and the outcome and toxicity post-SCT (autologous and allogenic) in a large retrospective UK wide analysis (n = 99).

Table 1: Summary of Brentuximab Vedotin in the transplant-naïve setting

Patient number	Criteria	Median cycles of BV	Response data	Transplantation data	Reference
30	PET-positive disease after conventional chemotherapy salvage treatments	4	Normalization of PET (Deauville ≤2) in 30% (9/30).	9 proceeded to ASCT	Zinzani et al, 2015
15	FDG PET positive disease after platinum-based salvage	4	Normalization of FDG PET (Deauville ≤2) in 53% (8/15). Only observed in patients achieving PR or SD after platinum-salvage	All (n =15) proceeded to ASCT, regardless of FDG PET status	Onishi et al, 2015
14	No prior autologous SCT due to refractory disease (n = 9), co-morbidity (n = 4) and unknown reasons (n = 1).		ORR 71% (10/14) with 5 PR and 5 CR	Consolidating ASCT (n = 4) or allogeneic SCT (n = 1)	Sasse et al, 2013
20	10 transplant-naïve patients from study SG035–0001 10 transplant-naïve patients from study SG035–0002. Median prior systemic chemotherapy regimens was 3 (range, 1–7).	3	ORR 30% (6/20) including 2 CR and 4 PR	3 of 4 'eligible' patients received an ASCT	Forero-Torres et al, 2012
12	No prior autologous SCT due to relapsed, refractory disease	5.5	ORR was 58% (2 CR, 5 PR)	1 proceeded to allogenic SCT	Gibb et al, 2013
37	Second-line therapy at first relapse	4	ORR was 68% (25/37) (13 CR, 12 PR).	32 proceed to ASCT (18 directly post-BV; 14 required salvage chemotherapy post-BV, pre-ASCT)	Chen et al, 2015

Material and Methods

Patient Characteristics

The purpose of this study was to investigate the efficacy of BV monotherapy in a retrospective, multicentre population of patients with relapsed, refractory cHL from across the UK prior to planned SCT. The majority of the data was collected from 9 major UK centres, all of whom had treated at least three patients. Patients received BV monotherapy from May 2011 to July 2016 when the data was censored. Paper and electronic clinical notes were reviewed in all cases. Data was collected typically by the physician who had overseen that patient's care whilst on BV monotherapy. Standard clinical baseline characteristics (age, gender, lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status (Oken *et al*., 1982), extranodal disease, B symptoms, Ann Arbor stage, disease bulk, histological subtype) were collected. Known

risk factors for poor progression free survival (PFS) at first relapse were also collected (haemoglobin, extranodal disease, B symptoms, Ann Arbor stage). In addition, details on first, second and third line therapy were collected including: a) regimen b) best ORR by PET-CT or CT alone c) length of first remission if obtained d) number of lines of prior therapy. Radiotherapy was typically included within a combined treatment modality approach and hence was not included as a separate line of prior treatment.

Adverse event (AE) data were collected including allergic reaction, cytopenias, neutropenic fever (NF), non-neutropenic fever (NNF), and peripheral neuropathy. Grading of AEs was collected wherever possible. Patient follow up was censored at the most recent hospital visit or death. The data were locked and analysed in September 2016.

Treatment and Statistical analysis

Patients received BV monotherapy at 1.8 mg / kg once every three weeks until progression, toxicity or death from other causes. PFS was calculated from the initiation of BV to the time of relapse, disease progression, death, or censored at the last follow-up. OS was calculated from the initiation of BV monotherapy to date of death and was also censored at the last follow-up. Cox regression was used to determine univariate predictors of PFS. Independent predictors were identified using multivariate Cox regression. All univariate predictors with $p < 0.2$ were eligible for inclusion in the initial multivariate model, followed by backward selection with the Akaike information criterion, AIC (Burnham & Anderson, 2002). Fractional polynomials were used to allow for non-linear effects of continuous variables (Royston & Altman, 1994). All analyses were performed in Stata 13 (StataCorp, College Station, TX).

Results

Table II: Baseline Characteristics

Characteristics	BV SCT-naive patients (n = 99)
At Diagnosis	
Median age (years) at diagnosis	32 years (range 13-70 years)
Gender	
Male	45 (45%)
Female	54 (55%)
ECOG at diagnosis (n = 86)	

0	45 (52%)
1	36 (42%)
2	3 (3%)
3	0 (0%)
4	2 (2%)
Histological subtype at diagnosis (n =89)	
Nodular Sclerosis	75 (84%)
Mixed Cellularity	12 (13%)
Lymphocyte Deplete	1 (1%)
Lymphocyte Rich	1 (1%)
Ann Arbor staging at diagnosis (n = 98)	
1-2	28 (29%)
3-4	70 (71%)
Bulk at diagnosis > 10 cm (n = 95)	
N	75 (79%)
Y	20 (21%)
Length of first remission: earliest remission to relapse (n = 66)	Median 6.00 months (range 0.66 – 74.07 months)
Risk factors at relapse	
Haemoglobin (n = 80)	Median 12.2 g/dL (range 6.6 – 15.3 g/dL)
≥ 12	41 (51%)
< 12	39 (49%)
Extranodal disease at first relapse (n = 94)	
Y	44 (47%)
N	50 (53%)
B symptoms at first relapse (n = 88)	
Y	33 (38%)
N	55 (62%)
Ann Arbor stage at first relapse (n = 94)	
1-2	27 (29%)
3-4	67 (71%)
Median time from last treatment to BV (n = 94)	2.53 months (range 0.72 – 34.8 months)
Median time from initial diagnosis to BV (n = 99)	14.53 months (range 4.01 – 190.95 months)
Prior lines of therapy pre BV (n = 99)	
2	70
3	24
4	5
Median number of prior chemotherapy lines	2 (range 2-4)
Response to BV (n = 96)	
ORR	54 (56%)
CMR / CR / CRu	24 (25%) / 3 (3%) / 1 (1%)
PMR / PR	2 (2%) / 24 (24%)
SD	8 (8%)
PD	34 (35%)
Cycles of BV given	Median 4 (range 1-9)
Received stem-cell transplantation following BV	
Yes	61 (61%)
Autologous SCT	23 (23%)
Allogenic SCT	38 (38%)
No	38 (38%)

Abbreviations: BV; *brentuximab vedotin, ORR; overall response rate, P(M)R;* Partial (metabolic) response, C(M)R/CRu; complete (metabolic) response / unconfirmed complete response, SD; stable disease, PD; progressive disease, SCT; stem cell transplantation

The key baseline characteristics of the 99 patients are outlined in Table II. The median age of the cohort treated with BV monotherapy was 32 years (range 13-70 years) with an equal gender distribution (male 45%; female 55%). The majority of patients within the cohort had nodular sclerosis histological subtype (n = 75; 84%) and presented with an ECOG performance status of 0-1 in 94% of cases. Most patients presented with advanced stage disease (n = 69; (71%)) with bulky disease > 10 cm present in 21% of patients.

Table III: Treatments received pre and post BV and response rates

Treatment lines and response rates	BV SCT-naive patients (n = 99)
First line therapy (n = 99)	
ABVD alone	73 (74%)
ABVD to eBEACOPP/BEACOPP	7 (7%)
CHLVPP / ABVD	3 (3%)
ABVD to AVD	4 (4%)
OEPA/COPDAC	7 (7%)
Other	5 (5%)
RT as part of first line treatment	7
Response to first line chemotherapy	
ORR	75 (76%)
CR total (CMR / CR / Cru)	44 (44%) (25 (25%) / 16 (16%) / 3 (3%))
PR total (PMR / PR)	31 (31%) (10 (10%) / 21 (21%))
SD	5 (5%)
PD	19 (19%)
Second line therapy (n = 99)	
ESHAP	42 (42%)
DHAP	24 (24%)
IGEV	8 (8%)
ICE	7 (7%)
IVE	4 (4%)
BEACOPP/eBEACOPP	4 (4%)
ChVLLP based	4 (4%)
RT	3 (3%)
Other	3 (3%)
RT adjunct	3
Response to second line chemotherapy (n = 98)	
ORR	47 (48%)
CMR / CR	4 (4%) / 6 (6%)
PMR / PR	4 (4%)/ 33 (34%)
SD	15 (15%)
PD	36 (37%)
3rd line therapy if not BV (n= 28)	
Mini-LEAM / Mini-BEAM	9 (32%) / 1 (4%)
GEM-P	7 (25%)
DHAP	4 (14%)
IGEV	3 (11%)
IVE	2 (7%)
ESHAP	1 (4%)
RT	1 (4%)
Response to non-BV third line chemotherapy (n = 28)	
ORR	11 (39%)
CMR / CR	1 (4%) / 2 (7%)
PMR / PR	2 (7%)/ 6 (21%)

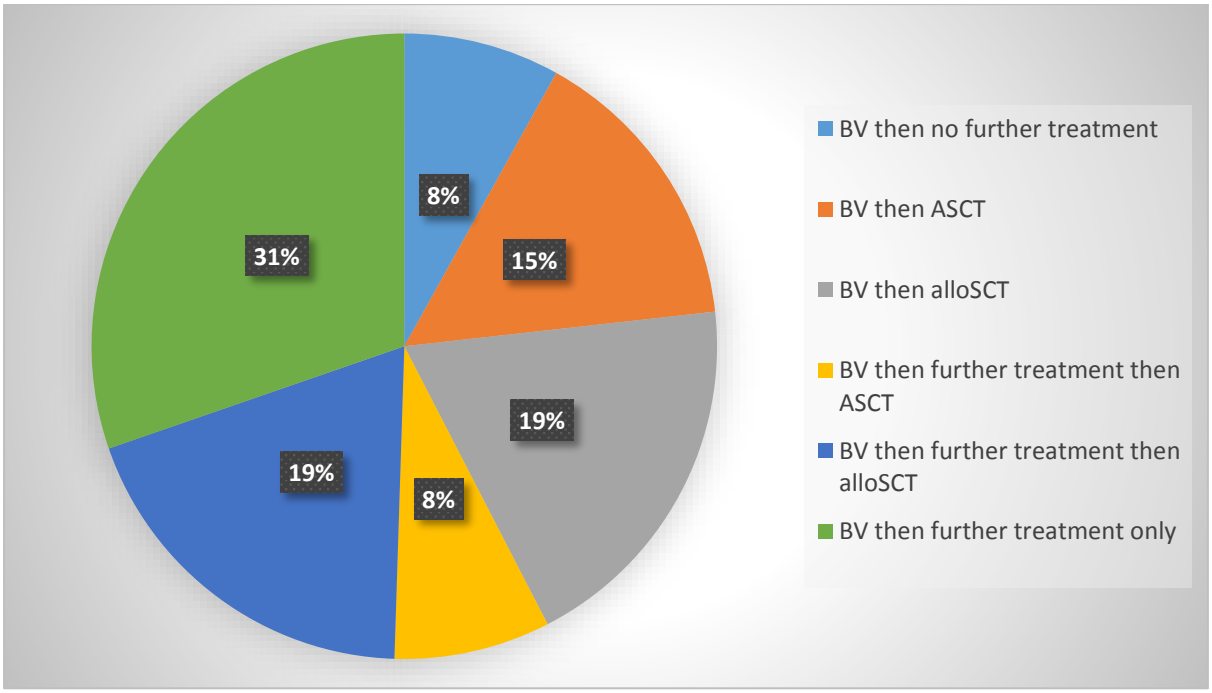
SD	4 (14%)
PD	13 (46%)
Treatment post BV pre SCT	
Cohort failing to reach SCT	
Bendamustine	11
Gemcitabine-based	6
Mini-BEAM	6
DECC	3
RT	5
Others	14
Cohort successfully reaching SCT	
Bendamustine	7
Gemcitabine-based	3
Mini-BEAM/mini-LEAM	12
RT	4
Others	5
Response to BV according to subsequent transplantation	
Autologous SCT (n = 23)	
CMR/CR	10
PMR/PR	7
SD	2
PD	3
N/A	1
ORR	77%
Allogenic SCT (n = 38)	
CMR/CR	16
PMR/PR	9
SD	3
PD	10
N/A	0
ORR	69%

Abbreviations: ABVD; adriamycin, bleomycin, vinblastine, dacarbazine, (e)BEACOPP; (escalated) bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisolone, procarbazine; CHLVPP; chlorambucil, vinblastine, prednisolone, procarbazine; OEPA/COPDAC; Vincristine, etoposide, prednisone, doxorubicin, cyclophosphamide, vincristine, prednisone, and dacarbazine; B(L)EAM; carmustine (lomustine), etoposide, cytarabine, melphalan; DECC; lomustine, etoposide, chlorambucil, dexamethasone; BV; *brentuximab vedotin, ICE; ifosfamide, carboplatin, etoposide, GEM-P; gemcitabine, methylprednisolone, cisplatin, DHAP; dexamethasone, high dose cytarabine, cisplatin; ESHAP; etoposide, high dose cytarabine, methylprednisolone, cisplatin, IVE; ifosfamide, epirubicin, etoposide, IGEV; ifosfamide, gemcitabine,* vinorelbine *RT; radiotherapy, ORR; overall response rate P(M)R;* Partial (metabolic) response, C(M)R/CRu; complete (metabolic) response / unconfirmed complete response, SD; stable disease, PD; progressive disease,

Table III displays the treatment patients received in our cohort both prior to and following BV monotherapy. The vast majority (74%) received ABVD induction regimen, either 2-4 cycles with involved field radiotherapy in early stage disease or 6 cycles (with bleomycin dropped in some more recently treated, iPET negative patients

(4%)). Seven patients (7%) escalated intensity following a positive iPET to escalated BEACOPP or BEACOPP-14. The ORR to first line therapy was 76% (CR/CRu/CMR rate 41%; PR/PMR rate 25%) and the median length of the first remission in all measurable patients was 6 months (range 0.7 – 74 months). Second line therapy was most commonly ESHAP (42%) (etoposide, high dose cytarabine, methylprednisolone, cisplatin) or DHAP (24%) (dexamethasone, high dose cytarabine, cisplatin). IGEV (Ifosfamide, gemcitabine, vinorelbine) and ICE (ifosfamide, carboplatin, etoposide), and IVE (ifosfamide, epirubicin, etoposide) were all also regularly used second line regimens. Mini-BEAM / mini-LEAM (carmustine (lomustine), etoposide, cytarabine, melphalan) and GEM-P (gemcitabine, cisplatin, methylprednisolone) were often used third line. Response rates incrementally decreased with subsequent lines of therapy pre-BV (second line; ORR 48%; CR/CMR 10%; PR/PMR 38% and third line; ORR 39%; CR/CMR 11%' PR/PMR 28%).

Figure 1: treatment following BV



Response to BV monotherapy

The overall median follow up from the start of BV was 12.0 months (range 0.4 - 56.7 months). The median time from prior therapy to starting BV was only 2.53 months (range 0.72 – 34.8 months). The best radiological ORR recorded as assessed by the local treating physician was 56% (complete metabolic response/complete response/complete response unconfirmed (CMR/CR/CRu) 29% plus partial metabolic response/partial

response (PMR/PR) 27%) in the 96 patients assessable for response. Three patients developed toxicities and were never radiologically assessed. The median number of cycles of BV monotherapy received was 4 (range 1-9). Sixty one percent (n = 61) received consolidation with either an allogenic (n = 38; 38%) or autologous SCT (n = 23; 23%). However, only 32% (n = 32) proceeded to SCT without requiring further treatment with 29% (n = 29) requiring further treatment prior to receiving SCT (Figure 1). For those who proceed to ASCT (n = 14) immediately following BV, 64% were in CR and 36% were in PR. For those who proceeded to alloSCT immediately following BV (n = 18) the corresponding rates to BV were CR/CMR 67%, PR 22% and SD 11%.

Post BV therapy

Post BV therapy was variable, with the most commonly used options including bendamustine, gemcitabine, and radiotherapy. Of the 23 patients receiving an autologous SCT, 3 patients had progressive disease (PD) pre-SCT and received bendamustine (n = 2) and mini-BEAM followed by GEM-P (n = 1). Of the 38 receiving allogenic SCT, 10 patients had PD pre-SCT and were salvaged by mini-BEAM/LEAM (n = 6), bendamustine (n = 1), GEM-P (n = 1), R-IVE (n = 1) and radiotherapy (n = 1).

Figure 2: Survival of patients following BV monotherapy

Figure 2 panel (A-E) provides the key survival outcomes. The median PFS for all patients was 5.65 months (95% confidence interval (CI) 4.41 - 12.20 months) (panel A) and the median OS for all patients was 37.15 months (95% CI 18.28 months - not reached (NR)) (panel B). Patients who were consolidated with either an autologous or allogenic SCT had a superior PFS (panel C) and OS (panel D) ($p < 0.001$ for autologous and allogenic SCT when compared to non-SCT group for PFS and OS) to those patients that did not receive a consolidative SCT. The median OS and PFS of those groups were as follows: no SCT (median PFS 3.02 months (95% CI 2.50 - 4.41); median OS 12.19 months (95% CI 8.09 - 18.28 months)) vs autologous SCT (median PFS NR (95% CI 17.03 months - NR); median OS NR (95% CI 27.02 months - NR)) vs allogenic SCT (median PFS NR (95% CI 5.59 months - NR); median OS NR (95% CI 37.15 months - NR)). Patients with an improved initial remission to BV translated that response into an improved PFS (Panel E).

Table IV summarises the findings of the univariate and multivariate analysis. Univariate predictors of PFS following BV treatment were baseline performance status at diagnosis ECOG 0 vs. 1 (Hazard ratio (HR) 2.19

(95% CI 1.23 - 3.92; p = 0.008), baseline ECOG 0 vs. 2 (HR 3.93 (95% CI 1.32 - 11.65; p = 0.014)), haemoglobin at first relapse (continuous variable HR 0.77 (95% CI 0.65 - 0.92; p = 0.004)) and extranodal disease at first relapse (HR 1.86 (95% CI 1.11 - 3.14; p = 0.020)). ECOG 0 vs. 1 at baseline and haemoglobin at first relapse factors remained statistically significant following multivariate analysis.

Table IV: Univariate and multivariate predictors of progression or death

A: Univariate predictors of progression or death		
Predictor	**Hazard ratio (95% CI)**	**p**
Male gender	1.00 (0.60 - 1.67)	0.995
ECOG 0 vs 1 at diagnosis	2.19 (1.23 - 3.92)	0.008
ECOG 0 vs 2 at diagnosis	3.93 (1.32 - 11.65)	0.014
Age (continuous)	1.01 (1.00 – 1.03)	0.152
Stage I vs II at diagnosis	0.73 (0.10 - 5.57)	0.766
Stage I vs III at diagnosis	0.82 (0.10 - 6.44)	0.852
Stage I vs IV at diagnosis	1.20 (0.16 - 8.79)	0.860
Bulk > 10 cm at diagnosis	0.85 (0.44 - 1.64)	0.621
NS vs MC	1.35 (0.63 - 2.88)	0.434
NS vs other	1.92 (0.59 - 6.21)	0.277
First remission (continuous)	1.00 (0.99 - 1.02)	0.652
Hb at first relapse (continuous)	0.77 (0.65 - 0.92)	0.004
Extranodal disease at first relapse Y	1.86 (1.11 - 3.14)	0.020
B symptoms at first relapse Y	1.61 (0.94 - 2.75)	0.084
Stage II at first relapse	2.32 (0.31 - 17.71)	0.415
Stage III at first relapse	2.36 (0.31 - 18.17)	0.409
Stage IV at first relapse	3.38 (0.46 - 24.79)	0.232
Prior lines of therapy 3	1.15 (0.64 - 2.05)	0.643
Prior lines of therapy 4	1.61 (0.57 - 4.49)	0.367
Time from last treatment to BV (continuous)	0.97 (0.92 - 1.03)	0.384
Total Duration of HL time frame (continuous)	1.00 (0.99 - 1.01)	0.892
B: Multivariate predictors of progression or death		
Characteristic	**Hazard ratio (95% CI)**	**p**
Male gender	2.04 (1.05 - 3.96)	0.035
ECOG 0 vs 1 at diagnosis	2.19 (1.18 - 4.04)	0.013
ECOG 0 vs 2 at diagnosis	2.40 (0.76 - 7.54)	0.136
Hb at first relapse (continuous)	0.66 (0.54 - 0.80)	0.000

Table V describes the AEs reported by local physicians during BV monotherapy. Causality and CTCAE v 4.03 grading was formally assessed where possible given the retrospective nature of this study. BV was generally well tolerated, with no AEs reported in 63 (64%) of the 99 patients. The commonest reported AEs were neutropenia (grade 1-2 n =9; grade 3-4 n = 6; not known n = 2), anaemia (n = 7; all grade 1), non-neutropenic infection (grade 1-2 n = 5; grade 3-4 n = 4; grade 5 n = 1) and sensory peripheral neuropathy (grade 1-2 n = 7; grade 3-4 n = 2). There were no previously undescribed AEs thought related to BV.

Table V: Adverse Events – possible, probably or definitely related to brentuximab vedotin

Adverse Events reported (n = 99)	Total number of events
Patients experiencing no related toxicity	63
Neutropenic Fever	0
Non neutropenic Infection	
G2	5
G3	4
G5	1
Haematological	
Neutropenia	
G1	4
G2	5
G3	4
G4	2
NK	2
Anaemia	
G1	7
Thrombocytopenia	
G1	1
Allergic Reaction	
G2	2
G3	1
Gastroenterological	
Mucositis	
G1	1
Vomiting	
G1	1
Nausea	
G1	1
Constipation	
G2	1
Peripheral Neuropathy	
G1	4
G2	3
G3	2
Rash	
G1	1
G3	1
Flu-like Symptoms	
G1	3
Fatigue	
G1	2
Myalgia	
G1	4
Others	3

Discussion

Despite the unavoidable limitations of a retrospective non-randomized study, this is the largest series to date outlining the efficacy and survival of patients with relapsed / refractory cHL treated with BV monotherapy

prior to planned SCT. Our series (n = 99) provides extensive coverage across the United Kingdom, with data provided from major tertiary referral units and provides an accurate representation of the patient population in need of novel therapies in this area. The ORR of 56% (complete metabolic response/complete response/complete response unconfirmed (CMR/CR/CRu) 29% plus partial metabolic response/partial response (PMR/PR) 27%) highlights the efficacy of BV in this difficult-to-treat, chemotherapy-refractory population. Response rates recorded in our cohort are consistent with that reported within the summarised literature in Table 1. The overall PFS for all patients of 5.65 months (95% CI 4.41 - 12.20 months) is however modest. This is reflected in the fact that over half of patient who were consolidated with a SCT required at least 1 further line of therapy post-BV before consolidation SCT. Patients who initially only responded partially had a short median PFS of 6.48 months (95% 4.73 – NR) and therefore required consolidation therapy in remission as responses were non-durable. Patients with a complete response had more durable remissions with the median duration of remission not reached.

It is very difficult to conclude from this data as to which form of SCT consolidation is superior. The ORR to BV in those receiving autologous SCT may have had some influence over the seemingly improved PFS curve when compared to those receiving allogenic SCT. There was no OS difference between the two strategies and type of SCT was very dependent of physician and centre preference within the cohort as a whole rather than direct patient characteristics *per se*. Our study was not designed to answer the question of whether alternative treatment options are superior to BV or which consolidation SCT strategy is best. Overall, BV was very well tolerated in this setting and highlights the value of relatively non-toxic regimens in the preparation for more toxic SCT subsequent therapy.

Univariate and multivariate analysis were performed to provide potential predictors of outcome in patients treated with BV monotherapy. Patients with a superior ECOG performance status had an overall superior outcome. However as this was not a randomised trial we cannot state which patients would definitely derive most benefit from BV.

The potential weaknesses of our retrospective study include the lack of centralised pathology review of biopsies from diagnosis or relapse, the lack of formalised radiological reporting according to published criteria (Barrington et al., 2014; Cheson et al., 2014) and the lack of prospective reporting of AEs and documentation of causality.

Section on other R/R HL data + concluding statement – GC input please.

Contributions: Conception and design: TE and GC made substantial contributions to conception and design. Collection and assembly of data: TE co-ordinated the collection of national data. TE, BP, KML, SK, AG, SA, KP, CB, GS, RLeD, CB, WLO, FM, KA, GC all managed patients in the study and were involved in collection and assembly of data. Data analysis and interpretation: TE, GC were involved in data analysis and interpretation. DE performed the statistical analysis. Manuscript writing: TE wrote the manuscript, which all authors critically reviewed. Final approval of manuscript: All authors were involved in research design, or the acquisition, analysis or interpretation of data, critically revising the manuscript and the final approval. TE is funded by the Julian Starmer-Smith lymphoma fund. GC acknowledges support by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme. KA is supported by the UCL/UCLH Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the funding bodies.

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