Title: Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma who are Ineligible for Autologous Stem Cell Transplant: A Germany and UK Retrospective Study

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**Abstract**

**Objective**

Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate licensed for the treatment of relapsed/refractory Hodgkin lymphoma (rrHL) following autologous stem cell transplant (ASCT) or at least two prior therapies when ASCT or multi-agent chemotherapy is not an option. The objective of this study was to describe real-world outcomes with BV in rrHL patients considered ASCT-ineligible or who refuse ASCT.

**Methods**

This was a retrospective medical chart review study that enrolled patients ≥18 years old who were initially diagnosed with HL between 1 January 2008 and 30 June 2014, considered ASCT-ineligible, and treated in routine care with BV for progressive disease after multi-drug chemotherapy regimens. Clinical outcomes included best response to treatment, progression-free survival (PFS), overall survival (OS), and adverse events.

**Results**

A total of 136 patients were included, with a median age of 70 years at initial HL diagnosis. The most common reasons for ASCT-ineligibility were comorbidities (74%) and age (57%). Overall response rate was 74% and PFS and OS were 15.1 and 17.8 months, respectively. Peripheral neuropathy was observed in 9.6% of patients.

**Conclusion**

The results of this study provide real-world evidence on the feasibility and effectiveness of BV in elderly or frail ASCT-ineligible patients with rrHL in a real-world setting.

**Introduction**

A high proportion of patients with Hodgkin lymphoma (HL) respond to front-line chemotherapy regimens but depending on initial therapy however, up to 20% of patients progress or relapse after initial treatment.[1-4] The current standard of practice in these patients is salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (ASCT), which has been shown to prolong progression-free survival (PFS).[5-7] However, a relevant proportion of patients who have chemorefractory disease, advanced age, or significant medical comorbidities are not considered candidates for ASCT, or do not undergo ASCT due to patient preference, and therefore have a poor prognosis.[8] Until recently, treatment options for these patients have been limited to palliative approaches including gemcitabine-based chemotherapy, bendamustine, or local radiotherapy for symptom control.[5]

Brentuximab vedotin (BV) is an antibody-drug conjugate targeted to CD30, a cell surface marker that is highly expressed on malignant HL cells,[9,10] with limited expression in healthy tissue and on resting leukocytes,[11,12] making it a rational target for antibody-based therapies. BV is licensed for the treatment of relapsed/refractory Hodgkin lymphoma (rrHL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

Previous prospective studies of BV in ASCT-ineligible patients include a *post hoc* analysis of a phase 1 trial,[8] and a single-arm, phase 4 trial.[13] Small retrospective studies,[14-16] including data from the BV Named Patient Program (NPP)[17] have also been reported. Clinical outcomes in the ASCT-ineligible population receiving BV have not yet been evaluated in routine clinical practice under real-world conditions in a large, multinational study. The objectives of this study were thus to characterize the population of patients with rrHL in Germany and the UK who are either considered ASCT-ineligible by their treating physicians or elect not to undergo ASCT, and to describe treatment patterns and outcomes with BV in ASCT-ineligible rrHL patients treated in routine clinical practice in two European countries known to have different practice patterns in HL.

**Patients and Methods**

This was a retrospective medical chart review study that enrolled patients at 45 clinical sites representative of routine practice in Germany and the UK. Study investigators within the UK and Germany were hematologists and oncologists selected at random to participate. Additionally, study investigators were required to currently manage or treat at least 10 patients with HL, at least 5 who have received ASCT, and at least 3 who have been treated with BV. Ethics approval for the study was granted by the Freiburg Ethics Commission International (FECI) in Germany and the Medicines & Healthcare Products Regulatory Agency (MHRA) in the UK, with a waiver of patient consent.

The study included anonymized patients ≥18 years old at the time of HL diagnosis, who were first diagnosed with HL between 1 January 2008 and 30 June 2014, progressed after multi-drug chemotherapy regimens, were not ASCT candidates as identified by their clinicians or elected not to undergo ASCT, were subsequently treated with BV, and were not enrolled in an HL-related clinical trial. Patients were selected at random by the study investigator who selected study subjects from the entire pool of eligible patients within their respective practice. Specifically, investigators selected patients based on the month of the patient’s last clinic/office visit, with each investigator assigned a unique set of months.

A standardized case report form was developed for use by investigators to collect medical chart data, and was pilot tested prior to implementation. Data collected included demographic and baseline clinical characteristics; potentially multiple reasons for ASCT-ineligibility; all prior regimens administered for the treatment of HL; BV dosing and number of cycles; best response to therapy and date of relapse after all regimens, as assessed by the study investigator; adverse events occurring during BV treatment, as assessed by the study investigator; and dates of disease progression and death from any cause.

Patient demographics, clinical characteristics, and treatment characteristics were described. Clinical outcomes included best response to treatment, progression-free survival (PFS), overall survival (OS), and adverse events (AEs). Given the retrospective nature of the study, no assessment of causality was made for AEs. Outcomes were primarily descriptive, and reported in the full study population and by country. PFS and OS were analyzed using the nonparametric Kaplan-Meier method, where patients were censored at their last available follow-up. A *post hoc* analysis comparing best response to therapy on BV compared to the line of therapy received just prior to BV was conducted using Chi-square tests in order to explore the relative effectiveness of BV compared to other regimens while having each patient serve as his or her own control.

**Results**

A total of 136 patients (78 in Germany and 58 in the UK) were included in this study. The median duration of follow-up was 10.9 months (range, 0.4 to 47.0 months) from initiation of BV. Study investigators represented primarily hospital-based practice (90% in Germany, 100% in the UK) and were mostly affiliated with academic/teaching hospitals (70% in Germany, 60% in the UK).

Across both countries, the mean age at first HL diagnosis was 66.7 years and 40% of patients had bulky disease at diagnosis (Table 1). At first diagnosis patients in Germany appeared to be older, have more often advanced disease, worse ECOG status, and were more likely to have bulky disease compared to patients in the UK. According to treating physicians the most common reasons for ASCT-ineligibility were comorbidities (73.5%) and age (56.6%; Table 2). Front-line therapy consisted of ABVD in the majority of patients in Germany (67.9%) and UK (75.9%), with 28% of patients in Germany and no patients in UK receiving BEACOPP and the remainder receiving other regimens. Second-line therapy was heterogeneous and consisted of mostly ABVD, BEACOPP, DHAP, ESHAP, gemcitabine-based regimens, and CHLVPP. Several other regimens were used in second-line including but not limited to single-agent bendamustine, ICE, and CHOP.

Over the course of therapy radiotherapy was administered in 48 (61.5%) patients in Germany and 14 (24.1%) in the UK; 52% of radiotherapy was given as part of the front-line regimen, with the remainder in Germany and all radiotherapy in UK given between lines of treatment prior to BV. Fourteen of the 78 patients in Germany (17.9%) and 6 of the 58 patients in UK (10.3%) had documented use of BV as the first line of therapy after their initial relapse. Of note, the study investigators confirmed that all patients met study eligibility criteria, and thus it is possible that radiotherapy was counted as a line of therapy. The remaining patients received BV as indicated for the second or later post-relapse line of therapy. At the relapse treated with BV, 54% of patients had stage III or IV disease, 9.6% had bulky disease, and 61.0% had an ECOG status ≥2 (Table 2).

**Efficacy Outcomes**

Patients received a median of 8 cycles of BV (range, 6-15 cycles). The overall response rate was 74.3% of patients and 34.6% of patients achieved a complete response to BV across the study population from both countries (Table 2). ORR with BV and the preceding line of therapy were not significantly different. One patient in Germany (1.3%) and 2 in the UK (3.4%) went on to receive allogeneic SCT after BV.

Median PFS from initiation of BV was 15.1 months (95% CI, 8.9-22.0 months), with 52.1% (43.0%-61.2%) of patients progression-free at 12 months. Median OS from initiation of BV was 17.8 months (95% CI, 13.7 to 33.5 months), with 68.2% (59.2%-77.1%) of patients alive at 12 months. Among the 51 patients who died during the follow-up period, cause of death was HL-related in 33 (64.7%). Other causes of death included myocardial infarction/acute coronary syndrome (n=9), pneumonia (n=4), pulmonary embolism (n=2), multiple organ failure (n=1), and unknown (n=1).

**Adverse Events**

The most common adverse events reported during treatment with BV included leukopenia, anemia, and diarrhea (Table 3). The documented incidence of peripheral neuropathy during BV treatment was 9.6%, of which 92.3% of cases were non-serious.

**Discussion**

This multinational rrHL population receiving BV in routine clinical care is different from those previously published in being older (median age 67 years vs. 38 and 45 years in previous studies) and less likely to be ASCT-ineligible due to refractory disease (12% vs. 64% and 75% in previous studies). In addition, our study also included a small proportion of patients who elected not to undergo ASCT. It thereby better reflects the real-world challenges of treating elderly patients or those with significant comorbidities. Nevertheless, the ORR (74.3%) was similar to previous retrospective studies (71% and 75%),[14,15] while the ORR in previous prospective studies was lower (30% and 50%).[8,13] Lower response rates in the BV phase 1 study might partially be due to low doses applied during dose escalation, while the difference In the phase 4 study might be explained by the utilization of an independent review facility to assess outcomes as opposed to the investigator’s clinical judgment. The median OS in our study was 17.1 months compared to 40.1 months in the pivotal BV phase II study, likely reflecting differences in median age (66.7 vs. 31 years), prior treatments (no-ASCT vs. ASCT) and comorbidities of the studied population.[18] Nevertheless 64.7% of deaths were HL-related potentially indicative of poorer disease control in an ASCT-naïve population.

Despite their advanced age and comorbidities of patients in this sample, peripheral neuropathy was reported less frequently than in patients enrolled in the pivotal BV trial (9.6% vs. 42%)[19] and in the Named Patient Program (20%).[17] However, given the retrospective nature of the study and data derived from real-world patient files rather than study documentation, it is possible and indeed likely that such AEs were under-reported.

Of note, the results of the study highlight differences in the standard of practice or treatment of ASCT-ineligible rrHL patients in Germany and the UK. Selection of front-line therapy (ABVD and BEACOPP in Germany, ABVD only in the UK) and use of radiotherapy (nearly 2/3 of patients in Germany and only 1/4 in the UK) differed between countries. It is possible that the more frequent use of BEACOPP in Germany is correlated with the trend towards a higher prevalence of ASCT-impeding comorbidities, given the greater incidence of acute hematologic and non-hematologic toxicities with BEACOPP compared to ABVD.[20] However, because patients in Germany already had more comorbidities at initial HL diagnosis reflected by a mean Charlson Comorbidity Index of 2.9 compared to 1.5 in the UK, it seems likely that this trend is rather due to underlying differences in the population studied in each country instead of BEACOPP application.

To our knowledge, this is the first study of safety and efficacy of BV in ASCT-ineligible patients in real-world clinical practice. The chart review design allowed for the collection of detailed clinical data related to treatment, response, and adverse events, which could not be accomplished with secondary data. Moreover, study data were collected by physician investigators, further contributing to the overall study strength and accuracy of the data. The sample size in this multicenter study of 136 patients from across two European countries is also larger than previously published studies. The retrospective nature of the study however means that the data collected were limited to those documented in the medical chart. Furthermore the study lacks a control group, meaning that no definitive conclusions about the relative effectiveness of BV versus other treatments can be made. In view of the fact that individual study investigators determined response and progression, and identified adverse events, different criteria may have been used across study sites. Finally, 20 of the 136 patients in the study received BV outside its original indication after only one prior line of treatment, which may be due to the application of different criteria for identifying lines of therapy.

In conclusion, the results of this study in a population of advanced age with relevant comorbidities are encouraging, and suggest that BV demonstrates real-world clinical effectiveness for patients with rrHL who are ineligible for ASCT. BV would appear to be a useful treatment option in this population where there is a great clinical need with limited treatment options and currently poor outcomes. Further comparative effectiveness data are needed to evaluate these outcomes relative to other therapeutic interventions.

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**Conflict of Interest Statement**

PJB: advisory role to Takeda, honoraria and research funding by Bristol-Myers Squibb

TI: advisory role to Takeda

SLC, VC, CJ, CM: paid consultant to Takeda

EAZ, MRD: employees of Takeda

BS: employee of Takeda at the time the research was conducted

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**Table 1. Characteristics of ASCT-Ineligible Patients with rrHL at First Diagnosis**

| **Characteristic** | **GermanyN=78** | **United KingdomN=58** | **All CountriesN=136** |
| --- | --- | --- | --- |
| Male, n (%) | 46 (59.0) | 33 (56.9) | 79 (58.1) |
| Age at HL diagnosis, mean (SD), y | 69.4 (7.6) | 63.2 (15.0) | 66.7 (11.7) |
| Charlson Comorbidity Index, mean (SD) | 2.9 (2.1) | 1.5 (1.4) | 2.3 (2.0) |
| Ann Arbor clinical stage at diagnosis, n (%)IAIBIIAIIBIIIAIIIBIVAIVBUnknown |  1 (1.3)1 (1.3)9 (11.5)11 (14.1)7 (9.0)10 (12.8)7 (9.0)32 (41.0)0 (0) |  1 (1.7)0 (0.0)3 (5.2)7 (12.1)10 (17.2)10 (17.2)5 (8.6)20 (34.5)2 (3.4) |  2 (1.5)1 (0.7)12 (8.8)18 (13.2)17 (12.5)20 (14.7)12 (8.8)52 (38.2)2 (1.5) |
| Sites of diseaseLymph nodeBoneSpleenLiverSkinLungOsseousPleuralOther |  76 (97.4)28 (35.9)19 (24.4)7 (9.0)2 (2.6)1 (1.3)1 (1.3)0 (0.0)0 (0.0) |  58 (100.0)11 (19.0)18 (31.0)9 (15.5)0 (0.0)8 (13.8)1 (1.7)0 (0.0)1 (1.7) |  134 (98.5)39 (28.7)37 (27.2)16 (11.8)2 (1.5)2 (1.5)2 (1.5)1 (0.7)1 (0.7) |
| Bulkiness at HL diagnosisBulky (≥ 5 cm)Non-bulky (< 5 cm)Unknown |  36 (46.2)36 (46.2)6 (7.7) |  19 (32.8)39 (67.2)0 (0) |  55 (40.4)75 (55.1)6 (4.4) |
| ECOG performance status at diagnosis, n (%)01234Unknown |  3 (3.8)46 (59.0)23 (29.5)3 (3.8)1 (1.3)2 (2.6) |  13 (22.4)33 (56.9)8 (13.8)2 (3.4)0 (0.0)2 (3.4) |  16 (11.8)79 (58.1)31 (22.8)5 (3.7)1 (0.7)4 (2.9) |

**Table 2. Characteristics of ASCT-Ineligible Patients with rrHL at Relapse Treated with BV**

| **Characteristic** | **GermanyN=78** | **United KingdomN=58** | **All CountriesN=136** |
| --- | --- | --- | --- |
| Ann Arbor clinical stage at relapse, n (%)IAIIAIIBIIIAIIIBIVAIVBUnknown | 1 (1.3)17 (21.8)17 (21.8)9 (11.5)5 (6.4)9 (11.5)12 (15.4)8 (10.3) | 0 (0.0)6 (10.3)12 (20.7)6 (10.3)13 (22.4)4 (6.9)15 (25.9)1 (1.7) | 1 (0.7)23 (16.9)29 (21.3)15 (11.0)18 (13.2)13 (9.6)27 (19.9)9 (6.6) |
| Bulkiness at relapseBulky (≥ 5 cm)Non-bulky (< 5 cm)Unknown | 3 (3.8)72 (92.3)3 (3.8) | 10 (17.2)46 (79.3)2 (3.4) | 13 (9.6)118 (86.8)5 (3.7) |
| ECOG performance status at relapse, n (%)01234Unknown | 0 (0.0)24 (30.8)42 (53.8)11 (14.1)0 (0.0) | 3 (5.2)24 (41.4)28 (48.3)1 (1.7)1 (1.7) | 3 (2.2)48 (35.3)70 (51.5)12 (8.8)1 (0.7) |
| Reason for ASCT ineligibility, n (%)\*ComorbiditiesAgePatient choiceRefractory diseaseFailure to mobilize stem cellsHad eligible unrelated allo-SCT donors | 63 (80.8)55 (70.5)13 (16.7)6 (7.7)2 (2.6)0 (0.0) | 37 (63.8)22 (37.9)7 (12.1)10 (17.2)2 (3.4)1 (1.7) | 100 (73.5)77 (56.6)20 (14.7)16 (11.8)4 (2.9)1 (0.7) |

\* Multiple reasons for ASCT ineligibility could be selected.

**Table 3. Best Response to BV and the Treatment Immediately Preceding BV**

|  |  |  |  |
| --- | --- | --- | --- |
| **Best response** | **GermanyN=78** | **United Kingdom****N=58** | **All CountriesN=136** |
| BV | Prior therapy | P-value | BV | Prior therapy | P-value | BV | Prior therapy | P-value |
| Complete responsePartial responseStable diseaseProgressive disease | 28 (35.9)36 (46.2)3 (3.8)11 (14.1) | 49 (62.8)19 (24.4)5(6.4)5(6.4) | 0.003 | 19 (32.8)18 (31.0)15 (25.9)6 (10.3) | 7(12.1)27 (46.6)19 (32.8)5(8.6) | 0.048 | 47 (34.6)54 (39.7)18 (13.2)17 (12.5) | 56 (41.2)46 (33.8)24 (17.6)10(7.4) | 0.251 |

**Table 4: Adverse Events of any Grade Occurring during Treatment with BV**

|  |  |  |  |
| --- | --- | --- | --- |
| **Events during regimen, n (%)** | **GermanyN=78** | **United KingdomN=58** | **All CountriesN=136** |
| Leukopenia | 8 (10.3) | 9 (15.5) | 17 (12.5) |
| Anemia | 8 (10.3) | 4 (6.9) | 12 (8.8) |
| Diarrhea | 5 (6.4) | 2 (3.4) | 7 (5.1) |
| Peripheral neuropathy | 5 (6.4) | 8 (13.8) | 13 (9.6) |
| Nausea/vomiting | 4 (5.1) | 1 (1.7) | 5 (3.7) |
| Thrombocytopenia | 3 (3.8) | 3 (5.2) | 6 (4.4) |

**Figure 1. Kaplan-Meier Curve for Progression-Free Survival from initiation of BV for rrHL**



**Figure 2.** **Kaplan-Meier Curve for Overall Survival from initiation of BV for rrHL**

