# Effect of cumulative dose of brentuximab vedotin maintenance in relapsed/refractory classical Hodgkin lymphoma after autologous stem cell transplant: an analysis of real-world outcomes

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## Abstract

Sixteen cycles of Brentuximab vedotin (BV) after autologous stem cell transplant (ASCT) in high-risk relapsed/refractory classical Hodgkin lymphoma demonstrated an improved 2-year progression-free survival (PFS) over placebo. However, most patients are unable to complete all 16 cycles at full dose due to toxicity. This retrospective, multicenter study investigated the effect of cumulative maintenance BV dose on 2-year PFS. Data were collected from patients who received at least one cycle of BV maintenance after ASCT with one of the following high-risk features: primary refractory disease (PRD), extra-nodal disease (END), or relapse <12 months (RL<12) from the end of frontline therapy. Cohort 1 had patients with >75% of the planned total cumulative dose, cohort 2 with 51-75% of dose, and cohort 3 with ≤50% of dose. The primary outcome was 2-year PFS. A total of 118 patients were included. Fifty percent had PRD, 29% had RL<12, and 39% had END. Forty-four percent of patients had prior exposure to BV and 65% were in complete remission before ASCT. Only 14% of patients received the full planned BV dose. Sixty-one percent of patients discontinued maintenance early and majority of those (72%) were due to toxicity. The 2-year PFS for the entire population was 80.7%. The 2-year PFS was 89.2% for cohort 1 (n=39), 86.2% for cohort 2 (n=33), and 77.9% for cohort 3 (n=46) (*P*=0.70). These data are reassuring for patients who require dose reductions or discontinuation to manage toxicity.

## Introduction

In patients with relapsed/refractory classical Hodgkin lymphoma (r/r cHL) high-dose chemotherapy followed by autologous stem cell transplant (ASCT) leads to improved progression-free survival (PFS) over chemotherapy alone and is the accepted standard to achieve durable disease response.[1] Historically, this treatment strategy cures approximately half of the patients with r/r cHL.[1] Risk factors associated with poor outcomes after ASCT include chemo-resistant disease, B symptoms at relapse, residual disease before ASCT, and extra-nodal involvement at relapse.[2-4]

Brentuximab vedotin (BV) is an antibody drug conjugate targeting CD30 that carries monomethyl auristatin E (MMAE) payload.[5,6] The phase III AETHERA trial assessed whether early maintenance with BV after ASCT improved PFS compared to placebo in patients deemed high-risk for relapse after ASCT by the following risk factors primary refractory disease (PRD), extra-nodal disease (END) at re-

lapse <12 months (RL<12). Patients treated on the BV arm received 16 cycles at 1.8 mg/kg and had a significantly longer 2-year PFS compared to placebo, 63% compared to 51%, respectively.[7] In an updated 5-year analysis, the PFS improvement was sustained, 59% in the BV arm compared to 41% in the placebo arm.[8] The most common adverse events were peripheral neuropathy (PN) (56%), infections (60%) and neutropenia (35%); additionally, 53% of patients on the BV arm discontinued treatment early, with the main reason for discontinuation being adverse events (69%).[7] In this study, PN was managed by dose delays or reductions. Those who required dose delay or reduction due to PN had a similar PFS to the entire population in a *post hoc* analysis.[9]

In the real world, patients are rarely able to tolerate all 16 cycles of BV maintenance at full dose, mainly due to toxicity. In a study conducted in Italy, early treatment discontinuations were reported at a rate of 44%, with the most common reason for discontinuation being toxicity.[10] A real-world study assessing patients who received BV maintenance in Europe found that the median cycles of BV maintenance completed was 11.[11] A similar study from Colombia also illustrated that the median number of cycles for BV maintenance was 12 and 18% of patients had grade 3 or higher PN.[12] However, none of these studies examined cumulative dose of BV maintenance and its effect on PFS.

Patients on AETHERA trial had no prior exposure to BV in front-line or in the pre-ASCT salvage setting. The landscape of frontline and salvage treatment of cHL has shifted dramatically since the publication of the AETHERA trial. The ECHELON-1 trial showed both improved PFS and OS of BV-AVD compared to ABVD in frontline advanced cHL.[13,14] Additionally, many phase II studies have showed excellent results with combination of BV and chemotherapy (such as ifosfamide, carboplatin, etoposide or bendamustine) during salvage before ASCT, resulting in high complete remission (CR) rates.[15,16] Anti-programmed death receptor antibodies (anti-PD1) such as nivolumab or pembrolizumab have also been combined with either chemotherapy (ifosfamide, carboplatin, etoposide or gemcitabine, vinorelbine, liposomal doxorubicin) or BV for patients needing salvage therapy, also illustrating high CR rates in the range of 80-90%.[17-19]

The role of 16 cycles of BV maintenance in patients who might have had previous exposure to BV or anti-PD1 therapy before ASCT has not been determined. Due to physical and financial toxicity related to 16 cycles of BV maintenance, it is important to determine whether the full planned cumulative dose of BV maintenance is beneficial to patients in the era of earlier use of BV and anti-PD1 therapies. We set out to determine if dose reduction or treatment discontinuation, measured by cumulative dose of BV maintenance received, affects the 2-year PFS in patients with r/r cHL who received BV maintenance after ASCT.

# Methods

## Patients

This is a retrospective, multicenter study of patients with r/r cHL who were administered at least one dose of BV maintenance after ASCT. We included patients ≥18 years of age who underwent ASCT from July 1, 2015 through June 30, 2019 from 13 institutions across the United States. Patients were required to have at least one high-risk disease feature as defined in AETHERA:[7] PRD, END, or RL <12.

We used an Excel ® (Microsoft ®, Redmond WA) database with built in data validation to capture variables uniformly across institutions. This project was exempt by the Institutional Review Board (IRB) at the University of Utah as the lead site. Each participating center obtained local IRB approval or exemption and a data use agreement.

## Cumulative dose of Brentuximab vedotin maintenance

Patients were divided into three different cohorts based on total cumulative dose of BV maintenance (in mg/kg) received. Cohort 1 (C1) included those who received >75% of the planned total cumulative dose, cohort 2 (C2) included those who received 51-75% and cohort 3 (C3) included those who received ≤50%. In order to avoid bias from conditioning on future exposure, the total cumulative dose was treated as a time-varying exposure.[20] For example, if a hypothetical patient was administered 100% of the total dose uniformly over exactly 1 year, then for the first 6 months the patient is in the “BV ≤50%” category. For the next 3 months the patient is in the “BV 51-75%” category, and for the remainder of follow-up time until censoring or progression the patient is in the “BV >75%” category. The other covariates in the analysis are fixed. We linearly interpolated when each dose was administered based on when the first and last dose of BV maintenance were administered. Patients were excluded if we did not have a date of first or last BV maintenance treatment.

## Study objectives

The primary objective of the study was to determine the difference in 2-year PFS between the three cohorts of patients in each of the cumulative dosing cohorts. The secondary objectives of this study were to examine adverse events related to BV, treatment discontinuation rate and to examine the effect of prior chosen factors on the 2-year PFS.

## Statistical analysis

Fisher’s exact tests were used to compare categorical variables and Wilcoxon rank-sum tests were used for continuous variables. Patients were censored at the date of last observation. PFS was defined as the time from the date of ASCT to the date of progression or death from any cause, whichever occurred first. Kaplan-Meier estimates were used

to summarize the distributions of PFS. Univariable Cox proportional hazards regression models were fit to assess associations between prior chosen predictors. Due to small sample size, *P* values are not reported for the multivariate analysis but the effect size for the odds ratio (OR) is reported assuming small, medium and large are 1.5, 2 and 3, respectively.[21] Adverse events were defined using CTCAE v. 5 criteria. Response criteria was defined by Lugano criteria.[22]

# Results

## Patient characteristics

There were a total of 123 patients identified from 13 institutions. After excluding five patients who did not have a known date of first and/or last BV maintenance dose, 118 patient records were included for evaluation (Figure 1). There were 39 patients who received >75% of the total adjusted cumulative dose of BV maintenance (C1), 33 patients who received 51-75% of the total adjusted cumulative dose of BV maintenance (C2) and 46 patients who received ≤50% of the total adjusted cumulative dose of BV maintenance (C3).

The median age of this population was 36 (range, 27-42) years at the time of ASCT, 53% were men, and the majority (95%) received ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as frontline therapy (Table 1). Sixty-nine percent of patients had advanced stage disease at diagnosis. High-risk features at relapse were as follows: 50% of patients had PRD, 29% had RL<12 and 39% had END. Eighteen percent of patients had B symptoms at relapse. Twenty-three percent had more than one line of salvage therapy before ASCT (Table 2). The majority of patients achieved a CR (65%) prior to ASCT. Forty-four percent of patients had BV exposure prior to ASCT, mostly during salvage therapy (98%). Fifty-six percent of patients received a traditional chemotherapy only salvage regimen, while rest (44%) had exposure to a novel agent (anti-PD1 or BV) during salvage. Of the novel salvage patients, 27% patients had BV-Bendamustine, 60% had BV single agent, and 19% had any exposure to an anti-PD1 agent during salvage (Table 1). BEAM (etoposide, cytarabine and melphalan) was the most common conditioning regimen, reported in 94% of the patients. Table 1 describes the baseline characteristics of the patients by total cumulative dosing cohorts of BV maintenance and Table 2 describes the salvage treatment by dosing cohorts. There were no statistically significant differences in baseline characteristics or salvage treatment between the three cohorts.

## Toxicity and treatment discontinuation

The median number of BV maintenance cycles completed was 12 (range, 1-25) with the majority (61%, 72/118) of patients discontinuing BV maintenance prior to completing all 16 cycles. Reasons for early discontinuation were as follows:

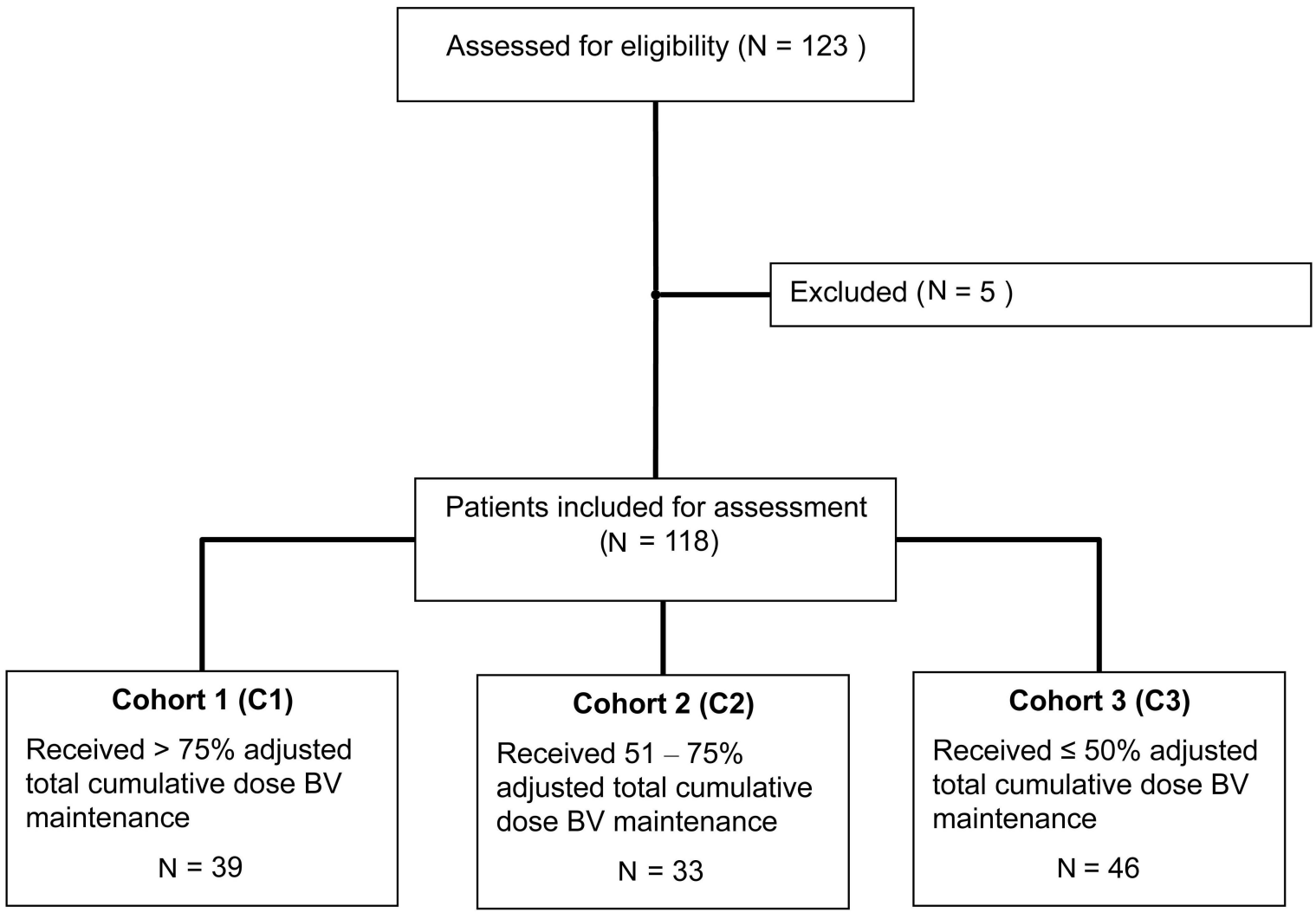


**Figure 1. Consort diagram for eligibility of enrollment.** BV: Brentuximab vedotin.

52 for toxicity (72%), ten for progression (14%), eight for patient preference (11%) and two for other reasons (3%). Forty-eight patients (41%) had a dose-reduction prior to discontinuation or completion of maintenance. Eighty-six percent of patients required either a dose reduction or discontinued BV maintenance early and only 14% of patients (16/118) received the full planned cumulative dose of BV (28.8 mg/kg). One patient continued maintenance past 16 cycles and received a total of 25 cycles. Any grade adverse events for peripheral neuropathy, neutropenia and infections were 79%, 20%, and 14% respectively and grade ≥3 adverse events were 17%, 7%, and 4% respectively. There was no difference in incidence of any grade neuropathy and grade ≥3 neuropathy in those who had prior BV exposure and those who did not have prior BV exposure (*P*=0.87). Additionally, there was no difference in the mean number of cycles between those who had prior BV exposure (10.64) and those who did not have prior BV exposure (10.97) (*P*=0.73).

## Progression-free survival

With a median follow up of 2.96 years 2-year PFS for all patients was 80.7% (95% confidence interval [CI]: 73.8-88.2) (Figure 2A). Analyzing PFS according to cumulative BV dose cohorts in the time-variable analysis, the 2-year PFS was 89.2% (95% CI: 79.7-99.8) for C1, 86.2% (95% CI: 75.5-98.4) for C2, and 77.9% (95% CI: 67.2-90.2) for C3 (*P*=0.70) (Figure 2B). There was no statistically significant difference when comparing the 2-year PFS for C3 to C1 (*P*=0.68) or C2 to C1 (*P*=0.69) (Figure 2B). These findings were also supported in the time-independent analysis of 2-year PFS with no statistical difference between the three cohorts (*Online Supplementary Figure S1*). Only one death occurred in the entire population and, therefore, a difference in overall survival could not be estimated.

In the multivariate analysis for PFS, ≤50% of adjusted total cumulative BV maintenance dose had OR of 1.57, predicting a trend towards worse PFS with a medium effect size. Prior BV exposure (OR=0.19) had large effect size for PFS and predicted for a trend towards improved PFS with post-ASCT BV maintenance. PRD (OR=5.91) and receiving ≥2 lines of salvage treatment (OR=9.34) had the largest effect size on PFS, predicting a trend for worse PFS (Table 3). Prior BV exposure and use of novel agents in salvage were almost perfectly correlated in the univariate analysis as there are only three

**Table 1.** Baseline characteristics by total cumulative dose of Brentuximab vedotin maintenance.

| Baseline characteristics | Entire population N (%) | C1 N (%) | C2 N (%) | C3 N (%) | *P* |
|---|---|---|---|---|---|
| Total N | 118 | 39 | 33 | 46 | - |
| Age in years, median (SD) | 36 (12) | 39 (12) | 35 (12) | 36 (12) | 0.37 |
| Sex | | | | | |
| Male | 62 (53) | 20 (51) | 13 (39) | 29 (63) | 0.12 |
| Female | 56 (47) | 19 (49) | 20 (61) | 17 (37) | |
| Stage at diagnosis | | | | | 0.81 |
| Early favorable | 9 (8) | 3 (8) | 4 (12) | 2 (4) | |
| Early unfavorable | 24 (20) | 10 (26) | 5 (15) | 9 (20) | |
| Advanced | 82 (70) | 25 (64) | 23 (70) | 34 (74) | |
| Unknown | 3 (2) | 1 (2) | 1 (3) | 1(20) | |
| Frontline therapy | | | | | |
| ABVD | 110 (93) | 37 (97) | 30 (91) | 43 (93) | 0.68 |
| BV-AVD | 2 (2) | 1 (3) | 0 (0) | 1 (2) | |
| BEACOPP | 3 (3) | 0 (0) | 2 (6) | 1 (2) | |
| Other | 1 (1) | 0 (0) | 0 (0) | 1 (2) | |
| Unknown | 2 (2) | 1 (2) | 1 (3) | 0 (0) | |
| cHL status after frontline therapy | | | | | 0.18 |
| PRD | 59 (50) | 17 (44) | 21 (64) | 21 (47) | |
| RL <12 months | 34 (29) | 12 (31) | 5 (15) | 17(38) | |
| RL ≥12 months | 24 (20) | 10 (26) | 7 (21) | 7 (16) | |
| Unknown | 1 (1) | 0 (0) | 0 (0) | 1 (2) | |
| Extra-nodal disease | 46 (39) | 21 (49) | 9 (27) | 16 (40) | 0.17 |
| B symptoms at relapse | 21 (18) | 5 (13) | 8 (24) | 8 (18) | 0.42 |

CI: cohort 1; C2: cohort 2; C3: cohort 3; SD: standard deviation; BV: Brentuximab vedotin; ABVD: doxorubicin, bleomycin, vinblastine and dacarbazine; BEACOPP: bleomycin, etoposide, adriamycine, cyclophosphamide, vincristine, procarbazine, and prednisone; cHL: classical Hodgkin lymphoma; PRD: primary refractory disease; RL: relapse.

instances when these variables disagree. Therefore "novel agents" variable was omitted in the multivariate analysis as there is no information to separate the effect of these variables on PFS.

## Discussion

In this large, retrospective, multicenter study from 13 academic medical centers across the United States, the 2-year PFS was robust (80.7%) regardless of cumulative dose of BV maintenance and higher than the 63% reported in the AETHERA trial.[7] The higher 2-year PFS observed in this study was most likely due to the recent incorporation of novel agents into salvage treatments prior to ASCT, which achieved a higher CR rate of 65% as compared to historical CR rates of 30-40% with chemotherapy-only salvage regimens. Furthermore, in the AETHERA trial,[7] patients were excluded if they had previously received BV, while half of our population had BV exposure in their salvage regimens. Additionally, anti-PD-1 antibodies are being studied earlier in the treatment course for cHL, and we had 8% of total patients who had received anti-PD-1 antibodies prior to ASCT during salvage. The use of these novel therapies prior to ASCT could contribute to the increased CR rate of 65% prior to ASCT compared to the 37% in AETHERA.[7] These results suggest achievement of a CR prior to ASCT remains an important treatment goal and that the use of novel agents in the salvage setting can help more readily achieve this CR. However, it should be noted that computed tomography (CT) scans were used to assess response criteria in the AETHERA trial while positron emission tomography/CT has become the standard which captures more instances of CR than CT alone.

The cumulative dose of BV maintenance received did not appear to have a significant impact on 2-year PFS in this population, even when controlling for other variables in a multivariate analysis. This is reassuring as up to 72% of patients stopped treatment early due to toxicity. Seventy-nine percent of patients had neuropathy and 18% of total patients had grade ≥3, highlighting significant impact on quality of life and instrumental ADL. The data from this

**Table 2.** Salvage characteristics by total cumulative dose of Brentuximab vedotin maintenance.

| Salvage characteristics | Entire population N (%) | C1 N (%) | C2 N (%) | C3 N (%) | *P* |
|---|---|---|---|---|---|
| Total N | 118 | 39 | 33 | 46 | - |
| Salvage therapies before ASCT, N | | | | | 0.60 |
| 1 | 90 (77) | 30 (77) | 27 (82) | 33 (72) | |
| >1 | 27 (23) | 8 (21) | 6 (18) | 13 (28) | |
| Unknown | 1 | 1 (2) | 0 (0) | 0 (0) | |
| Best response to salvage therapy | | | | | 0.45 |
| CR | 77 (65) | 23 (59) | 25 (75) | 29 (63) | |
| PR | 39 (33) | 15 (38) | 8 (25) | 16 (35) | |
| SD | 1 (1) | 1 (3) | 0 (0) | (0) | |
| PD | 1 (1) | 0 (0) | 0 (0) | 1 (2) | |
| Prior BV exposure | 53 (44) | 19 (49) | 15 (45) | 19 (41) | 0.78 |
| Type of salvage regimen | | | | | |
| Traditional Chemotherapy only | 66 (56) | 21 (54) | 18 (55) | 27 (59) | 0.89 |
| Novel Agents in any salvage line | 52 (44) | 18 (46) | 15 (45) | 19 (41) | |
| BV Bendamustine | 14 (26) | 5 (27) | 4 (27) | 5 (26) | 1.00 |
| BV monotherapy | 31 (60) | 11 (61) | 10 (67) | 10 (52) | 0.65 |
| BV Nivolumab | 7 (12) | 2 (12) | 1 (6) | 4 (20) | 0.62 |
| Pembrolizumab | 1 (1) | 0 (0) | 0 (0) | 1 (1) | 1.00 |
| Nivolumab | 2 (1) | 0 (0) | 0 (0) | 2 (1) | 0.33 |
| Median number of BV maintenance cycles* | 12 (2-25) | 16 (13-25) | 12 (8-16) | 5 (1-10) | - |
| ASCT conditioning regimen | | | | | 0.62 |
| BEAM | 110 (93) | 37 (95) | 32 (97) | 41 (91) | |
| CVP | 7 (6) | 2 (5) | 1 (3) | 4 (9) | |
| Unknown | 1 (1) | 0 (0) | 0 (0) | 1 (0) | |

*Median and range. No *P* value because the difference in number of cycles is a design feature. CI: cohort 1; C2: cohort 2; C3: cohort 3; BV: Brentuximab vedotin; BEAM: etoposide, cytarabine and melphalan; CVP: cyclophosphamide, vincristine, and prednisone; ASCT: autologous stem cell transplantation; CR: complete remission; PR: partial response; SD: stable disease; PD: progressive disease.

study suggest that receiving 51-75% of total planned dose had no impact on PFS (OR=0.94) when compared to >75% dose and receipt of ≤50% of the total planned cumulative dose of BV maintenance (equivalent to ≤8 cycles) had only a moderate effect size on PFS (OR=1.57) indicating that the 2-year PFS benefit is not significantly different from those who received a higher cumulative dose and was higher than reported in the AETHERA trial.

Findings from our study highlight the difficulty in being able to deliver all 16 cycles of BV maintenance post-ASCT. In the AETHERA study, 47% of the patients received all 16 cycles of BV, however only 39% received all 16 cycles in the present real-world study; additionally, only 14% (16/118) received all 16 cycles at full cumulative dose of 28.8 mg/kg. A median number of 12 cycles were delivered to all patients, which is comparable to previously reported studies.[10-12] Despite 44%

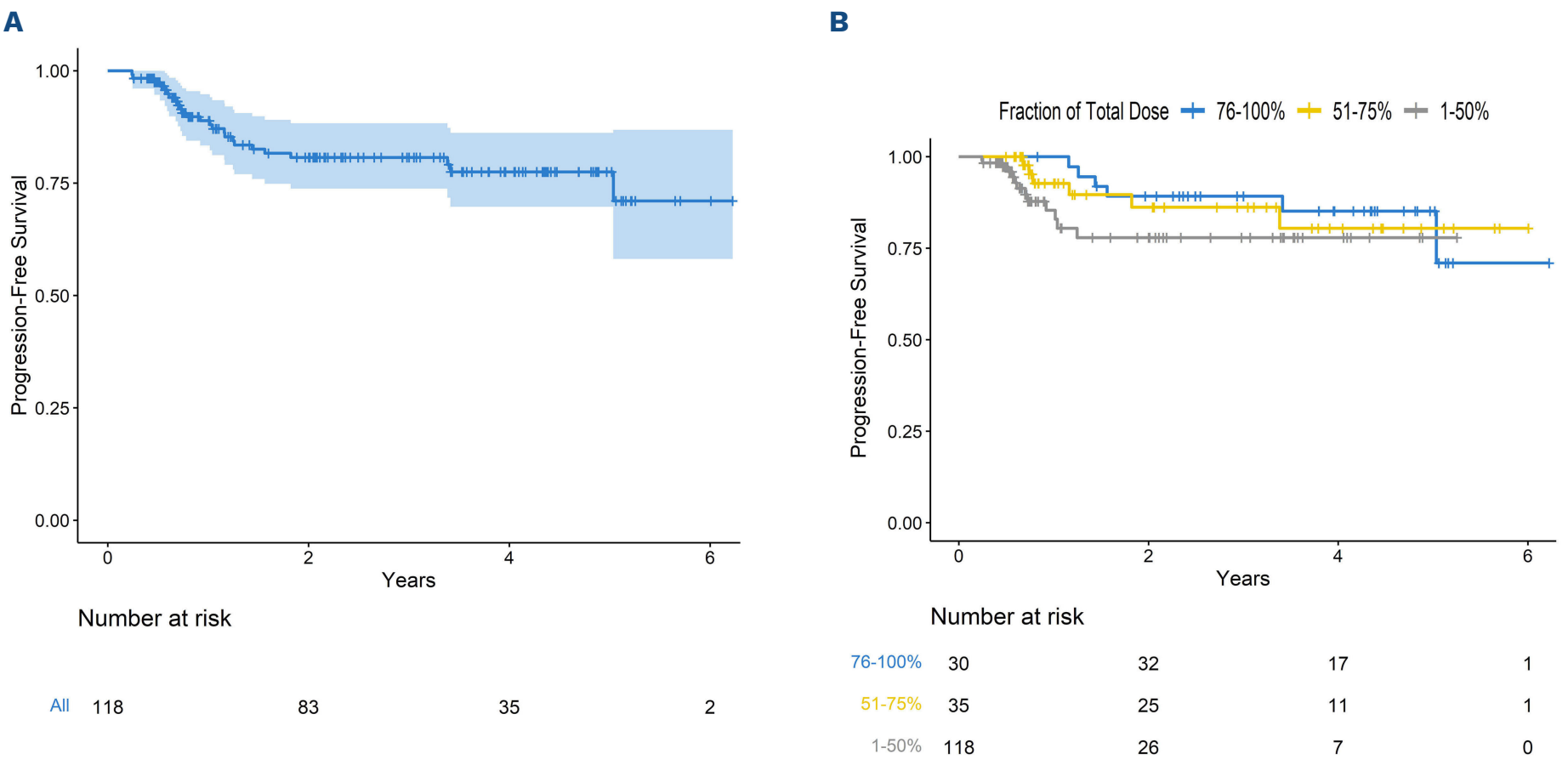


**Figure 2. Two-year progression-free survival.** (A) Progression-free survival of the entire study population. (B) Progression-free survival stratified by cohort, based on total planned cumulative dose, time-dependent analysis.

**Table 3.** Univariate and multivariate analysis of progression-free survival.

| Conditional logistic regression for progression | | | | |
|---|---|---|---|---|
| **Predictor** | **Category** | **Univariate** | **Multivariate** | **Effect size** |
| | | **OR (95% CI)** | **OR (95% CI)** | |
| Fraction of total BV dose% | BV >75% | Reference | Reference | - |
| | BV 51-75% | 1.20 (0.34-4.22) | 0.94 (0.19-4.62) | 0.94 (none) |
| | BV ≤50% | 2.19 (0.74-6.55) | 1.57 (0.43-5.69) | 1.57 (small) |
| Type of salvage regimen | Standard chemotherapy | Reference | Reference | - |
| | Novel agent | 0.54 (0.21-1.39) | - | - |
| cHL Status | Relapse >12 months | Reference | Reference | - |
| | Relapse <12 months | 1.40 (0.25-7.96) | 1.46 (0.22-9.95) | 1.46 (small) |
| | Primary refractory disease | 5.02 (1.09-23.1) | 5.91 (0.99-35.1) | 5.91 (large) |
| Best response to salvage therapy | CR | Reference | Reference | - |
| | No CR | 2.31 (0.97-5.49) | 1.88 (0.65-5.47) | 1.88 (small) |
| Lines of prior therapy, N | 1 | Reference | Reference | - |
| | 2+ | 1.85 (0.70-4.90) | 9.34 (1.57-55.4) | 9.34 (large) |
| Prior BV? | No | Reference | Reference | - |
| | Yes | 0.51 (0.20-1.33) | 0.19 (0.03-1.01) | 5.26 (large) |

BV: Brentuximab vedotin; OR: overall response; cHL: classical Hodgkin lymphoma, CR: complete remission; CI: confidence interval.

of patients having prior BV exposure, total mean number of BV cycles during maintenance was similar in the BV-exposed *versus* BV-naïve patients (10.6 *vs*. 11 cycles) which highlights that toxicity management and dose reductions were appropriate. Additionally, prior BV exposure had a large effect size on the 2-year PFS (OR=0.19) indicating a trend towards improved PFS compared to those without prior BV exposure. Seven patients had BV-refractory disease during salvage and yet still received BV maintenance therapy. Overall these findings suggest that prior response to BV during salvage may be an indicator of potential benefit of BV maintenance post-ASCT.

During the time our study was conducted, multiple new treatment strategies including the use of novel therapies such as BV and anti-PD1 inhibitors have become incorporated into the treatment landscape of cHL. The replacement of bleomycin with BV in frontline therapy (BV + AVD) has demonstrated an overall survival benefit compared to ABVD in patients with late stage cHL.[13] Additionally, both pembrolizumab and nivolumab have been studied in combination with chemotherapy in the front-line setting, and are being explored in the multipole prospective randomized phase III clinical trials such as *clinicaltrials gov. Identifier: NCT03907488*.[23,24] There have also been studies indicating that adding an anti-PD-1 antibody to traditional chemotherapy salvage yields high complete response rates.[18,19] These advances in both front-line and relapsed setting highlight the relevance of our data in a cohort with exposure to novel agents prior to ASCT, which leaves the role of BV maintenance less well defined within the modern treatment landscape. Many patients may have pre-existing neuropathy due to exposure to BV as initial therapy or salvage, which may limit further use of BV maintenance. The data presented support that ongoing toxicity from BV can be managed with dose reduction and/or discontinuation without effect on long-term outcomes. Furthermore, post-ASCT maintenance with single agent anti-PD1 inhibitors and in combination with BV are being explored, which have demonstrated favorable safety and efficacy outcomes, which may supplant BV maintenance in the future.[25]

There are limitations to this study that impact the conclusions that we are able to draw. First, this study is retrospective in design, and, therefore, it should be viewed as hypothesis generating. We did not have data on previous cumulative dose of BV before maintenance, which could have some clinical implications, however we still highlighted impact of prior BV on PFS and toxicity. We also did not collect data on patients who may have qualified for BV maintenance, but did not receive it which could have further elucidated what role, if any, BV maintenance provides in the current treatment landscape. Additionally, a longer follow-up is necessary in order to validate the findings from our study.

In summary, the 2-year PFS was high regardless of the cumulative BV maintenance dose received. This may be due to a shift in the treatment paradigm overall for cHL which is incorporating novel agents such as BV and anti-PD1 therapy earlier during salvage prior to ASCT, ultimately resulting in higher CR rate before ASCT. This study adds valuable contribution to the field of cHL that could have some important clinical implications. For example, for patients who have prior exposure to BV during salvage therapy with a response, there may still be a benefit of BV maintenance but reduced number of BV cycles (for example 8-12 cycles equivalent to 51-75% total cumulative dose of BV) could be considered to avoid unnecessary toxicity. For patients who are refractory to BV during frontline or salvage, maintenance BV has an unclear role as AETHERA study did not have such population and our study had had limited number of patients who were BV-refractory. Overall, our data is reassuring for clinicians who can feel comfortable dose reducing or discontinuing BV maintenance when facing toxicities that may impact quality of life in cHL patients.

## Disclosures

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**Contributions**

*HS conceived the study question. CW and HS designed the data collection tool, cleaned and analyzed the data. CW, AN, HH, EZ, AS, CS, SB, KM, SR, KF, ET, SA and NC collected data. CW drafted the manuscript. KB performed the statistical analysis. All authors reviewed and provided input on the manuscript*

**Data-sharing statement**

*The data supporting the findings of this study are available within the article. Additional data are available, upon request, from the corresponding author.*

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