ARTICLE

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Outcomes of patients with Hodgkin lymphoma receiving Brentuximab Vedotin (BV) as maintenance therapy after ASCT according to previous exposure to BV. A retrospective analysis of the EBMT Lymphoma Working Party in collaboration with GELTAMO, FIL, LYSA, and Turkish Lymphoma Group

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We evaluated brentuximab vedotin (BV) as maintenance therapy after autologous stem cell transplantation (ASCT) in 353 patients with relapsed/refractory Hodgkin lymphoma (HL). Of these, 52.6% received BV prior to ASCT. The five-year overall survival (OS) and progression-free survival (PFS) from the start of BV maintenance were 85.1% and 69.9%, respectively. Multivariable analysis revealed that age at ASCT (HR 1.17, $P = 0.037$), disease status (HR 3.61, $P = 0.002$), and BV treatment before ASCT (HR 0.40, $P = 0.033$) significantly impacted OS. Disease status at ASCT was the only factor significantly associated with PFS (HR 3.09, $p < 0.001$) and relapse risk (HR 3.33, $p < 0.001$). Although a trend toward improved PFS (HR 0.59, $p = 0.053$) and lower relapse risk (HR 0.57, $p = 0.051$) was observed in patients treated with BV before ASCT, the data were not statistically significant. Patients in complete remission (CR) at ASCT showed similar 2-year OS (94.6% vs. 99.2%, $P = 0.3$) and PFS (84.6% vs. 89%, $P = 0.3$) regardless of BV pre-transplant. In those not in CR, OS (83.1% vs. 93.6%, $P = 0.076$) and PFS (51.5% vs. 75.3%, $P = 0.039$) were higher in those previously treated with BV. This large study emphasizes BV maintenance post-ASCT, even in patients pre-treated with BV, ang highlights disease status as a key prognostic factor.

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INTRODUCTION

The optimal treatment for patients with classical Hodgkin lymphoma (HL) who do not respond to first-line therapy is high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (ASCT) [1]. Disease relapse remains the leading cause of treatment failure and mortality after ASCT. Several risk factors that predict relapse after transplantation include poor performance status, primary refractory disease, relapse within 12 months of the initial remission, extranodal disease at relapse, and metabolically active disease on positron emission tomography (PET) prior to transplantation [2–8].

Most HL patients who experience a relapse do so within the first 1–3 years following ASCT, which provides a rationale for the use of post-transplant maintenance or consolidation strategies to reduce the risk of relapse. In the AETHERA trial, HL patients at high risk for relapse or progression—defined as those with one or more trial-specified risk factors (primary refractory disease, complete remission (CR) of less than 12 months, or extranodal involvement

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at the start of salvage chemotherapy)—were randomized to receive consolidation therapy with brentuximab vedotin (BV) or placebo [9]. The trial results demonstrated that BV consolidation significantly improved progression-free survival (PFS) compared to placebo, with 5-year PFS rates of 59% versus 41%, respectively (hazard ratio [HR] 0.57, $P = 0.001$) [9, 10]. Consequently, BV was approved for this indication by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [11, 12].

The approval of BV for the treatment of relapsed/refractory (R/R) HL after ASCT, as well as for post-ASCT consolidation, along with the emergence of other highly effective agents like checkpoint inhibitors (CPIs), has dramatically transformed the management of HL patients. These agents have been incorporated into earlier lines of therapy, including front-line treatment and pre-ASCT salvage therapy, either within or outside of clinical trials. This shift in clinical practice has resulted in more HL patients, previously treated with BV as monotherapy or in combination with chemotherapy, becoming eligible for BV consolidation after ASCT. While the AETHERA trial excluded patients with prior BV exposure, four real-world studies on BV consolidation included many patients who had been treated with BV before ASCT [14–17]. Another limitation of the AETHERA trial was that PET scans were not routinely used for disease assessment before ASCT, even though pre-transplant PET status is now recognized as a critical determinant of prognosis and is considered standard practice for evaluating the response to salvage therapy before transplant.

These observations suggest that the patients enrolled in the AETHERA trial may not have been entirely representative of real-world patients receiving BV consolidation. The use of maintenance BV post-ASCT carries significant implications. Firstly, its efficacy in the current context of widespread use of BV pre-ASCT is crucial. Moreover, it is equally important to consider safety aspects, as BV is not without side effects, particularly peripheral neuropathy. Furthermore, economic factors must be addressed, as post-transplant BV use leads to a notable increase in the overall therapeutic costs associated with patient management. For these reasons, we believe that real-world studies of this nature can profoundly influence therapeutic decision-making in clinical practice.

The current study was designed to assess the efficacy of BV as a consolidation treatment post-ASCT in high-risk HL patients from several national registries and reported to the European Society for Blood and Marrow Transplantation (EBMT) registry, and to explore the impact of pre-transplant exposure to BV on PFS.

PATIENTS AND METHODS

Study design and patients

In this cooperative retrospective study, data were collected in a database specifically designed for this study from the Lymphoma Study Association (LYSA), the Fondazione Italiana Linfomi (FIL), the Spanish Group of Lymphoma and Bone Marrow Transplantation-Spanish Group of Hematopoietic Transplantation (GELTAMO-GETH), and Turkish institutions. The study population included patients who met the following inclusion criteria: age over 18 years at the time of ASCT, a diagnosis of classical HL, first ASCT performed between May 2011 and January 2021, and patients who received BV as consolidation therapy post-ASCT. Exclusion criteria included patients diagnosed with lymphomas other than HL, those who received BV after ASCT as treatment for relapse or progression of HL, and patients treated with tandem ASCT.

The study was approved by the Lymphoma Working Party review board of the EBMT. All transplantation centers were required to obtain written informed consent from all participants before data registration with the EBMT in accordance with the 1975 Declaration of Helsinki. Collection of patient's data was approved by local ethical committees in each registry.

Statistical analysis

Patients' characteristics were described according to BV use pre-ASCT (yes vs. no). Pearson's chi-squared test or Fisher's exact test was used for categorical variables and the Wilcoxon rank-sum test was used for continuous variables.

The primary study endpoint was progression-free survival (PFS) after ASCT defined as survival without relapse or progression. Secondary endpoints were overall survival (OS) defined as survival from BV initiation after ASCT to death from any cause, non-relapse mortality (NRM) defined as death without previous relapse and relapse incidence (RI) defined as disease recurrence following BV initiation after ASCT. Outcomes were all measured from the day of BV initiation after ASCT. Lymphoma status assessment was based on local PET/CT results and on previously published recommendations and response criteria [17, 18]. A positive PET was defined as a Deauville score ≥ 4.

We used the Kaplan Meier method to compute the OS and the PFS and the Fine-Gray subdistribution hazard model to compute the Cumulative incidence function with competing risks for the NRM and the RI. Univariable analyses were performed using the Cox proportional-hazards regression model as well as the Kaplan Meier method for BV use pre-ASCT and disease status at ASCT. Multivariable analyses were performed using the Cox proportional-hazards regression model. Results were reported as hazard ratios (HR) with a 95% confidence interval (95% CI). All analyses were performed using R version 4.3.3.

RESULTS

Characteristics of the patients

A total of 353 patients (33% from LYSA, 29% from FIL, 21% from Turkey, and 18% from GELTAMO-GETH registries) who fulfilled the eligibility criteria were included in the study. Baseline patient characteristics are listed in Table 1. Most patients (61%) had advanced stage HL (stages III-IV) at diagnosis and were treated mainly with ABVD (80%). No patient received first line treatment including BV. Regarding the high-risk factors for HL relapse following ASCT as documented in the AETHERA trial, a total of 152 patients (43%) exhibited primary refractory disease, 176 (50%) experienced relapse within 12 months of frontline therapy, 116 (34%) had extranodal disease at relapse, and 50 (21%) had B symptoms at relapse. Fifty percent of the patients received only 1 salvage therapy before ASCT, 37% 2 lines, 12% ≥3 lines, and 1.1% proceeded to transplant without additional treatment. A total of 186 patients (53%) received BV before ASCT; of these, 15% received BV alone, and 56% received it in combination with chemotherapy (29% with/without chemotherapy, not specified). At the time of ASCT, 247 (74%) patients were in complete remission (CR), 72 (22%) in partial remission (PR), 13 (3.9%) had stable disease, and 1 (0.3%) had refractory HL. PET-CT evaluation before ASCT was available in most patients (92%) and showed a metabolic CR in 66% of them. Compared to patients who did not receive BV prior to transplant, those treated with BV more frequently received two or more lines of salvage therapy (54% vs. 43%, $P = 0.013$), and a higher number were in CR at ASCT (80% vs. 68%, $P = 0.026$) or had a negative PET at ASCT (73% vs. 59%, $P < 0.001$).

BV consolidation after ASCT

The median time from ASCT to BV initiation was 2.1 months (interquartile range [IQR] 1.5–2.9). The median number of BV maintenance cycles was 12 (IQR 8–16). The administration of BV was interrupted in 50 (28%) patients due to BV-related adverse events, in 36 (20%) due to HL relapse/progression, in 11 (6.1%) due to physician/patient decision, and in 1 (0.6%) due to patient death.

Survival outcomes after ASCT

After a median follow-up of 2.5 years (2.2–2.6), the 2 and 5-year overall survival (OS) rates from BV initiation were 94.6% (95% CI 91.5–96.6) and 85.1% (95% CI 76–91), respectively, while the PFS rates were 79.5% (95% CI 74.3–83.7) and 69.9% (95% CI 57.8–79.1), respectively (Fig. 1). A total of 27 patients died during the period of the study. Of these, 9 (53%) died because of HL progression, 6 (35%) died due to infectious complications, and 2 (12%) died for

Table 1. Characteristics of the patients.

Characteristics	All patients $N = 353$	Patients without BV pre-ASCT $N = 167$	Patients with BV pre-ASCT $N = 186$	*P*-value
Median age at diagnosis, years (range)	30 (14–69)	30 (14–68)	31 (15–69)	0.4
Median age at ASCT, years (range)	33 (18–70)	32 (18–69)	34 (18–70)	0.2
Sex, male	190 (54%)	89 (53%)	101 (54%)	0.8
Ann Arbor HL stage at diagnosis				
I	7 (2%)	5 (3%)	2 (1.1%)	0.6
II	126 (37%)	60 (36%)	66 (37%)	
III	68 (20%)	30 (18%)	38 (21%)	
IV	142 (41%)	71 (43%)	71 (40%)	
Missing	10	1	9	
First-line therapy				
ABVD	282 (80%)	144 (86%)	138 (74%)	0.019
ABVD, BEACOPP	30 (8.5%)	7 (4.2%)	23 (12%)	
BEACOPP	20 (5.7%)	7 (4.2%)	13 (7%)	
Other	21 (5.9%)	9 (5.4%)	12 (6.5%)	
Primary refractory HL	152 (43%)	72 (43%)	80 (43%)	>0.9
HL relapse ≤ 12 months after 1st-line therapy	177 (50%)	86 (51%)	91 (49%)	0.6
B symptoms at relapse/progression	50 (21%)	29 (25%)	21 (17%)	0.14
Missing	113	50	63	
Bulky disease at relapse/progression	13 (8%)	1 (1.8%)	12 (11%)	0.034
Missing	191	110	81	
Extranodal disease at relapse/progression	116 (34%)	51 (31%)	65 (36%)	0.3
Missing	7	2	5	
Number of salvage therapy lines				0.013
0	4 (1.1%)	0 (0%)	4 (2.2%)	
1	177 (50%)	96 (57%)	81 (44%)	
2	129 (37%)	56 (34%)	73 (39%)	
≥ 3	43 (12%)	15 (9%)	28 (15%)	
BV before ASCT				-
No	167 (47%)			
Yes, in monotherapy	28 (7.9%)			
Yes, in combination with chemotherapy	104 (29%)			
Yes, not detailed	54 (15%)			
PET-CT pre-ASCT				< 0.001
Metabolic CR	222 (66%)	92 (59%)	130 (73%)	
No metabolic CR	86 (26%)	55 (35%)	31 (17%)	
Not performed	26 (7.8%)	8 (5.2%)	18 (10%)	
Missing	19	12	7	
Disease status at ASCT				0.026
CR	247 (74%)	112 (68%)	135 (80%)	
PR	72 (22%)	41 (25%)	31 (18%)	
Stable disease	13 (3.9%)	10 (6.1%)	3 (1.8%)	
Progressive disease	1 (0.3%)	1 (6.1%)	0 (0%)	
Missing	20	3	17	

BV brentuximab vedotin, *ASCT* autologous stem cell transplantation, *HL* Hodgkin lymphoma, *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine, *BEACOPP* bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone, *PET-CT* positron emission tomography, *CR* complete remission, *PR* partial remission

reasons unrelated to HL or ASCT. In the case of 10 patients, the cause of death was not available for review. The cumulative incidences of non-relapse mortality and relapse rate at 1 and 2 years were 0.3% (95% CI 0–1.7), 0.7% (95% CI 0.1–2.3), and 14.7% (95% CI 11.0–18.9), 19.9% (95% CI 15.5–24.7), respectively.

In univariable analysis, relapse within 12 months of frontline therapy (HR 3.27, 95% CI 1.32–8.11, $P = 0.01$), receiving ≥ 2 salvage therapy lines (HR 2.87, 95% CI 1.21–6.79, $P = 0.016$), and non-CR at ASCT (HR 3.42, 95% CI 1.58–7.40, $P = 0.002$) were associated with worse OS (Table 2). Patients who had primary refractory HL (HR

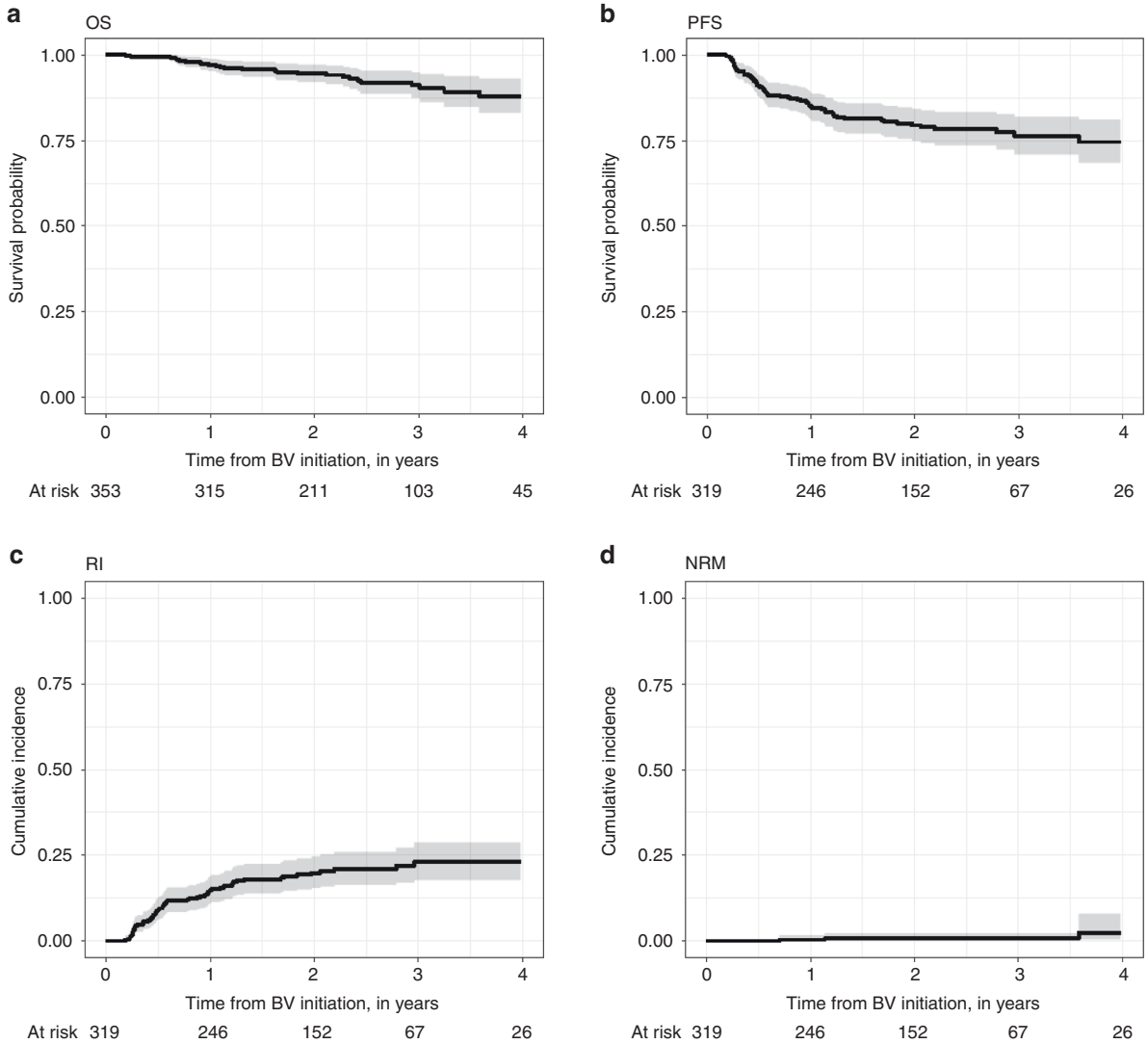

Fig. 1 Survival outcomes. Kaplan-Meier plots showing overall survival (OS) (**a**) progression-free survival (PFS) (**b**) relapse incidence (RI) (**c**) and non-relapse mortality (NRM) (**d**) from BV maintenance initiation after ASCT for all patients.

Table 2. Univariable analysis of factors associated with survival outcomes.

Variable	Overall survival		Progression-free survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age at ASCT, years	1.03 (1.00–1.06)	0.075	0.99 (0.97–1.01)	0.3
Sex, male	1.72 (0.34–1.55)	0.4	1.18 (0.72–1.91)	0.5
Primary refractory disease	0.59 (0.27–1.32)	0.2	1.85 (1.14–2.99)	0.013
Relapse ≤12 months	3.27 (1.32–8.11)	0.01	1.00 (0.62–1.62)	> 0.9
Extranodal disease at relapse/progression	0.67 (0.29–1.52)	0.3	0.87 (0.52–1.47)	0.6
B symptoms at relapse/progression	0.77 (0.22–2.69)	0.7	0.56 (0.22–1.45)	0.2
Number of salvage therapy lines ≥2	2.87 (1.21–6.79)	0.016	0.91 (0.56–1.47)	0.7
No CR at ASCT	3.42 (1.58–7.40	0.002	3.61 (2.19–5.97)	< 0.001
BV before ASCT	0.43 (0.20–0.97)	0.042	0.58 (0.36–0.96)	0.032

HR hazard ratio, *95% CI* 95% confidence interval, *ASCT* autologous stem cell transplantation, *CR* complete response, *BV* brentuximab vedotin.

1.85, 95% CI 1.14–2.99, $P = 0.013$), and those with non-CR at ASCT (HR 3.61, 95% CI 2.19–5.97, $P < 0.001$) had significantly lower PFS (Table 2) (Fig. 2). Patients treated with BV before transplant had better 2-year OS (97.7% vs. 91.2%, HR 0.43, 95% CI 0.20–0.97, $P = 0.042$) and 2-year PFS (84.4% vs. 74.3%, HR 0.58, 95% CI 0.36–0.96, $P = 0.032$) than those who did not receive it (Fig. 3). The multivariable analysis showed that the only variables with a significant impact on OS were age at ASCT (HR 1.17, 95% CI

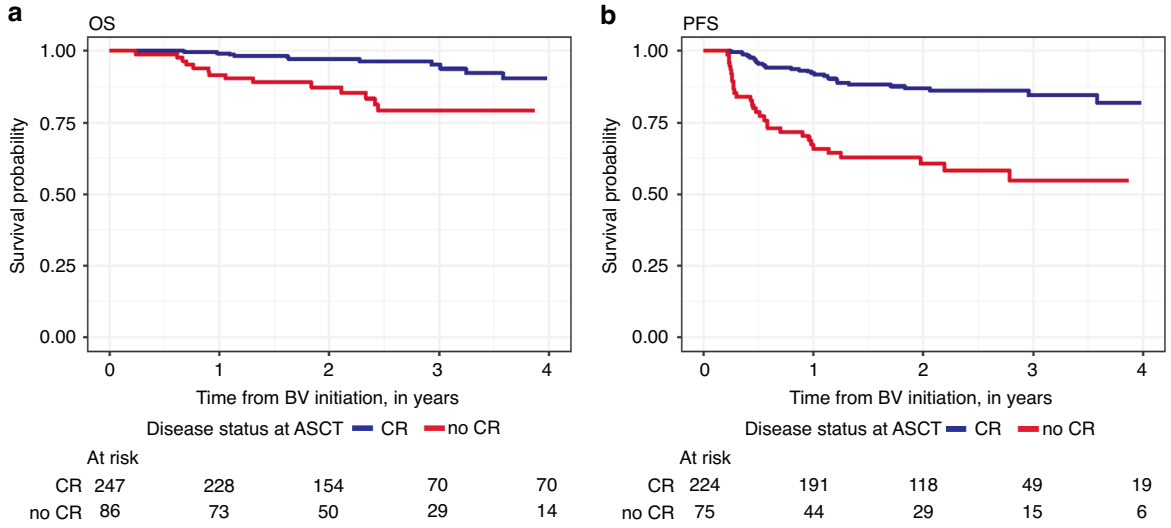

Fig. 2 Survival outcomes according to disease status at ASCT (CR vs. No-CR). Kaplan-Meier plots showing overall survival (OS) (**a**) and progression-free survival (PFS) (**b**) from BV maintenance initiation after ASCT.

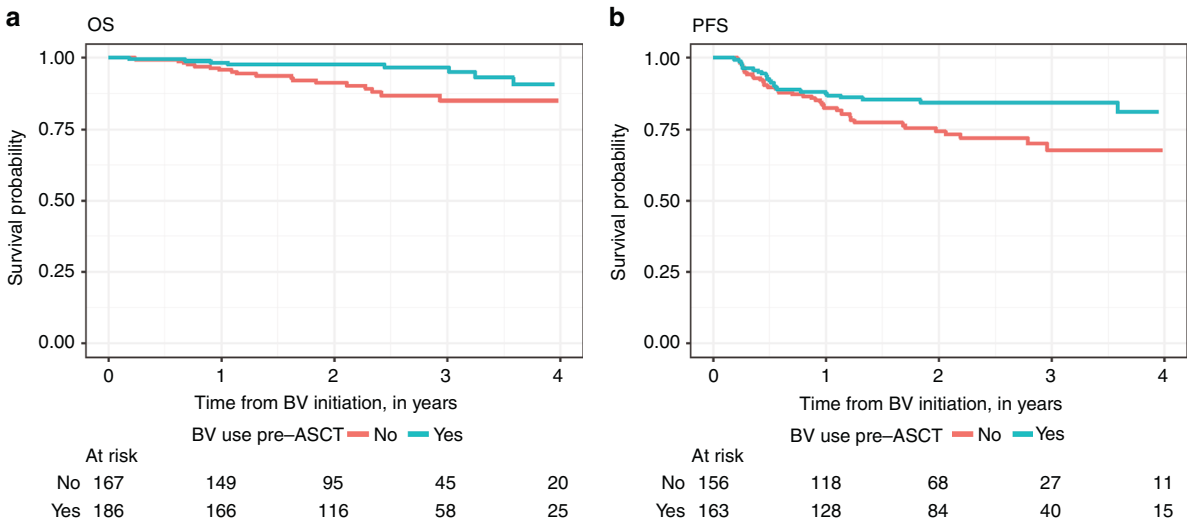

Fig. 3 Survival outcomes in patients treated or not with BV before ASCT. Kaplan-Meier plots showing overall survival (OS) (**a**) and progression-free survival (PFS) (**b**) from BV maintenance initiation after ASCT.

Table 3. Multivariable Cox regression analysis of factors associated with post-ASCT outcomes.

Variable	Overall survival		Progression-free survival		Relapse incidence		Non-relapse mortality	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age at ASCT, 5-year interval	1.17 (1.01–1.36)	0.037	0.98 (0.88–1.09)	0.7	0.97 (0.86–1.08)	0.6	1.18 (0.79–1.77)	0.4
Primary refractory disease	0.52 (0.22–1.21)	0.13	1.50 (0.88–2.54)	0.13	1.48 (0.86–2.55)	0.2	1.58 (0.21–11.7)	0.7
No CR at ASCT	3.61 (1.62–9.05)	0.002	3.09 (1.84–5.20)	< 0.001	3.33 (1.94–5.70	< 0.001	1 (0.10–9.92)	> 0.9
BV before ASCT	0.40 (0.17–0.93)	0.033	0.59 (0.34–1.01)	0.053	0.57 (0.33–1.00)	0.051	0.74 (0.10–5.58)	0.8

HR hazard ratio, *95% CI* 95% confidence interval, *ASCT* autologous stem cell transplantation, *CR* complete response, *BV* brentuximab vedotin.

1.01–1.36, $P = 0.037$), disease status at ASCT (HR 3.61, 95% CI 1.62–8.05, $P = 0.002$), and BV treatment prior to ASCT (HR 0.40, 95% CI 0.17–0.93, $P = 0.033$) (Table 3). Disease status at ASCT was the only factor significantly correlated with PFS outcomes (HR 3.09, 95% CI 1.84–5.20, $P < 0.001$), with a trend towards better PFS for BV treatment before ASCT (HR 0.59, 95% CI 0.34–1.01, $P = 0.053$) (Table 3).

The aforementioned factors did not affect non-relapse mortality. Non-CR status was correlated with an increased risk of HL relapse (HR 3.33, 95% CI 1.94–5.70, $P < 0.001$) (Table 3). While a

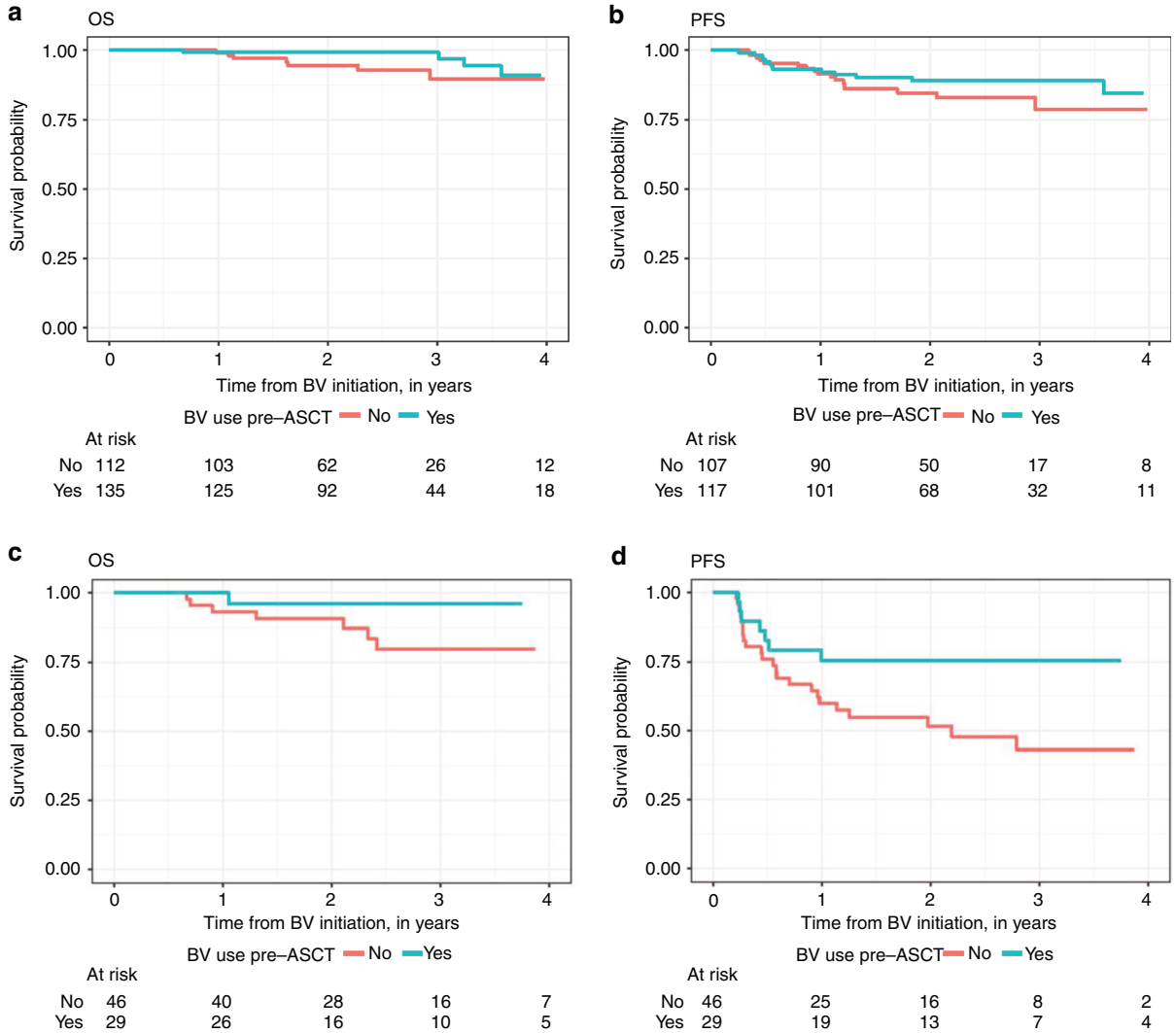

Fig. 4 Survival outcomes. Kaplan-Meier plots showing overall survival (OS) and progression-free survival (PFS) from BV maintenance initiation after ASCT in patients treated or not with BV before ASCT and according to HL status at ASCT (CR [**a**, **b**] vs. No-CR [**c**, **d**]).

trend toward a lower risk of relapse (HR 0.57, $p = 0.051$) and improved PFS (HR 0.59, $p = 0.053$) was observed in patients treated with BV before ASCT, the current data were insufficient to establish this association with statistical significance (Table 3). Patients in CR at ASCT showed similar 2-year OS (94.6%, 95% CI 87.3–97.7 vs. 99.2%, 95% CI 94.8–99.9, $P = 0.3$) and PFS (84.6%, 95% CI 75.7–90.5 vs. 89%, 95% CI 81.3–93.6, $P = 0.3$) regardless of BV pre-transplant (Fig. 4). However, for those in non-CR at ASCT, both OS (83.1%, 95% CI 68.8–91.2 vs. 93.6%, 95% CI 76.9–98.4, $P = 0.076$) and PFS (51.5%, 95% CI 35.5–65.4 vs. 75.3%, 95% CI 55.0–87.4, $P = 0.039$) were higher in those who had been treated with BV before the transplant (Fig. 4). It should be noted that in the latter group the proportion of patients with chemosensitive HL (PR) at ASCT was lower in the group of patients who did not receive BV prior to transplantation (41 of 52 [78.8%]) compared to those who received BV-based salvage regimens (31 of 33 [93.9%]).

DISCUSSION

This is the largest study published to date that presents real-world outcomes of BV maintenance therapy following ASCT in patients with R/R high-risk HL, after the approval of BV for this indication. The results reflect clinical practice in European centers during the period of the study including the progressive incorporation of BV into pre-ASCT salvage therapies. This cohort of patients, larger than the group in the AETHERA trial that received BV maintenance, consists of patients who were previously published independently by the French, Italian, Turkish, and Spanish national groups [13–16]. This has enabled us to analyze the factors related to PFS with greater statistical power than each study individually.

The estimated 5-year PFS was 69.9%, with better outcomes observed in patients in CR at the time of transplantation and those who received BV-based salvage regimens prior to ASCT. In the AETHERA trial, the 5-year PFS rate for patients receiving BV maintenance was 63% [10]. Compared to AETHERA's BV maintenance cohort, our series had lower percentages of patients with primary refractory HL (43% vs. 60%) and B symptoms (21% vs. 28%), but higher rates of extranodal disease (34% vs. 28%), early relapse (50% vs. 32%) and more than 2 lines of salvage therapy (51.9% vs. 43%) [9, 10]. In contrast with AETHERA study in which BV before ASCT was not allowed, 53% of our patients received BV alone or in combination with chemotherapy as salvage therapy. The inclusion of a higher proportion of patients with HL in CR at ASCT (74% vs. 37% in AETHERA patients receiving BV maintenance) may explain the better observed PFS (69.9%) in our study. These results emphasize the value of CR status at the time of ASCT as one of the main prognostic factors for PFS, which has been previously

highlighted in several studies [6–8]. This finding would confirm what was observed in the French and Spanish studies with a smaller number of patients, all of them receiving BV maintenance, where the presence of a metabolic CR was the only factor associated with better PFS in the multivariable analyses [14, 16].

Indeed, the primary objective of salvage therapy prior to ASCT has become the achievement of metabolic CR. Consequently, over the past decade, several different treatment regimens have been developed that combine BV with chemotherapy. Notable examples include the combinations of BV-Bendamustine, BV-ICE, BV-DHAP, and BV-ESHAP, for which metabolic CR rates have been reported at 70–81% [19–23]. In these studies, the PFS rates after ASCT were reported to be in the range of 65–80%. A recent prospective phase IIb study (BRESELIBET trial) has shown, for the first time, that the combination of BV with chemotherapy was more efficacious than chemotherapy alone [24]. In the aforementioned trial, 53 out of 76 (69.7%) R/R HL patients who were randomized to the BV-ESHAP arm achieved a metabolic CR after three cycles, compared to 36 out of 75 (48.0%) in the ESHAP arm ($P = 0.007$) [24]. More recently, checkpoint inhibitors-based (CPIs) protocols have been demonstrated to achieve metabolic CR in up to 71–95% of cases, with post-ASCT PFS exceeding that observed with BV combinations (over 80%) [25–27]. The high efficacy of combinations of CPIs has prompted some studies to suggest that a selected group of patients could potentially obviate the need for ASCT. These results should be interpreted with caution due to the relatively low number of patients included in the studies and the short duration of post-transplant follow-up. CPIs and CPIs plus BV maintenance have also been explored to improve the outcome of high-risk R/R HL patients undergoing ASCT with very promising results [28, 29].

The introduction of BV and CPIs not only into pre-ASCT salvage treatments but also into front-line therapies has led to controversy regarding the value of maintenance with BV. In the study by Falade et al. presented as a poster at ASH in 2023, in the cohort of patients who had previously been exposed to BV and had shown sensitivity to it, maintenance with BV after ASCT did not improve PFS compared to those in the same situation who did not receive maintenance [30]. The authors suggest that, for patients with HL in response after salvage BV, the addition of BV maintenance would not be of benefit or would provide minimal benefit. It should be noted that, in the group that received maintenance with BV, the percentage of patients with primarily refractory HL or early relapse —both well-recognized adverse factors—was higher than in the group that did not receive maintenance. It could be argued that the addition of maintenance in this group of poor-prognosis patients who were sensitive to BV was beneficial, as it equalized the PFS outcomes with those of a group that had a better prognosis initially. The results of our study demonstrate that patients in CR at ASCT who receive BV maintenance have an excellent prognosis, regardless of whether they received BV pre-transplant. We did not have a cohort without BV maintenance for comparison. The prognosis for individuals undergoing ASCT in a non-CR situation is less favorable, even with the use of BV maintenance. However, it is encouraging to note that patients who have been previously exposed to BV prior to ASCT tend to experience a more favorable outcome. This is probably due to a reduction in the number of patients with salvage-resistant disease, given that, compared to the group not treated with BV, the group that received BV prior to ASCT had a higher number of patients with HL in partial remission (25% vs. 18%) and a lower number with SD (1.8% vs. 6.1%).

Considering recent scientific evidence, a review of BV maintenance after ASCT is warranted. In 2019, a consensus recommendation was issued by the ASBMT, CIBMTR, and EBMT on the use of maintenance therapies for HL [31]. BV maintenance was advised for BV-naive HL patients with at least one high-risk feature, as defined by the AETHERA study. It was also recommended for patients with limited prior BV exposure (< 4–6 cycles) undergoing ASCT, provided they met AETHERA risk criteria and showed no prior resistance or intolerance to BV. Our findings may support BV maintenance in previously treated patients. However, modifying these recommendations is challenging, as high-quality prospective studies demonstrating clear benefits in BV-exposed patients are unlikely. The situation is further complicated by the increasing use of BV and CPIs in first line and salvage regimens, and the growing prevalence of sequential treatments with BV and CPI before ASCT.

Regarding the toxicity of BV maintenance post-ASCT, unfortunately, our study was unable to collect detailed data on the incidence of peripheral neuropathy or other adverse effects. Nonetheless, the study does record how many patients discontinued BV maintenance due to adverse effects (28%). This figure reflects the percentage of cases where the adverse effect was sufficiently severe to prompt the discontinuation of BV. This proportion was higher than that reported in the AETHERA study, which was 18%. This difference is expected, as real-world settings do not involve the same level of patient selection as clinical trials, where individuals with pre-existing peripheral neuropathy or those at higher risk for its development are typically excluded. Additionally, our study included patients who were previously exposed to BV and more heavily treated, which may contribute to a higher incidence of adverse effects.

The limitations of our study are inherent to registry-based studies, where patient heterogeneity and the absence of certain relevant data, such as BV maintenance toxicity, are more pronounced than in prospective studies. Moreover, the present study did not include a control group comprising patients without BV maintenance, nor a group of patients treated with BV prior to ASCT who did not receive BV maintenance. Currently, a randomized study is not feasible; however, a comparison with a well-matched historical control group could be conducted. In this regard, the study published by the Spanish group (GELTAMO-GETH) and included in our series made this comparison with a historical cohort of patients without BV maintenance, some of whom were treated with BV pre-ASCT [16]. The authors observed that BV maintenance, regardless of prior exposure to the drug, resulted in a significantly superior PFS compared to the historical control group. Another limitation is the absence of patients who received BV or CPIs in first-line therapy, which is now a common practice. The impact of BV maintenance in these groups of patients is currently unknown.

In conclusion, our study shows that the use of BV maintenance in high-risk R/R HL after ASCT is associated with a PFS of 69.9%, with particularly good outcomes for patients who undergo ASCT in CR. Considering that in many countries the use of BV-based salvage therapies before ASCT is not yet approved and may be difficult to access, BV maintenance remains relevant and should be recommended.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

CM and AS conceived and designed the study; CM interpreted the statistical results and wrote the manuscript; IK collected and assembled data; MF performed the statistical analysis and interpreted the results; and CM, IK, MF, BDF, AM, HG, LMF, FM, PMS, FM, BB, BF, OMA, MÖ, MEH, SR, JEG, BG, AB, AS are physicians from LWP-EBMT centers who performed the transplants, took care of the patients, collected local data of patients, and made significant contributions to the discussion of the results. All authors approved the final version of the manuscript.

COMPETING INTERESTS

C. Martínez declares participation in Scientific Takeda Advisory Board. I. Khvedelidze declares no conflict of interest. M. Fekom declares no conflict of interest. B. Deau Fischer declares participation in Scientific Takeda and Abbvie Advisory board. A. Marouf declares no conflict of interest. H. Ghesquières declares Roche, BMS, Takeda consultancy; Honoraria: Gilead, Roche, BMS, Abbvie, Takeda. L.M. Fornecker declares no conflict of interest. F. Merli declares Honoraria/Advisory Board: Beigene, Gilead, Incyte, Janssen, Novartis, Roche, Sandoz, Takeda, Astrazeneca. P. M. Stefani declares participation in Advisory Board: Takeda, Roche, Janssen-Cilag, Incyte. Kiowa Kirin Gilead. F. Massaro declares no conflict of interest. B. Botto declares Takeda Speakers

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