Brentuximab-vedotin and bendamustine for relapsed or refractory Hodgkin lymphoma: the LYSA real-world experience

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Abstract

Classical Hodgkin lymphoma (HL) is often cured after a modern first-line regimen but relapsed or refractory (R/R) diseases remain a therapeutical challenge that few randomized clinical trials have addressed. Several combinations of brentuximab-vedotin (Bv) with chemotherapy have been reported in R/R HL so far, yet there are no randomized clinical trials or large-scale real-world evidence that comprehensively picture efficacy and toxicity of these distinct Bv-based regimen. By leveraging real-world data from 222 patients with R/R HL treated in France over ten years, we show that brentuximab-vedotin plus bendamustine (B2 regimen) was associated with an overall response rate (ORR), complete response (CR) rate, and 2-year progression-free survival (2y-PFS) of 82%, 69.8%, and 54.8%, respectively. The 2y-PFS of the 150 patients eligible for transplantation at B2 initiation was 64.2% and reached 79.9% for the 102 patients who successfully underwent transplantation, despite an infrequent use of Bv maintenance. Conversely and despite a CR rate of 69.6%, patients who were ineligible for transplant faced poor outcomes with a 2y-PFS of 35%. The B2 regimen was associated with low hematologic toxicities and neuropathy rates and was administered as outpatient treatment in 80% of cases. Considering that Bv combinations might remain important therapy options for R/R diseases, notably after front-line regimen containing checkpoint inhibitors, these results support the B2 regimen as a valid combination for patients eligible for transplantation while highlighting ineligible patients as a persistent unmet medical need.

Introduction

The therapeutic landscape of Hodgkin lymphoma (HL) has been largely refined over the last two decades owing to numerous large randomized controlled trials (RCT) that addressed the question of the best first-line regimen to use in previously untreated patients.[1-4] These efforts contributed to an improvement in patients' outcomes and have allowed the establishment of strong, widely-recognized evidence-based therapy guidelines. Despite significant improvements driven by the incorporation of innovative agents within historical polychemotherapy regimen, only a few RCT have been dedicated to relapsed and refractory (R/R) HL. This has led to highly variable practices across countries and centers, and to a notable absence of any recognized standard of care. The treatment paradigm for young and fit patients historically

consisted of multi-agent salvage therapy followed by high-dose chemotherapy (HDC) and autologous hematopoietic stem-cell transplantation (ASCT) in case of response,[5-9] only allowing less than 50% of cases to be cured overall. Following phase I-II trials demonstrating its efficacy in advanced-line HL,[10,11] brentuximab-vedotin (Bv), an immunoconjugated monoclonal antibody targeting CD30, has been shown to increase progression-free survival (PFS) when administered as maintenance after ASCT in the only RCT to include R/R HL over the last ten years.[12] The addition of Bv to salvage therapy also emerged as a potent tool to increase response and transplantation rates in several pivotal phase II trials. In these studies, Bv was combined with either bendamustine,[13,14] dexamethasone, high-dose cytarabine and cisplatin (DHAP),[15] ifosfamid, carboplatin and etoposide (ICE),[16,17] etoposide, solumedrol, cytarabine and cisplatin (ESHAP)[18] or nivolumab,[19] leading to a CR rate of approximately 60-80% and a sustained remission rate of approximately 60-80%. These favorable results led several collaborative groups to integrate the Bv-based regimen into the backbones of salvage treatment.[20,21] However large-scale data are still lacking and most evidence regarding specific Bv-based regimens relies on the aforementioned phase II trials and real-world studies which, however, only included very small numbers of patients.[22-24] Therefore, clinician choices are likely to be driven by clinical experience and habits or extrapolation from evidence in non-Hodgkin lymphoma. Besides this, few phase II trials have reported the impressive efficacy of checkpoint inhibitors (CPI) associated with chemotherapy as first salvage,[25,26] but the lack of market access in the second-line setting in many countries, including France, is a barrier to their use.

This incomplete and yet decisive issue has evolved with the paradigm shift that recently affected the front-line setting of HL. The outstanding results of the HD21[27] and SWOG1826[28] trials have set Bv or nivolumab, respectively, as legitimate parts of front-line regimen, leading to novel and personalized needs for the minority of patients who eventually experience disease progression. Defining the best second-line regimen to combine with Bv, especially in patients who did not receive it as part of their front-line therapy, thus remains a major challenge to address. Since RCT involving Bv in the second-line setting are now unlikely to be carried out, solid real-world evidence is warranted to guide therapy decision making. Even more urgent is the need for evidence regarding the subset of R/R patients unfit for ASCT, a population under-represented in the current literature that continues to face poor outcomes and to pose a serious therapeutical challenge to clinicians.

To address these questions, the HL-R2-B2 study evaluated the efficacy and toxicity of Bv in association with bendamustine (B2 regimen) in a large, real-life cohort of R/R HL recruited across French centers. We aimed to evaluate the outcomes of patients receiving this association, with a dedicated focus on both ASCT-eligible and non-eligible subgroups, as well as to highlight the different toxicity patterns associated with this regimen in the real-life setting.

Methods

Data source

French centers within the Lymphoma Study Association (LYSA) network were invited to participate in this retrospective study (HL-R2-B2 study) following approval by the LYSA Hodgkin scientific board. The research was supervised by the Direction de la Recherche Clinique du CHU de Bordeaux and was undertaken in accordance with the Declaration of Helsinki. It was approved by the ethics research committee of the Centre Hospitalier Universitaire de Bordeaux (reference: CER-BDX 2025-59).

Patients and treatments

Eligible patients were adults (aged ≥18 years) diagnosed with R/R HL and treated with at least one cycle of bendamustine in association with Bv. The first HL diagnosis was originally validated by an expert hematopathologist within the LYMPHOPATH network[29] and a new histological examination before B2 treatment was not required for inclusion in the study. B2 consisted of bendamustine 90 mg/m^2 day (D) 1 and D2, 21-day cycle with Bv (1.8 mg/kg) at D1. Dose reduction was possible at the physician's discretion, and the number of planned cycles could vary according to the physician's choice and ASCT eligibility. Granulocyte colony-stimulating factors (GCSF) were not routinely administered but could have been used according to physician's discretion. Considering the absence of indisputable criteria to define ASCT eligibility[20] and the selection bias that commonly affect consolidative therapy in retrospective studies, we allocated ASCT eligibility according to an initial intention-to-treat approach. Since the Plan Cancer 2006, all cancer therapy decisions in France have to be taken by a certified, multidisciplinary board. Any patient considered eligible for ASCT at the time of the decision to give B2 therapy, and before the start of salvage therapy, was identified as such in this study, whether or not he or she was eventually denied access to ASCT due to treatment toxicity, personal or physician choice, or any other reason. Age, absence of serious comorbidities or organ failure, good physical condition (including performance status ≤2), and no previous ASCT were decisive criteria for the multidisciplinary board decision, based on clinical expertise. Conditioning regimen consisted of BEAM (carmustine, etoposide, cytarabine, melphalan). Hematopoietic stem cells (HSC) were collected as per local guidelines following standard stimulation with a high dose of GCSF. Patients could receive Bv maintenance at the physician's discretion, regardless of whether they had been transplanted or met the high-risk AETHERA criteria.[12] Of note, during the study period, CPI were only licensed in case of progression after Bv exposure (2017-2021) or two or more progression events (2021).

Outcomes

The primary objective was to report the 2-year (2y) PFS of the study population. Other objectives included the evaluation of 4-year (4y) PFS, 2y and 4y overall survival (OS), best overall response rate (bORR), and duration of response (DOR). The bORR (best complete response [CR] and best partial response [PR]) was the best response recorded after completion of induction with B2 regimen (and before ASCT, if performed) according to the Lugano classification.[30] We also described PFS, OS and bORR separately in patients according to whether they were eligible or not for ASCT, and survival according to early positon emission tomography (PET) evaluation after 2 or 3 cycles using the 5-point scale Deauville score (DS). We also assessed adverse events (AE) of interest, including grade and frequency of infectious events, peripheral neuropathy (PN), cutaneous and infusion-related events, transfusion requirements, and rate of second primary malignancies (SPM, excluding non-melanoma skin tumors), including secondary myeloid neoplasia (SMN). We did not plan to report grade 1 events as we were uncertain as to the reliability of such retrospective data in the context of a mostly outpatient treatment. Only PN was assessed for grade 1 toxicity considering the careful focus of physicians on this toxicity in daily practice. Non relapse mortality (NRM) was reported. Grades of AE were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Statistical analysis

Duration of follow-up was estimated using reverse Kaplan-Meier method. Survival curves were generated using the Kaplan-Meier estimation method. PFS and OS were measured from the date of B2 initiation to the date of death from any cause or disease progression, or until the date of death from any cause, respectively. DOR was measured from the date of response to the date of disease progression or death from any cause. Cumulative incidence of non-relapse mortality was estimated by using relapse as a competitive risk. Survival distributions were compared using the log-rank test. A two-sided $P<0.05$ was considered statistically significant. Prognostic factors for PFS were estimated using proportional hazard Cox model. Covariates with univariate $P<0.20$ by AIC were selected for multivariable analysis. Prognostic factors for toxicity were estimated using logistic regression on toxicity indicators. Statistical analyses were performed using SAS software version 9.4 and R version 4.2.3. The maxstat package version 0.7 was used for cutoff analyses

Results

Patients

A total of 222 patients treated across 10 French centers from 2014 to 2024 were included. Among them, 150 were considered eligible for ASCT at B2 initiation and 72 were not. Clinical characteristics of the overall population are shown in Table 1. Median age of the study cohort was 44 years (36 in eligible patients, 68 in non-eligible patients), and the sex ratio (M/F) was 1.8. Patients had received a median of 1 previous line of treatment, with 59.9% of the patients being in a second-line setting, 27.8% having received 2 previous lines of therapy and 12.2% having been heavily pre-treated (≥3 prior lines). First-line regimen consisted of ABVD and BEACOPP-based regimen in 61.3% and 14.9% of cases, respectively, while 14% received another regimen, mostly anthracycline therapies (see *Online Supplementary Table S1* for details). Thirteen patients (6%, all unfit for transplantation) received prednisone, vinblastine, doxorubicin and bendamustine (PVAB regimen) at frontline.[31] Only one patient received Bv-AVD at first line, this regimen not being reimbursed in France, and 9 (4%) had prior exposure to CPI (3 in the context of a first-line clinical trial, and 6 in the context of advanced lines). In terms of disease status, 61% were refractory (no response, or progression within 3 months after completion of therapy) to their prior line, 15% had early relapse (3-12 months), and 24% had late relapse (>12 months). At B2 initiation, 64.9% of patients had stage III-IV disease (including 47% stage IV), 25.2% presented with B symptoms, and 11% had ECOG ≥2. Of note, 86% of patients presented at least one AETHERA risk factor (namely, refractory or early relapsed disease, B symptoms or stage IV disease). Reasons for ASCT ineligibility were previous transplantation in 19 out of 72 patients, and age or general frailty in 53 out of 72 patients. A flow chart of the study population is shown in *Online Supplementary Figure S1*.

Outcomes of the whole cohort and risk factors for events

After a median follow-up of 48 months, the 2y-PFS and 4y-PFS for the whole cohort were 54.8% (95%CI: 54.8-61.3%) and 50% (95%CI: 42.6-56.9%), respectively, while 2y-OS and 4y-OS were 82.1% (95%CI: 76.1-86.7%) and 73.8% (95%CI: 66.6-79.1%) (Figure 1). Median PFS (mPFS) and median OS (mOS) were 44.7 months and not reached (NR), respectively. In 212 patients for whom response was available after B2 induction according to the Lugano classification, the bORR was 82%, with 69.8% of patients achieving CR and 12.1% PR. The 2y-DOR was 70.2% (95%CI: 61.7-77.2%) for patients achieving CR and 40% (95%CI: 21.3-58.1%) for patients achieving PR. In multivariable analysis including only baseline characteristics, ECOG ≥2, stage III-IV disease and ineligibility to ASCT at B2 initiation were associated with both worse PFS and OS (Table 2). When early response to therapy assessed by PET was added to the model, DS 4 and DS 5 were associated with increased risk of progression or death. ECOG, stage III-IV and ASCT ineligibility also remained significant, indicating that the adverse prognosis carried by these factors is not fully reversed by early metabolic response (*Online Supplementary Table S2*).

A total of 91 patients experienced progression or relapse

Table 1. Characteristics of the study population.

Characteristics	All N=222	Eligible for ASCT at treatment initiation	
		Yes N=150	No N=72
Age			
Median (range)	44 (18-86)	36 (18-71)	68 (20-86)
≤60 y, N (%)	159 (71.6)	137 (91.3)	22 (30.6)
>60 y, N (%)	63 (28.4)	13 (8.7)	50 (69.4)
Gender, N (%)			
Male	142 (64.0)	98 (65.3)	44 (61.1)
Female	80 (36.0)	52 (37.4)	28 (38.9)
Previous treatment line			
Median (range)	1 (1-11)	1 (1-4)	1 (1-11)
1, N (%)	133 (59.9)	94 (62.7)	39 (54.2)
2, N (%)	62 (27.9)	44 (29.3)	18 (25.0)
≥3, N (%)	27 (12.2)	12 (8.0)	15 (20.8)
Previous ASCT, N (%)			
Yes	21 (9.5)	1 (0.1)	20 (27.8)
No	201 (90.5)	149 (99.9)	52 (72.2)
Previous Bv exposure, N (%)			
Yes	23 (10.3)	11 (7.3)	12 (16.7)
No	197 (88.7)	139 (92.7)	58 (80.5)
Not known	2	0	2
Previous bendamustine exposure, N (%)			
Yes	13 (6)	0	13 (18)
No	209 (94)	222 (100)	59 (82)
Previous CPI exposure, N (%)			
Yes	9 (4)	3 (2)	6 (8.3)
No	213 (96)	147 (98)	66 (91.7)
First-line treatment, N (%)			
ABVD-based	139 (62.6)	102 (68.0)	37 (51.4)
BEACOPP-based	33 (14.9)	30 (20.0)	3 (4.2)
Other	26 (11.7)	4 (2.7)	22 (30.6)
Not known	24	14	10
Delay between initial diagnosis and B2 initiation			
Median, months (range)	13.5 (0-253)	11.9 (0-253)	17.7 (0.6-199)
Disease status at B2 initiation, N (%)			
Refractory	135 (60.8)	99 (66.0)	36 (50)
Relapse	87 (39.2)	51 (34.0)	36 (50)
Early relapse, <1 y	33 (14.8)	22 (14.6)	11 (15.2)
Late relapse, ≥1 y	49 (22)	28 (18.6)	21 (29.1)
Not known	5	1	4
ECOG at B2 initiation, N (%)			
0-1	186 (83.8)	129 (86.0)	57 (79.2)
2-4	25 (11.3)	13 (8.7)	12 (16.7)
Not known	11	8	3
B symptoms at B2 initiation, N (%)			
Yes	55 (24.8)	35 (23.3)	20 (27.8)
No	163 (74.4)	112 (74.7)	51 (70.8)
Not known	4	3	1
Ann Arbor stage at B2 initiation, N (%)			
I-II	78 (35.1)	57 (38.0)	21 (29.2)
III-IV	144 (64.9)	93 (62.0)	51 (70.8)
Median N of cycles			
Bendamustine (range)	4 (1-7)	4 (1-6)	4 (1-7)
Bv (range)	4 (1-22)	4 (1-22)	6 (1-18)
B2 combination (range)	4 (1-7)	4 (1-6)	4 (1-7)

Continued on following page.

Characteristics	All N=222	Eligible for ASCT at treatment initiation	
		Yes N=150	No N=72
Bv maintenance administered, N (%) Yes No	47 (21) 175 (79)	32 (21) 118 (79)	15 (20) 57 (80)

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT: autologous stem cell transplantation; B2: brentuximab-vedotin/bendamustine association; Bv: brentuximab-vedotin; BEACOPP: escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CPI: checkpoint inhibitors; N: number; y: years.

after B2. Their 2y-OS2 and 4y-OS2 were 62.9% (95%CI: 51.5-72.4%) and 49.6% (95%CI: 37-61%), respectively, and were not significantly impacted by the period of relapse (2014-2017 *vs*. 2018-2024, *P*=0.66) (*Online Supplementary Figure S2*).

Outcomes of patients eligible for autologous hematopoietic stem cell transplantation

After a median follow-up of 48.1 months, the 2y-PFS and 4y-PFS for the 150 patients eligible for ASCT at B2 initiation were 64.2% (95%CI: 56.6-72.2%) and 59.2% (95%CI: 50-67.2%), respectively (Figure 2A, B), while 2y-OS and 4y-OS were 89.2% (95%CI: 82.7-93.4%) and 84.3% (95%CI: 76.5-89.6%), respectively. Median PFS and median OS were not reached. In 146 patients for whom response was available after B2 induction according to the Lugano criteria, the bORR was 84.2%, with 69.8% of patients achieving CR and 14.3% PR. The 2y-DOR was 79% (95%CI: 68-86.6%) for patients achieving CR and 50% (95%CI: 21.3-58.1%) for patients achieving PR.

Early PET evaluation findings were available in 117 patients (after 2 cycles for 56 and 3 cycles for 61), and consisted of DS 1-3 in 77 patients (66%), DS 4 in 17 patients (14.5%), and DS 5 in 23 patients (19.6%). Of note, the response achieved at early PET evaluation was the bORR in 94% of these cases. DS was strongly associated with outcomes, with a 2y-PFS of 81.9% for DS 1-3, 52.9% for DS 4 and 25% for DS 5 (*P*<0.001). DS at early PET evaluation was also associated with OS: 2y-OS 95.8% for DS 1-3, 81.9% for DS 4 and 69.6% for DS 5 (*P*=0.027) (*Online Supplementary Figure S3A, B*).

A total of 102 patients were eventually transplanted. Their 2y-PFS and 4y-PFS were 79.9% (95%: 70.3% to 86.7%) and 72.6% (95%: 61.1% to 81.3%), respectively. Their 2y-OS and 4y-OS were 96.8% (95%: 90.4% to 99%) and 95.1% (95%: 87.2% to 98.2%), respectively (Figure 2C, D). Disease status prior to transplantation was available in 99 patients: CR in 89%, PR in 9%, stable disease (SD) in 1% and uncertain in 1%. Among the 48 patients who were eventually not transplanted, the reason for non-transplantation was insufficient response in 25, failure to collect HSC in 7, patient's decision in 6, revision of initial indication due to late relapse in 5, insufficient fitness in 3 and not defined in 2. Of note, failure to collect HSC affected 4.6% of all eligible patients overall, but differed according to the temporality of the harvesting: 2.7% (3/112) when performed immediately prior to B2 initiation, and 22% (4/18) when performed after initiation of the treatment. The median number of harvest attempts was 1, with 18% of patients needing more than one harvest.

Although ATHERA high-risk criteria were met by 90% of transplanted patients, only 25% of them received Bv maintenance. These patients had comparable pre-transplant CR

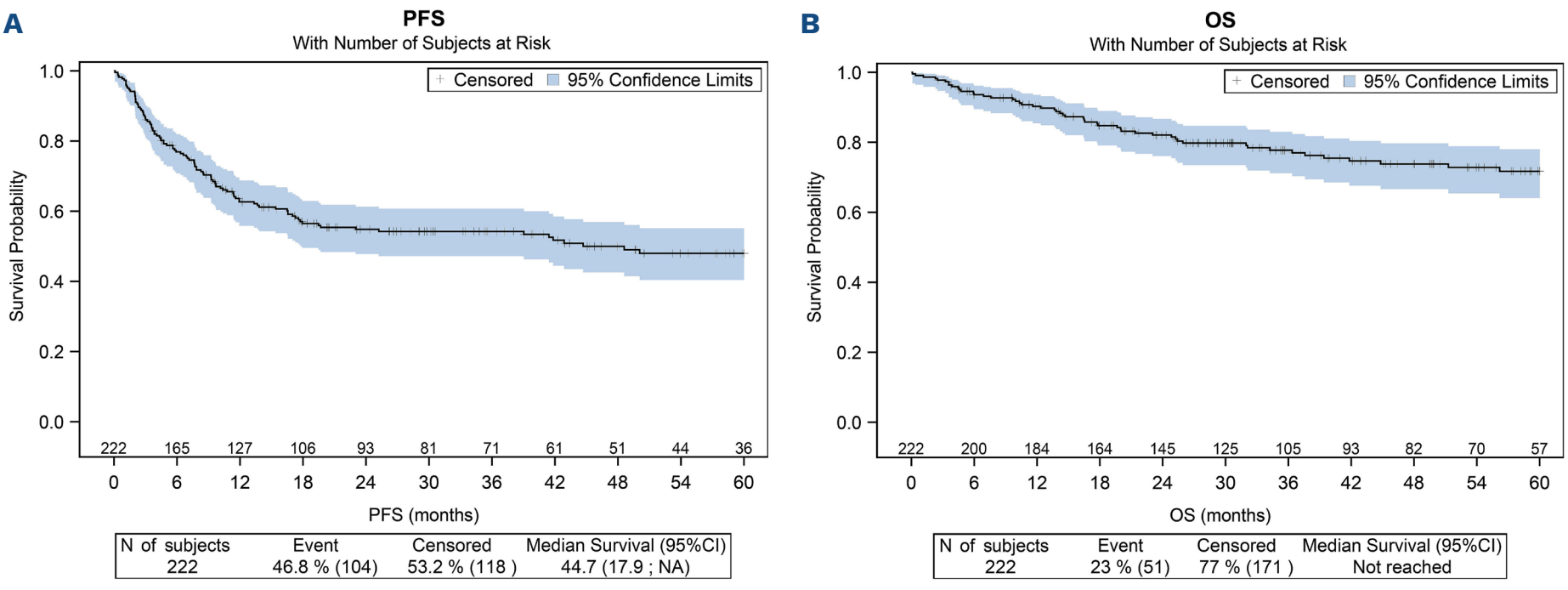


Figure 1. Outcomes of the study population. (A) Progression-free survival (PFS) and (B) overall survival (OS). NA: not assessable.

Table 2. Risk factors for progression-free survival and overall survival in multivariable analysis.

Parameter	Modality	Progression-free survival				Overall survival			
		Univariate		Multivariable		Univariate		Multivariable	
		HR	*P*	HR	*P*	HR	*P*	HR	*P*
ECOG	0-1 2-4	1 2.58 (1.6-4.3)	<0.001	1 2.07 (1.2-3.5)	0.005	1 3.70 (2.0-6.9)	<0.001	1 2.59 (1.4-4.9)	0.003
Ann Arbor stage	I-II III-IV	1 2.82 (1.7-4.6)	<0.001	1 2.37 (1.4-3.9)	<0.001	1 3.89 (1.7-9.1)	0.002	1 3.11 (1.3-7.4)	0.01
Presence of B symptoms	Yes	1.64 (1.1-2.5)	0.020	-	-	1.39 (0.7-2.6)	0.30	-	-
Gender	Female	0.91 (0.6-1.4)	0.63			0.76 (0.4-1.4)	0.36		
N of previous therapy lines	1 2 ≥3	1 0.94 (0.6-1.5) 2.43 (1.4-4.1)	 0.78 0.001	- - -	- - -	1 1.00 (0.5-2.0) 3.03 (1.6-5.9)	 0.99 0.001	- - -	- - -
First-line treatment	ABVD-based BEACOPP-based Other	1 1.17 (0.7-2.0) 1.57 (0.9-2.6)	 0.57 0.088	- - -	- - -	1 0.95 (0.4-2.3) 3.37 (1.8-6.4)	 0.90 <0.001	- - -	- - -
Delay between diagnosis and treatment	Continuous	0.999 (0.99-1.00)	0.83	-	-	1.003 (0.997-1.01)	0.33	-	-
Eligible for transplantation	Yes No	1 1.99 (1.4-2.9)	<0.001	1 1.83 (1.2-2.7)	0.003	1 3.34 (1.9-5.8)	<0.001	1 3.03 (1.7-5.3)	<0.001

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP: escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; ECOG: Eastern Cooperative Oncology Group; HR: Hazard Ratio; N: number.

rates and AETHERA risk factor rates (*P*=0.85 and *P*=0.25, respectively). Median number of maintenance cycles was 10 with 12/25 patients prematurely stopping treatment for adverse events (7 patients) or lack of compliance (5 patients). In an exploratory analysis, there was no difference in terms of PFS between patients who received at least one cycle of maintenance after transplantation and those who did not (*P*=0.61) (*Online Supplementary Figure S4*). Of note, 7 out of 23 patients who did not proceed to ASCT for reasons other than lack of response received off-label Bv maintenance.

Regarding the next therapy of the 25 patients who did not proceed to ASCT due to lack of response, 15 received CPI as standard-of-care salvage (monotherapy in 14) of whom 8 achieved CR and 2 PR. None of these patients proceeded to ASCT. Four patients received polychemotherapy and progressed (including one with DLBCL), 2 patients died without any further treatment, and one patient with false positive PET imaging remained alive without progression. Information was missing for three patients.

Outcomes of patients non-eligible for autologous hemopoietic stem-cell transplantation

After a median follow-up of 42.3 months, the 2y-PFS and 4y-PFS of the 72 non-eligible patients were poor: 35% (95%: 23.7% to 46.5%) and 30.6% (95%: 19.5% to 42.4%), respectively, while 2y-OS and 4y-OS was 66.8% (95%: 54% to 76.8%) and 51.5% (95%: 37.3 to 64%), respectively (Figure 3A, B). This led to a mPFS of 11.9 months and a mOS NR. The bORR according to Lugano classification was 77.2%, with 69.6% of patients achieving CR and 7.5% PR. These rates were not statistically different from those of eligible patients (*P*=0.89), suggesting that the poor outcomes observed in non-eligible patients was driven by a lack of sustained response. Accordingly, the 2y-DOR was only 40.1% (95%: 22.9% to 56.8%) for patients achieving CR as best response. Early PET evaluation findings were available in 45 patients (after 2 cycles in 17 patients and 3 cycles in 28 patients) and consisted of DS 1 – 3 in 31 patients (69%) and DS 4 and DS 5 in 7 patients (15.5%) each. Response achieved at early PET was the bORR in 91% of these cases, DS 1 – 3 being associated with a 2y-PFS of 42.9% while all patients with DS 4 or 5 eventually progressed or died. PFS and OS of non-eligible patients according to early PET evaluation are depicted in *Online Supplementary Figure S5*. Of note, a total of 15 patients received an off-label maintenance with Bv, with a median of 12 administered cycles. Due to the heterogeneity of maintenance starting timepoint and the low number of patients treated, we did not address the clinical benefit of this strategy.

Toxicity of B2 regimen

Adverse events of interest in the study population are shown in Table 3. (Details of transplant-eligible and non-eligible patients are provided in *Online Supplementary Table S3*).

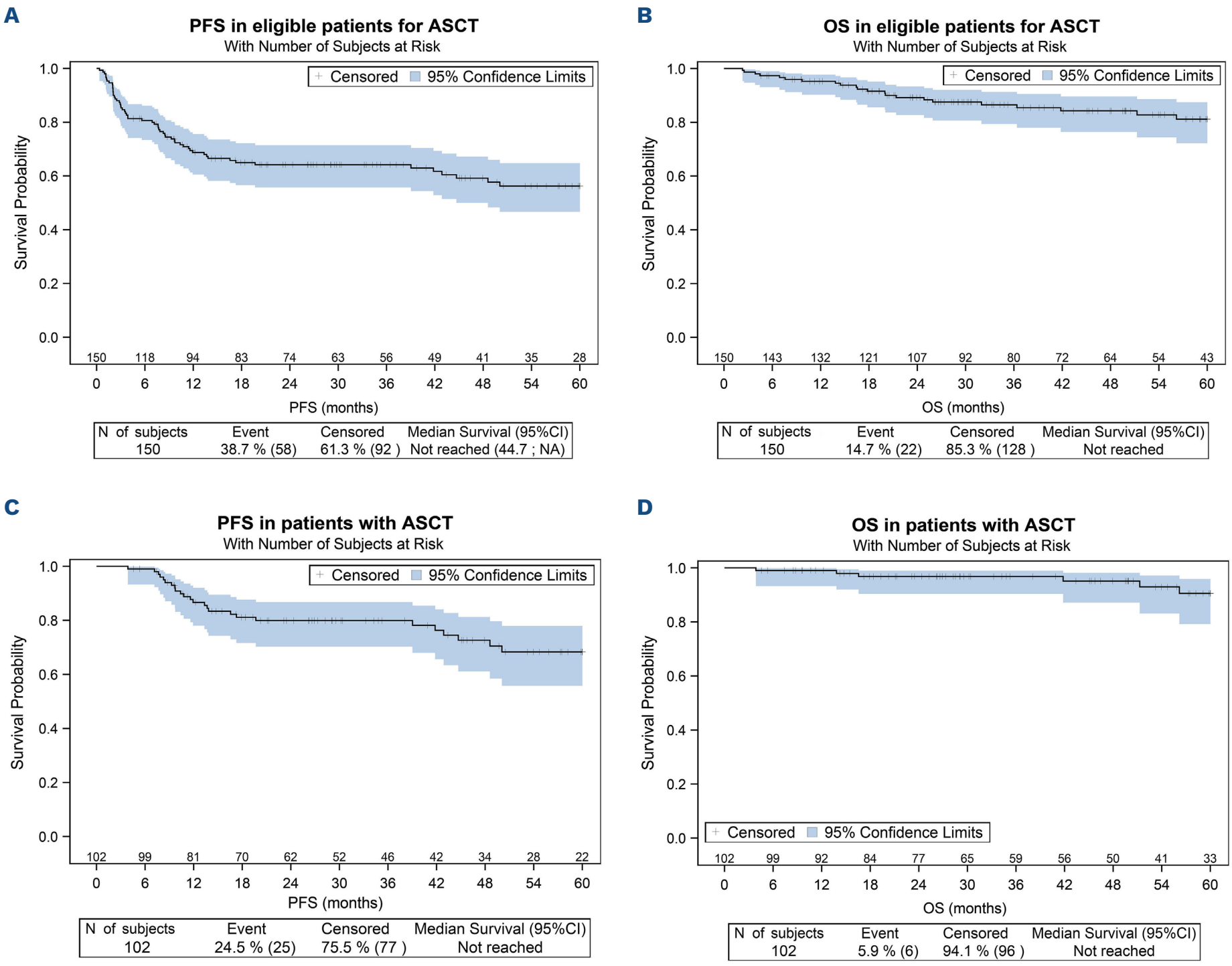


Figure 2. Outcomes of patients eligible for transplantation. (A) Progression-free survival (PFS) and (B) overall survival (OS) of the 150 patients deemed eligible for autologous stem cell transplantation (ASCT) at initiation of brentuximab-vedotin/bendamustine association (B2). (C) PFS and (D) OS of the 102 patients transplanted.

Ninety-four percent of patients remained transfusion-free during the B2 treatment period, with 5.4% and 4.5% of patients requiring at least one red blood cell or platelet transfusion, respectively. Grade ≥2 infectious events (including febrile neutropenia) affected 20.3% of patients, consisting of 7.7% grade 2, 9% grade 3, 1% grade 4, and 2.7% grade 5 (fatal) events. Fatal infectious events consisted of 4 septic shocks (3 in patients >65 years of age, and one in a heavily pre-treated patient) and one progressive multifocal leukoencephalopathy (PML) in a patient living with HIV (PLWH) with undetectable T CD4⁺ level. Interestingly, in 2 patients without HIV, there was one grade 3 cytomegalovirus (CMV) hepatitis and one grade 3 pneumocystis pneumonia (the latter not receiving pneumocystis prophylaxis). Grade ≥2 cutaneous events and grade ≥2 infusion-related reactions affected 14% and 15% of patients, respectively. Overall, all non-hematologic severe AE (grade ≥3) affected 23.9% of patients. For bendamustine, dose adaptation was required in 15.3% and treatment was prematurely discontinued in 13.5%. For Bv, dose adaptation was required in 9% and treatment was discontinued for toxicity in 7.2%. Only 3.8% of patients required bendamustine dose adaptation due to hematologic toxicity. Thirty-six percent of bendamustine dose reduction or discontinuation and 14% of Bv dose reduction or discontinuation were linked to infusion-related reactions (anaphylactic-like or toxidermic-like reactions) occurring at a median cycle of 2. The reasons for therapy reduction or discontinuation are provided in *Online Supplementary Table S4*. Nevertheless, B2 regimen was fully and exclusively delivered as an outpatient treatment in 80% of cases. In multivariable analysis, the only risk factor for severe AE was age at treatment initiation (*Online Supplementary Table S5*).

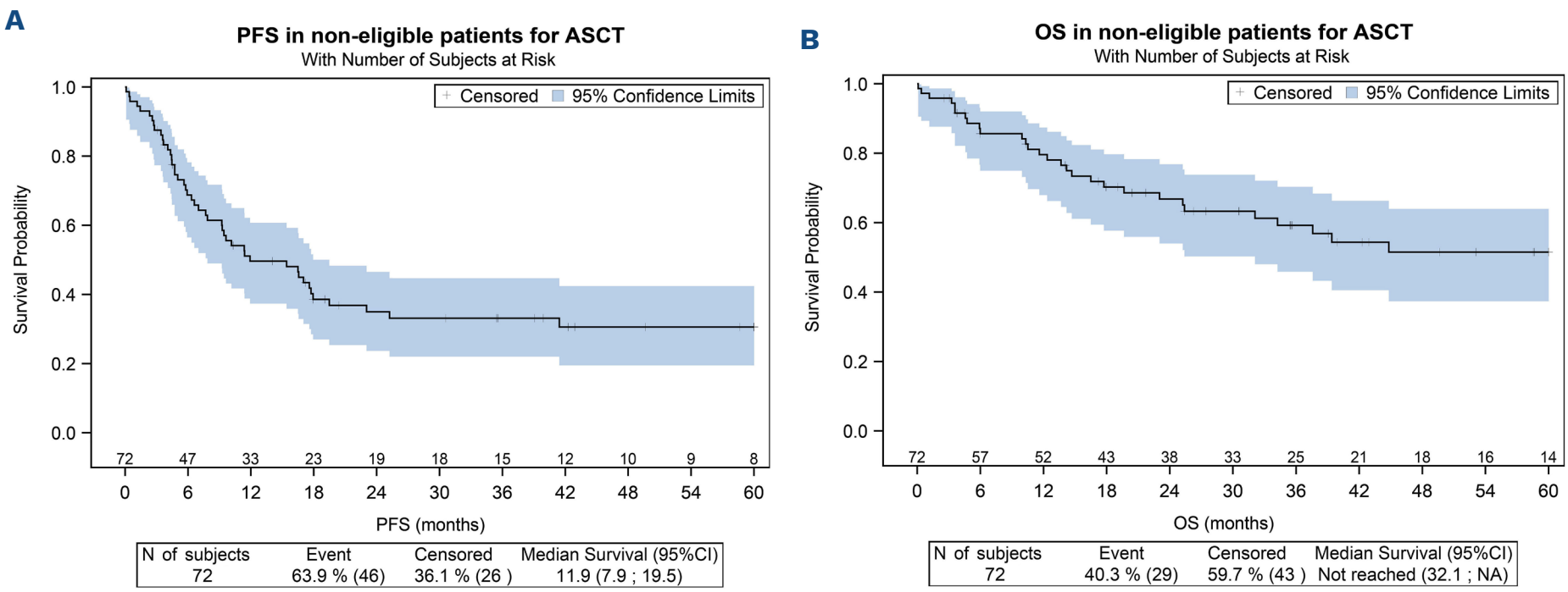


Figure 3. Outcomes of patients non-eligible for autologous stem cell transplantation at initiation of brentuximab-vedotin/bendamustine association. (A) Progression-free survival (PFS) and (B) overall survival (OS) of patients deemed non-eligible for autologous stem cell transplantation (ASCT) at initiation of brentuximab-vedotin/bendamustine association (B2).

Regarding PN, all grade events affected 19.4% of patients, consisting of grade 1, grade 2, and grade 3 in 10.8%, 6.3%, and 2.3% of patients, respectively. Grade 1 PN resolved in 15 out of 20 cases and were stable in 5; grade 2 PN resolved in 7 out of 14 cases, was down-graded in 3 cases and were stable in 4 cases; grade 3 PN resolved in 2 out of 5 cases, was down-graded to grade 1 in 2 cases, and was stable in one patient who died one year after completion of treatment. Data regarding disease evolution were missing for 4 patients. The median time to best downgrade or resolution was 14 months. In multivariable analysis, the only factor associated with occurrence of PN grade ≥2 was the total number of Bv cycles administered (*Online Supplementary Table S6*). Notably, 83% (15/18) of PN grade ≥2 events affected patients who received ≥6 cycles of Bv.

Regarding secondary malignancies, the rate of SPM was 7.2% leading to an overall 4-year cumulative incidence of 8.8% (Figure 4A). Details of SPM are shown in *Online Sup-*

Table 3. Adverse events of interest in the entire study cohort.

Adverse events	N=222
All transfusions, N (%)	
No	208 (93.6)
Yes	14 (6.4)
Red blood cell	12 (5.4)
Platelets	10 (4.5)
All non-hematologic toxicity grade ≥3, N (%)	
No	169 (76.1)
Yes	53 (23.9)
Infections ≥ grade 2, N (%)	
No	177 (79.7)
Yes	45 (20.3)
Grade 2	17 (7.7)
Grade 3	20 (9.0)
Grade 4	2 (0.9)
Grade 5	6 (2.7)
Peripheral neuropathy, N (%)	
No	179 (80.6)
Yes	53 (19.4)
Grade 1	24 (10.8)
Grade 2	14 (6.3)
Grade 3	5 (2.3)
Digestive toxicity ≥ grade 2, N (%)	
No	186 (83.8)
Yes	36 (16.2)
Grade 2	26 (11.7)
Grade 3	10 (4.5)
Skin toxicity ≥ grade 2, N (%)	
No	191 (86.1)
Yes	31 (13.9
Grade 2	12 (5.4)
Grade 3	19 (8.6)
Perfusion reactions ≥ grade 2, N (%)	
No	173 (77.9)
Yes	49 (15)
Grade 2	21 (9.5)
Grade 3	11 (5.0)
Grade 4	1 (0.5)
N of days of hospitalization	
Median (IQR)	0 (0-0)

IQR: interquartile range; N: number.

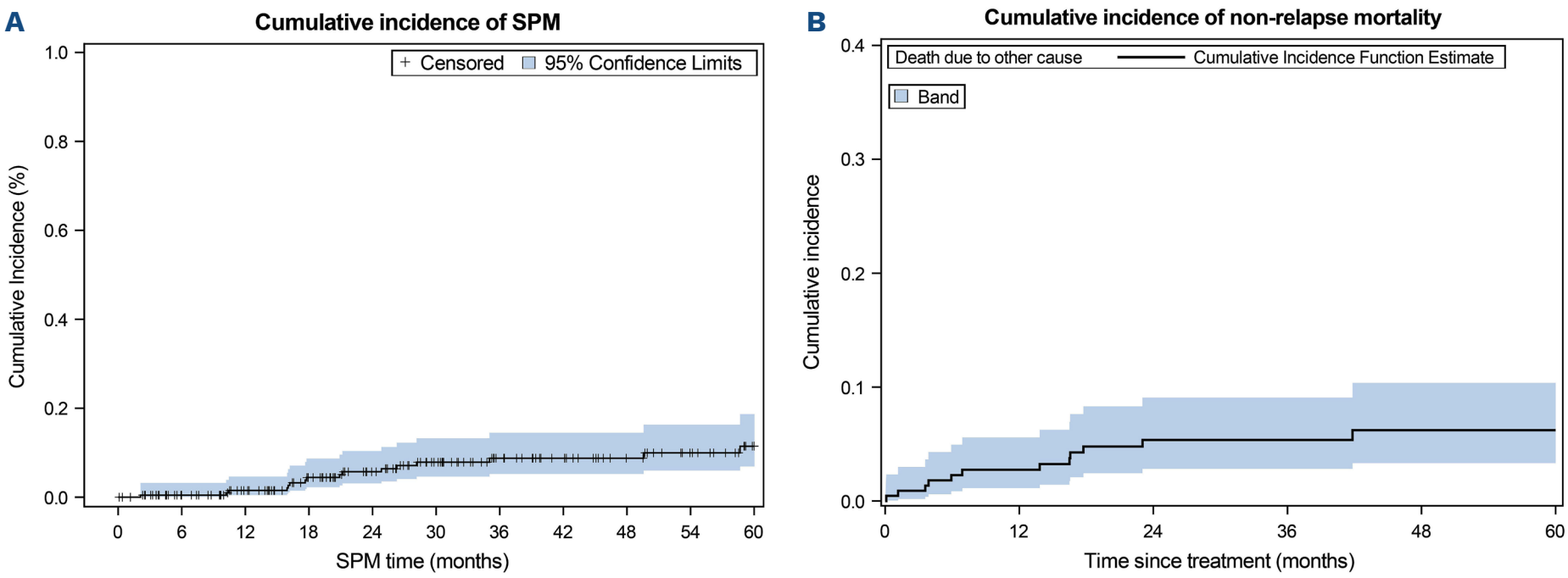


Figure 4. Cumulative incidence of second primary malignancies and non-relapse mortality in the study population. (A) Cumulative incidence of second primary malignancies (SPM). (B) Cumulative incidence of non-relapse mortality.

plementary Table S7. SMN occurred in 4 patients (1.8%, 3 myelodysplastic syndrome and one acute myeloid leukemia): 3 were >70 years of age and another had received 11 previous lines of therapy. Of note, the 4-year cumulative incidence of SPM in transplanted patients was 5.4%, without any SMN.

Finally, the NRM was evaluated at 4.2% at 2 years and 5.2% at 5 years (Figure 4B), but was significantly higher in non-eligible patients (Hazard Ratio = 4.1 [95%CI:1.3-12], *P*=0.0136).

Discussion

Relapsed and refractory HL remains an unmet medical need for which strong evidence is still scarce. To our knowledge, this cohort is the largest to date focusing on a single Bv-based regimen in R/R HL. This enabled us to address pivotal questions such as the efficacy of this regimen in the real-world setting (overcoming the possible selection bias affecting phase II trials), its efficacy in specific subsets of patients, and its main toxicity patterns. Overall, B2 produces high rates of CR (69.8%) despite a high rate of clinical risk factors (with roughly 40% of patients being in 3rd line treatment or more, and with approx. 90% of them carrying AETHERA risk factors). Patients eligible for ASCT experienced a 2y-PFS of 64.2%; this falls within the range of reports from phase II trials (62.6-63.7% for B2, 73.5% for Bv-DHAP, 64.3-80.4% for Bv-ICE)[13-17] and the 2y-PFS of transplanted patients was high at 79.9%. On the contrary, patients who did not reach CR at early PET evaluation experienced poor outcomes. It is noteworthy that these excellent results have been achieved while Bv maintenance was only performed in a minority of cases (25%). The infrequent use of maintenance in our cohort was mainly related to the fact that some clinicians considered it to be of uncertain benefit to patients pre-exposed to BV (an exclusion criterion in the AETHERA trial). Even though this explanatory comparison lacked power and is only hypothesis-generating, we did not observe any signal favoring Bv maintenance in our cohort suggesting that maintenance strategies could be tailored to the individual patient's risk to reduce treatment burden and unnecessary use of healthcare resources. Taken together, these data suggest that B2 is an attractive Bv-based pre-transplant salvage regimen for patients with R/R HL. Conversely this study highlights the unfavorable outcomes achieved in patients unfit for transplantation. Older patients are markedly under-represented in the current literature of HL but their prognosis in second or more advanced lines seems dismal.[32] Despite impressive CR rates for this population (similar to those of transplant-eligible patients), very few patients in our cohort sustained response after the B2 regimen. This pattern of treatment failure is noteworthy and may suggest that there is room for off-label maintenance strategies used as "ASCT replacement" in this subset of patients in order to prolong response; however, this consideration would warrant further dedicated studies. Enhancing the rate of sustained response in elderly and/or frail R/R patients should be a research priority, with limited progress achieved to date. More studies in this area are urgently needed.

In terms of toxicities, the B2 regimen was overall well tolerated and easily administered with only 20% of patients requiring hospitalization (outside of the ASCT procedure). Acute hematologic toxicities appeared to be very low with very few transfusion requirements and a very low rate of dose adaptation due to cytopenia. Failure to collect stem cells is a common concern associated with the use of bendamustine, and indeed, we observed a high rate of failure when collection was attempted during treatment, while pre-treatment collection was largely successful (97.3%) and should be strongly encouraged in this context. Severe

infectious events were infrequent but some cases of fatal events in frail or heavily pre-treated patients must be acknowledged. We did not observe a major outbreak of opportunistic infections (another concern associated with the use of bendamustine, a strongly lymphodepletive agent[33]) with only 3 events reported, but the severity of these events clearly warrants special attention in case of severe pre-existing immunodepression. The PN rate was also relatively low (20% of all grade events and 2.3% of grade 3 events) and compares favorably with those reported after BV use in the R/R setting[12,34] or even in the first-line setting.[35] This might be due to the short Bv exposure in our cohort (median 4 cycles), as well as the absence of neurotoxicity of bendamustine. Finally, the incidence of SPM appeared to be moderate especially in transplanted patients for which the cumulative incidence rate at four years was around 5% without any SMN; cumulative 5-year incidence of 10% and 3%, respectively, was reported in patients transplanted for lymphoma.[36] These data are reassuring and suggest that the B2 regimen, especially when few cycles are planned, can be safely administered to young patients.

It is essential to acknowledge that the recent shift in front-line HL therapy might impact the applicability of our findings, both in transplant-eligible and -ineligible patients. A majority of upcoming patients with R/R HL will present with prior exposure to Bv or CPI (following BRECADD and N-AVD regimen, respectively), with potentially worse outcomes and personalized therapeutic needs which cannot be represented in our cohort which is mostly composed of Bv-naïve and CPI-naïve patients. This said, the outstanding survival rates achieved with these modern first-line regimens might reduce the feasibility and attractivity of clinical trials dedicated to R/R disease in the near future, translating into modest changes in salvage strategies.[37] Good quality evidence is lacking and will become even more challenging to generate, yet Bv-based regimen may remain a key option for salvage therapy for patients who are Bv-naïve at relapse following the new standard N-AVD regimen. Continuous efforts to provide large-scale studies depicting efficacy and toxicities of these regimen are still needed. By demonstrating that the B2 regimen achieves real-life outcomes comparable to those reported in clinical trials conducted in a similar therapeutical background, our data consolidate a place in the current landscape of salvage therapies while informing on important unmet needs that remain to be addressed. On the other hand, CPI-based salvage regimens are associated with very high response rates and post-ASCT survivals[25,38,39] and might be preferred for R/R patients who are CPI-naïve after front-line therapy.

In conclusion, this study is the largest to date reporting the efficacy and toxicity of a single Bv-based salvage regimen in R/R HL and confirms B2 as a safe, effective, and convenient outpatient treatment option for patients eligible for transplantation. Improving the duration of response and cure rates of patients unfit for transplantation should be an ongoing research priority.

Disclosures

JG reports honoraria and travel expenses from Takeda and Gilead. KB reports honoraria, travel expenses, and consultancy for Takeda. KL reports honoraria and travel expenses from Takeda, Jansen, Abbvie, Novartis, and Pfizer. SB reports honoraria from Abbvie, Kite, and Roche. SD reports honoraria from Takeda, Abbvie, and Johnson & Johnson Innovative Medicine. GD reports honoraria from Takeda and Amgen; travel support from Takeda; and research support from Takeda and Ideogen. All the other authors have no conflict of interests to disclose.

Contributions

KB is responsible for study concept and design, data analysis and interpretation, and wrote the manuscript. JG is responsible for study concept and design, collected, assembled, analyzed and interpreted the data, and wrote the manuscript. AN, DM, BD, SD, RN, ED, AC, GL and KL collected and assembled the data. LC is responsible for data analysis and interpretation. GB collected, assembled, analyzed and interpreted the data, and wrote the manuscript. All authors are accountable for all aspects of the work, provided study material or patients, and approved the final manuscript for publication.

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Data-sharing statement

Data are subject to controlled access by Centre Hospitalier Universitaire de Bordeaux owing to privacy and legal requirements and proprietary reasons. Requests for anonymized IPD will be reviewed by the corresponding author.

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