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

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Data sharing statement

Data are subject to controlled access by Centre Universitaire de Bordeaux owing to privacy and legal requirements and proprietary reasons. Anonymized IPD requests will be reviewed by the corresponding author (JG).

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KEYPOINTS

- In this large high-risk cohort of R/R HL, B2 regimen produces high rate of remission leading to excellent outcomes in transplanted patients
- Patients unfit for transplantation exhibit unsatisfactory survivals that should prompt novel adapted strategies

ABSTRACT :

Classical Hodgkin lymphoma (HL) is often cured after modern first line regimen but relapsed or refractory (R/R) diseases remain a therapeutical challenge that has been addressed by little randomized clinical trials. Several combinations of brentuximab-vedotin (Bv) with chemotherapy have been reported in R/R HL so far, yet neither randomized clinical trials nor large scale real world evidence exist 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 during 10 years, we showed 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 in which transplantation was successfully performed, despite an infrequent use of Bv maintenance. Conversely and despite a CR rate of 69.6%, patients ineligible for transplantation faced poor outcomes with a 2y-PFS of 35%. B2 regimen was associated with low hematological toxicities and of neuropathy rates, and was administered as an outpatient treatment in 80% of cases. Considering the fact that Bv combinations might remain important therapy options for R/R diseases, notably after frontline regimen containing checkpoint inhibitors, these results support 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 improve patients' outcomes and allowed to establish strong, widely recognized evidence-based therapy guidelines. Despite significant improvements driven by the incorporation of innovative agents within historical polychemotherapy regimen, only few RCTs have been dedicated to relapsed and refractory (R/R) HL. This led to highly variable practices across countries and centers, and to a notable absence of a recognized standard of care.

Treatment paradigm for young and fit patients historically consisted of multi-agent salvage therapy followed by HDC and ASCT in case of response[5–9], allowing to cure less than 50% of cases 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 administrated as maintenance after autologous stem cell transplantation (ASCT) in the only RCT including R/R HL over the last 10 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 ≈ 60 – 80% and a sustained remission rate of ≈ 60 – 80%. These favorable results led the Bv-based regimen to be integrated by several collaborative groups within 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 of very small sample size[22–24]. Therefore, clinician choices are likely to be driven by clinical habits or extrapolation from non-Hodgkin lymphoma evidence. Besides, few phase II trials reported the impressive efficacy of checkpoint inhibitors (CPI) associated with chemotherapy as fist

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 under-pictured and yet decisive issue has evolved with the paradigm shift that recently affected the frontline setting of HL. The outstanding results of the HD21[27] and SWOG1826[28] trials have set Bv or nivolumab, respectively, as legitimate parts of frontline regimen, leading to novel and personalized needs for the minority of patients eventually progressing. Defining the best second-line regimen to combine with Bv, especially in patients who did not receive it as part of their frontline therapy, thus remains a major point 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 underrepresented 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 sought 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 toxicities patterns associated with this regimen in the real-life setting.

Methods

Data source

French centers within the LYSA (Lymphoma Study Association) 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 Ethic 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 90mg/m^2 D1 and D2, 21-day cycle with Bv (1.8mg/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[30] and the selection bias that commonly affect consolidative therapy in retrospective studies, we allocated ASCT eligibility according to an initial intent of treatment approach. Since the Plan Cancer 2006, all cancer therapy-decisions in France have to be taken by a certified, multidisciplinary board. A patient considered eligible for ASCT at the time of B2 therapy-decision and before the start of the salvage was identified as such in this study, whether or not he was eventually denied for ASCT due to treatment toxicity, personal or physician choice, or any other reason. Age, absence of heavy 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, whether or not 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 (2021).

Outcomes

The primary objective was to report the 2 years (2y) PFS of the study population. Other objectives included the evaluation of 4years (4y)PFS, 2y and 4y overall survival (OS), best overall response rate (bORR) and duration of response (DOR). The bORR (best CR and best PR) was the best response recorded after completion of induction with B2 regimen (and before ASCT if performed) according to Lugano classification[31]. We also described PFS, OS and bORR separately in patients according to their eligibility or not to 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 could not assure 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 to this toxicity in daily practice. Finally, non-relapse mortality (NRM) was reported. Grade was reported according to CTCAE v5.

Statistical analysis

The follow-up duration was 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 for 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 value of less than 0.05 was considered significant. Prognostic factors for PFS were estimated using proportional hazard Cox model. Covariates with univariate p values < 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 were included across 10 French centers from 2014 to 2024. Among them, 150 were considered eligible for ASCT at B2 initiation and 72 were not. Clinical characteristics of the overall population are displayed in **Table 1**. Briefly, the 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. The median number of previous lines was 1, 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 other regimen, mostly anthracycline therapies (see details in **supplemental table 1**). Thirteen patients (6%, all unfit for transplantation) received prednisone, vinblastine, doxorubicin and bendamustine (PVAB regimen) at frontline[32]. 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 was 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 **supplemental figure 1**.

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% to 61.3%) and 50% (95%CI 42.6% to 56.9%), respectively, while 2y-OS and 4y-OS were 82.1% (95%CI 76.1% to 86.7%) and 73.8% (95%CI 66.6% to 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 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% to 77.2%) for patients achieving CR and 40% (95%CI 21.3% to 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 **(Supplemental table 2**).

A total of 91 patients experienced progression or relapse after B2. Their 2y-OS2 and 4y-OS2 were 62.9% (95%CI 51.5% to 72.4%) and 49.6% (95%CI 37% to 61%), respectively, and were not significantly impacted by the period of relapse (2014 – 2017 vs 2018 – 2024, p = 0.66 ; **supplemental figure 2**).

Outcomes of patients eligible for ASCT

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% to 72.2%) and 59.2% (95%CI 50% to 67.2%), respectively (**figure 2A and 2B**), while 2y OS and 4y OS were 89.2% (95%CI 82.7% to 93.4%) and 84.3% (95%CI 76.5% to 89.6%) respectively. Median PFS and median OS were not reached. In 146 patients for whom response was available after B2 induction according to 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% to 86.6%) for patients achieving CR and 50% (95%CI 21.3% to 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 ($p = 0.027$, **supplemental figure 3A and 3B**).

A total of 102 patients were eventually transplanted. Their 2y-PFS and 4y-PFS were 79.9% (95%CI 70.3% to 86.7%) and 72.6% (95%CI 61.1% to 81.3%), respectively. Their 2y-OS and 4y-OS were 96.8% (95%CI 90.4% to 99%) and 95.1% (95%CI 87.2% to 98.2%), respectively (**Figure 2C and 2D**). Disease status prior to transplantation was available in 99 patients : CR in 89%, PR in 9%, 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 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 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 were no difference in terms of PFS between patients who received at least one cycle of maintenance after transplantation and those who did not ($p = 0.61$, **supplemental figure 4)**. Of note, 7 out of 23 patients who did not proceed to ASCT for reason 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 ASCT

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%CI 23.7% to 46.5%) and 30.6% (95%CI 19.5% to 42.4%), respectively, while 2y-OS and 4y-OS was 66.8% (95%CI 54% to 76.8%) and 51.5% (95%CI 37.3 to 64%), respectively (**figure 3A and 3B**). 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%CI 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 **supplemental figure 5**. Of note, a total of 15 patients received an off-label maintenance with Bv, with a median number of administered cycles of 12. 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

AEs of interest in the study population are shown in **Table 3** (details for transplant-eligible and non-eligible patients are displayed in **Supplemental Table 3**). Ninety-four per cent 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 older than 65 years, 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. Of interest were also one grade 3 CMV hepatitis and one grade 3 pneumocystis pneumonia in two patients without HIV (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-hematological 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 hematological 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. A description of reason for therapy reduction or discontinuation is given in **supplemental table 4**. 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 (**supplemental table 5**).

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, downgraded in 3 cases and were stable in 4 cases ; grade 3 PN resolved in 2 out of 5 cases, downgraded to grade 1 in 2 cases, and was stable in one patient who died one year after completion of treatment. Data regarding 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 (**supplemental table 6)**. 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 **Supplemental Table 7**. SMN occurred in 4 patients (1.8%, 3 myelodysplastic syndrome and one acute myeloid leukemia) : 3 were older than 70 years and another 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 non-relapse mortality was evaluated at 4.2% at 2 years and 5.2% at 5 years (**Figure 4B**), but was significantly higher in non-eligible patients (HR = 4.1 [95%CI:1.3-12], p=0.0136).

DISCUSSION

R/R HL remains a medical need to address 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 possible selection bias affecting phase II trials), its efficacy in specific subsets of patients, and its main toxicity patterns. Overall, B2 produces high rate of CR (69.8%) despite a high rate of clinical risk factors (with roughly 40% of patients being in 3rd line or more, and with ≈ 90% of them carrying AETHERA risk factors). Patients eligible for ASCT experienced a 2y-PFS of 64.2% falling within the range of what has been reported in 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 very 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 clinician considered its benefit as uncertain in 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 individual's risk to reduce treatment burden and unnecessary healthcare resources consumption. Taken together, this 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[33]. Despite impressive CR rates for this population, similar to those of transplant eligible patients, sustained response after B2 regimen remained infrequent in our cohort. This pattern of treatment failure is noteworthy and may suggest that a room exists for off-label maintenance strategies used as "ASCT replacement" in this subset of patients in order to prolong response – but this point 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 progresses achieved to date. More studies in this area are urgently needed.

In term of toxicities, B2 regimen was overall well tolerated and easily administered with only 20% of patients requiring hospitalization (outside of ASCT procedure). Acute hematological 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 we indeed observed a high rate of failure when 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[34]) 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[12,35] or even in the first-line setting[36] . This might be due to the short Bv exposure in our cohort (4 cycle median), 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 4 years was around 5% without any SMN – cumulative 5 years incidence of 10% and 3%, respectively, being reported in patients transplanted for lymphoma[37]. These data are reassuring and suggest that B2 regimen, especially when few cycles are planned, can be safely administered in young patients.

It is essential to acknowledge that the shift that recently affected the frontline therapy of HL 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 exposition 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 mostly composed of Bv-naive and CPI-naive patients. This said, the outstanding survivals achieved with these modern first line regimen 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[38]. Good quality evidence are lacking and will become even more challenging to generate, yet Bv-based regimen may remain key options of salvage therapy for patients being Bv-naive 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 B2 regimen achieves real-life outcomes comparable to those reported in clinical trials conducted in a similar therapeutical background, our data consolidate its place in the current landscape of salvage therapies while informing on important unmet needs that still have to be addressed. On another hand, CPI-based salvage regimen are associated with very high response rates and post-ASCT survivals[25,39,40] and may be preferred for R/R patients being CPI-naive after frontline 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 a current research priority.

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Table 1 : characteristics of the study population

	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)
≤ 60y	159 (71.6%)	137 (91.3%)	22 (30.6%)
> 60y	63 (28.4%)	13 (8.7%)	50 (69.4%)
Gender			
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	133 (59.9%)	94 (62.7%)	39 (54.2%)
2	62 (27.9%)	44 (29.3%)	18 (25.0%)
≥ 3	27 (12.2%)	12 (8.0%)	15 (20.8%)
Previous ASCT			
Yes	21 (9.5%)	1 (0.1%)	20 (27.8%)
No	201 (90.5%)	149 (99.9%)	52 (72.2%)
Previous Bv exposure			
Yes	23 (10.3%)	11 (7.3%)	12 (16.7%)
No	197 (88.7%)	139 (92.7%)	58 (80.5%)
NK	2	0	2
Previous Bendamustine exposure			
Yes	13 (6%)	0	13 (18%)
No	209 (94%)	222 (100%)	59 (82%)
Previous CPI exposure			
Yes	9 (4%)	3 (2%)	6 (8.3 %)
No	213 (96%)	147 (98%)	66 (91.7%)
First line treatment			
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%)
NK	24	14	10
Delay between initial diagnosis and B2 initiation			
Median (ranges), months	13.5 (0 - 253)	11.9 (0 – 253)	17.7 (0.6 - 199)
Disease status at B2 initiation			
Refractory	135 (60.8%)	99 (66.0%)	36 (50%)
Relapse	87 (39.2%)	51 (34.0%)	36 (50%)
Early relapse (< 1y)	33 (14.8%)	22 (14.6%)	11 (15.2%)

Late relapse (≥ 1y)	49 (22%)	28 (18.6%)	21 (29.1%)
NK	5	1	4
ECOG at B2 initation			
0-1	186 (83.8%)	129 (86.0%)	57 (79.2%)
2-4	25 (11.3%)	13 (8.7%)	12 (16.7%)
NK	11	8	3
B symptoms at B2 initiation			
Yes	55 (24.8%)	35 (23.3%)	20 (27.8%)
No	163 (74.4%)	112 (74.7%)	51 (70.8%)
NK	4	3	1
Ann Arbor stage at B2 initiation			
I-II	78 (35.1%)	57 (38.0)	21 (29.2%)
III-IV	144 (64.9%)	93 (62.0%)	51 (70.8%)
Number of cycles			
Bendamustine, median (ranges)	4 (1 – 7)	4 (1 – 6)	4 (1 – 7)
Bv, median (ranges)	4 (1 – 22)	4 (1 – 22)	6 (1 – 18)
B2 combination, median (ranges)	4 (1 – 7)	4 (1 – 6)	4 (1 – 7)
Bv maintenance administered			
Yes	47 (21%)	32 (21%)	15 (20%)
No	175 (79%)	118 (79%)	57 (80%)

Data are presented as No. (%) unless otherwise indicated.

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; NK: not known

Table 2 : risk factors for PFS and OS in multivariable analysis

		Progression-free survival				Overall survival			
		Univariate		Multivariable		Univariate		Multivariable	
Parameter	**Modality**	HR	P-value	HR	P-value	HR	P-value	HR	P-value
ECOG	0 - 1	1		1		1		1	
	2 – 4	2.58 (1.6-4.3)	<0.001	2.07 (1.2-3.5)	0.005	3.70 (2.0-6.9)	<0.001	2.59 (1.4-4.9)	0.003
Ann Arbor stage	I - II	1		1		1		1	
	III - IV	2.82 (1.7-4.6)	<0.001	2.37 (1.4-3.9)	<0.001	3.89 (1.7-9.1)	0.002	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		
Number of previous lines	1	1				1			
	2	0.94 (0.6-1.5)	0.78			1.00 (0.5-2.0)	0.99		
	≥ 3	2.43 (1.4-4.1)	0.001			3.03 (1.6-5.9)	0.001		
First line treatment	ABVD-based	1				1			
	BEACOPP-based	1.17 (0.7-2.0)	0.57			0.95 (0.4-2.3)	0.90		
	Other	1.57 (0.9-2.6)	0.088			3.37 (1.8-6.4)	<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	1		1		1		1	
	No	1.99 (1.4-2.9)	<0.001	1.83 (1.2-2.7)	0.003	3.34 (1.9-5.8)	<0.001	3.03 (1.7-5.3)	<0.001

Table 3: Adverse events of interest in the study cohort

	All (n = 222)
All transfusion	
No	208 (93.6%)
Yes	14 (6.4%)
Red blood cell	12 (5.4%)
Platelets	10 (4.5%)
All non-hematological toxicity grade ≥ 3	
No	169 (76.1%)
Yes	53 (23.9%)
Infections (≥ grade 2)	
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	
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)	
No	186 (83.8%)
Yes	36 (16.2%)
Grade 2	26 (11.7%)
Grade 3	10 (4.5%)
Skin toxicity (≥ grade 2)	
No	191 (86.1%)
Yes	31 (13.9%)
Grade 2	12 (5.4%)
Grade 3	19 (8.6%)
Perfusion reactions (≥ grade 2)	
No	173 (77.9%)
Yes	49 (15%)
Grade 2	21 (9.5%)
Grade 3	11 (5.0%)
Grade 4	1 (0.5%)
Number of days of hospitalization	
Median (IQR)	0 (0-0)

IQR : interquartile range

LEGENDS OF THE FIGURES :

Figure 1 : Outcomes of the study population. **A.** Progression-free survival and **B.** overall survival.

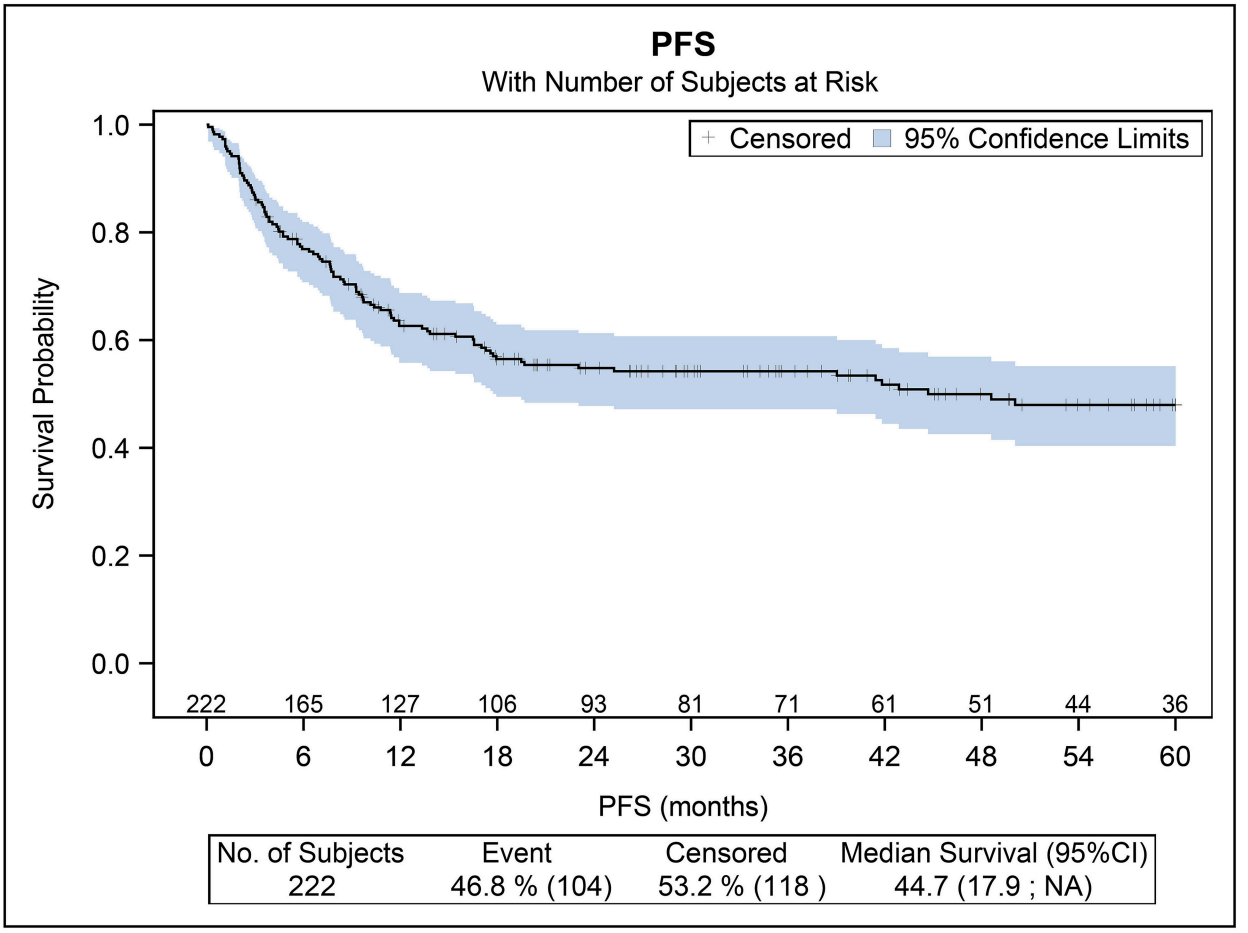
Figure 2 : Outcomes of patients eligible for transplantation. **A**. Progression-free survival and **B.** overall survival of the 150 patients deemed eligible for ASCT at B2 initiation. **C.** Progression-free survival and **D.** overall survival of the 102 patients transplanted.

Figure 3 : Outcomes of patients non-eligible for ASCT at B2 initiation**. A.** Progression-free survival and **B**. overall survival of patients deemed non-eligible for ASCT at B2 initiation.

Figure 4 : Cumulative incidence of second primary malignancies and non-relapse mortality in the study population. **A.** Cumulative incidence of second primary malignancies. **B.** cumulative incidence of non-relapse mortality .

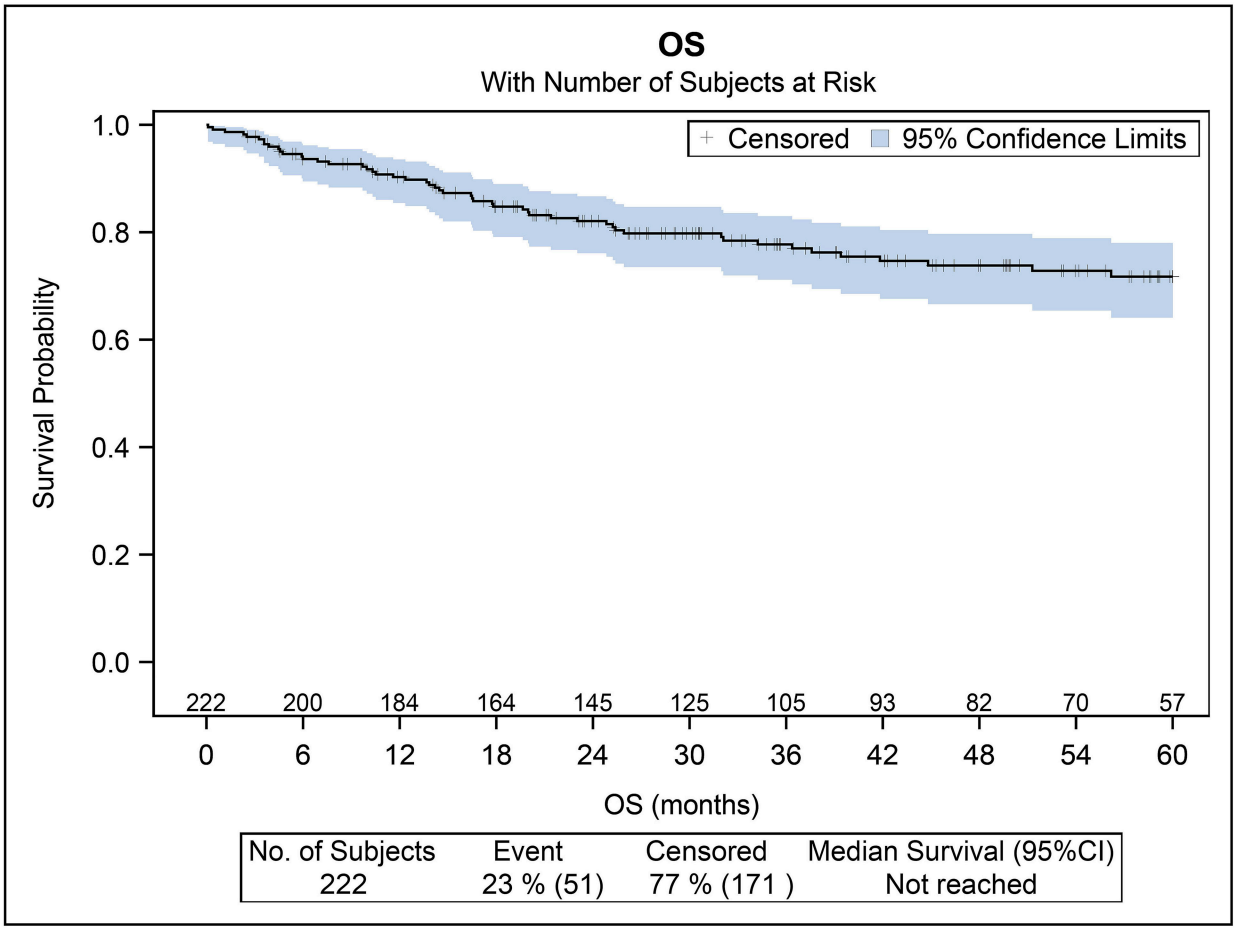
SPM : second primary malignancies

A



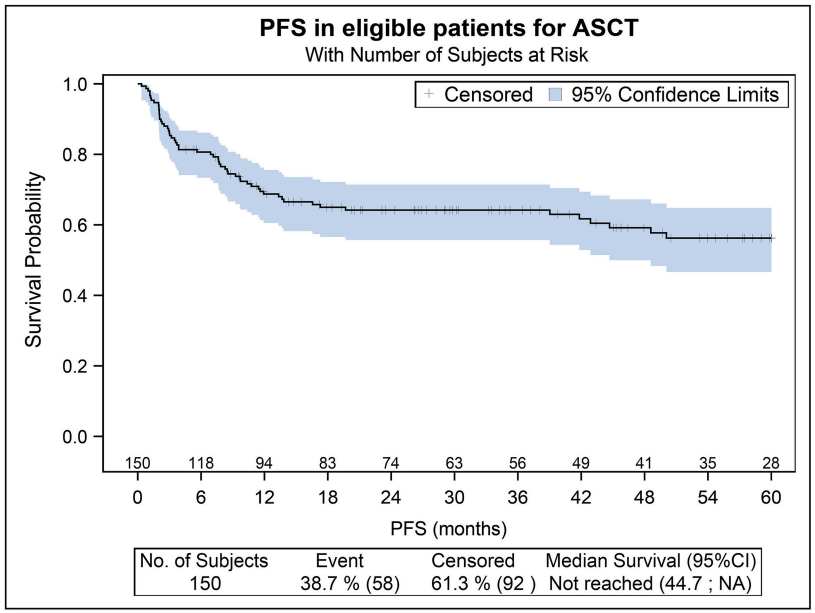
No. of Subjects	Event	Censored	Median Survival (95%CI)
222	46.8 % (104)	53.2 % (118)	44.7 (17.9 ; NA)

B

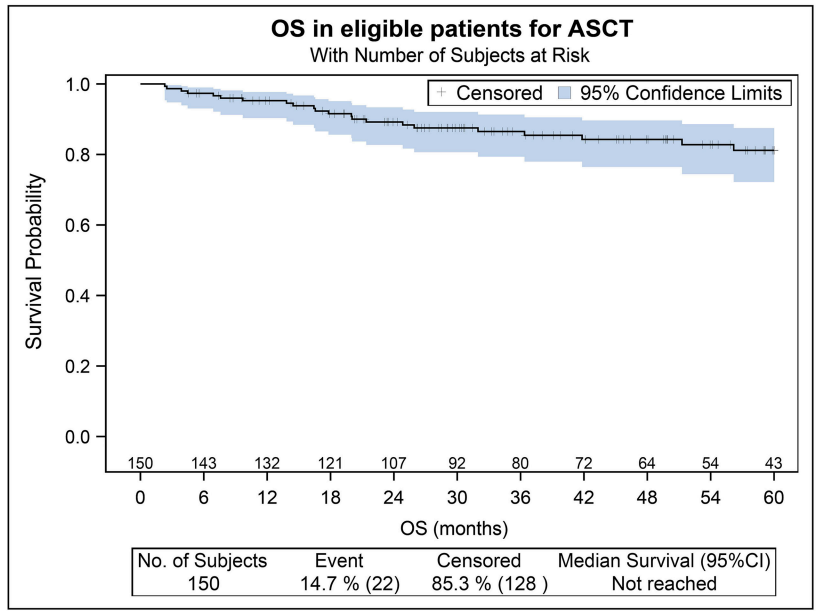


No. of Subjects	Event	Censored	Median Survival (95%CI)
222	23 % (51)	77 % (171)	Not reached

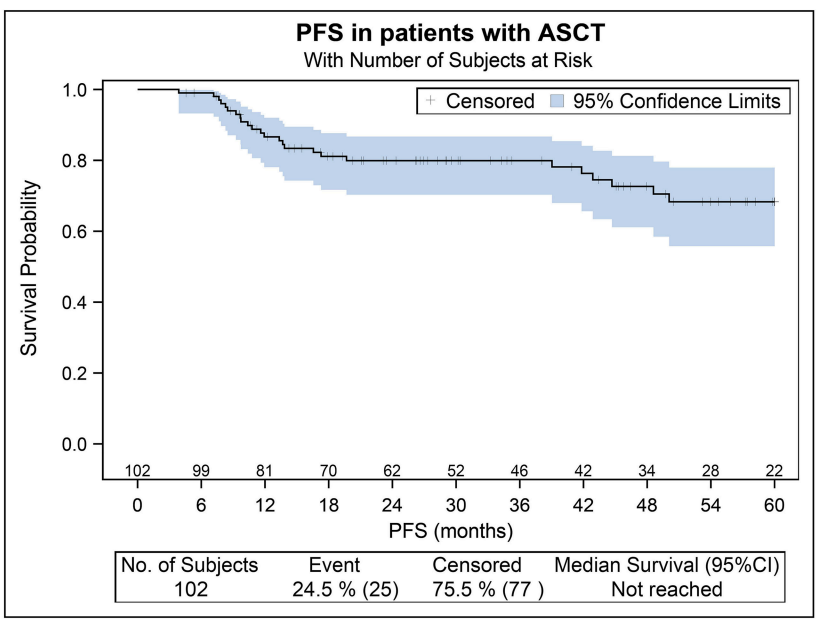
A


PFS in eligible patients for ASCT
With Number of Subjects at Risk
Censored
95% Confidence Limits
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
150 118 94 83 74 63 56 49 41 35 28
0 6 12 18 24 30 36 42 48 54 60
PFS (months)
No. of Subjects | Event | Censored | Median Survival (95%CI)
150 | 38.7 % (58) | 61.3 % (92) | Not reached (44.7 ; NA)

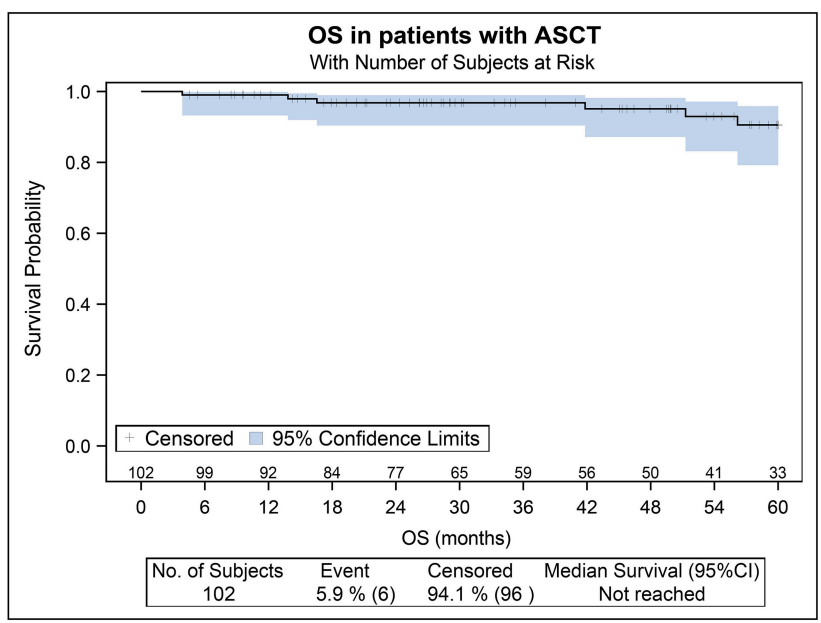
B


OS in eligible patients for ASCT
With Number of Subjects at Risk
Censored
95% Confidence Limits
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
150 143 132 121 107 92 80 72 64 54 43
0 6 12 18 24 30 36 42 48 54 60
OS (months)
No. of Subjects | Event | Censored | Median Survival (95%CI)
150 | 14.7 % (22) | 85.3 % (128) | Not reached

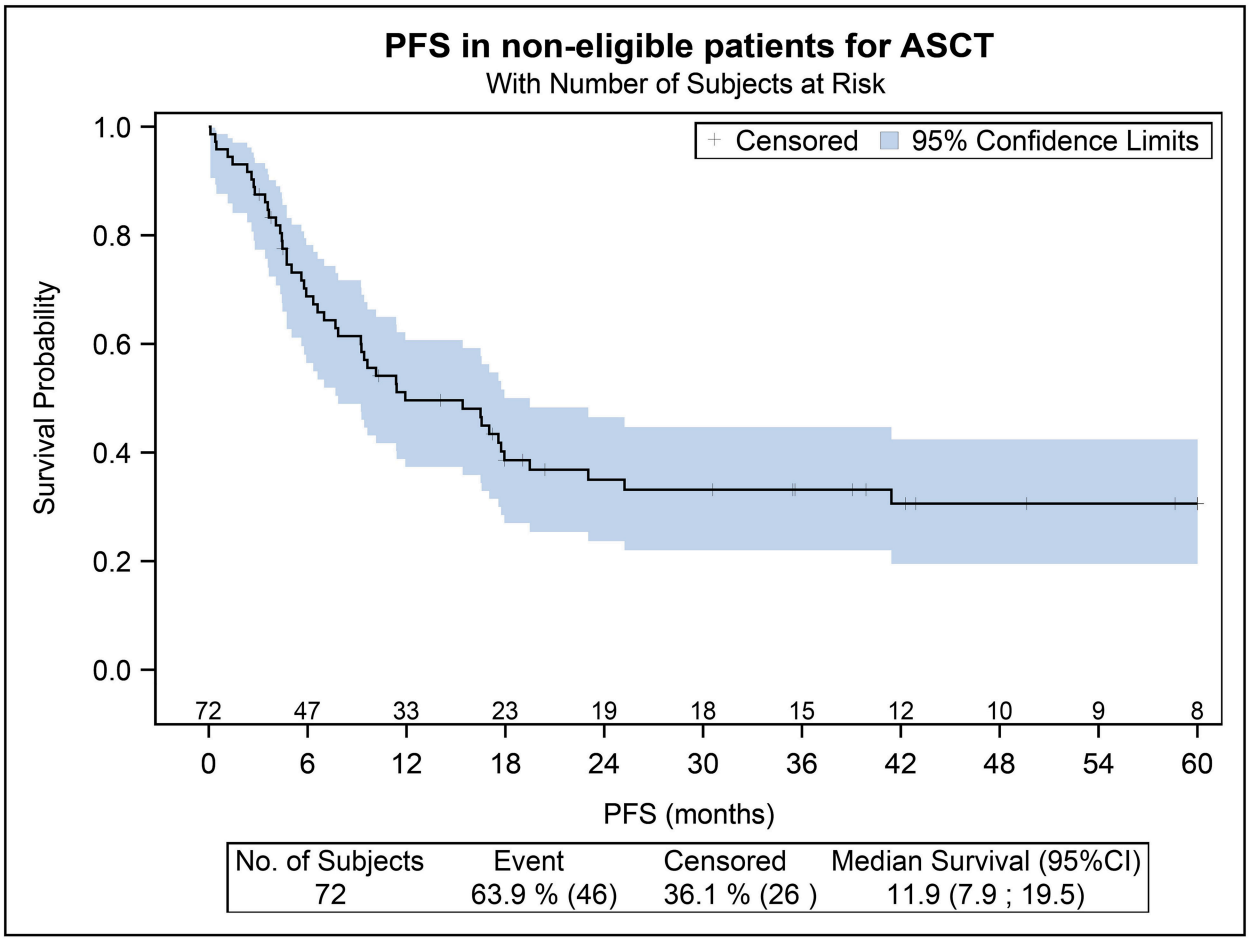
C


PFS in patients with ASCT
With Number of Subjects at Risk
Censored
95% Confidence Limits
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
102 99 81 70 62 52 46 42 34 28 22
0 6 12 18 24 30 36 42 48 54 60
PFS (months)
No. of Subjects | Event | Censored | Median Survival (95%CI)
102 | 24.5 % (25) | 75.5 % (77) | Not reached

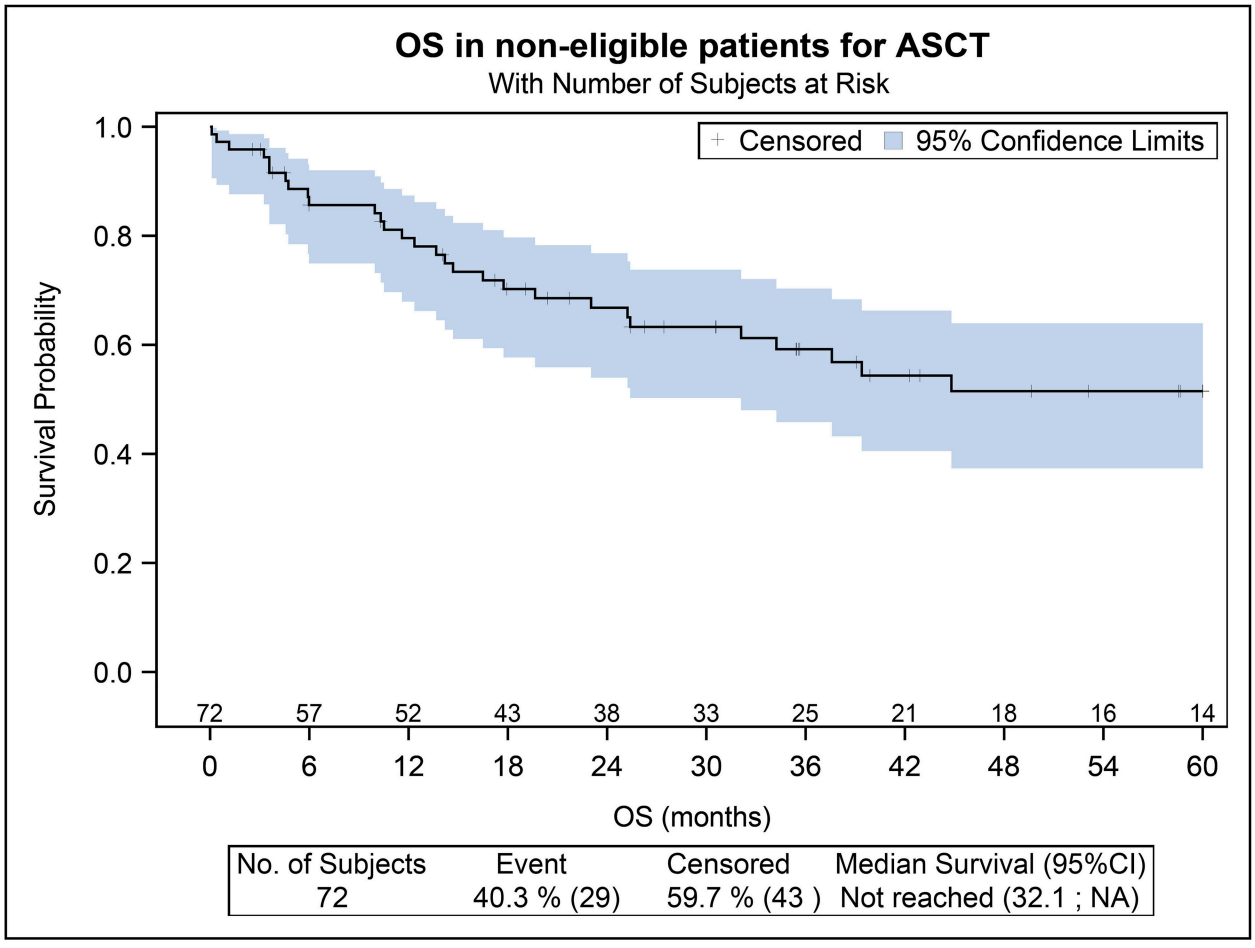
D


OS in patients with ASCT
With Number of Subjects at Risk
Censored
95% Confidence Limits
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
102 99 92 84 77 65 59 56 50 41 33
0 6 12 18 24 30 36 42 48 54 60
OS (months)
No. of Subjects | Event | Censored | Median Survival (95%CI)
102 | 5.9 % (6) | 94.1 % (96) | Not reached

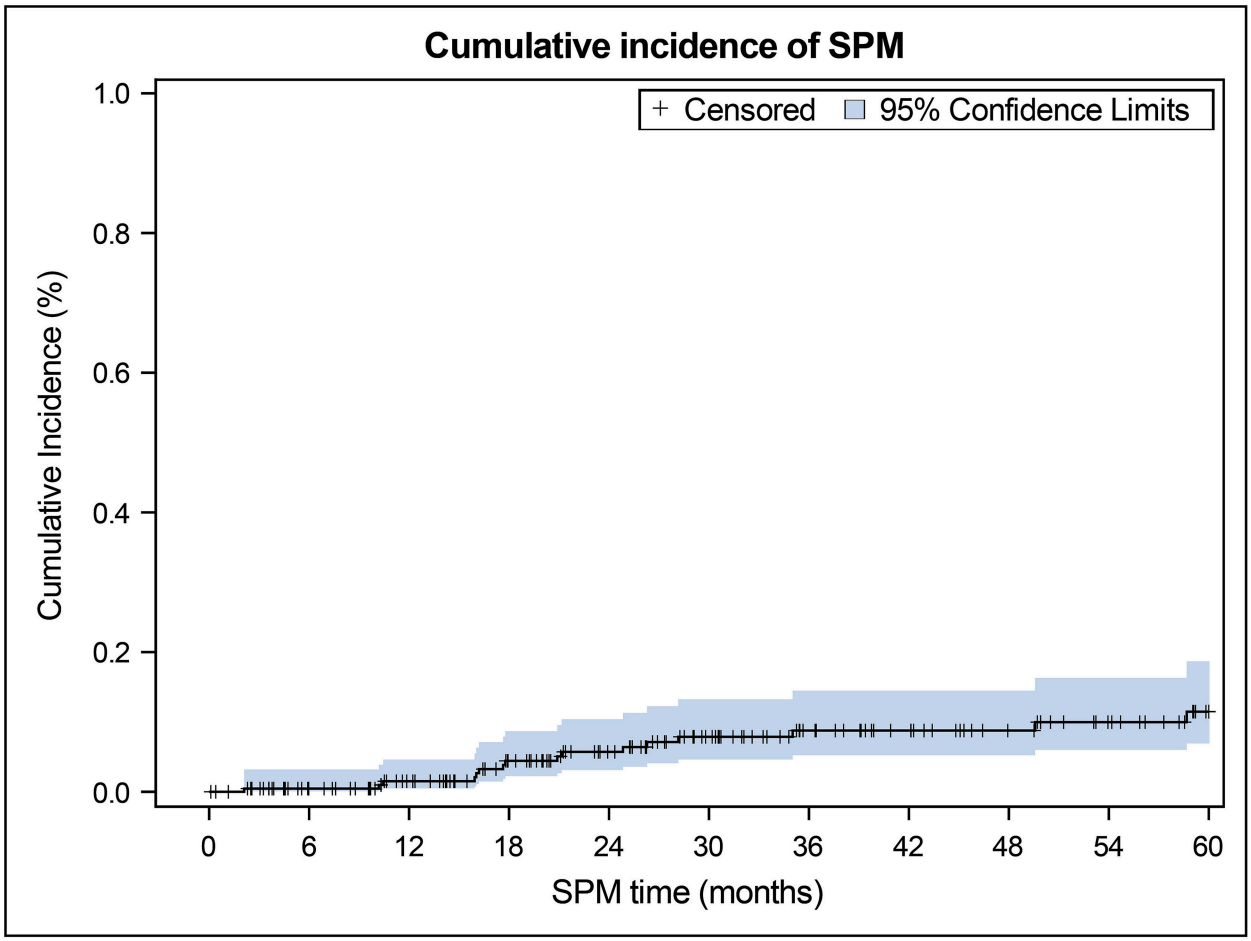
A


PFS in non-eligible patients for ASCT
With Number of Subjects at Risk
Censored
95% Confidence Limits
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
72 47 33 23 19 18 15 12 10 9 8
0 6 12 18 24 30 36 42 48 54 60
PFS (months)
No. of Subjects
72
Event
63.9 % (46)
Censored
36.1 % (26)
Median Survival (95%CI)
11.9 (7.9 ; 19.5)

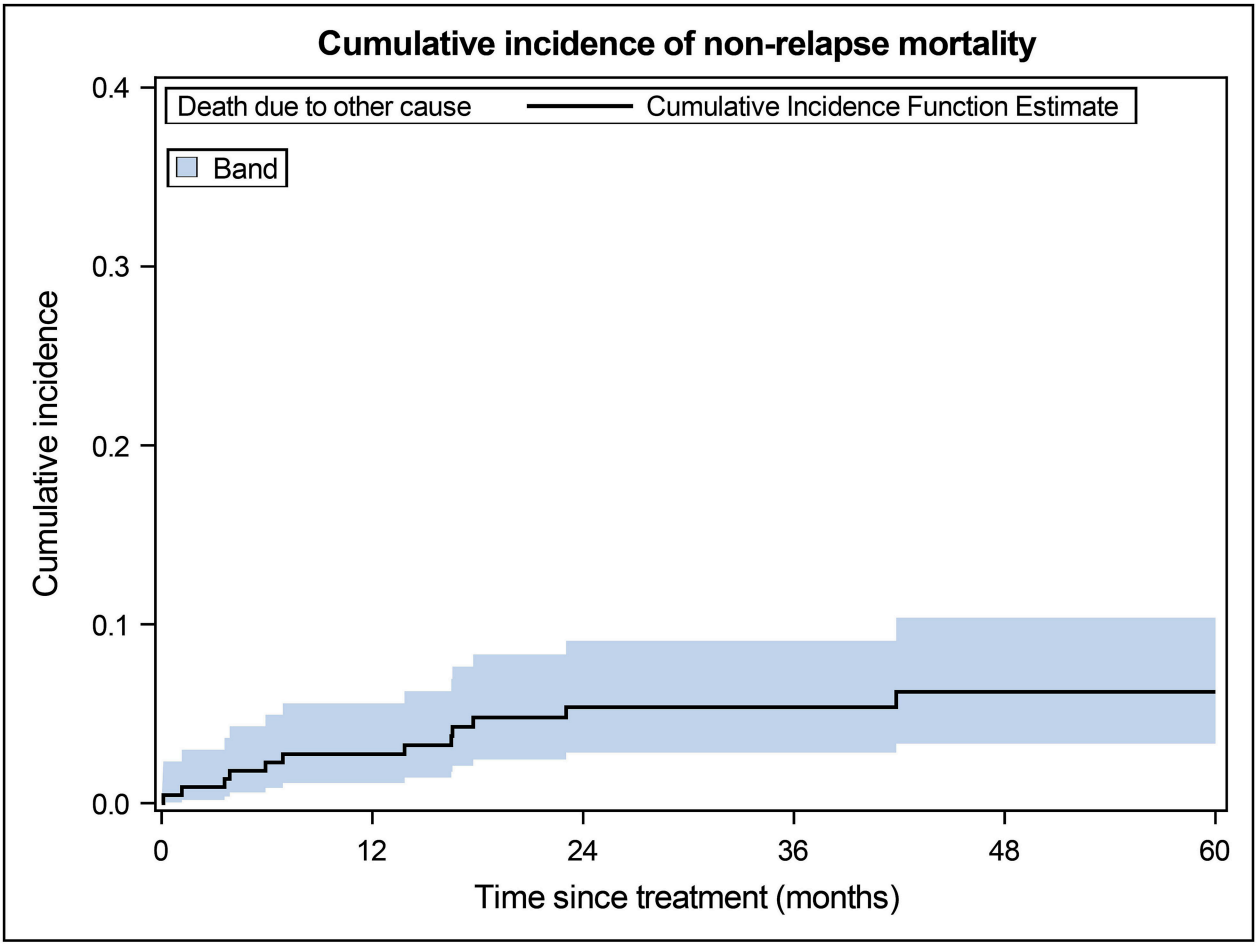
B


OS in non-eligible patients for ASCT
With Number of Subjects at Risk
Censored
95% Confidence Limits
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
72 57 52 43 38 33 25 21 18 16 14
0 6 12 18 24 30 36 42 48 54 60
OS (months)
No. of Subjects
72
Event
40.3 % (29)
Censored
59.7 % (43)
Median Survival (95%CI)
Not reached (32.1 ; NA)

A


Cumulative incidence of SPM
Censored
95% Confidence Limits
Cumulative Incidence (%)
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
36
42
48
54
60
SPM time (months)

B


Cumulative incidence of non-relapse mortality
Death due to other cause
Cumulative Incidence Function Estimate
Band
Cumulative incidence
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
Time since treatment (months)

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

SUPPLEMENTAL DATA

Summary

Supplemental table 1 : details of first line therapy of the study population

First line regimen		N = 222
ABVD based		139
BEACOPP based		33
Other	PVAG/PVAB	13 (12/1)
	Nivolumab + Vinblastin	3
	Bv-based (Bv-AVD/Bv-DHA)	2 (1/1)
	Platinum-based (DHAP, DHAOx)	3 (2/1)
	EBVP	1
	COPP-ABV	1
	VABEM	1
	ACVP/HD-MTX/Holoxan-VP16/HDAC	1
	R-CHOP	1
Not known		24

ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine, ; ACVP : doxorubicin, cyclophosphamide, vindesine, prednisone ; Bv: brentuximab-vedotin; BEACOPP: escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP-ABV : cyclophosphamide, prednisone, procarbazine, adriamycin, bleomycin, vinblastine ; DHAP/OX : dexamethasone, high dose cytarabine, cisplatin/oxaliplatin EBVP : epicirubicin, bleomycin, vinblastine, prednisone ; PVAG/PVAB : prednisone, vinblastine, doxorubicin, gemcitabine/bendamustine ; R-CHOP : rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone ; VABEM : vindesine, doxorubicin, carmustine, etoposide, methylprednisolone

Supplemental table 2 : risk factors for PFS in multivariable analysis when response on interim PET is considered.

Parameter	Modality	Univariate		Multivariable	
		HR	p-value	HR	p-value
ECOG	0-1	1		1	
	2-4	2.34 (1.1-5.0)	0.0260	2.22 (1.0-4.8)	0.0438
Ann Arbor stage	3-4	2.93 (1.5-5.7)	0.0013	2.30 (1.2-4.6)	0.0173
Presence of symptoms	Yes	1.17 (0.6-2.2)	0.61		
Gender	Female	0.81 (0.5-1.4)	0.43		
Number of previous lines	1	1			
	2	2.08 (0.9-4.6)	0.07		
	>3	37.54 (4.2-337.2)	0.0012		
Disease status	Relapse	0.82 (0.5-1.4)	0.48		
First line treatment	ABVD based	1			
	BEACOPP based	0.99 (0.5-2.1)	0.98		
	Other	2.21 (1.2-4.2)	0.0156		
Delay between diagnosis and treatment	Continuous	1.000 (0.993-1.008)	0.89		
Eligible for ASCT	No	2.88 (1.7-4.8)	<0.0001	3.23 (1.9-5.6)	<0.0001
Deauville score	1/2/3	1		1	
	4	2.70 (1.4-5.1)	0.0020	2.95 (1.5-5.7)	0.0011
	5	6.54 (3.3-12.8)	<0.0001	4.66 (2.3-9.4)	<0.0001

Supplemental table 3 : adverse events of interest in transplant eligible and non-eligible patients.

	Eligible for ASCT at B2 initiation	
	No (n = 72)	**Yes (n = 150)**
Red blood cell transfusion		
No	65 (90.3%)	145 (96.7%)
Yes	7 (9.7%)	5 (3.3%)
Platelet transfusion		
No	68 (94.4%)	144 (96.0%)
Yes	4 (5.6%)	6 (4.0%)
Non hematological toxicity grade ≥ 3		
No	46 (63.9%)	123 (82.0%)
Yes	26 (36.1%)	27 (18.0%)
Infection grade ≥ 2		
No	53 (73.6%)	124 (82.7%)
Yes	19 (26.4%)	26 (17.3%)
2	6 (8.3%)	11 (7.3%)
3	8 (11.1%)	12 (8.0%)
4	1 (1.4%)	1 (0.7%)
5	4 (5.6%)	2 (1.3%)
Peripheral neuropathy		
No	57 (79.2%)	122 (81.3%)
Yes	17 (21.8%)	28 (18.7%)
1	9 (12.5%)	15 (10.0%)
2	4 (5.6%)	10 (6.7%)
3	2 (2.8%)	3 (2.0%)
Digestive toxicity ≥ grade 2		
No	57 (79.2%)	129 (86.0%)
Yes	15 (20.8%)	21 (14.0%)
2	10 (13.9%)	16 (10.7%)
3	5 (6.9%)	5 (3.3%)
Skin toxicity ≥ grade 2		
No	57 (82%)	132 (88%)
Yes	15 (18%)	18 (12%)
2	6 (8.3%)	6 (4.0%)
3	7 (9.7%)	12 (8.0%)
Perfusion reactions ≥ grade 2		
No	60 (83.4%)	131 (86.0%)
Yes	12 (16.6%)	19 (14%)
2	7 (9.7%)	14 (9.3%)
3	5 (6.9%)	6 (4.0%)
4	0 (0.0%)	1 (0.7%)
Number of days for hospitalization		
Median (IQR)	0.0 (0-3)	0.0 (0-0)

Supplemental table 4 : reason for treatment reduction or discontinuation in the study cohort

	All (n = 222)	Eligible for ASCT at treatment initiation	
		No (n = 72)	Yes (n = 150)
Dose adaptation for bendamustine			
No	158 (71.2%)	40 (55.6%)	118 (78.7%)
Dose reduction	34 (15.3%)	19 (26.4%)	15 (10.0%)
Permanent stop	30 (13.5%)	13 (18.1%)	17 (11.3%)
Reason of dose adaptation for bendamustine			
Hematologic toxicities	8 (3.6%)	3 (4.2%)	5 (3.3%)
Other toxicities	36 (16.2%)	20 (27.8%)	16 (10.6%)
Cutaneous toxicity / perfusion reaction	23 (10.4%)	10 (13.9%)	13 (8.7%)
Digestive toxicity	6 (2.7%)	4 (5.5%)	2 (1.3%)
Infection	1 (0.4%)	0	1 (0.6%)
Frailty	6 (2.7%)	6 (8.3%)	0
Logistical (harvesting, ASCT, COVID pandemia)	8 (3.6%)	1 (1.4%)	7 (4.7%)
Unknown	14 (6.3%)	10 (13.8%)	4 (2.7%)
Dose adaptation for Bv			
No	186 (83.8%)	58 (80.6%)	128 (85.3%)
Dose reduction	20 (9.0%)	11 (15.3%)	9 (6.0%)
Permanent stop	16 (7.2%)	3 (4.2%)	13 (8.7%)
Reason of dose adaptation for Bv			
Hematologic toxicities	4 (1.8%)	0	4 (2.7%)
Other toxicities	23 (10.3%)	8 (11.1%)	15 (10%)
Peripheral neuropathy	10 (4.5%)	5 (6.9%)	5 (3.3%)
Cutaneous toxicity / perfusion reaction	5 (2.3%)	1 (1.4%)	4 (2.7%)
Infection	3 (1.4%)	0	3 (2.0%)
Interstitial lung disease	2 (0.9%)	1 (1.4%)	1 (0.6%)
Digestive toxicity	2 (0.9%)	0	2 (1.3%)
Frailty	1 (0.4%)	1 (1.4%)	0
Logistical (harvesting, ASCT, COVID pandemia)	1 (0.4%)	0	1 (0.6%)
Unknown	8 (3.6%)	6 (8.3%)	2 (1.3%)

ASCT: autologous stem cell transplantation; Bv: brentuximab-vedotin

Supplemental table 5 : risk factors for all grade ≥ 3 adverse events in multivariable analysis

Parameter	Modality	Univariate		Multivariable	
		OR	p-value	OR	p-value
ECOG	0-1	1			
	2-4	2.43 (1.0-5.8)	0.0459		
Ann Arbor stage	1-2	1			
	3-4	1.20 (0.6-2.3)	0.59		
Presence of symptoms	Yes	1.12 (0.6-2.3)	0.75		
Gender	Female	1.10 (0.6-2.1)	0.77		
Number of previous lines	1	1			
	2	0.97 (0.5-2.0)	0.93		
	>3	0.69 (0.2-2.0)	0.49		
Age	Continuous	1.033 (1.02-1.05)	0.0003	1.033 (1.02-1.05)	0.0003
Number of BV cycles	Continuous	1.05 (0.98-1.1)	0.15		

Supplemental table 6 : risk factors for neuropathy grade ≥ 2 in multivariable analysis

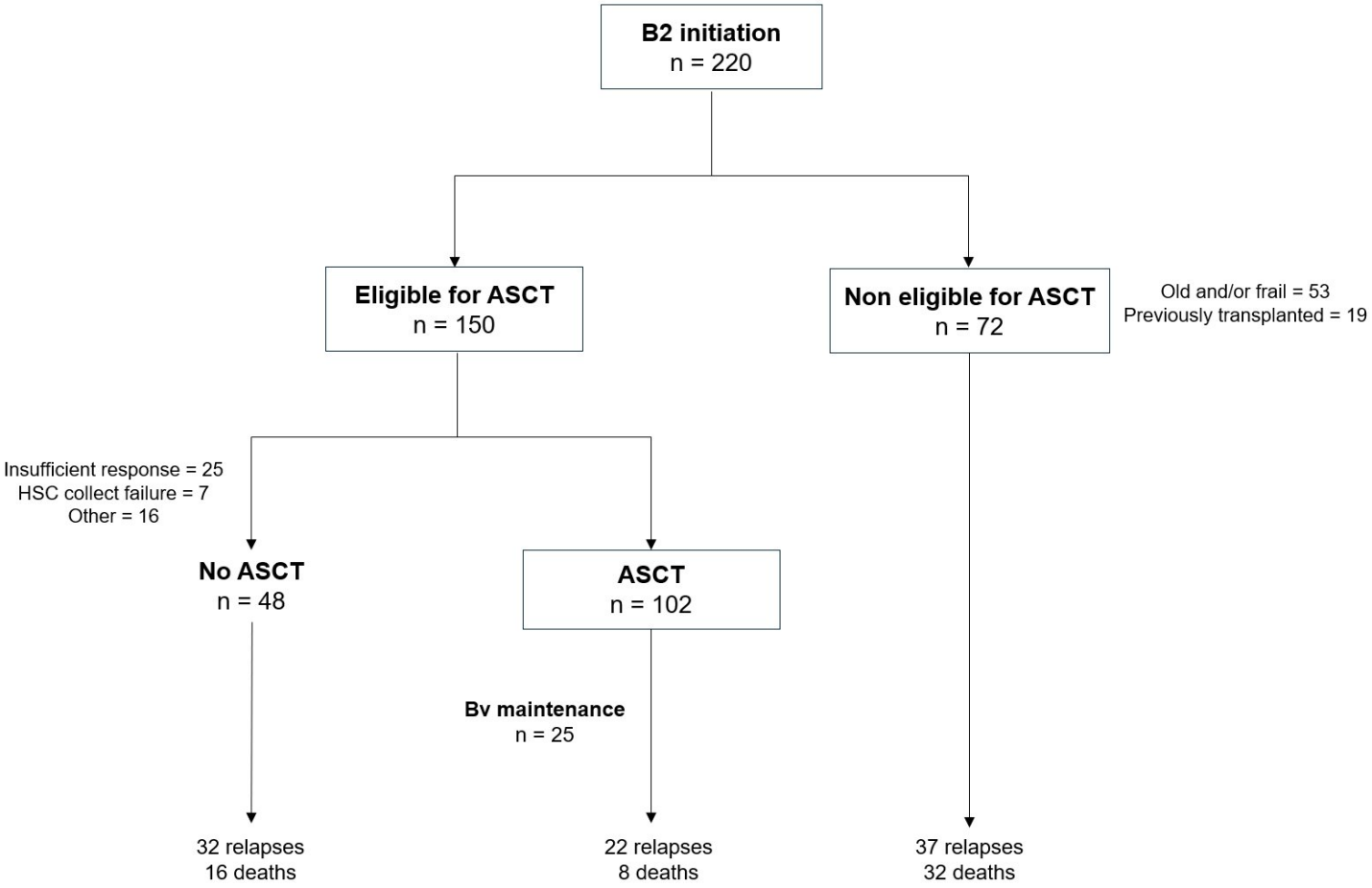
Parameter	Modality	Univariate		Multivariable	
		OR	p-value	OR	p-value
ECOG	0-1	1			
	2-4	0.41 (0.1-3.3)	0.40		
Ann Arbor stage	1-2	1			
	3-4	0.72 (0.3-1.9)	0.59		
Presence of symptoms	Yes	0.53 (0.1-1.9)	0.33		
Gender	Female	1.67 (0.7-4.3)	0.29		
Number of previous lines	2	0.99 (0.4-2.7)	0.98		
	>3	NA	NA		
Age	Continuous	1.011 (0.99-1.04)	0.39		
Number of BV cycles	Continuous	1.17 (1.1-1.3)	<0.001	1.17 (1.1-1.3)	<0.001

Supplemental table 7 : details of second primary malignancies in the study cohort

Age at B2 initiation	Gender	Eligible for ASCT at B2 initiation	Details of SPM	Delay between treatment initiation and SPM (months)	Death due to SPM
39	Male	Yes	AITL	28.1	No
78	Male	No	Prostatic cancer	17.6	No
52	Male	Yes	Small cell lung cancer	24.8	No
53	Male	Yes	DLBCL	35	No
59	Male	Yes	Prostatic cancer	10.4	No
56	Female	Yes	AITL	20.9	No
71	Female	No	MDS	10.1	No
71	Male	No	Urothelial carcinoma	2.0	No
68	Male	No	Squamous cell lung cancer	16.0	No
72	Male	No	Small cell lung cancer	16.2	No
83	Female	No	MDS	58.6	No
25	Male	Yes	PTLD after HSCT	49.5	No
60	Male	Yes	DLBCL	21.1	No
82	Male	No	MDS followed by AML	17.7	Yes
69	Male	No	Gastric cancer	15.9	Yes
27	Female	No	AML	26.2	Yes

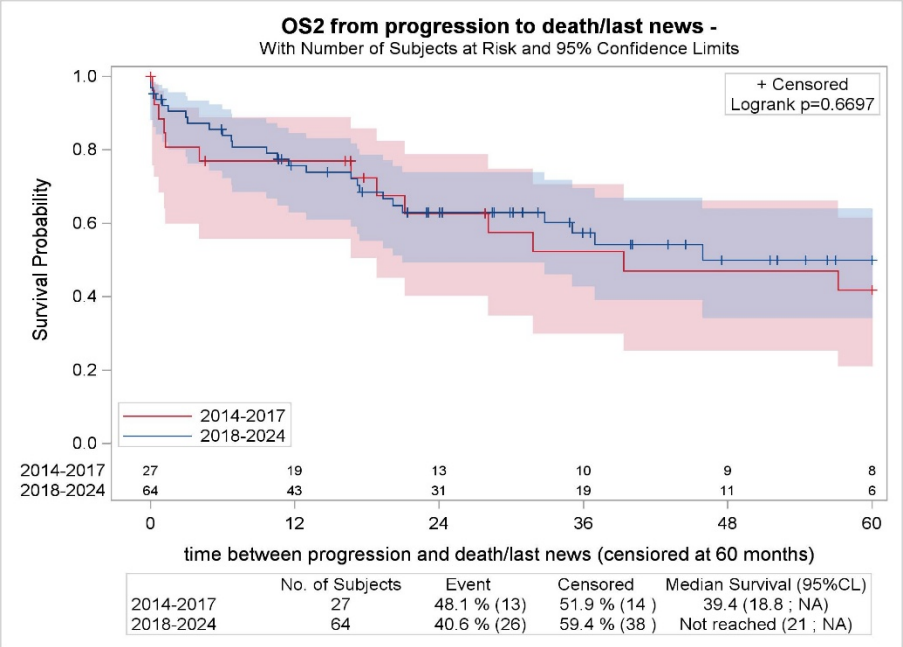
AITL: angioimmunoblastic T-cell lymphoma; AML: acute myeloid leukemia; ASCT: autologous stem cell transplantation; DLBCL: diffuse large B-cell lymphoma; HSCT: heterologous stem cell transplantation; MDS: myelodysplastic syndrome; PTLD: post-transplant lymphoproliferative disorder; SPM: second primary malignancies.

Supplemental figure 1 : flow chart of the study population



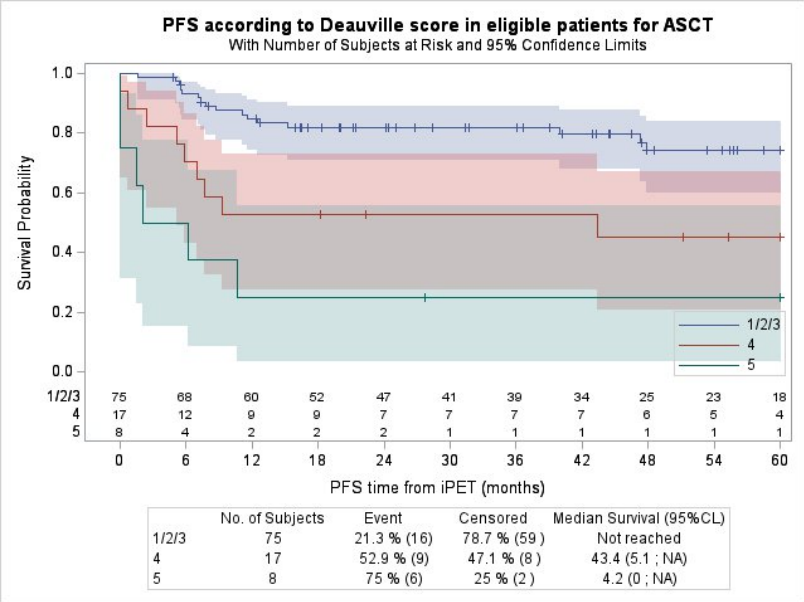
ASCT : autologous stem cells transplantation ; B2 : Bendamustine and brentuximab-vedotin ; Bv : brentuximab-vedotin ; HSC : hematopoietic stem cells

Supplemental figure 2 : OS2 of patients experiencing progression or relapse after B2 salvage

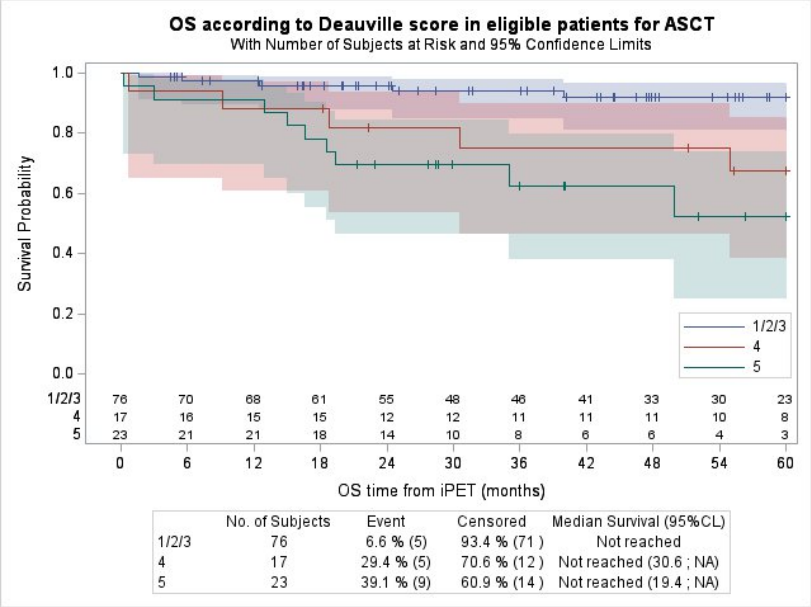


Supplemental figure 3 : PFS (A) and OS (B) of patients eligible for ASCT stratified by early PET results

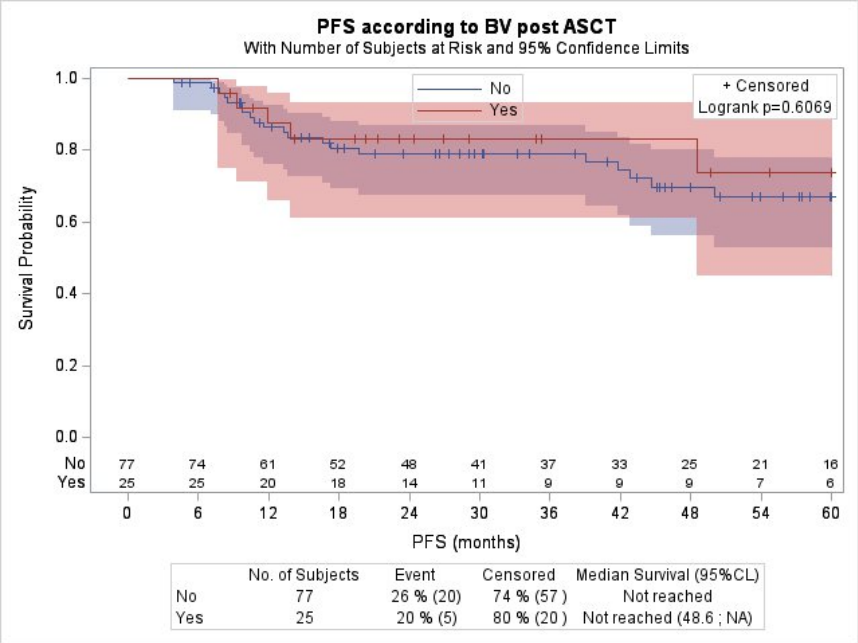
A.



B.

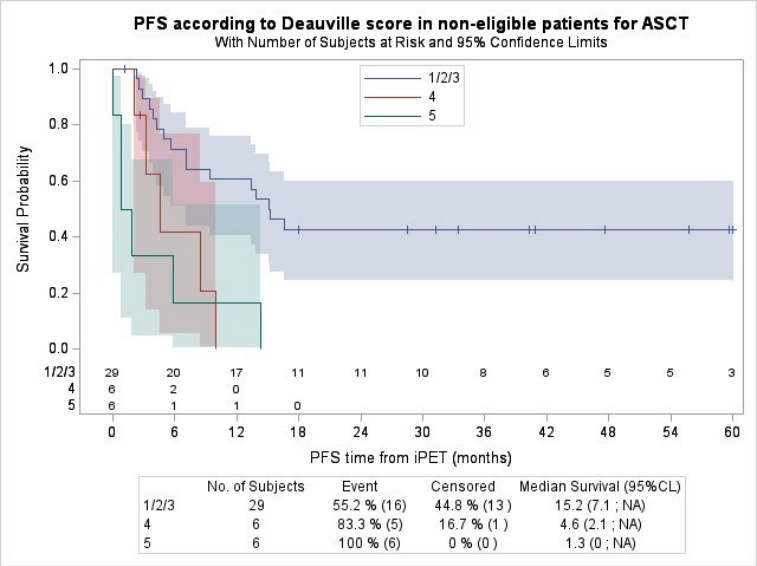


Supplemental figure 4 : PFS of transplanted patients stratified by use of Bv maintenance



Supplemental figure 5 : PFS (A) and OS (B) of patients non-eligible for ASCT stratified by early PET results

A.



B.