REGULAR ARTICLE

blood advances

Salvage therapy with brentuximab-vedotin and bendamustine for patients with R/R PTCL: a retrospective study from the LYSA group

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Key Points

- Brentuximab-vedotin in combination with bendamustine is highly active salvage therapy in R/R PTCL with an ORR of 68% and CR of 49%.
- Patients who underwent an allo-stem cell transplantation in CR had better outcome. m-PFS and OS was 19.3 months and not reached.

Patients with relapsed or refractory (R/R) peripheral T-cell lymphomas (PTCL) have a poor prognosis. Bendamustine (B) and brentuximab-vedotin (Bv) have shown interesting results in this setting. However, little information is available about their efficacy in combination. This multicenter and retrospective study aimed to evaluate the efficacy and safety of the combination of BBv in patients with noncutaneous R/R PTCL among 21 LYSA centers in France and Belgium. The primary objective was the overall response rate. A total of 82 patients with R/R PTCL were included. The best overall response rate (ORR) was 68%, with 49% of patients in complete response (CR). In multivariable analysis, only the disease status after the last regimen (relapse vs refractory) was associated with the response with an ORR of 83% vs 57%. Median duration of response was 15.4 months for patients in CR. With a median follow-up of 22 months, the median progression free survival (PFS) and overall survival (OS) were 8.3 and 26.3 months respectively. Moreover, patients in CR, who underwent an allogeneic transplant, had a better outcome than patients who did not with a median PFS and OS of 19.3 vs 4.8 months and not reached vs 12.4 months, respectively. Fifty-nine percent of patients experienced grade 3/4 adverse events that were mainly hematologic. BBv is highly active in patients with R/R PTCL and should be considered as a one of the best options of immunochemotherapy salvage combination in this setting and particularly as a bridge to allogeneic transplant for eligible patients.

Submitted 8 July 2022; accepted 8 November 2022; prepublished online on *Blood Advances* First Edition 7 December 2022; final version published online 27 September 2023. https://doi.org/10.1182/bloodadvances.2022008524.

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Presented in abstract form at the 63rd annual meeting of the American Society of Hematology, Atlanta, GA, 11 December 2021.

Data are available on request from the corresponding author, Gandhi Damaj (damaj-gl@chu-caen.fr).

The full-text version of this article contains a data supplement.

Introduction

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of diseases that account for about 10% to 15% of aggressive lymphomas. The most common histologic subtypes in Europe are T-cell lymphomas with T follicular helper (TFH) phenotype (angioimmunoblastic T-cell lymphomas [AITL] are the most common) and PTCL not otherwise specified (PTCL NOS), which represent around 60% of all TCL.[1,2]

Patients with relapsed or refractory (R/R) PTCL have a poor prognosis with a median progression free survival (PFS) of about 3 months and a median overall survival (OS) of 5 to 11 months.[3-5] Salvage therapies are of limited efficacy and there is still an unmet medical need in this setting. The duration of response (<12 vs >12 months) after the first line and the disease status at progression (relapse vs refractory) were found to be a major prognostic factor for survival. In addition, patients who can proceed to stem cell transplantation (SCT) consolidation have a better outcome with a 3-year OS of 48% (autologous or allogeneic [allo]) vs only 18% for patients who did not undergo SCT.[3] These results emphasize the importance of optimizing the efficacy of the salvage regimens. Many regimens have been tested. Among them, cytarabine or platinum-based chemotherapy regimens such as ICE (ifosfamide, carboplatin, and etoposide) or ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) remain the most common, with an overall response rate (ORR) and a median PFS between 30% to 70% and 3 to 6 months, respectively.[6]

Bendamustine, a bifunctional cytotoxic agent, has already demonstrated its efficacy in several lymphoid malignancies, as single agent or in combination with other drugs.[7-10] Recently, bendamustine was evaluated as single agent in patients with R/R PTCL. It demonstrated encouraging results with an ORR between 30% and 50% and a median OS ranging from 4 to 6.2 months.[11,12]

Brentuximab-vedotin (Bv), an anti-CD30 antibody-drug conjugate, showed an interesting efficacy in first line and also in R/R CD-30 positive PTCL.[13-15]

The combination of bendamustine and Bv (BBv) has been shown to be very effective with a manageable toxicity in R/R Hodgkin lymphoma.[16] In PTCL, this combination has been less frequently evaluated with only few patients reported in only 5 studies.[17-21] Therefore, the efficacy of this combination in the treatment of PTCL is yet to be established.

The objective of our study was to evaluate the efficacy and the safety of the BBv combination in the treatment of R/R non-cutaneous PTCL.

Patients and methods

We retrospectively included 82 patients with R/R PTCL and treated with BBv from 21 LYSA centers. Patients had to be 18 years old or older, must have received at least 1 previous line of treatment and a confirmed histopathological diagnosis of PTCL. Patients who received prior Bv treatment were allowed in this study independently of the CD30 expression on tissue samples. Patients with a diagnosis of primary cutaneous T-cell lymphoma were excluded. This study has been approved by the institutional review board of the University of Bordeaux and was performed according to the Declaration of Helsinki.

All the data were collected through an electronic questionnaire after validation by the referent physicians.

Patients received Bv at the standard dose of 1.8 mg/kg on the first day of each cycle and bendamustine was given at the dose of 90 mg/m^2 on days 1 and 2, every cycle, for most patients. Cycles were repeated every 3 weeks.

Histological diagnosis and CD30 assessment per the institutional laboratory using immunohistochemical (IHC) staining, were centrally reviewed and confirmed by an expert pathologist from the French lymphopath network for most patients. Histological subtypes were determined accordingly to the most recent World Health Organization classification at the time of diagnosis.[22-24] CD30 positivity was determined by immunochemistry staining, considering only tumor cells with a threshold of 5%.[25]

Responses to treatment were assessed by the patient's referent physician based on positron emission tomography or computed tomography scanner (depending on physician's choice) according to Lugano 2014 revised response criteria.[26] Refractory status was defined by a stable or progressive disease after the last regimen.

Toxicity was assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) applicable at the time of the patient's evaluation.

The primary objective was the best ORR (complete [CR] and partial response [PR]) after BBv. Secondary objectives were PFS, OS, duration of response (DoR), and impact of transplantation on outcome and safety. We also tried to identify potential prognosis factors for response, PFS and OS. PFS was measured from the date of the first cycle of BBv to the date of death from any cause, disease progression or relapse, or the date of last contact. OS was calculated from the date of the first cycle of BBv to the onset of death from any cause or the date of last contact. DoR was calculated from the date of the best documented response to the date of death from any cause, disease progression or relapse, or the date of last contact. ORR was defined as the best documented response (CR or PR) by the referent hematologist.

Survival functions were calculated by Kaplan-Meier estimates, and comparison between categories using the log-rank test. Analysis of hematopoietic SCT (HSCT) impact in survival endpoints used Landmark at the time of HSCT or at the time of last BV administration for patients in CR without HSCT. Responder and nonresponder groups were compared by using the chi-square or Fisher exact tests for discrete variables. The variables potentially associated with ORR, PFS or OS ($P \leq .20$) were included in the multivariable analyses. Stepwise logistic (backward) regression was undertaken for ORR. Multivariable analyses were performed for PFS and OS by using Cox proportional hazards models. All P values $\leq .05$ were considered statistically significant. Statistical analyses were performed using SAS software, version 9.3.

Results

Patients' characteristics

A total of 82 patients were included between January 2013 and October 2020. Median age was 60 years (range, 25-85). The TFH phenotype was the most common histological subtype in 42 (51%) patients, most patients were male (n=50; 61%), with advanced

Table 1. Patients' demographic and disease characteristics at study baseline

Characteristic	Number of patients (N = 82)	n (%)
Age (y)		
Median	60	
Range	25-85	
≤70 y	70	85
Sex		
Male	50	61
Female	32	39
Ratio	1:6	
Lymphoma histology		
TFH	42	51
AITL	40	49
Other TFH	2	2
PTCL NOS	13	16
ALCL	22	27
Alk−	17	21
Alk+	5	6
EATL	3	4
T/NK extranodal	1	1
Subcutaneous panniculitis	1	1
CD30 status*		
Positive	52	63
Negative	21	26
Missing	9	11
Stage		
1-2	10	12
3-4	71	87
Missing	1	1
IPI		
0-2	40	49
3-5	30	37
Missing	12	14
Number of previous regimen		
Median	1	
Range	1-6	
Status at last regimen		
Refractory	41	50
Early relapse (<1 y)	29	35
Late relapse (≥1 y)	12	15
Previous therapy		
CHOP-like regimen	79	96
Cytarabine- and/or platine-based regimen	29	35
Other polychimiotherapy	13	16
New treatments		
HDACi	4	5
BV	9	11
Lenalidomide	2	2
SC transplantation	25	30
Autologous	21	84
Allogeneic	2	8
Autologous + allogeneic	2	8

Alk; EATL, enteropathy associated T-cell lymphoma; HDACi, histone deacetylase inhibitor; SC, stem cell.

*CD30 status determined by immunochemistry, considering only tumor cells with a threshold of 5%.

stage (n=71; 87%). Half of patients were refractory to their last treatment. Median number of previous regimens was 1 (range, 1-6).

Almost all patients (n=79; 96%) received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimen as first-line treatment and 29 patients (35%) received a cytarabine or platinum-based regimen before BBv. Thirteen patients (16%) had previously received ifosfamide or gemcitabine-based regimens. Nine patients (11%) had already received Bv in previous lines. Twenty-five (30%) patients had a SCT before BBv. Baseline patients' characteristics, at the start of BBv, are summarized in Table 1.

Efficacy

A total of 81 patients were assessable for response (1 patient was lost to follow-up). The median number of cycles was 4 (range, 1-7). Twenty-seven patients received <3 cycles (32.9%), mainly owing to disease progression (21 patients, 77.8%), transplantation (2 patients, 7.4%), toxicity (2 patients, 7.4%), and loss of follow-up (2 patients, 7.4%). The 2 patients who received transplantion before the third cycle were in CR after 2 cycles.

The ORR was 68% (55 patients) with 49% (40 patients) in CR and 19% (15 patients) in PR (Table 2). The median DoR was 15.4 months (range, 0.6-50.2). A total of 24 patients (31%) had a prolonged response lasting >1 year. Twenty-two patients ≤70 years (30%) received SCT after BBv (16 allogeneic and 6 autologous).

The median PFS (calculated for 81 patients) was 8.3 months (95% confidence interval [CI], 4.8-13.1) and the median OS was 26.3 months (95% CI, 12.2-not reached [NR]) (Figure 1). The estimated 1-year PFS and OS were 40.7% and 63.7% respectively.

The exclusion of the 5 patients who presented ALK+ anaplastic large-cell lymphoma (ALCL) from the analysis did not modify the survival rates of the whole cohort with a median PFS and OS remained the same at 8.3 and 26.3, respectively.

After a median follow-up of 22 (range, 0.4-52.2) months, 34 patients (41.5%) died from lymphoma progression and 1 patient died from toxicity while in PR.

Predictive factors for response

In univariate analysis, 2 factors were associated with a better ORR. (supplemental Table 1): the disease status after the last regimen (relapse vs refractory), (OR = 3.7; 95% CI, 1.3-10.5; $P = .014$) and the International Prognostic Index (IPI) at relapse (0-2 vs 3-5) (OR = 3.88; 95% CI, 1.1-13.9; $P = .037$). In multivariate analysis, only the disease status at time of BBv treatment remained

Table 2. Response to brentuximab-vedotin plus bendamustine

Best response		
ORR	55	68
CR	40	49
PR	15	19
SD	2	2
PD	24	30
DoR (mo)		
Median	15.4	
Range	0.6-50.2	

significantly associated with response: patients with relapsed disease had a better response with an ORR of 83% (CR, 56%) compared with 53% (CR, 43%) for refractory ones (OR = 3.70; 95% CI, 1.3-10.5; $P = .014$).

Previous treatment with BV doesn't seem to reduce the efficacy of BBv. Among 9 patients previously treated with BV monotherapy or in association with chemotherapy (gemcitabine and vinorelbine), 5 patients responded, with 4 of them achieving a CR. Of note, 2 of them were initially refractory to BV.

The histological subtype seemed to have an impact on efficacy. The best results were observed in patients with ALCL in whom the ORR was 82% with 64% of CR. For TFH and PTCL NOS/other subgroups, the ORR were 67% (CR, 50%) and 53% (CR, 29%) respectively. However, the difference was not statistically significant.

Furthermore, among patients in CR, the DoR was significantly longer in patients who underwent transplantation (mDoR NR) vs 8.4 months ($P = .0055$) for the patients who did not.

Predictive factors for survival

In univariate analysis, SCT, type of response (CR vs PR and CR vs stable disease [SD] or progressive disease [PD]), histological subtype (TFH vs ALCL and TFH vs PTCL NOS/other) and IPI at relapse (0-2 vs 3-5) were significantly associated with better PFS and OS. (supplemental Figures 1 and 2)

In multivariable analysis, only 2 factors had a significant impact on PFS and OS: response to treatment and transplantation.

Patients who achieved a good response (CR or PR) had a better survival than patients who did not (SD/PD). Median PFS and OS were 17.4 vs 1.9 months ($P < .0001$) and NR vs 5.9 months ($P < .0001$) respectively (Figure 2).

Moreover, PFS was significantly longer for patients in CR than in PR with a median PFS of 19.3 vs 7.2 months (HR = 2.65; 95% CI, 1.2-5.7; $P = .013$), respectively but not OS (HR = 2.51; 95% CI, 0.9-7.2; $P = .0895$).

Patients who underwent an allo-SCT (n = 16) had also a better outcome than patients who were not transplanted, regardless of the response status (CR or PR). The median PFS and OS for patients who underwent allo-transplantation vs the patients who did not were 19.3 (95% CI, 9.3-NR) vs 4.8 months (95% CI, 2.4-8.3) (HR = 0.241; 95% CI, 0.101-0.571; $P = .0005$) and NR (95% CI, 26.3-NR) vs 12.4 (95% CI, 9.3-34.6) months (HR = 0.133; 95% CI, 0.133-0.560; $P = .0013$), respectively (Figure 3). When considering only patients in CR, the median OS for patients who underwent transplantation vs patients who did not was still statistically significant with a median OS not reached (95% CI, NR-NR) vs 20.7 months (95% CI, 7.5-NR) ($P = .014$). Almost twice more events were observed in patients who did not undergo allo-SCT transplantation than patients who did (50% vs 26.3%) where the median PFS was not reached (95% CI, 9.7-NR) vs 11.1 (95% CI, 2.5-NR; $P = .066$) months (Figure 4). Only 6 patients with ALK– ALCL underwent an autologous SCT while in CR. All the 6 patients were still alive and in CR at the end of the follow-up.

Patients who did not respond had a very poor outcome with a 1-year PFS of 4.3% (HR = 15.72; 95% CI, 62-39.7; $P < .001$) compared with 44.8% (HR = 3.46; 95%CI, 1.4-8.6; $P = .0077$) for responding patients (CR or PR) without HSCT and 77.5% after HSCT.

Furthermore, the histological subtype was also significantly associated with PFS ($P = .004$) and OS ($P = .022$). Patients with PTCL NOS/other subtypes had a worse PFS (median PFS, 2.7 months) than patients with TFH subtypes (median PFS, 9.7 months) and those with ALCL (median, 16.5 months). PFS differed significantly between PTCL NOS/other and TFH phenotype (HR = 2.37; 95% CI, 1.3-4.5; $P = .0074$) but not between TFH phenotype and ALCL ($P = .23$) (supplemental Figure 3).

In the multivariable analysis for OS, IPI at relapse was at the edge of significance level (HR = 2.59; 95% CI, 0.99-6.8; for IPI 3 to 5, $P = .0535$).

There was no influence of age, number of previous lines, Ann Arbor stage at relapse, refractory or relapsing status, or early vs late relapse. Interestingly, CD30 positivity had no impact on ORR ($P = .55$) or survival ($P = .97$) for PFS and ($P = .35$) for OS.

Safety

Grade 3 to 4 adverse events were reported in 48 patients (59%). Hematologic, infectious, and neurologic toxicities were the most frequent adverse events with neutropenia in 22 cases (27%), thrombopenia in 19 cases (23%), anemia in 13 cases (16%), infections in 7 cases (9%), and peripheral neuropathy in 7 cases (9%).

Doses had to be reduced in 27 patients (33%) and the treatment had to be stopped early in 9 patients (11%). Causes of dose reduction were mainly hematologic toxicities (16 cases), neurotoxicity (7 cases), rash (2 cases), and gastro-intestinal toxicity (2 cases). Causes of discontinuation were hematologic toxicity in 6 cases and neurotoxicity in 5 cases. Two patients stopped the treatment for both hematologic and neurologic toxicity (supplemental Table 2)

Discussion

The use of bendamustine in combination with brentuximab-vedotin in patients at high-risk for R/R PTCL provided an excellent ORR of 68%, a CR rate of 49%, and a median DoR of 15.4 months for patients in CR.

To the best of our knowledge, this study is the first to evaluate the efficacy of BBv in such a large cohort of noncutaneous PTCL.

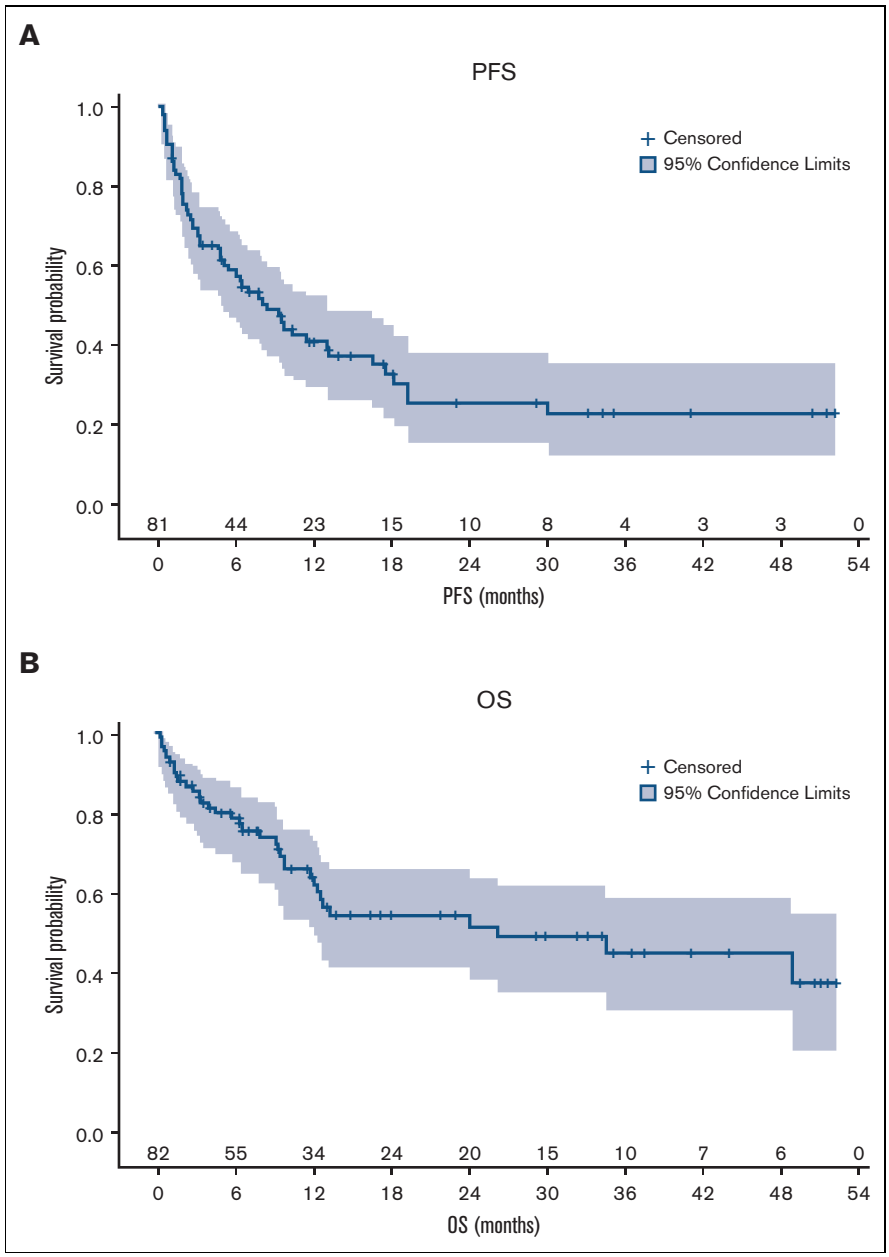


Figure 1. Survival for the whole cohort. (A) PFS and (B) OS.

These results are very encouraging and have never been reported in this setting, either with multidrug combination or with single agents.

The patient characteristics in this cohort were similar to those reported in previous studies except for a higher proportion of ALCL where BV is more likely to be effective. It should be emphasized that this study is retrospective and reflecting the real-life data for patients treated outside of clinical trials.

This combination seems to improve the results reported with both BV and bendamustine when used separately, suggesting a synergistic effect of this association. In the prospective phase 2 BENTLY trial conducted by Damaj et al evaluating the benefit of bendamustine in R/R PTCL, the ORR was 50% and the CR rate was 28%.[11] Median PFS and OS were however short of 3.6 and 6.2 months respectively. In another retrospective study with bendamustine in real-life setting, including 138 patients with PTCL, the ORR was 32.6% with a CR rate of 24.6% and a median DoR of 3.3 months. Patients with AITL seemed to be more sensitive than patients with PTCL-NOS (ORR, 45.1% vs 20%; $P = .01$). The median PFS and OS were 3.1 and 4.4 months respectively.[12]

BV monotherapy showed the best results in patients with ALCL with an ORR of 86%, a CR rate of 57%, and a median PFS of 13.3 months.[14] In contrast, the efficacy of BV is also noticeable in patients with R/R CD30-positive non-ALCL as reported by Horwitz et al. The ORR was 54% (38% CR) and 33% (14% CR) with a median PFS of 6.7 months and 1.6 months in patients with AITL and PTCL NOS respectively.[15]

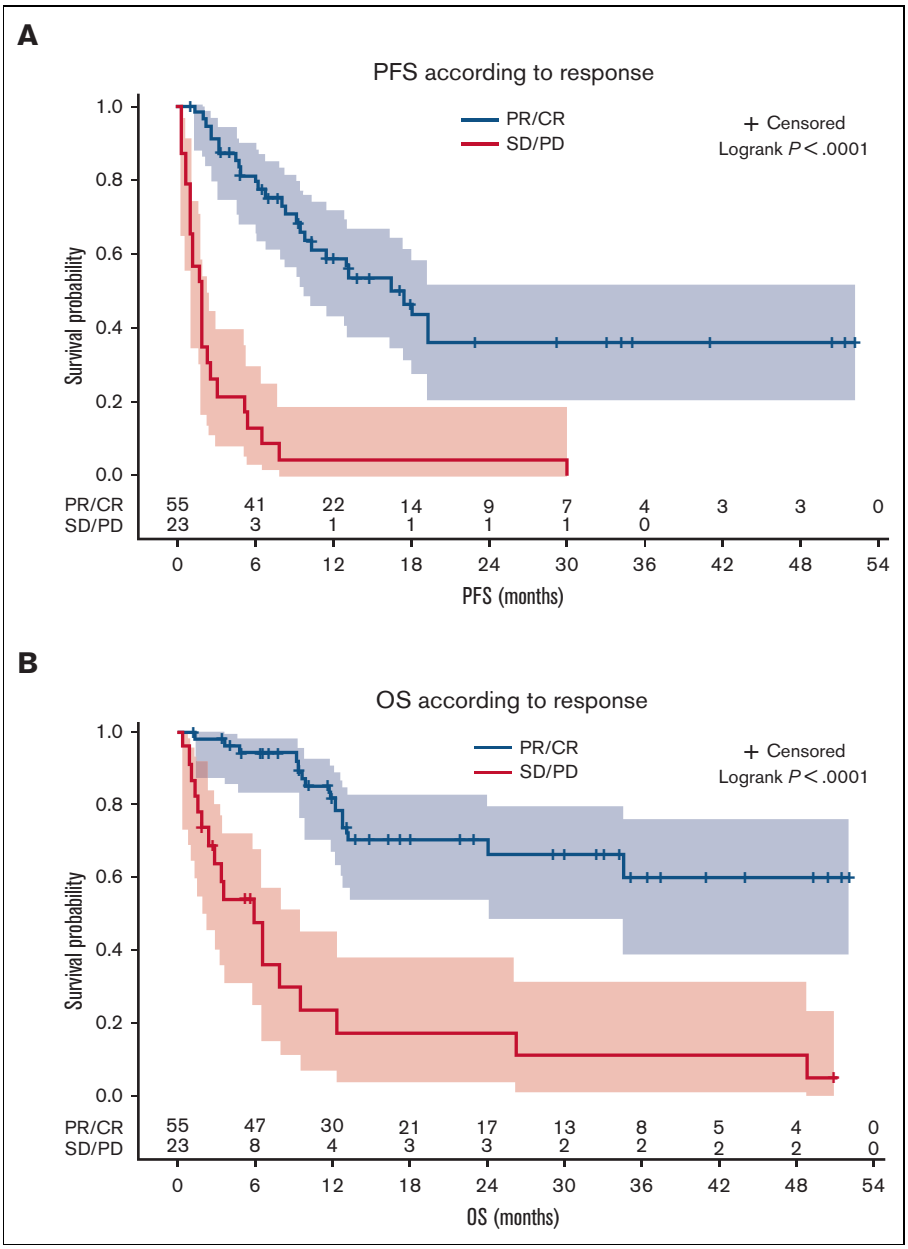


Figure 2. PFS and OS according to response. (A) PFS according to response (PR/CR vs SD/PD). (B) OS according to response (PR/CR vs SD/PD).

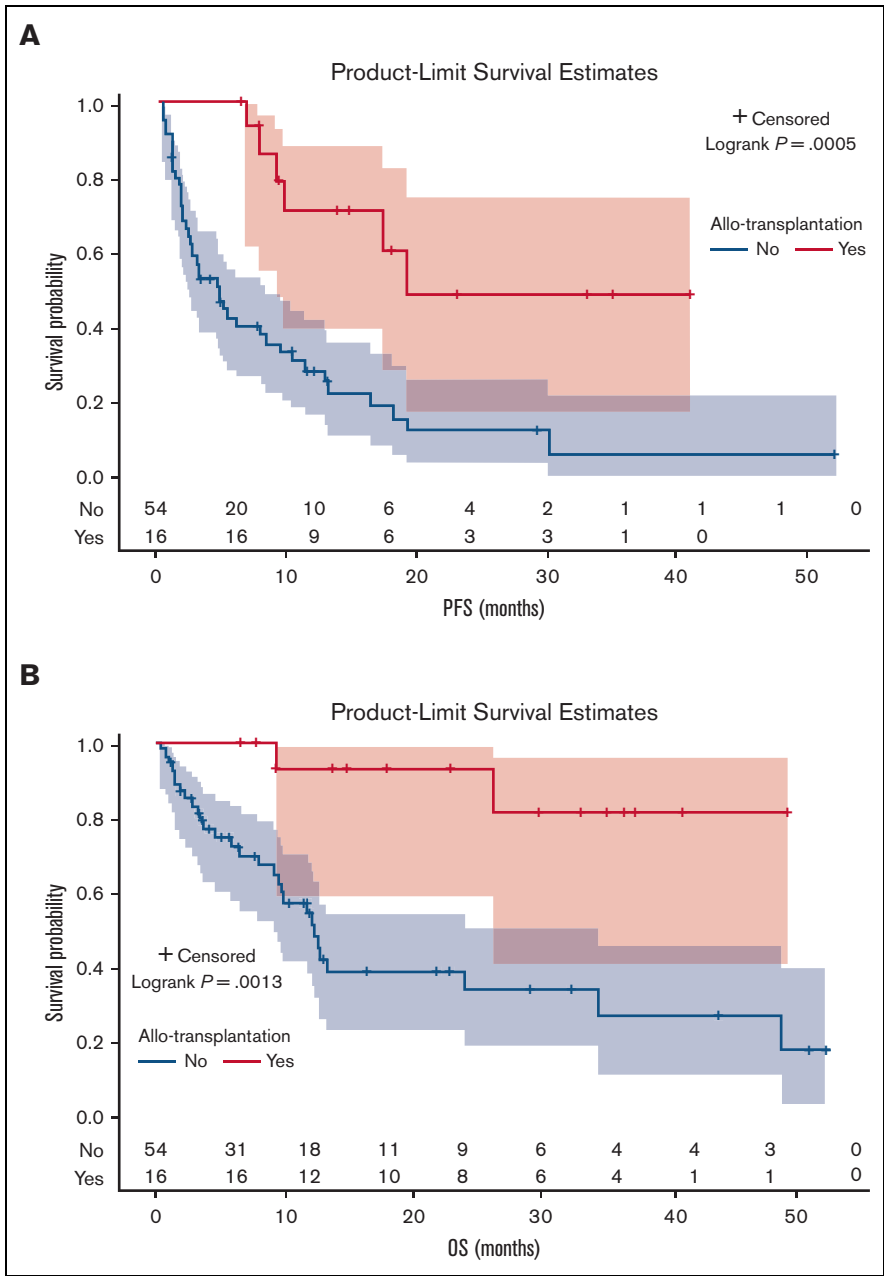
Our results compare favorably with the results of both bendamustine and BV as single agents. They also compare favorably with many other single new agents such as romidepsine, pralatrexate, and gemcitabine that have been approved for use by the US Food and Drug Administration for R/R PTCL. The ORR and CR rates ranged from 25% to 30% and 11% to 15%, respectively, with a median PFS around 3 to 6 months.[27-29]

Thus, these results are also better than those reported with numerous drugs combination such as platinum-based (eg, ESHAP and ICE) or gemcitabine-based (eg, GDP) regimens. The ORR, CR, and PFS reported with these drugs ranged between 32% to 70%, 18% to 35%, and 2.5 to 6 months with more toxic side effects.[6,30] The combination of BV plus ICE (BV-ICE) has been used successfully in R/R Hodgkin disease.[31] However, in the setting of R/R PTCL, the results are disappointing with an ORR of 29% and a 1-year PFS of 14%.[32]

In multivariable analysis, the disease status at the start of BBv was the only factor found to be associated with response. However, it is important to note that, even in patients with refractory PTCL, these results are encouraging with an ORR and a CR rate of 57% and 46% respectively.

Moreover, the histological subtype seems to influence the response rate and the survival. Although the ORR, CR, and PFS in ALCL and TFH subtypes were noteworthy and similar (82%, 64%, and 16.5 months vs 67%, 50%, and 9.7 months, respectively), PTCL NOS/other had a bad outcome (53%, 29%, and 2.7 months). This may suggest that BBv may be considered as a

Figure 3. PFS and OS according to allotransplantation for patients in CR or PR (Landmark approach). (A) PFS according to allotransplantation status for patients in CR or PR. (B) OS according to transplantation status for patients in CR or PR only.



backbone to which many other drugs could be associated to improve these results (ie, azacytidine, duvelisib or JAK-STAT inhibitor molecules).[33-35]

We found no impact of the CD30 level expression neither on response nor survival. This is in accordance with some studies published previously, where no apparent correlation between CD30 expression and response was found.[15,36] In addition, there are some ongoing trials addressing this question specifically (Jagadesh D, #NCT02588651; Seagen Inc., #NCT04404283).

Interestingly, previous treatment with brentuximab does not seem to have a negative impact on the results that we observed after retreatment with BBv. This is consistent with previous reports with an ORR of 88% and a CR rate of 63% for patients with ALCL after a second regimen containing BV.[37] The question of the reintroduction of BV at relapse is relevant now that the ECHELON-2 study demonstrated an advantage to use BV in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) in front-line therapy of CD30-positive PTCL and that this combination have been approved for use in the United States and many other European countries.[13]

Finally, our results support the need of SCT consolidation in responding patients and particularly in patients who achieve CR, where both PFS and OS were not reached. Notwithstanding the good outcome after SCT, we would also like to stress the good results achieved in patients who achieved a CR, but were not

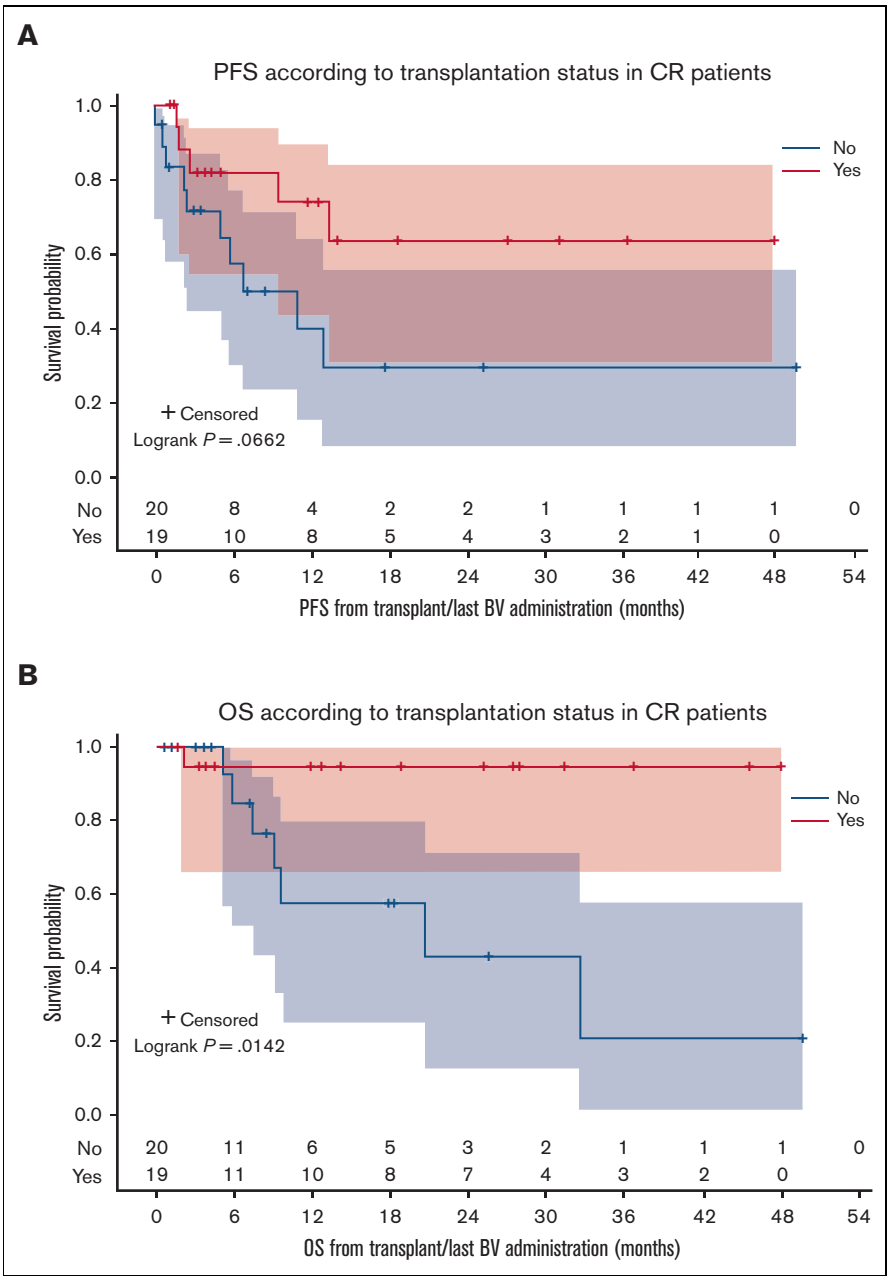


Figure 4. PFS and OS according to transplantation status for patients in CR (Landmark approach). (A) PFS according to transplantation status for patients in CR only. (B) OS according to transplantation status for patients in CR only.

transplanted with a median PFS and OS of 13.1 and 34.6 months respectively, making this combination very attractive.

Toxicity was as expected with mainly hematologic, and peripheral neuropathy that is consistent with the known toxicity profile of these 2 drugs. BV related neurologic toxicity is known to improve after treatment discontinuation.[14] Therefore, toxicity profile of BBv regimen is acceptable.

In conclusion, the overall response rate, the complete response rate, and the DoR achieved after the combination of brentuximab-vedotin and bendamustine therapy as well as the long survival in patients who achieved a CR and underwent an allogeneic transplantation are, to the best of our knowledge, among the best results ever reported so far in patients with R/R PTCL. Should this combination become a standard of care in this setting is an important question to be optimally evaluated in prospective trials.

Authorship

Contribution: R.A., K.B., and G.D. designed the research, analyzed the data, wrote the manuscript, and gave the final approval; L.C. analyzed the data and wrote the manuscript; and all authors collected data and approved the manuscript.

Conflict-of-interest disclosure: G.D., K.B., O.T., D.S., and P.B. received travel grant from Takeda. G.D. received travel grant from AbbVie, Pfizer, and is a member on the scientific board for blueprint of Takeda, AbbVie, and Roche. The remaining authors declare no competing financial interests.

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