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

Tracking no: ADV-2022-008524R2

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Abstract:
ABSTRACT: Purpose: 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. Patients and Methods: This multicenter and retrospective study aimed to evaluate the efficacy and safety of the combination of BBv in patients with non-cutaneous R/R PTCL among 21 LYSA centers in France and Belgium. The primary objective was the overall response rate. Results: Eighty-two patients with R/R PTCL were included. The best ORR was 68%, with 49% of patients in CR. In multivariable analysis, only the relapse status after the last regimen (relapse vs refractory) was associated with the response with an ORR of 83% vs 57% (OR=3.70 (95%CI:1.3-10.5); p=0.014). Median DoR was 15.4 (0.6-50.2) months for patients in CR. With a median follow-up of 22 (0-52) months, the median PFS and 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 versus 4.8 months (p=0.0005) and NR versus 12.4 months (p=0.0013) respectively. Fifty-nine percent of patients experienced grade 3/4 adverse events which were mainly hematologic. Conclusion: BBv is highly active in patients with R/R PTCL and should be considered as a one of the best option of immunochemotherapy salvage combination in this setting and particularly as a bridge to allogeneic transplant for eligible patients.

Conflict of interest: COI declared - see note

COI notes: GD, KB, OT, DS, PB : travel grant from takeda; GD : travel grant from abbvie, pfizer, GD scientific board for blueprint, takeda, abbvie, roche

Preprint server: No;

Author contributions and disclosures: RA, KB, GD: designed research, data analysis, manuscript writing, final approval LC; data analysis, wrote the paper all authors : data collection, manuscript approval

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: NA

Clinical trial registration information (if any):

ORIGINAL REPORT:

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

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Presented in abstract form at the 63rd American Society of Hematology Annual Meeting in December 2021.

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Running title: Brentuximab vedotin and bendamustine for R/R PTCL
Abstract: 247 words

Article: 3041 words

ABSTRACT:

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 non-cutaneous R/R PTCL among 21 LYSA centers in France and Belgium. The primary objective was the overall response rate. Eighty-two patients with R/R PTCL were included. The best ORR was 68%, with 49% of patients in CR. In multivariable analysis, only the relapse status after the last regimen (relapse vs refractory) was associated with the response with an ORR of 83% vs 57% (OR=3.70 (95%CI:1.3-10.5); *p=0.014*). Median DoR was 15.4 (0.6-50.2) months for patients in CR. With a median follow-up of 22 (0-52) months, the median PFS and 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 versus 4.8 months (*p=0.0005*) and NR versus 12.4 months (*p=0.0013*) respectively. Fifty-nine percent of patients experienced grade 3/4 adverse events which were mainly hematologic. BBv is highly active in patients with R/R PTCL and should be considered as a one of the best option of immunochemotherapy salvage combination in this setting and particularly as a bridge to allogeneic transplant for eligible patients.

KEY POINTS:

Brentuximab-vedotin in combination with bendamustine is highly active salvage therapy in R/R PTCL with an ORR was 68% and CR was 49%.

Patient who underwent an allo-stem cell transplantation in CR, had better outcome. m-PFS and OS was 19.3 months and not reached

Introduction

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

Relapsed or Refractory (R/R) PTCL patients have a poor prognosis with a median progression free survival (PFS) 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 as major prognostic factors for survival. Additionally, patients who can proceed to stem cell transplantation (SCT) consolidation have a better outcome with a 3-year OS of 48% (autologous or allogeneic) versus only 18% for non-transplanted patients.[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, 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 30-70% and 3-6 months respectively.[6,7]

Bendamustine, a bifunctional cytotoxic agent, has already demonstrated its efficacy in several lymphoid malignancies, as single agent or in combination with other drugs.[8-11] Recently, Bendamustine was evaluated as single agent in R/R patients with PTCL. It demonstrated encouraging results with an ORR between 30 and 50% and a median OS ranging from 4 to 6.2 months.[12,13]

Brentuximab Vedotin (Bv), an anti-CD30 antibody-drug conjugate, showed an interesting efficacy in first line as well as in R/R CD-30 positive PTCL [14-16.]

The combination of Bendamustine and BV (BBv) has been shown to be very effective with a manageable toxicity in R/R Hodgkin's lymphoma.[17] In PTCL, this combination has been less frequently evaluated with only few patients reported in only 5 articles.[18-22] Therefore, the efficacy of this combination in the treatment of PTCL is still 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 from 21 LYSA centers 82 patients with R/R PTCL and treated with BBv. Patients had to be 18 years-old or older, must have received at least one prior 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 IRB 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 1.8mg/Kg on the first day of each cycle and Bendamustine was given at the dose of 90mg/m2 on days 1 and 2 for the majority of patients. Cycles were repeated every 3 weeks.

Histological diagnosis and CD30 assessment per institutional laboratory using immunohistochemical (IHC) staining were centrally reviewed and confirmed by an expert pathologist from the French *Lymphopath network* for the majority of patients. Histological subtypes were determined accordingly to the most recent WHO classification at time of diagnosis.[23,24,25] CD30 positivity was determined by immunochemistry staining, considering only tumor cells with a threshold of 5%.[26]

Responses to treatment were assessed by the patient's referent physician based on PET or CT scanner (depending on physician's choice) according to Lugano 2014 revised response criteria.[25] 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), 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 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 non-responder groups were compared by using the chi-square (chi^2) or Fisher's exact tests for discrete variables. The variables potentially associated with ORR, PFS or OS ($p \leq 0.20$) 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 ≤ 0.05 were considered statistically significant. Statistical analyses used SAS 9.3.

Results

Patient's characteristics

Eighty-two patients were included between January 2013 and October 2020. Median age was 60 years (range 25 to 85 years). The TFH phenotype was the most common histological subtype (51%), most patients were male (61%), with advanced stage (87%). Half of patients were refractory to their last treatment. Median number of prior regimens was 1 (range 1 to 6).

Almost all patients (96%) received CHOP or CHOP-like regimen as first-line treatment and 35% received a cytarabine or platinum-based regimen before BBv. Sixteen percent of patients had previously received Ifosfamide or gemcitabine-based regimens. Nine patients (11%) had already received Bv in previous lines. Twenty-five patients had a SCT before BBv. Baseline patients' characteristics, at the start of BBv, are summarized in table 1.

Efficacy

Eighty one patients were assessable for response (1 patient was lost to follow-up). The median number of cycles was 4 (range 1 to 7). Twenty-seven patients received less than 3 cycles (32.9%), mainly due to 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 two patients who were transplanted 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 duration of response was 15.4 months (range 0.6 – 50.2). Twenty-four patients (31%) had a prolonged response lasting more than one year. Twenty-two patients ≤ 70 years (30%) received SCT after BBv (16 allogeneic and 6 autologous).

The median PFS (calculated for 81 pts) was 8.3 months (95%CI: 4.8-13.1) and the median OS was 26.3 months (95%CI: 12.2-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+ ALCL from the analysis did not modify the survival rates of the whole cohort with a median PFS and OS still remain 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 partial response.

Predictive factors for response

In univariate analysis, two factors were associated with a better ORR. *(Appendix, table A1, online only)*: the disease status after the last regimen (relapse vs refractory), (OR=3.7 (95% CI, 1.3-10.5), *p=.014*)) and the 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 significantly associated with

response: patients with relapsed disease had a better response with an ORR of 83% (CR 56%) compared to 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 did respond 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 ALCL patients 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 transplanted patients (mDoR not reached (NR) versus 8.4 months (*p=.0055*) for non-transplanted patients).

Predictive factors for survival

In univariate analysis, SCT, type of response (CR vs PR and CR vs SD or 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. *(Appendix, figure A1 and A2, online only)*

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 versus 7.2 months (HR=2.65 (95% CI: 1.2-5.7), p=0.013), respectively but not OS (HR=2.51 (95% CI: 0.9-7.2), p=0.0895).

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 allo-transplanted versus not allo-transplanted patients were 19.3 (95% CI: 9.3-NR) versus 4.8 months (95% CI: 2.4-8.3) (HR=0.241 (95% CI: 0.101-0.571, *p=0.0005*) and NR (95% CI: 26.3-NR) versus 12.4 (95% CI: 9.3-34.6) months (HR=0.133 (95% CI: 0.133-0.560), *p=0.0013*) respectively (figure 4). When considering only patients in CR, the median OS for transplanted versus non-transplanted patients was still statistically significant with a median OS not reached (95%CI: NR-NR) versus 20.7 months (95% CI: 7.5-NR) (*p=0.014*). Almost twice more events were observed in non-transplanted patients compared to transplanted patients (50% vs 26.3%) where the median PFS was not reached (95%CI: 9.7-NR) versus 11.1 (95% CI: 2.5-NR, *p=0.066*) months (*Figure 3*). Only 6 patients with ALK-neg. 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 to 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.

Additionally, 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 of 2.7 months) than patients with TFH subtypes (median PFS of 9.7 months) and those with ALCL (median of 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) *(Appendix, Figure A3, online only)*

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 3-5, p=0.0535).

There was no influence of age, number of previous lines, Ann Arbor stage at relapse, refractory or relapsing status, or early versus 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. (*Appendix, Table A2, online only)*

Discussion

The use of Bendamustine in combination with Brentuximab-Vedotin in this high-risk R/R PTCL patients provided an excellent ORR of 68%, a CR rate of 49% and a median DoR of 15.4 months for patients in CR.

To our knowledge, this study is the first one to evaluate the efficacy of BBv in such a large cohort of non-cutaneous PTCL. These results are very encouraging and have never been reported in this setting, either with multidrug combination or with single agents.

The patients' 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 and al evaluating the benefit of Bendamustine in R/R PTCL, the ORR was 50% and the CR rate was 28%.[12] 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 PTCL patients, the ORR was 32.6% with a CR rate of 24.6% and a median DoR of 3.3 months. AITL patients seemed to be more sensitive than PTCL-NOS patients (ORR: 45.1% versus 20%, $p = 0.01$). The median PFS and OS were 3.1 and 4.4 months respectively.[13]

BV monotherapy showed the best results in ALCL patients with an ORR of 86%, a CR rate of 57% and a median PFS of 13.3 months.[15] On the other hand, 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 AITL and PTCL NOS patients respectively. [16]

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 like Romidepsine, pralatrexate, gemcitabine that have been approved for use by the FDA for R/R PTCL. The ORR and CR rates range from 25% to 30% and 11% to 15% respectively with a median PFS around 3 to 6 months. [28-30]

Thus, these results are also better than those reported with numerous drugs combination such as platinum based (e.g., ESHAP, ICE) or gemcitabine-based (e.g. 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. [6,7,31] The combination of BV plus ICE (BV-ICE) has been used successfully in R/R Hodgkin disease.[32] However, in the setting of R/R PTCL, the results are disappointing with an ORR of 29% and a 1-year PFS of 14%. [33]

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 refractory patients, these results are encouraging with an ORR and a CR rate of 57% and 46% respectively.

Additionally, the histological subtype seems to influence the response rate and the survival. While the ORR, CR and PFS in ALCL and TFH subtypes were noteworthy and similar (82%, 64% and 16.5 months versus 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 backbone to which many other drugs could be associated in order to improve these results (ie azacytidine, duvelisib or Jak-STAT inhibitor molecules).[34-36]

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.[16,37] Additionally, there are some ongoing trials addressing specifically this question (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.[38] 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 in front-line therapy of CD30-positive PTCL and that this combination have been approved for use in USA and many other European countries.[14]

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 complete response but were not 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 which is consistent with the known toxicity profile of these 2 drugs. BV related neurologic toxicity is known to improve after treatment discontinuation.[15] Therefore, toxicity profile of BBV regimen is acceptable.

In conclusion, the overall response, the complete response rate and the duration of response acheived 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 among the best results ever reported so far in R/R PTCL patients. Should this combination become a standard of care in this setting is an important question to be optimally evaluated in prospective trials.

Authorship

Contribution: RA, KB, GD: designed research, data analysis, manuscript writing, final approval LC; data analysis, wrote the paper all authors : data collection, manuscript approval.

Conflicts of interest: GD, KB, OT, DS, PB : travel grant from Takeda; GD : travel grant from AbbVie, Pfizer, GD scientific board for blueprint, Takeda, AbbVie, Roche.

References

1. Laurent C, Baron M, Amara N et al. Impact of Expert Pathologic Review of Lymphoma Diagnosis: Study of Patients From the French Lymphopath Network. Journal of clinical Oncology, 2017.
2. De Leval L, Parrens M, Le Bras F, et al. Angioimmunoblastic T-cell lymphoma is the most common T-cell lymphoma in two distinct French information data sets. *Haematologica 2015, 100(9): e361-4*.
3. Bellei M, Foss FM, Shustov AR et al. The outcome of peripheral T-cell lymphoma patients failing first-line therapy: a report from the prospective, International T-Cell Project. Haematologica. 2018;103(7):1191-7.
4. Chihara D, Fanale MA, Miranda RN et al. The survival outcome of patients with relapsed/refractory peripheral T-cell lymphoma-not otherwise specified and angioimmunoblastic T-cell lymphoma. Br J Haematol. mars 2017;176(5):750-8.
5. Mak V, Hamm J, Chhanabhai M, et al. Survival of Patients With Peripheral T-Cell Lymphoma After First Relapse or Progression: Spectrum of Disease and Rare Long-Term Survivors. J Clin Oncol. 2013; 31(16):1970-6.
6. Kogure Y, Yoshimi A, Ueda K et al. Modified ESHAP regimen for relapsed/refractory T cell lymphoma: a retrospective analysis. Annals of Oncology. June 2015
7. Horwitz S, Moskowitz C, Kewalramani T, et al. Second-Line Therapy with ICE Followed by High Dose Therapy and Autologous Stem Cell Transplantation for Relapsed/Refractory Peripheral T-Cell Lymphomas: Minimal Benefit When Analyzed by Intent To Treat. Blood. 2005; 106:2679-2679.
8. Pönisch W, Mitrou PS, Merkle K, et al. Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone--a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). J Cancer Res Clin Oncol. avr 2006;132(4):205-12.
9. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol Off J Am Soc Clin Oncol. 10 janv 2008;26(2):204-10.
10. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol Off J Am Soc Clin Oncol. 20 sept 2008;26(27):4473-9.
11. Niederle N, Megdenberg D, Balleisen L, et al. Bendamustine compared to fludarabine as second-line treatment in chronic lymphocytic leukemia. Ann Hematol. mai 2013;92(5):653-60.
12. Damaj G, Gressin R, Bouabdallah K, et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. J Clin Oncol 2013;31(1):104-10.
13. Reboursiere E, Bras FL, Herbaux C, et al. Bendamustine for the treatment of relapsed or refractory peripheral T cell lymphomas: A French retrospective multicenter study. Oncotarget. 2016;7(51):85573-83.
14. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab Vedotin with Chemotherapy for CD30-Positive Peripheral T-cell Lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet Lond Engl. jan 2019;393(10168):229-40.
15. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol 2012, 30(18): 2190-6.
16. Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood. 2014;123(20):3095-100.
17. LaCasce AS, Bociek RG, Sawas A, Caimi P, Agura E, Matous J, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood. 5 juill 2018;132(1):40-8.
18. Dumont M, Ram-Wolff C, Roelens M, et al. Efficacy and safety of brentuximab vedotin plus bendamustine in advanced-stage primary cutaneous T-cell lymphomas. Br J Dermatol. déc 2019;181(6):1315-7.
19. O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1–2 trial. Lancet Oncol. févr 2018;19(2):257-66.
20. Wagner SM, Melchardt T, Egle A, et al. Treatment with brentuximab vedotin plus bendamustine in unselected patients with CD30-positive aggressive lymphomas. Eur J Haematol. mars 2020;104(3):251-8.

21. Sawas A, Connors JM, Kuruvilla JG, et al. The Combination of Brentuximab Vedotin (Bv) and Bendamustine (B) Demonstrates Marked Activity in Heavily Treated Patients with Relapsed or Refractory Hodgkin Lymphoma (HL) and Anaplastic Large T-Cell Lymphoma (ALCL): Results of an International Multi Center Phase I/II Experience. Blood. 2015;126(23):586-586.
22. Poon L-M, Kwong Y-L. Complete remission of refractory disseminated NK/T cell lymphoma with brentuximab vedotin and bendamustine. Ann Hematol. 2016;95(5):847-9.
23. Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematol Am Soc Hematol Educ Program. 2009;523-31.
24. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 19 2016;127(20):2375-90.
25. Campo E, Jaffe E, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. *Blood 2022. Jun 2:blood.2022015851. doi: 10.1182/blood.2022015851. Online ahead of print*.
26. Bossard C, Dobay MP, Parrens M, et al. Immunohistochemistry as a valuable tool to assess CD30 expression in peripheral T-cell lymphomas: high correlation with mRNA levels. Blood. 6 nov 2014;124(19):2983-6.
27. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol Off J Am Soc Clin Oncol. 20 sept 2014;32(27):3059-68.
28. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol Off J Am Soc Clin Oncol. 20 févr 2012;30(6):631-6.
29. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol Off J Am Soc Clin Oncol. 20 mars 2011;29(9):
30. O'Connor OA, Ozcan M, Jacobsen ED, Roncero JM, Trotman J, Demeter J, et al. Randomized Phase III Study of Alisertib or Investigator's Choice (Selected Single Agent) in Patients With Relapsed of Refractory Peripheral T-Cell Lymphoma. J Clin Oncol. 2019;37(8)
31. Qi F, Dong M, He X, Li Y, Wang W, Liu P, et al. Gemcitabine, dexamethasone, and cisplatin (GDP) as salvage chemotherapy for patients with relapsed or refractory peripheral T cell lymphoma—not otherwise specified. Ann Hematol. 2017;96(2)
32. Lynch R, Cassaday R, Smith S et al. Dose-dense brentuximab vedotin plus ifosfamide, carboplatin, and etoposide for second-line treatment of relapsed or refractory classical Hodgkin lymphoma: a single centre, phase 1/2 study. The Lancet Haematology, August 2021
33. Van de Wyngaert Z, Coppo P, Cervera P, et al. Combination of brentuximab-vedotin and ifosfamide, carboplatin, etoposide in relapsed/refractory peripheral T-cell lymphoma. Eur J Haematol. avr 2021;106(4):467-72.
34. Lemonnier F, Dupuis J, Sujobert P et al. Treatment with 5-azacytidine induces a sustained response in patients with angioimmunoblastic T-cell lymphoma. Blood, Nov 2018
35. Horwitz S, Koch R, Procu P et al. Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. Blood 2018
36. Moskowitz A, Ghione P, Jacobsen E et al. Final Results of a Phase II Biomarker-Driven Study of Ruxolitinib in Relapsed and Refractory T-Cell Lymphoma. Blood 2019
37. Krathen M, Sundram U, Bashey S, et al. Brentuximab Vedotin Demonstrates Significant Clinical Activity in Relapsed or Refractory Mycosis Fungoides with Variable CD30 Expression. Blood. 2012;120(21):797-797.
38. Bartlett NL, Chen R, Fanale MA, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. J Hematol OncolJ Hematol Oncol. 2014; 7:24.

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

*CD30 status determined by immunochemistry, considering only tumor cells with a threshold of 5%.Abbreviations: TFH, T Follicular Helper; AITL, angioimmunoblastic lymphoma; ALCL, anaplastic large-cell lymphoma; PTCL-NOS, peripheral T cell lymphoma non other specified; EATL, Enteropathy associated T cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; IPI, International Prognostic Index; CR, complete response; PR, Partial Response; HDACi, histone deacetylase inhibitor; BV, Brentuximab Vedotin; SC, Stem cell

Characteristic		No. of patients (N = 82)	%
Age			
	Median	60	
	Range	25 - 85	
	≤ 70 y.o.	70	85%
Sexe			
	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 prior regimen			
	Median	1	
	Range	1 - 6	
Status at last regimen			
	Refractory	41	50%
	Early relapse (<1 year)	29	35%
	Late relapse (≥1year)	12	15%
Prior 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%
	allogenic	2	8%
	Autologous + allogenic	2	8%

Table 2: Response to Brentuximab Vedotin plus Bendamustine

Abbréviations : ORR, Overall Response Rate; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; DoR, Duration of Response

		N = 81	%
Best Response			
	ORR	55	68
	CR	40	49
	PR	15	19
	SD	2	2
	PD	24	30
DoR (months)			
	Median	15.4	
	Range	0.6-50.2	

Figure legends

Figure 1: (A) Progression-free-Survival (PFS) and (B) Overall Survival (OS)

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)

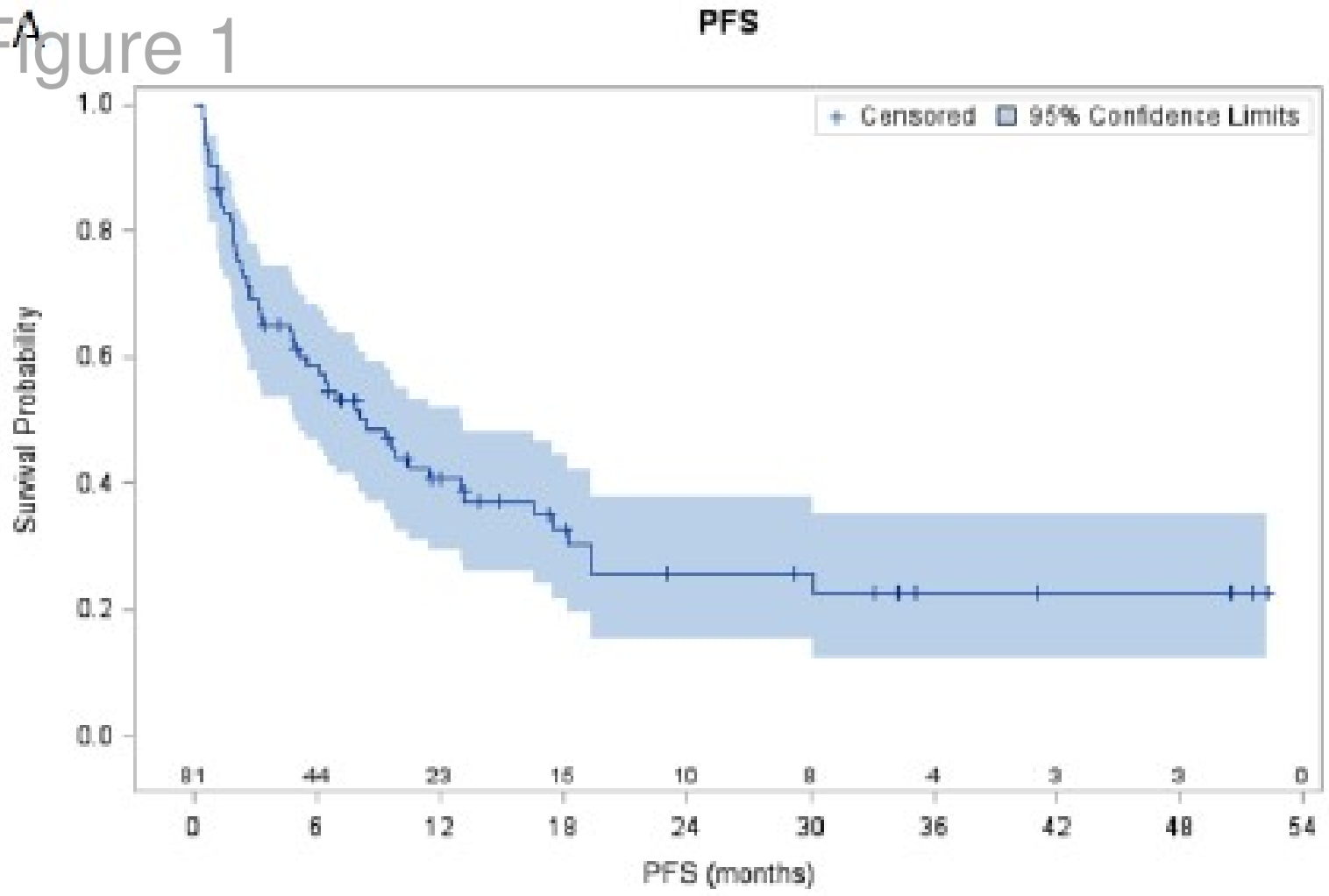
Figure 3: PFS and OS according to transplantation status for patients in CR (Landmark approach).

(A) PFS according to transplantation status for patients in CR only, (B) OS according to transplantation status for patients in CR only

Figure 4: 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

Figure 1



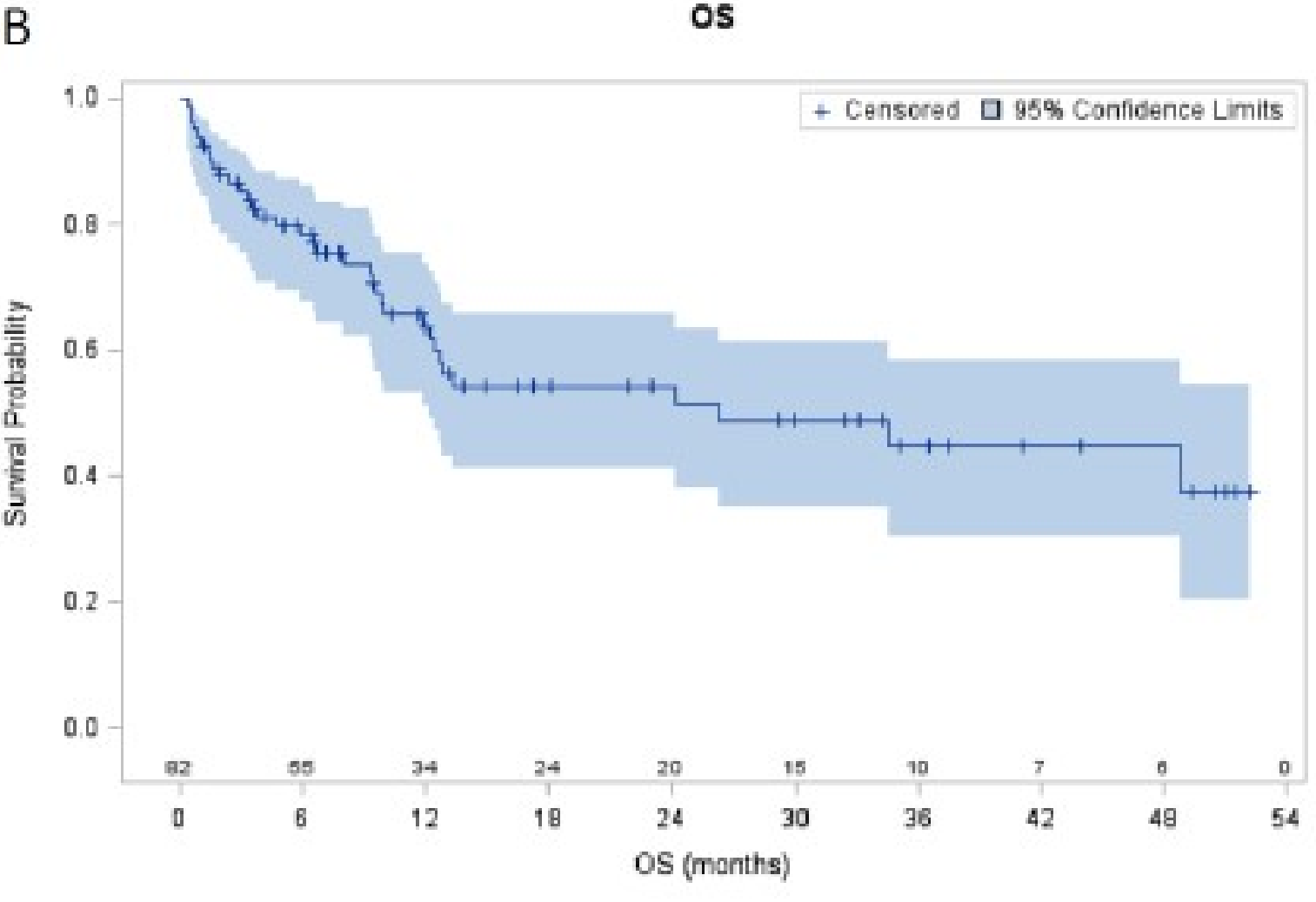
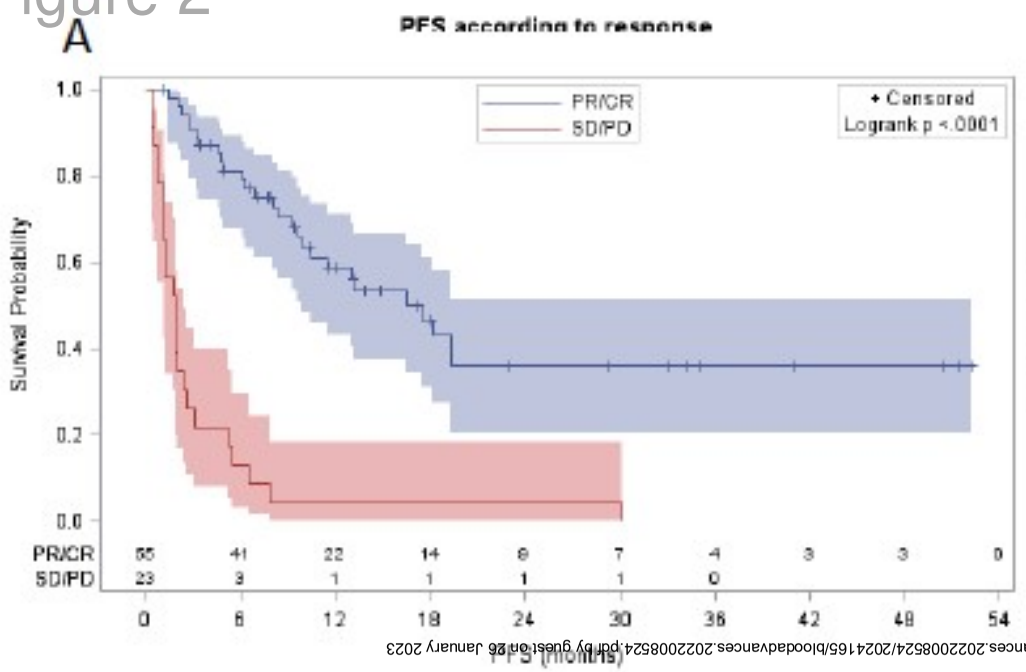


Figure 2



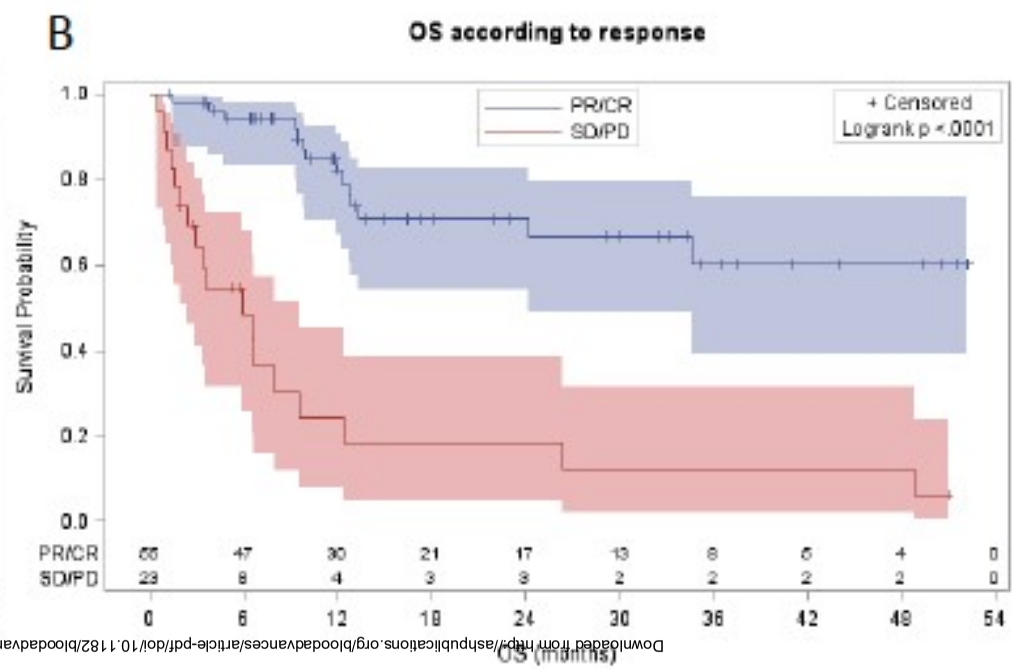
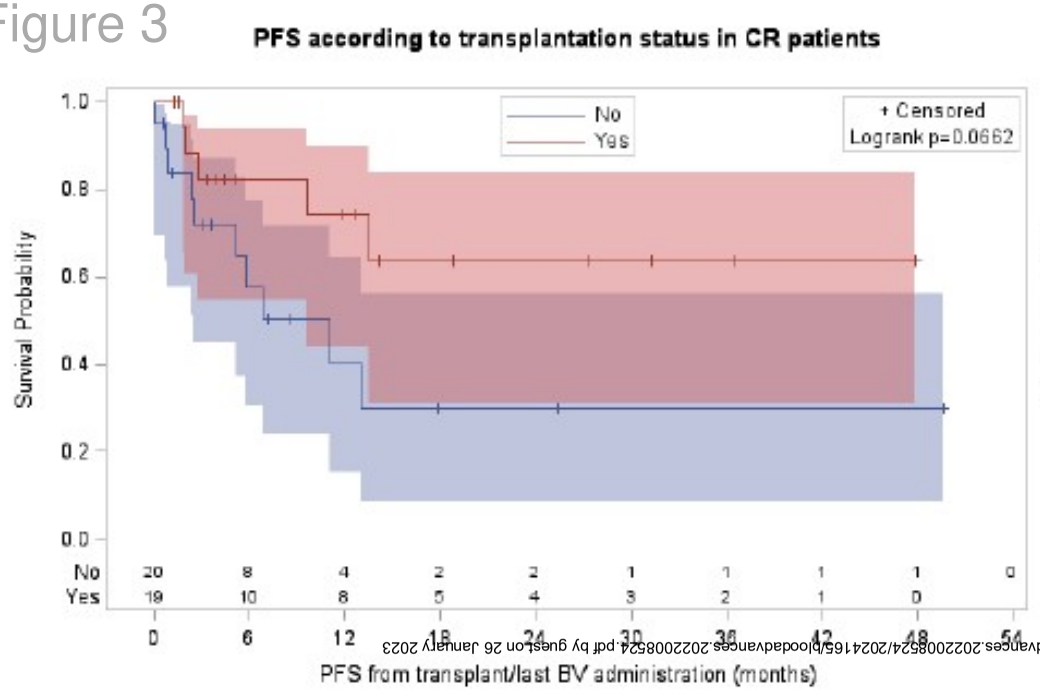


Figure 3



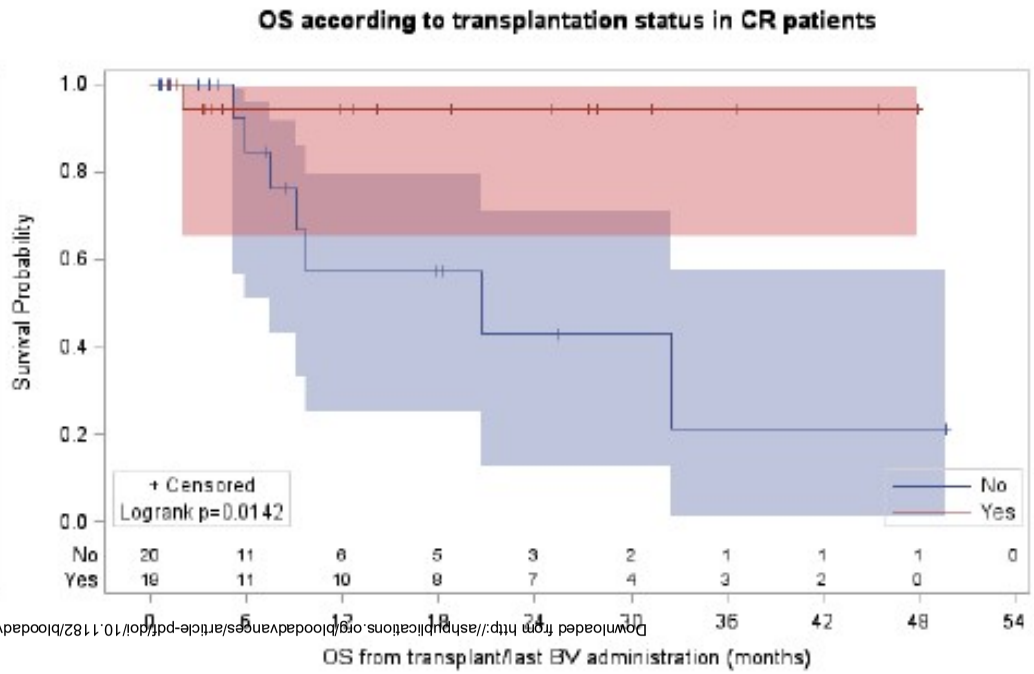


Figure 4