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Polatuzumab vedotin-containing regimens as bridge to CART: analysis from the CART-SIE study

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Abstract:
High tumor burden negatively affects responses to anti-CD19 chimeric antigen receptor T-cell (CART) therapy in large B-cell lymphoma (LBCL). Therefore, bridging therapy (BT) is crucial for disease control before infusion. Here, we retrospectively compared polatuzumab vedotin (PV) combined with rituximab (R) bendamustine (B) in a cohort of 200 LBCL patients enrolled in the prospective, multicenter, observational CART-SIE study. Commercial CART were infused between July 2020 and January 2025. Patients received BT with either PV-BR (n=122) or PV-R (n=78). At median follow-up of 11.9 months, median progression-free (PFS) and overall survival (OS) in the entire cohort were 10.1 and 35.1 months after CART, respectively. When comparing PV-BR with PV-R treated groups, patient characteristics at CART eligibility, objective response rates to BT (52.5% vs 49.4%, p=0.775), median PFS (13.4 months vs 7.4 months, p=0.556), and median OS (not reached vs 29.0 months, p=0.954) were similar. Hematological toxicities after BT were higher with PV-BR than PV-R (36.4% vs 18.2%, p=0.010; grade≥3 16.1% vs 6.5%, p=0.048), as were rates of neurotoxicity after CART (31.1% vs 15.4%, p=0.019). Rates of cytokine release syndrome and infections were comparable between the two groups. High tumor burden at CART infusion was independent risk factor for both PFS and OS. Our findings confirmed the role of BT and suggested that PV-regimens may effectively control the disease during T-cell manufacturing. Responses and survivals were similar between PV-R and PV-BR, with PV-R showing a trend toward lower toxicity, including reduced neurotoxicity, supporting its potential as a targeted, well-tolerated bridging regimen.

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Key points

- Polatuzumab vedotin associated with rituximab is safe and effective as a bridge to anti-CD19 CART in LBCL.
- The addition of bendamustine to PV-R induces higher rates of toxicities with no differences in tumor control or in survival after CART.

Abstract

High tumor burden negatively affects responses to anti-CD19 chimeric antigen receptor T-cell (CART) therapy in large B-cell lymphoma (LBCL). Therefore, bridging therapy (BT) is crucial for disease control before infusion. Here, we retrospectively compared polatuzumab vedotin (PV) combined with rituximab (R) ± bendamustine (B) in a cohort of 200 LBCL patients enrolled in the prospective, multicenter, observational CART-SIE study. Commercial CART were infused between July 2020 and January 2025. Patients received BT with either PV-BR (n=122) or PV-R (n=78). At median follow-up of 11.9 months, median progression-free (PFS) and overall survival (OS) in the entire cohort were 10.1 and 35.1 months after CART, respectively. When comparing PV-BR with PV-R treated groups, patient characteristics at CART eligibility, objective response rates to BT (52.5% vs 49.4%, p=0.775), median PFS (13.4 months vs 7.4 months, p=0.556), and median OS (not reached vs 29.0 months, p=0.954) were similar. Hematological toxicities after BT were higher with PV-BR than PV-R (36.4% vs 18.2%, p=0.010; grade≥3 16.1% vs 6.5%, p=0.048), as were rates of neurotoxicity after CART (31.1% vs 15.4%, p=0.019). Rates of cytokine release syndrome and infections were comparable between the two groups. High tumor burden at CART infusion was independent risk factor for both PFS and OS. Our findings confirmed the role of BT and suggested that PV-regimens may effectively control the disease during T-cell manufacturing. Responses and survivals were similar between PV-R and PV-BR, with PV-R showing a trend toward lower toxicity, including reduced neurotoxicity, supporting its potential as a targeted, well-tolerated bridging regimen.

Introduction

Chimeric antigen receptor T-cell (CART) therapies targeting CD19 are standard treatments for patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL),[1-7] and have recently been approved for use in the second-line setting.[8-13] Patients with rapidly progressive or symptomatic disease at the time of CART eligibility have a dismal prognosis and often fail to proceed to infusion.[14-19] Moreover, high tumor burden has been associated with lower efficacy and increased immune cell-mediated toxicities.[18,20-22]

Bridging therapy (BT) is the antineoplastic treatment administered between leukapheresis and CART infusion, with the aim of controlling the disease during T-cell manufacturing, especially when a long turnaround time is expected.[15,19,23-25] Given the aggressiveness of LBCL and the risk of progression during the CART production period, BT may reduce pre-infusion dropout and influence CART responses and long-term outcomes. Since the registrational trials, BT has lacked standardization, as it was allowed in JULIET[4] but not in ZUMA-1.[1] A variety of regimens have been used as BT in real-world studies, selected according to disease presentation, treatment history and physician discretion. These have included steroids, focal and comprehensive radiotherapy (defined as radiotherapy to all active sites of disease seen on imaging),[26] chemotherapy, immunotherapy, and targeted agents.[14-17,27-29] Therefore, identifying a BT regimen that effectively reduces tumor burden without adding toxicity is crucial for the overall success of CART therapies.[30]

Polatuzumab vedotin (PV) is an antibody-drug conjugate composed of the anti-mitotic agent monomethyl auristatin E (MMAE) covalently linked to a monoclonal antibody targeting CD79b, a key component of the B-cell receptor complex that is highly expressed on malignant B cells, including more than 95% of LBCL.[31] On this basis, encouraging antitumor activity was anticipated in this setting. However, PV has shown low complete response rates when used as monotherapy[32,33] or with rituximab (R) in R/R LBCL,[34] supporting the need for additional combination strategies. The cytotoxic agent bendamustine (B) was therefore added to PV-R to enhance efficacy, and based on the results of the phase 1b/2 GO29365 trial,[35] PV-BR was approved in R/R LBCL, achieving an objective response rate of 45% with a manageable safety profile. Nevertheless,

responses were not durable, suggesting a potential role for PV-based regimens as BT to CART infusion.[24]

Bendamustine is a unique chemotherapeutic agent with both alkylating and purine analog properties, which can overcome cross-resistance to other alkylators and has potent B-cell lymphocytotoxic activity. It is highly effective in indolent non-Hodgkin lymphomas when combined with rituximab,[36,37] but has shown only modest activity in R/R LBCL.[38-41] Consequently, its use in this setting is largely limited to patients with R/R LBCL ineligible for CART and autologous stem-cell transplantation, in combination with PV-R.[42,43]

Owing to its dual antitumor activity and lymphocytotoxic effect, bendamustine has been extensively studied both as a lymphodepleting strategy, showing a favorable toxicity profile,[44-47] and in BT regimens.[23] Whether the inclusion of this cytotoxic agent into PV-R BT is associated with different outcomes and additional toxicities remains to be determined.

Although several real-world experiences have shown that PV-containing regimens enable patients to successfully proceed with CART infusion,[23,24,29,30] a systematic characterization of PV as BT is lacking.

Since November 2019, the Italian Society of Hematology (Società Italiana di Ematologia, SIE) has conducted a prospective, multicenter, observational study (CART-SIE) evaluating the efficacy and safety of CD19-directed CART in lymphomas. In this sub-analysis of CART-SIE, we aimed to assess the impact of PV as a bridge to CART, comparing PV-BR with the alkylator-free regimen (PV-R) in terms of response and toxicity.

Methods

The CART-SIE study is an ongoing prospective, observational, multicenter study, which collects clinical data from patients diagnosed with diffuse large B-cell lymphoma (DLCBL), primary mediastinal B-cell lymphoma (PMBCL), mantle cell lymphoma, and follicular lymphoma (FL) who are eligible for commercially available CART therapy in Italy[48]. Eligibility criteria for CART are defined by the "Agenzia Italiana del Farmaco" (AIFA, Italian drug agency). The detailed list of criteria is provided in the Supplemental Materials. The CART-SIE study is conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines and has been approved by the institutional review board at each site (INT 180/19, approval number 431/DG, 2019. ClinicalTrials.gov ID: NCT06339255).[48] All patients provided written informed consent.

This study is a sub-analysis of CART-SIE, evaluating PV-containing regimens as BT to CART. Patients diagnosed with refractory or relapsed LBCL who received CART infusion and had been administered PV-R or PV-BR as BT were eligible. Patients treated with PV in the first-line setting or who had received holding therapies (defined as any systemic treatment or radiotherapy administered just before apheresis) were excluded. Bridging therapy was defined as any antineoplastic treatment administered between leukapheresis and CART infusion. The choice of BT and the number of cycles was at the treating physician's discretion. For the purpose of this sub-analysis, patient- and disease-related variables were retrospectively extracted from the CART-SIE database and from institutional clinical records, aggregated as de-identified data in a single password-protected dataset.

All patients were administered axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), or lisocabtagene maraleucel (liso-cel) between July 2020 and January 2025 at 17 Italian CART centers. The data collection cutoff date was April 1, 2025.

Pre-leukapheresis and pre-lymphodepletion (pre-LD) lactate dehydrogenase (LDH) values were collected as surrogate markers of tumor burden. Pre-LD LDH referred to measurements obtained after BT and prior to LD. LDH was considered elevated when above the upper limit of normal per center-specific reference ranges. Bulky disease was defined as a longest diameter >10 cm of the largest node or mass.

Responses after BT (pre-LD) and at 1 and 3 months after CART infusion were assessed according to the Lugano criteria using PET and/or CT scans in routine clinical practice and were evaluated by local physicians.[49,50] Best response was defined as the best response achieved by day +90.

Adverse events encompassed hematological toxicities and infections occurring after BT and within 30 days after CART, as well as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) after CART. Hematological toxicities and infections were graded according to the Common Terminology Criteria for Adverse Events (version 5.0), whereas CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy criteria.[51] No other adverse event data were collected.

Progression-free survival (PFS) was defined as the time from CART infusion to disease progression or death from any cause. Overall survival (OS) was defined as the time from CART infusion to death from any cause.

The aims of the study were to assess response rates and the incidence of adverse events after BT. Efficacy endpoints included best overall response rate (ORR) after CART, overall survival (OS) and progression-free survival (PFS) stratified by BT, as well as rates of CRS and ICANS within 30 days after CART infusion.

Descriptive statistics were used to summarize patient and disease characteristics, BT, toxicities and responses. Continuous variables were summarized as median with interquartile range (IQR), unless otherwise specified, whereas categorical variables were reported as counts and frequencies. Differences in distribution were tested with the chi-square test and Fisher's exact test for categorical variables, unpaired Student's t-test or ANOVA for continuous variables, as appropriate. A multivariable logistic regression model was fitted to assess the effect of key covariates on the occurrence of ICANS.

PFS and OS were analyzed using Kaplan-Meier curves and compared with the log-rank test or Gehan-Breslow-Wilcoxon as applicable. Cox proportional hazards regression models were used for multivariable analyses for PFS and OS to include significant covariates, reported as hazard ratios (HR) and two-sided 95% confidence intervals (CI 95%). Variables with at least marginal association with PFS/OS from the univariable analysis (p-value < 0.1) were included in the multivariable model.

All statistical tests were 2-sided, and a p-value less than 0.05 was considered statistically significant. Analyses were performed with Statistical Package for the Social Sciences software v.22.0 (Chicago, IL, USA) and R version 4.1.3 (2022-03-10) - R Foundation for Statistical Computing, Vienna, Austria. Figures were generated using R.

Results

From November 2019 to January 2025, 1,132 patients were consecutively enrolled in CART-SIE, of whom 958 were infused and evaluable. Among the infused patients, 706 were diagnosed with LBCL. Of these, 200 received PV-BR or PV-R as BT and were included in the current study. One hundred twenty-two patients (61.0%) received PV-BR, while 78 (39.0%) received PV-R. Patient characteristics are shown in **Table 1**, stratified by BT regimen received; the patient flow diagram is provided in the Supplemental Materials (**supplemental Figure 1**).

The median age was 61 years, and 39.5% of patients were female. Among LBCL patients, 66.0% were diagnosed with diffuse LBCL, 16.5% with high-grade B-cell lymphoma, and 17% with transformed indolent lymphoma (13.5% from follicular lymphoma and 3.5% from marginal zone lymphoma). There were no significant differences between the two groups in terms of histology. Most patients had advanced-stage disease (n=168, 84.4%) at leukapheresis and a high tumor burden, as indicated by elevated LDH (n=118, 64.8%). The most infused product was axi-cel (n=152, 76.0%), followed by tisa-cel (n=46, 23.0%) and liso-cel (n=2, 1.0%). The median number of prior therapies was 2 (range, 1-6), with 37 patients (18.5%) treated with CART as second-line therapy. As aforementioned, patients who received PV as first-line therapy were not included in this study.

The median number of BT cycles was 1. The median time from leukapheresis to CART infusion was 53 days (IQR, 41-75), with a median manufacturing time of 28 days (IQR, 26-33). A few patients also received radiotherapy before CART without differences between the two groups. Noteworthy, all the patient and disease baseline characteristics were well balanced between the two groups (**Table 1**). Only two patients received bendamustine as LD; otherwise, fludarabine-cyclophosphamide was the most infused regimen.

Responses and toxicities after BT

Of the 197 patients evaluable for response to BT, 101 (51.3%) achieved an objective response prior to LD, including 47 (23.9%) with complete response (CR) and 54 (27.4%) with partial response (PR). These percentages exclude 3 of 200 patients, for whom response after BT was not assessed (**Table 2**). Accordingly, we evaluated the impact of LDH reduction from pre-leukapheresis to pre-LD (after BT), as a surrogate marker of tumor burden. Pairwise pre-leukapheresis and pre-LD LDH values were available for 181 patients, creating four groups: 69 patients (38.1%) had high LDH values at both timepoints (high/high); 48 patients (26.5%) experienced LDH normalization after BT (high/normal); 8 patients (4.4%) showed an increase in LDH after BT (normal/high); 56 patients (31.0%) maintained normal LDH throughout BT (normal/normal). Normalization of LDH values significantly correlated with response to BT, both complete and overall response ($p<0.001$; **supplemental Figure 2**).

No statistically significant differences in response to BT were identified between the PV-BR and PV-R groups (ORR 52.5% vs 49.4%, p=0.775; CR rate 25.0% vs 22.1%, p=0.765; **Figure 1** and **Table 2**). Adverse events occurred more frequently in bendamustine-treated patients compare to those in the PV-R group (42.4% vs 24.7%, p=0.018), with hematological toxicities being predominant (all-grade 36.4% vs 18.2%, p=0.010; grade≥3 16.1% vs 6.5%, p=0.048; **Figure 1**). No significant differences in infection rates were observed after BT (**Table 2**).

Ferritin values at the time of CART infusion, serving as a marker of inflammation, were significantly higher in the PV-BR group than the PV-R group (mean 781.9 vs 411.6 ng/dL, p=0.016; **Table 2**). The interval between leukapheresis and CART infusion did not differ significantly between the groups. However, the time from the end of BT to CART infusion was longer in PV-BR than in PV-R (median 36 days [IQR 30–50] vs 32 days [IQR 24–37], p=0.034; **Table 1**).

Responses and toxicities after CART

The best ORR after CART was 79.6% (n=152/191), including 78.3% (n=90/115) in the PV-BR group and 81.6% (n=62/76) in the PV-R group, respectively (p=0.709, **Figure 2**). The best CR rate was significantly higher in the PV-R than in the PV-BR (72.4% vs

56.5%, p=0.039; **Table 2**). Disease response was not assessable in nine patients due to early death, one of which was caused by disease progression (**supplemental Table 1**).

The median follow-up for the full cohort was 11.9 months (95% CI 11.0-12.9), longer in PV-BR than in PV-R (13.6 vs 10.1 months, p=0.039). The median PFS was 10.1 months (95% CI 5.8-14.4), with comparable results for the BT groups (HR 0.89, 95% CI 0.60-1.33, p=0.556; **Figure 2**). Restricting the analysis to axi-cel, the 12-month PFS was 49.0% in the PV-BR group versus 39.1% in the PV-R (p=0.798; **Figure 3**).

The median OS for the entire cohort was 35.4 months (95% CI 22.8-48.1), with no differences based on BT (HR 1.01, 95% CI 0.58-1.77, p=0.954). In the axi-cel cohort, the 12-month OS was 71.2% in the PV-BR group and 70.7% in the PV-R group (p=0.827; **Figure 3**).

The PFS and OS of patients who received CAR-T infusion with a high tumor burden or who did not respond to BT were significantly shorter than those of patients with controlled disease or a response to BT (**Figure 4**). In univariable analysis for PFS, high LDH at LD (HR 2.16, 95% CI 1.45-3.21, p <0.001) and stable/progressive disease (SD/PD) after BT (HR 2.46, 95% CI 1.63-3.72, p <0.001) were risk factors. When combined with advanced-stage disease, extranodal involvement, and bulky disease before leukapheresis, high LDH at LD and lack of response to BT remained independently associated with PFS (**Table 3**).

Similarly, in univariable analysis for OS, extranodal disease (HR 1.84, 95% CI 1.02-3.33, p=0.044), bulky disease before BT (HR 2.26, 95% CI 1.29-3.97, p=0.005), three or more prior lines of therapy (HR 1.93, 95% CI 1.09-3.44, p=0.025), high LDH at LD (HR 2.14, 95% CI 1.23-3.73, p=0.007), and SD/PD after BT (HR 3.01, 95% CI 1.65-4.48, p<0.001) were risk factors for death. Multivariable analysis identified extranodal disease (HR 2.06, 95% CI 1.07–3.95, p=0.030), three or more prior therapies (HR 2.27, 95% CI 1.18–4.41, p=0.014), high LDH at lymphodepletion (HR 2.03, 95% CI 1.10–3.77, p=0.024), and absence of response to BT (HR 2.10, 95% CI 1.11–3.99, p=0.023) as independent risk factors for death (**Table 4**). Notably, the type of BT regimen did not influence survival outcomes.

All-grade CRS occurred in 89.0% of patients (n=178/200), with 4.0% being grade≥3 events (n=9/200; **Table 2** and **Figure 5**). The overall ICANS rate was 25.0%

(n=50/200), with grade≥3 events in 5 patients (2.5%). No differences in CRS rate were observed between BT regimens, while ICANS was more frequent in the PV-BR group (all-grade 31.1% vs 15.4%, p=0.019; grade≥3 4.1% vs 0.0%, p=0.178). Infections occurring within 30 days after CART infusion were reported in 27/199 patients (13.6%), including grade≥3 in 6/199 patients (3.0%), equally distributed by the two BT cohorts. Three grade 5 immune-related toxicities occurred within 30 days of infusion: two CRS (one in PV-BR and one in PV-R) and one ICANS (in PV-BR; **supplemental Table 1**).

Discussion

This sub-analysis of the observational CART-SIE study included 200 patients with LBCL who received CART across 17 Italian centers in a real-world setting. Consistent with other European real-world studies, axi-cel was the most infused product, followed by tisa-cel and liso-cel, reflecting both the predominant use of axi-cel in Europe and the more recent approval of liso-cel[14-16,27,29].

Polatuzumab-vedotin combined with rituximab as BT was effective in controlling tumor burden prior to CART and showed a more favorable toxicity profile than PV-BR. Notably, a higher rate of adverse events after BT was observed in the PV-BR group (42.4% vs 24.7%, p=0.018), primarily hematological toxicities, as well as a higher incidence of ICANS (all-grade event 31.1% vs 15.4%, p=0.019).

Overall, the response rate after CART in our cohort was consistent with real-world reports,[14-17,27-29,52] with a best ORR of 79.6% (81.6% and 78.3% in the PV-R and PV-BR group, respectively, p=0.578). Interestingly, a higher best CR rate after CART infusion was achieved with PV-R than PV-BR (72.4% vs 56.5%, p=0.027), but this did not translate into a difference in survival.

The median PFS for the entire cohort was 10.1 months, with 7.4 vs 13.4 months in the PV-R vs PV-BR groups, respectively (p=0.556), exceeding that reported in other studies[52] and confirmed in analyses stratified by CART product (**Figures 2** and **3, Table 3**). Similarly, the median OS for the full cohort was 35.4 months, also longer than previously reported,[14-16,27,29] with no differences according to BT regimen or CART product (**Figures 2** and **3**, **Table 4**). These differences may reflect the selection of the BT population, which excluded LBCL patients bridged to CART with other regimens

(**supplemental Figure 1**). Whether the inclusion of second-line CART might have prolonged PFS was not supported by univariable and multivariable analyses, in which neither the number of prior lines of therapy nor the CART product was associated with survival.

In contrast, tumor burden at the time of CART infusion - represented by both pre-LD LDH and response to BT - was independently associated with PFS and OS, consistent with the literature.[15,18,23,30,53] Interestingly, extranodal disease was associated with worse OS but not PFS, as recently reported by Iacoboni et al.[54] These findings highlight the need to control disease prior to CART infusion in LBCL patients and support the crucial role of BT in achieving longer PFS and OS (**Figure 4**).

We then analyzed toxicities after CART according to BT. Rates of CRS were similar between the PV-BR and the PV-R groups, with an overall frequency of 4.0% grade≥3 events. This frequency is lower than that reported in other studies,[14-17,27,29] likely reflecting earlier recognition and improved management of CRS in clinical practice.[55-57]

In contrast, all-grade ICANS was more frequent in the PV-BR group, an association confirmed in univariable and multivariable analyses, in which both PV-BR and elevated pre-LD LDH were independently associated with neurotoxicity (**supplemental Table 2**). Based on previous evidence,[58] the addition of bendamustine to PV-R might have induced a higher inflammatory state, which in turn might have contributed to the occurrence of ICANS. Supporting this, ferritin levels before CART were higher in PV-BR than in PV-R patients (mean 781.9 vs 411.6 ng/dL, p=0.016), although a comprehensive assessment of the inflammatory status was not available.

It should be noted that in the multivariable analysis, a statistically significant association between grade≥3 CRS and ICANS was not observed, probably due to the small sample size, as reflected by the wide confidence interval (**supplemental Table 2**).

To ensure a more homogeneous cohort, we performed these analyses for the axi-cel subgroup. Baseline characteristics were well balanced between the two subgroups, and we confirmed the results obtained in the full cohort (**Figure 3, supplemental Table 3, supplemental Figures 3-4**).

Taking all this evidence together, we confirmed the strong prognostic value of tumor burden at LD on post-CART survival, as shown in **Figure 4**, supporting the rationale

for the use of BT. A response was achieved with both PV regimens in approximately half of the cohort, with a reduction in LDH from leukapheresis to infusion (**supplemental Figure 2**), demonstrating effective disease control during CART manufacturing.

However, patients receiving bendamustine experienced a higher frequency of all-grade and grade≥3 adverse events, particularly hematologic toxicities. This is consistent with the toxicity profile of PV-BR reported in both clinical trial and real-world experiences,[35,59-61] which is higher than that observed with PV-R,[62] with neutropenia, thrombocytopenia, anemia, and febrile neutropenia being the most frequent grade≥3 events.

Furthermore, while the manufacturing time was similar between the two groups, the interval from BT completion to CART infusion was significantly longer in PV-BR than in PV-R. Several factors may have contributed to this delay, including logistical issues related to patient recovery; however, it is reasonable to infer that the management of complications and resolution of cytopenias after BT may have contributed to postponing the infusion. Although a longer time to infusion *per se* does not affect outcomes after CART[15], it may reflect underlying patient conditions that could impact performance status, increase the risk of infections, or necessitate antibiotic prophylaxis - all factors that have been associated with post-CART survival.[14-16,21,27,63,64]

Several factors should be considered when selecting the optimal BT to CART in LBCL, including tumor debulking, toxicity profile, myelosuppression, and recovery time. Various approaches - including chemoimmunotherapy, steroids, targeted therapies, and radiotherapy - have been used and compared as BT, but an extensive analysis of these strategies is beyond the scope of this study. Based on the favorable toxicity profile and the efficacy of PV combined with BR[35] or R,[34] Liebers et al. were the first to investigate PV as BT, reporting that approximately half of the patients successfully proceeded with infusion.[24] Iacoboni et al. evaluated bendamustine-containing regimens as BT, demonstrating improved disease control; however, the small sample size precluded a direct comparison between PV-BR and PV-R.[23]

In this scenario, our study compared PV-R and PV-BR in a real-world setting, showing that PV-R was similarly efficacious in controlling tumor burden while exhibiting a potentially safer toxicity profile than PV-BR during T-cell manufacturing. Moreover, the omission of bendamustine as BT allows for its use in the lymphodepleting regimen, which

has been extensively studied and associated with comparable survival, but lower toxicity than fludarabine-cyclophosphamide for each product analyzed.[44-46]

Among other bridging strategies, it is worth mentioning radiotherapy. Several studies have reported that disease progression or recurrence after CART often has a local component, supporting the use of local treatment along with systemic therapy.[25,26,65-68] In our study, patients with bulky diseases or who received radiotherapy were equally distributed between PV-BR and PV-R, minimizing confounding and allowing direct comparisons.

We acknowledge several limitations of this study, primarily stemming from the retrospective extraction of data for this sub-analysis. Although CART-SIE is a prospective, observational study, data for the current analysis were collected retrospectively from both CART-SIE and institutional clinical records. The allocation of BT in our cohort may reflect selection bias, limiting direct comparisons with non-PV regimens. Similarly, unbiased selection of the CART construct was not feasible. The recent introduction of PV into first-line treatment for LBCL[69] precluded these patients from receiving PV as BT, and they were therefore automatically excluded. Including only patients who received CART infused prevented evaluation of the dropout rate from leukapheresis, which would be addressed by an intention-to-treat analysis. Furthermore, measuring endpoints from the time of CART infusion rather than from BT initiation - and consequently, excluding 174 subjects enrolled in CART-SIE who did not proceed with CART infusion, among whom there may have been LBCL patients eligible for PV-based BT - may have limited the identification of potential efficacy or toxicity signals of these regimens.

On the other hand, the strengths of this study include the large sample size and the relatively homogeneous management across Italian CART centers. Baseline characteristics were well balanced between the groups, supporting valid comparisons and statistically significant results. Furthermore, secondary analyses within the axi-cel subgroup allowed evaluation in an even more uniform population, minimizing the influence of CART product on outcomes. The effects of potential confounders were further explored through univariable and multivariable analyses for the primary endpoints.

To the best of our knowledge, this is the largest cohort of LBCL patients bridged to anti-CD19 CART using PV-containing regimens. Our findings confirm the poor outcomes of patients infused with a high tumor burden and suggest that PV-containing regimens may effectively control disease during T-cell manufacturing. Objective responses after BT and survival outcomes following CART were generally similar between PV-R and PV-BR, with PV-R showing a trend toward lower toxicity, including a reduced rate of ICANS.

In conclusion, these results shed light on PV-R as a widely available, targeted regimen capable of controlling tumor with a favorable toxicity profile. Further prospective studies are warranted to better define the most effective bridging strategies and understand the biological mechanisms underlying treatment resistance and disease recurrence.

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Authorship Contributions

GG, BC, PLZ conceptualized and designed the study, interpreted and discussed results. GG collected clinical data, performed data analysis and interpretation. LA contributed to statistical analysis. GG, BC, LA, PLZ drafted the manuscript. All authors participated in manuscript writing and review, and provided final approval of the manuscript.

Conflict of Interest Disclosures

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678 **Tables**

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680 **Table 1.** Baseline patient characteristics divided by bridging therapy received.

Variables, n (%)	Total, n=200 (100%)	PV-BR, n=122 (61%)	PV-R, n=78 (39%)	p-value
Female	79 (39.5)	46 (37.7)	33 (42.3)	0.516
Age at infusion, median (range)	61 (24-76)	62 (24-76)	61 (29-76)	0.881
Diagnosis				0.253
DLBCL, NOS	132 (66.0)	78 (63.9)	54 (69.2)	
HGBL	33 (16.5)	23 (18.9)	10 (12.8)	
FL, transformed	27 (13.5)	18 (14.8)	9 (11.6)	
MZL, transformed	7 (3.5)	2 (1.6)	5 (6.4)	
PMBCL	1 (0.5)	1 (0.8)	0 (0.0)	
Disease status at CART eligibility[a]				0.450
Primary refractory (<6 months)	36 (18.2)	24 (19.8)	12 (15.6)	
Relapsed (>6 months)	162 (81.8)	97 (80.2)	65 (84.4)	
Ann Arbor stage[b], **III-IV**	168 (84.4)	101 (82.8)	67 (85.9)	0.645
Prior lines of therapy				0.558
1	37 (18.5)	21 (17.2)	16 (20.5)	
≥2	163 (81.5)	101 (82.8)	62 (79.5)	
Median lines, n° (range)	2 (1-6)	2 (1-5)	2 (1-6)	0.727
Previous ASCT	28 (14.0)	17 (13.9)	11 (14.1)	0.973
Bulky disease at BT (>10 cm)	55 (27.4)	30 (27.5)	25 (32.5)	0.467
Extra-nodal disease	108 (54.0)	67 (57.8)	41 (54.7)	0.674
ECOG pre-CART ≥2	7 (3.5)	6 (4.9)	1 (1.3)	0.250
Pre-leukapheresis LDH [c] >1 ULN	118 (64.8)	79 (68.1)	39 (59.1)	0.221
Pre-LD LDH [d] >1 ULN	82 (41.8)	54 (45.0)	28 (36.8)	0.259
Radiotherapy before CART	16 (8.0)	13 (10.7)	3 (3.8)	0.110
CART product				0.057
axi-cel	152 (76.0)	89 (73.0)	63 (80.8)	
tisa-cel	46 (23.0)	33 (27.0)	13 (16.7)	
liso-cel	2 (1.0)	0 (0.0)	2 (2.6)	
n° of BT cycles, median (range)	1 (1-5)	1 (1-4)	1.5 (1-5)	0.069
Duration of BT, median days [IQR]	20 [1-23]	20 [1-22]	16 [1-25]	0.551
Time apheresis-CART infusion,				0.394
median days [IQR]	53 [41-75]	53 [42-75]	50 [40-76]	
Axi-cel	49 [40-70]			
Tisa-cel	68 [49-94]			
Liso-cel	52 [48-56]			
Time of manufacturing, median				0.081
days [IQR]	28 [26-33]	28 [26-33]	28 [25-31]	
Axi-cel	27 [25-29]			
Tisa-cel	36 [31-56]			
Liso-cel	37 [35-39]			

681 PV, polatuzumab vedotin; BR, bendamustine rituximab; R, rituximab; CART, chimeric antigen receptor T-cell; DLBCL,
682 diffuse large B-cell lymphoma; NOS, not otherwise specified; HGBL, high grade B-cell lymphoma; FL, follicular
683 lymphoma; MZL, marginal zone lymphoma; PMBCL, primary mediastinal B-cell lymphoma; ASCT, autologous stem
684 cell transplantation; BT, bridging therapy; ECOG, Eastern Cooperative Oncology Group; LDH, lactate
685 dehydrogenase; ULN, upper limit normal; LD, lymphodepletion; axi-cel, axicabtagene ciloleucel; tisa-cel,
686 tisagenlecleucel, liso-cel lisocabtagene maraleucel; IQR, interquartile range.
687 [a]missing 2 patients

[b]missing 1 patient
[c]missing 18 patients
[d]missing 4 patients; LDH pre-LD refers to measurements obtained after bridging therapy and prior to lymphodepletion.
[e]data available for 131 pts, missing 69 pts

Table 2. Results divided by bridging therapy received.

Outcome	Total, n=200 (100%)	PV-BR, n=122 (61%)	PV-R, n=78 (39%)	p-value
Response to BT[a]				ORR 0.775
CR	47 (23.9)	30 (25.0)	17 (22.1)	CRR 0.765
PR	54 (27.4)	33 (27.5)	21 (27.3)	
SD	35 (17.8)	22 (18.3)	13 (16.9)	
PD	61 (30.9)	35 (29.2)	26 (33.8)	
Adverse events after BT[a]	69 (35.4)	50 (42.4)	19 (24.7)	**0.018**
Hematologic AE after BT[a]	57 (29.2)	43 (36.4)	14 (18.2)	**0.010**
Hematologic AE after BT grade≥3[a]	24 (12.3)	19 (16.1)	5 (6.5)	**0.048**
Infections after BT	10 (5.8)	6 (5.8)	4 (5.9)	>0.999
Ferritin at CART infusion[b] Mean, ng/dL (standard deviation)	634.9 (865.2)	781.9 (1039.0)	411.6 (415.5)	**0.016**
Best response to CART[c]				ORR 0.709
CR	120 (62.8)	65 (56.5)	55 (72.4)	**CRR 0.027**
PR	32 (16.8)	25 (21.7)	7 (9.2)	
SD	8 (4.2)	4 (3.5)	4 (5.3)	
PD	31 (16.2)	21 (18.3)	10 (13.2)	
CRS	178 (89.0)	113 (92.6)	69 (88.5)	0.453
CRS grade≥3	8 (4.3)	7 (5.7)	2 (2.6)	0.487
ICANS	50 (25.0)	38 (31.1)	12 (15.4)	**0.019**
ICANS grade≥3	5 (2.5)	5 (4.1)	0 (0.0)	0.159
ICU admission after CART[d]	17 (9.6)	12 (11.1)	5 (7.2)	0.395
Infections[e]	27 (13.6)	14 (11.6)	13 (16.7)	0.305
Infections grade≥3	6 (3.0)	2 (1.7)	4 (5.2)	0.212

PV, polatuzumab vedotin; BR, bendamustine rituximab; R, rituximab; BT, bridging therapy; AE, adverse event; CART, chimeric antigen receptor T-cell; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CRS, cytokine-release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome (ICANS); ICU, intensive care unit.

[a]missing data in 3 patients (2 in PV-BR group, 1 in PV-R)

[b]data available for 131 pts, missing in 69 patients

[c]not evaluable due to early death in 9 patients

[d]missing data in 23 patients

[e]missing data in 1 patient

Table 3. Uni- and multivariable analyses for PFS, Cox proportional hazards model.

Variable	Univariable HR	Univariable CI95%	p-value	Multivariate HR	Multivariate CI95%	p-value
Sex	0.90	0.59-1.37	0.633			
Age, continuous	0.99	0.98-1.01	0.620			
Diagnosis	0.95	0.88-1.03	0.193			
ECOG ≥2	0.82	0.30-2.23	0.692			
Stage III-IV	1.86	1.01-3.41	**0.045**	1.74	0.85-3.57	0.130
Extranodal disease	1.51	1.00-2.30	**0.049**	1.30	0.81-2.09	0.276
Bulky disease at BT	1.52	0.99-2.31	**0.052**	1.34	0.84-2.12	0.220
Previous lines 3 vs 2	1.44	0.91-2.26	0.120			
Prior ASCT	0.62	0.34-1.14	0.127			
Primary refractory	0.94	0.55-1.73	0.941			
Pre-leukapheresis LDH, >ULN	1.36	0.86-2.17	0.190			
Pre-LD LDH, >ULN	2.16	1.45-3.21	**<0.001**	1.63	1.06-2.50	**0.027**
CART product	1.22	0.80-1.87	0.350			
Bridging therapy (PV-BR vs PV-R)	0.89	0.60-1.33	0.570			
SD/PD after bridging therapy	2.46	1.63-3.72	**<0.001**	2.05	1.32-3.18	**0.001**

HR, hazards ratio; CI95%, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; BT, bridging therapy; ASCT, autologous stem cell transplantation; LDH, lactate dehydrogenase; ULN, upper limit normal; LD, lymphodepletion; CART, chimeric antigen receptor T-cell; PV, polatuzumab vedotin; BR, bendamustine rituximab; R, rituximab; SD, stable disease; PD, progressive disease.

Table 4. Uni- and multivariable analyses for OS, Cox proportional hazards model.

Variable	Univariable HR	Univariable CI95%	p-value	Multivariable HR	Multivariable CI95%	p-value
Sex	0.66	0.37-1.19	0.174			
Age, continuous	1.01	0.98-1.03	0.580			
Diagnosis	0.93	0.84-1.04	0.193			
ECOG≥2	0.89	0.22-3.66	0.872			
Stage III-IV	1.33	0.82-4.51	0.133			
Extranodal disease	1.84	1.02-3.33	**0.044**	2.06	1.07-3.95	**0.030**
Bulky disease at BT	2.26	1.29-3.97	**0.005**	1.74	0.90-3.36	0.098
Previous lines 3 vs 2	1.93	1.09-3.44	**0.025**	2.27	1.18-4.41	**0.014**
Prior ASCT	0.58	0.24-1.34	0.193			
Primary refractory	0.65	0.26-1.64	0.361			
Pre-leukapheresis LDH, >ULN	1.69	0.87-3.25	0.120			
Pre-LD LDH, >ULN	2.14	1.23-3.73	**0.007**	2.03	1.10-3.77	**0.024**
CART product	1.28	0.71-2.29	0.408			
Bridging therapy (PV-BR vs PV-R)	1.01	0.58-1.77	0.954			
SD/PD after bridging therapy	3.01	1.65-5.48	**<0.001**	2.10	1.11-3.99	**0.023**

HR, hazards ratio; CI95%, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; BT, bridging therapy; ASCT, autologous stem cell transplantation; LDH, lactate dehydrogenase; ULN, upper limit normal; LD, lymphodepletion; CART, chimeric antigen receptor T-cell; PV, polatuzumab vedotin; BR, bendamustine rituximab; R, rituximab; SD, stable disease; PD, progressive disease.

Figure legends

Figure 1. Overall response rates and hematological toxicity rates after bridging therapy. Response rates after bridging therapy (panel A; p-value refers to overall response, CR-PR vs SD-PD); all grade hematological toxicity rate after bridging therapy (panel B); grade ≥3 hematological toxicity rate after bridging therapy (panel C). Hematological toxicities were defined as anemia, thrombocytopenia and neutropenia occurring after bridging therapy and prior to lymphodepletion, graded according to the Common Terminology Criteria for Adverse Events, version 5.0. PV-R, polatuzumab vedotin-rituximab; PV-BR, polatuzumab vedotin-bendamustine and rituximab; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Figure 2. Best overall response rate and survivals after CART divided by bridging therapy, all cohort. Best overall response rate after CART divided by bridging therapy, calculated in all cohort (panel A; p-value refers to best overall response, CR-PR vs SD-PD); Kaplan-Meier curves of progression-free survival (panel B) and overall survival (panel C) divided by bridging therapy, calculated in all cohort. PV-R, polatuzumab vedotin-rituximab; PV-BR, polatuzumab vedotin-bendamustine and rituximab; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Figure 3. Best overall response rate and survivals after CART divided by bridging therapy, axi-cel recipients. Best overall response rate after CART divided by bridging therapy, calculated in axi-cel recipients (panel A, p-value refers to best overall response, CR-PR vs SD-PD); Kaplan-Meier curves of progression-free survival (panel B) and overall survival (panel C) divided by bridging therapy, calculated in axi-cel recipients. PV-R, polatuzumab vedotin-rituximab; PV-BR, polatuzumab vedotin- bendamustine and rituximab; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Figure 4. PFS and OS by response to BT and by LDH value pre-LD, all cohort. Kaplan-Meier curves of progression-free survival divided by LDH values pre-lymphodepletion (panel A) and overall response to bridging therapy (panel B), calculated in all cohort; Kaplan-Meier curves of overall survival divided by LDH values pre-lymphodepletion (panel C) and overall response to bridging therapy (panel D), calculated

749 in all cohort. PFS, progression-free survival; OS, overall survival; LDH, lactate
750 dehydrogenase; ORR, overall response rate; BT, bridging therapy; pre-LD, pre-
751 lymphodepletion; CR/PR, complete response/partial response; SD/PD, stable disease,
752 progressive disease.

753 **Figure 5. CRS and ICANS occurrence after CART, all cohort.** All grade
754 cytokine-release syndrome rate (panel A) and all grade immune effector cell-associated
755 neurotoxicity syndrome rate (panel B) after CART, calculated in all cohort. Grade ≥3
756 cytokine-release syndrome rate (panel C) and all grade immune effector cell-associated
757 neurotoxicity syndrome rate (panel D) after CART, calculated in all cohort. PV-R,
758 polatuzumab vedotin-rituximab; PV-BR, polatuzumab vedotin- bendamustine and
759 rituximab; CRS, cytokine-release syndrome; ICANS, immune effector cell-associated
760 neurotoxicity syndrome.

Figure 1.

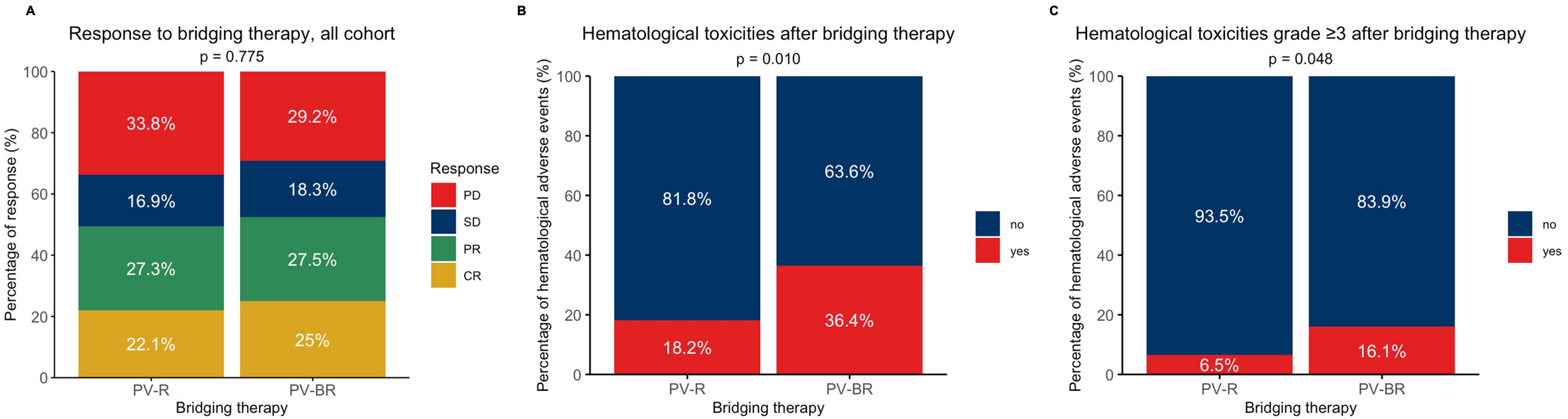


Figure 2.

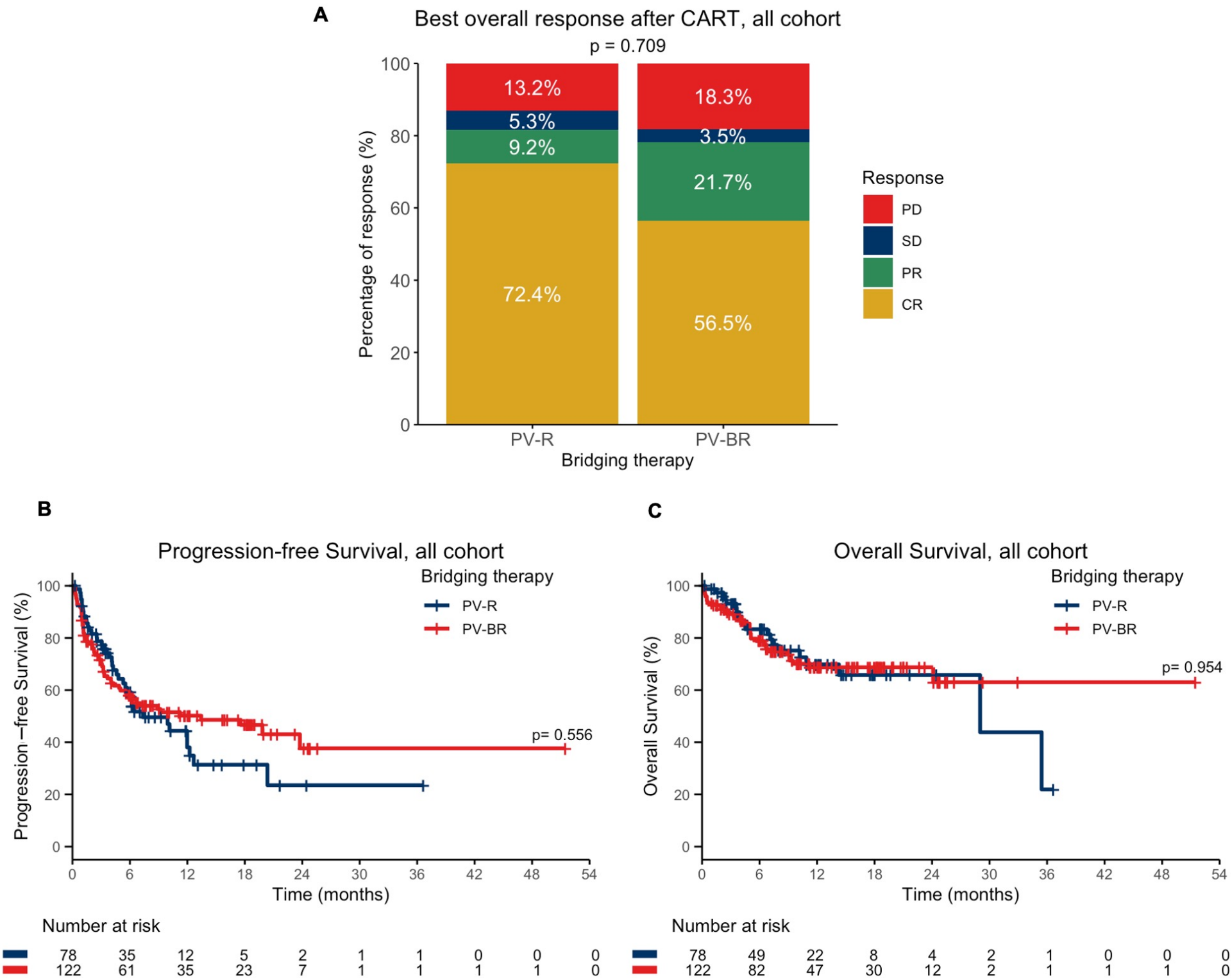
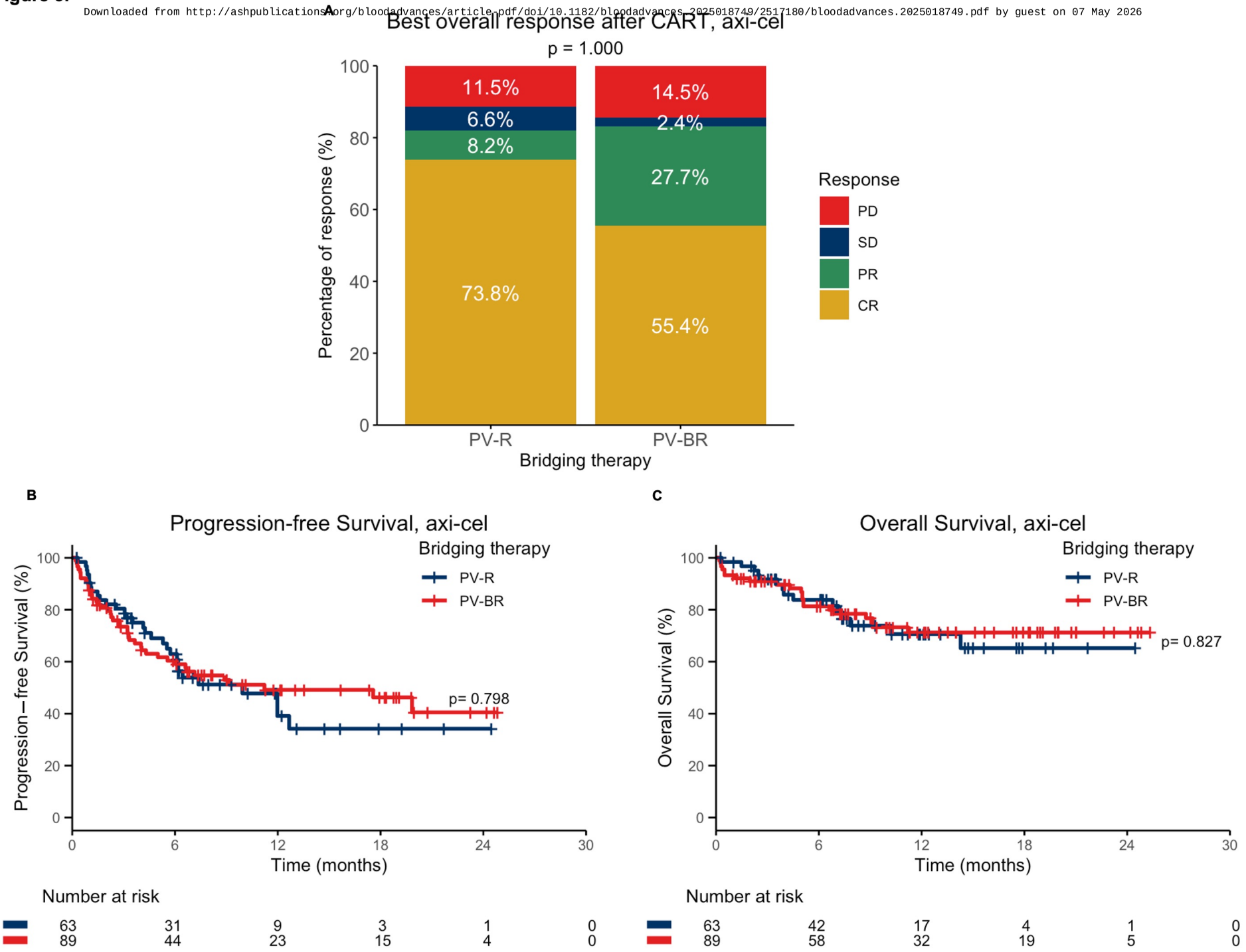


Figure 3.



12-month PFS: PV-R 39.1% vs PV-BR 49.0%, p=0.798

12-month OS: PV-R 70.7% vs PV-BR 71.2%, p=0.827

Figure 4.

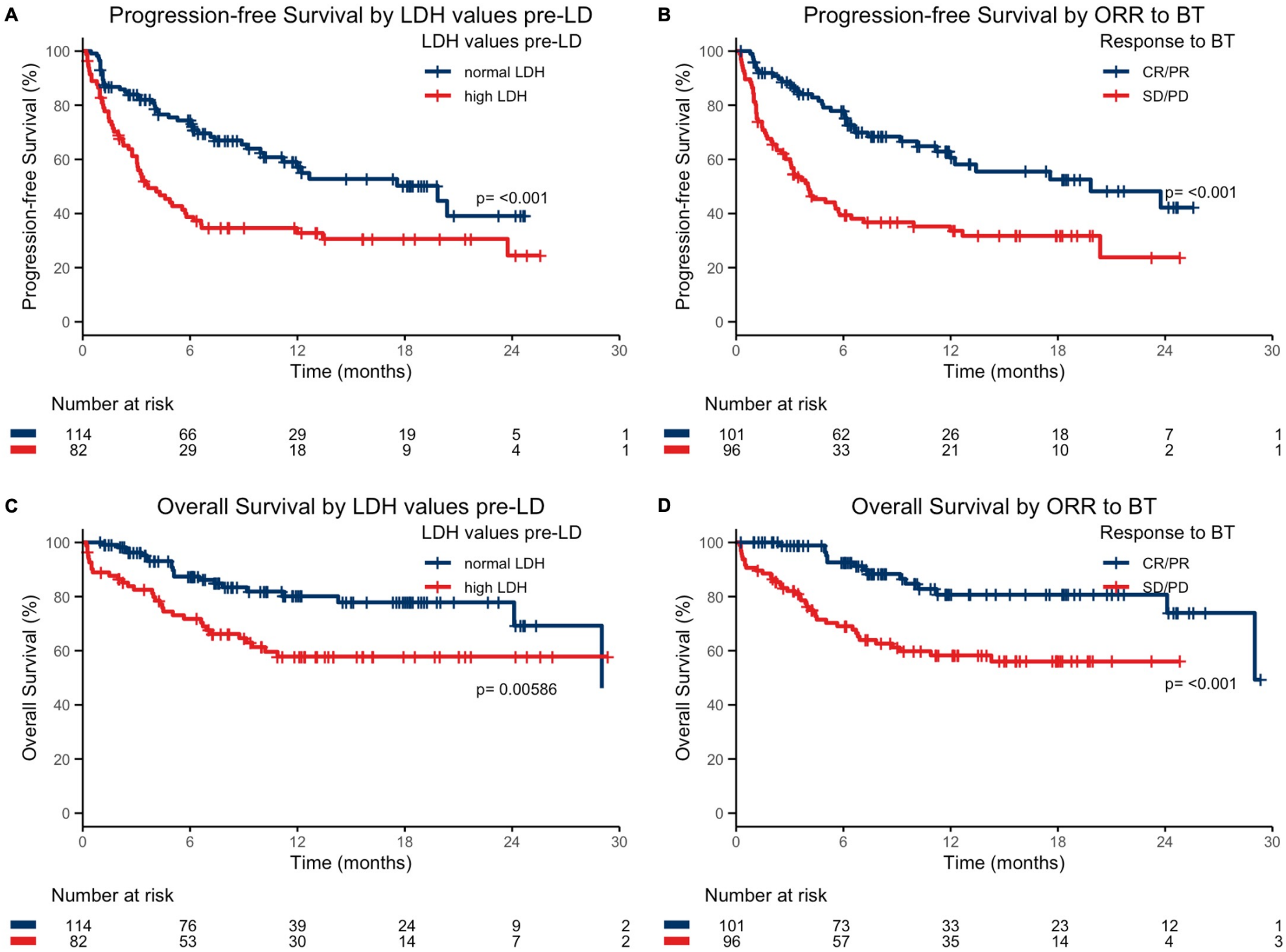


Figure 5.