

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

Giulia Gabrielli,^{1,*} Beatrice Casadei,^{2,*} Annalisa Chiappella,³ Maria Chiara Tisi,⁴ Eugenio Galli,⁵ Ilaria Cutini,⁶ Alice Di Rocco,⁷ Livia Donzelli,⁷ Massimo Martino,⁸ Giorgia Policastro,⁸ Alessandra Crescimanno,⁹ Giuseppe Petruzzellis,¹⁰ Federico Stella,³ Carlo Visco,¹¹ Mauro Krampere,¹¹ Mirko Farina,¹² Piera Angelillo,¹³ Lucia Brunello,¹⁴ Benedetto Bruno,¹⁵ Daniele Mannina,¹⁶ Mattia Novo,¹⁷ Giovanni Grillo,¹⁸ Lisa Argnani,¹ Francesca Bonifazi,¹⁹ Paolo Corradini,³ and Pier Luigi Zinzani¹

¹Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; ²Istituto di Ricovero e Cura a Carattere Scientifico Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Bologna, Italy; ³Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy; ⁴Hematology Unit, San Bortolo Hospital, Azienda Unità Locale Socio-Sanitaria n. 8 "Berica," Vicenza, Italy; ⁵Fondazione Policlinico Universitario A. Gemelli Istituto di Ricovero e Cura a Carattere Scientifico, Dipartimento di Scienze di Laboratorio ed Ematologiche, Rome, Italy; ⁶Struttura Organizzativa Dipartimentale Ematologia, Azienda Ospedaliero Universitaria Careggi, Florence, Italy; ⁷Hematology, Department of Translational and Precision Medicine, University Sapienza, Rome, Italy; ⁸Department of Hemato-Oncology and Radiotherapy, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli," Reggio Calabria, Italy; ⁹Unità Operativa Oncoematologia e Programma Trapianti Cellule Staminali Ematopoietiche e Immunoterapia Cellulare Dipartimento Oncologico La Maddalena, Palermo, Italy; ¹⁰Division of Hematology and Bone Marrow Transplant, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; ¹¹Unità di Ematologia e Centro Trapianto di Midollo Osseo, Sezione di Biomedicina di Innovazione, Dipartimento di Ingegneria per la Medicina di Innovazione, Università degli Studi di Verona, Verona, Italy; ¹²Unit of Blood Disease and Stem Cell Transplantation, Department of Clinical and Experimental Sciences, University of Brescia, Azienda Socio Sanitaria Territoriale-Spedali Civili, Brescia, Italy; ¹³Lymphoma Unit, University Vita-Salute San Raffaele, Milan, Italy; ¹⁴Struttura Complessa a Direzione Universitaria Ematologia, Azienda Ospedaliero-Universitaria SS Antonio e Biagio e C. Arrigo, Alessandria, Italy; ¹⁵Division of Hematology, Department of Molecular Biotechnology and Health Sciences, University of Torino, and Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Turin, Italy; ¹⁶Istituto di Ricovero e Cura a Carattere Scientifico Humanitas Research Hospital, Humanitas, Cancer Center, Rozzano, Milan, Italy; ¹⁷Division of Hematology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza, Turin, Italy; ¹⁸Dipartimento di Ematologia e trapianto di midollo, Azienda Socio Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda, Milan, Italy; and ¹⁹Istituto di Ricovero e Cura a Carattere Scientifico Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Key Points

- PV-R 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 survival after CART.

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 (PV-R) ± bendamustine (PV-BR) in a cohort of 200 patients with LBCL enrolled in the prospective, multicenter, observational CART-Società Italiana di Ematologia (SIE) study. Commercial CARTs 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, the median progression-free survival (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%; $P = .775$), median PFS (13.4 months vs 7.4 months; $P = .556$), and median OS (not reached vs 29.0 months; $P = .954$) were similar. Hematological toxicities after BT were higher with PV-BR than PV-R (36.4% vs 18.2%; $P = .010$; grade ≥ 3 , 16.1% vs 6.5%; $P = .048$), as were rates of neurotoxicity after CART (31.1% vs 15.4%; $P = .019$). Rates of cytokine release syndrome and infections were comparable between the 2 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

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*G. Gabrielli and B.C. contributed equally to this work.

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

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and survival 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 preinfusion dropout and influence CART responses and long-term outcomes. Since the registrational trials, BT has lacked standardization, because it was allowed in JULIET⁴ 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 antimetabolic agent monomethyl auristatin E 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 >95% of LBCL.³¹ On this basis, encouraging antitumor activity was anticipated in this setting. However, PV has shown low complete response (CR) rates when used as monotherapy^{32,33} or with rituximab (PV-R) in R/R LBCL,³⁴ supporting the need for additional combination strategies. The cytotoxic agent bendamustine was therefore added to PV-R (PV-BR) to enhance efficacy, and based on the results of the phase 1b/2 GO29365 trial,³⁵ PV-BR was approved for 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 subanalysis 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 LBCL, primary mediastinal B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma who are eligible for commercially available CART therapy in Italy.⁴⁸ Eligibility criteria for CART are defined by the "Agenzia Italiana del Farmaco" (Italian drug agency). The detailed list of criteria is provided in the supplemental Methods.

This study is a subanalysis of CART-SIE, evaluating PV-containing regimens as BT to CART. Patients diagnosed with R/R 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. BT 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 subanalysis, patient- and disease-related variables were retrospectively extracted from the CART-SIE database and institutional clinical records, aggregated as deidentified data in a single password-protected data set.

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 1 April 2025.

Preleukapheresis and prelymphodepletion (pre-LD) lactate dehydrogenase (LDH) values were collected as surrogate markers of tumor burden. Pre-LD LDH referred to measurements obtained after BT and before 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 for 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 positron emission tomography and/or computed tomography 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 end points included best overall response rate (ORR) after CART, OS and PFS stratified by BT, and 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 χ^2 test and Fisher exact test for categorical variables and unpaired Student *t* test or analysis of variance 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 test, 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 2-sided 95% confidence intervals (CI). Variables with at least marginal association with PFS/OS from the univariable analysis ($P < .1$) were included in the multivariable model.

All statistical tests were 2 sided, and a *P* value $< .05$ was considered statistically significant. Analyses were performed with Statistical Package for the Social Sciences software v.22.0 (Chicago, IL) and R version 4.1.3 (2022-03-10; R Foundation for Statistical Computing, Vienna, Austria). Figures were generated using R.

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](https://clinicaltrials.gov) identifier: NCT06339255).⁴⁸ All patients provided written informed consent.

Results

From November 2019 to January 2025, a total of 1132 patients were consecutively enrolled in CART-SIE, of whom 958 received infusion and were evaluable. Among the patients who received infusion, 706 were diagnosed with LBCL. Of these, 200 received PV-BR or PV-R as BT and were included in this study. A total of 122 patients (61.0%) received PV-BR, whereas 78 (39.0%) received PV-R. Patient characteristics are shown in [Table 1](#), stratified by the 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 patients with LBCL, 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 2 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 2 groups. Noteworthy, all the patient and disease baseline characteristics were well balanced between the 2 groups ([Table 1](#)). Only 2 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 before LD, including 47 (23.9%) with CR and 54 (27.4%) with partial response. 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 preleukapheresis to pre-LD (after BT), as a surrogate marker of tumor burden. Pairwise preleukapheresis and pre-LD LDH values were available for 181 patients, creating 4 groups: 69 patients (38.1%) had high LDH values at both time points (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); and 56 patients (31.0%) maintained normal LDH throughout BT (normal/normal). Normalization of LDH values significantly correlated with response to BT, both CR and overall response ($P < .001$; 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%; $P = .775$; CR rate, 25.0% vs 22.1%; $P = .765$; [Figure 1](#); [Table 2](#)). Adverse events occurred more frequently in bendamustine-treated patients than those in the PV-R group (42.4% vs 24.7%; $P = .018$), with hematological toxicities being predominant (all grade, 36.4% vs 18.2%; $P = .010$; grade ≥ 3 , 16.1% vs 6.5%; $P = .048$; [Figure 1](#)). No significant differences in infection rates were observed after BT ([Table 2](#)).

Table 1. Baseline patient characteristics stratified by BT 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)	.516
Age at infusion, median (range), y	61 (24-76)	62 (24-76)	61 (29-76)	.881
Diagnosis				.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*				.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† III-IV	168 (84.4)	101 (82.8)	67 (85.9)	.645
Prior lines of therapy				.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)	.727
Previous ASCT	28 (14.0)	17 (13.9)	11 (14.1)	.973
Bulky disease at BT (>10 cm)	55 (27.4)	30 (27.5)	25 (32.5)	.467
Extranodal disease	108 (54.0)	67 (57.8)	41 (54.7)	.674
Pre-CART ECOG ≥2	7 (3.5)	6 (4.9)	1 (1.3)	.250
Preleukapheresis LDH‡ >1 ULN	118 (64.8)	79 (68.1)	39 (59.1)	.221
Pre-LD LDH§ >1 ULN	82 (41.8)	54 (45.0)	28 (36.8)	.259
Radiotherapy before CART	16 (8.0)	13 (10.7)	3 (3.8)	.110
CART product				.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)	
No. of BT cycles, median (range)	1 (1-5)	1 (1-4)	1.5 (1-5)	.069
Duration of BT, median (IQR), d	20 (1-23)	20 (1-22)	16 (1-25)	.551
Time from apheresis to CART infusion, median (IQR), d	53 (41-75)	53 (42-75)	50 (40-76)	.394
Axi-cel	49 (40-70)			
Tisa-cel	68 (49-94)			
Liso-cel	52 (48-56)			
Manufacturing time, median (IQR), d	28 (26-33)	28 (26-33)	28 (25-31)	.081
Axi-cel	27 (25-29)			
Tisa-cel	36 (31-56)			
Liso-cel	37 (35-39)			

ASCT, autologous stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; HGBL, high grade B-cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; PMBCL, primary mediastinal B-cell lymphoma; ULN, upper limit normal.

*Missing 2 patients.

†Missing 1 patient.

‡Missing 18 patients.

§Missing 4 patients; LDH pre-LD refers to measurements obtained after BT and before LD.

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; $P = .016$; 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]; $P = .034$; Table 1).

Table 2. Results stratified by BT received

Outcome	Total, N = 200 (100%)	PV-BR, n = 122 (61%)	PV-R, n = 78 (39%)	P value
Response to BT*				ORR .775
CR	47 (23.9)	30 (25.0)	17 (22.1)	CRR .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)	
AE after BT*	69 (35.4)	50 (42.4)	19 (24.7)	.018
Hematological AE after BT*	57 (29.2)	43 (36.4)	14 (18.2)	.010
Hematological AE after BT, grade ≥ 3 *	24 (12.3)	19 (16.1)	5 (6.5)	.048
Infections after BT	10 (5.8)	6 (5.8)	4 (5.9)	>.999
Ferritin at CART infusion†				.016
Mean (standard deviation), ng/dL	634.9 (865.2)	781.9 (1039.0)	411.6 (415.5)	
Best response to CART‡				ORR .709
CR	120 (62.8)	65 (56.5)	55 (72.4)	CRR .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)	.453
CRS, grade ≥ 3	8 (4.3)	7 (5.7)	2 (2.6)	.487
ICANS	50 (25.0)	38 (31.1)	12 (15.4)	.019
ICANS, grade ≥ 3	5 (2.5)	5 (4.1)	0 (0.0)	.159
ICU admission after CART§	17 (9.6)	12 (11.1)	5 (7.2)	.395
Infections	27 (13.6)	14 (11.6)	13 (16.7)	.305
Infections grade ≥ 3	6 (3.0)	2 (1.7)	4 (5.2)	.212

Significant *P* values are set in bold (*P* < .05).

AE, adverse events; CRR, complete response rate; ICU, intensive care unit; PD, progressive disease; PR, partial response; SD, stable disease.

*Missing data in 3 patients (2 in PV-BR group and 1 in PV-R).

†Data available for 131 patients and missing in 69 patients.

‡Not evaluable due to early death in 9 patients.

§Missing data in 23 patients.

||Missing data in 1 patient.

Responses and toxicities after CART

The best ORR after CART was 79.6% (152/191), including 78.3% (90/115) in the PV-BR group and 81.6% (62/76) in the PV-R group (*P* = .709; [Figure 2](#)). The best CR rate was

significantly higher in PV-R than in PV-BR (72.4% vs 56.5%; *P* = .039; [Table 2](#)). Disease response was not assessable in 9 patients due to early death, one of which was caused by disease progression (supplemental Table 1).

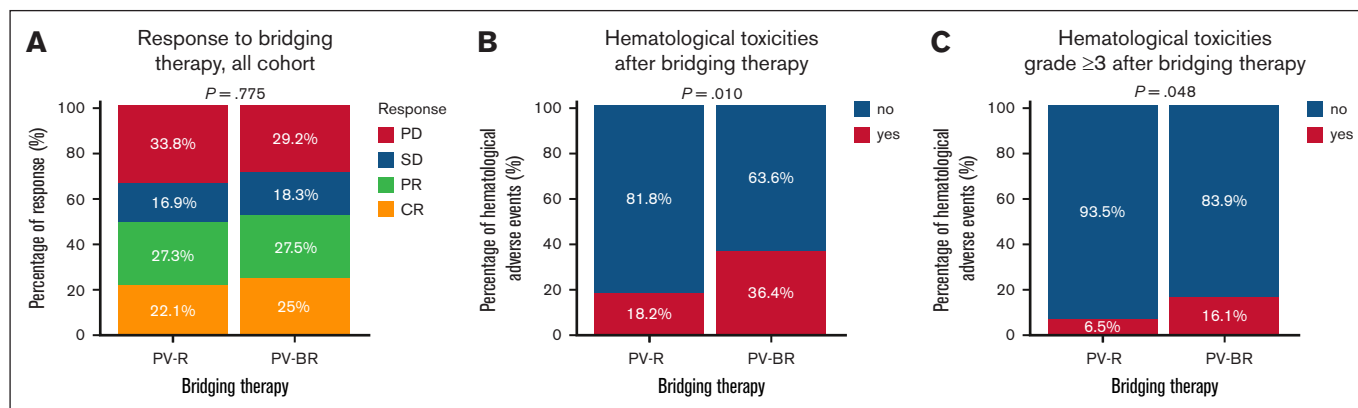


Figure 1. ORRs and hematological toxicity rates after BT. (A-C) Response rates after BT (A); *P* value refers to overall response (CR/partial response [PR] vs stable disease [SD]/progressive disease [PD]); all grade hematological toxicity rate after BT (B); grade ≥ 3 hematological toxicity rate after BT (C). Hematological toxicities were defined as anemia, thrombocytopenia and neutropenia occurring after BT and before LD, graded according to the Common Terminology Criteria for Adverse Events, version 5.0.

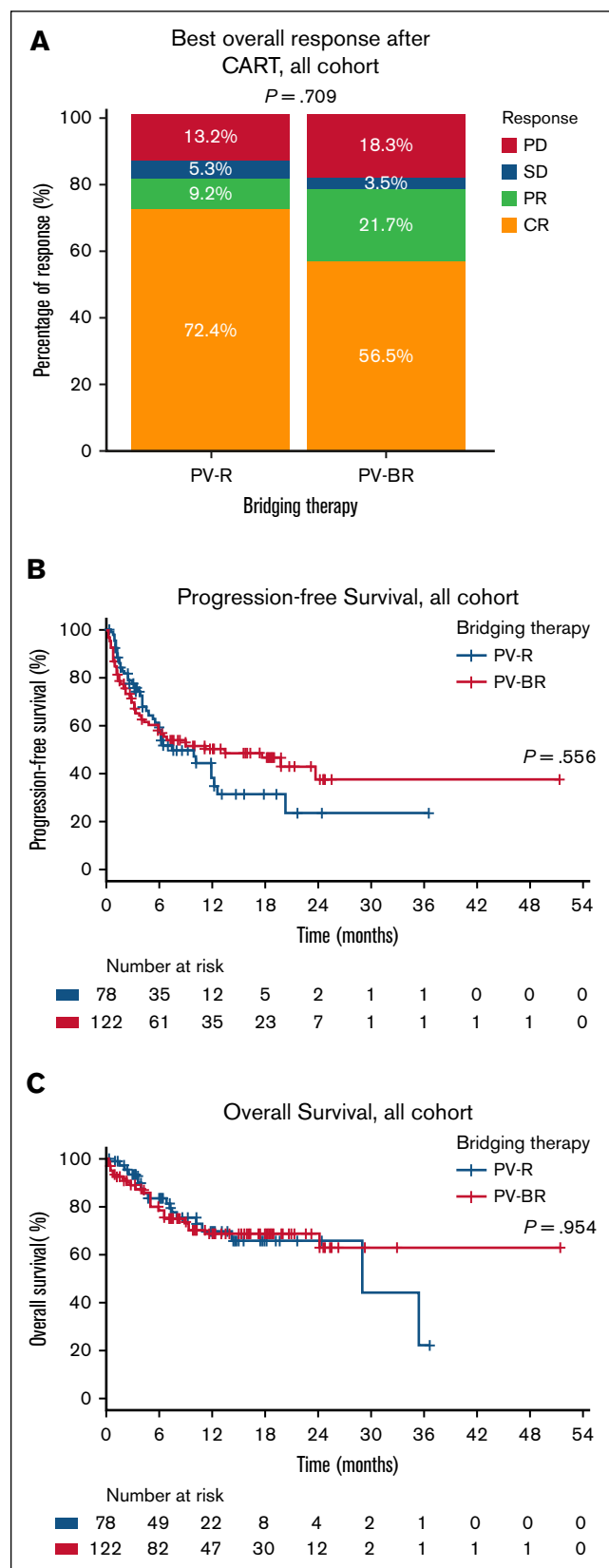


Figure 2. Best ORR and survival after CART stratified by BT in all cohorts. (A) Best ORR after CART stratified by BT, calculated in all cohorts; P value refers to best

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, $P = .039$). The median PFS was 10.1 months (95% CI, 5.8-14.4), with comparable results between the BT groups (HR, 0.89; 95% CI, 0.60-1.33; $P = .556$; **Figure 2**). Restricting the analysis to axi-cel, the 12-month PFS was 49.0% in the PV-BR group vs 39.1% in the PV-R ($P = .798$; **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; $P = .954$). 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 ($P = .827$; **Figure 3**).

The PFS and OS of patients who received CART 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; $P < .001$) and stable/progressive disease after BT (HR, 2.46, 95% CI, 1.63-3.72; $P < .001$) 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; $P = .044$), bulky disease before BT (HR, 2.26; 95% CI, 1.29-3.97; $P = .005$), ≥ 3 prior lines of therapy (HR, 1.93; 95% CI, 1.09-3.44; $P = .025$), high LDH at LD (HR, 2.14; 95% CI, 1.23-3.73; $P = .007$), and stable/progressive disease after BT (HR, 3.01; 95% CI, 1.65-4.48; $P < .001$) were risk factors for death. Multivariable analysis identified extranodal disease (HR, 2.06; 95% CI, 1.07-3.95; $P = .030$), ≥ 3 prior therapies (HR, 2.27; 95% CI, 1.18-4.41; $P = .014$), high LDH at LD (HR, 2.03; 95% CI, 1.10-3.77; $P = .024$), and absence of response to BT (HR, 2.10; 95% CI, 1.11-3.99; $P = .023$) as independent risk factors for death (**Table 4**). Notably, the type of BT regimen did not influence survival outcomes.

All-grade CRS occurred in 178 of 200 patients (89.0%), with 9 (4.0%) being grade ≥ 3 events (**Table 2**; **Figure 5**). The overall ICANS rate was 25.0% (50/200), with grade ≥ 3 events in 5 patients (2.5%). No differences in CRS rate were observed between BT regimens, whereas ICANS was more frequent in the PV-BR group (all grade, 31.1% vs 15.4%; $P = .019$; grade ≥ 3 , 4.1% vs 0.0%; $P = .178$). Infections occurring within 30 days after CART infusion were reported in 27 of 199 patients (13.6%), including grade ≥ 3 in 6 of 199 patients (3.0%), equally distributed between the 2 BT cohorts. Three grade 5 immune-related toxicities occurred within 30 days of infusion: 2 CRS (1 in PV-BR and 1 in PV-R) and 1 ICANS (in PV-BR; supplemental Table 1).

Discussion

This subanalysis 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

Figure 2 (continued) overall response (CR-PR vs SD-PD). (B-C) Kaplan-Meier curves of PFS (B) and OS (C) stratified by BT, calculated in all cohorts.

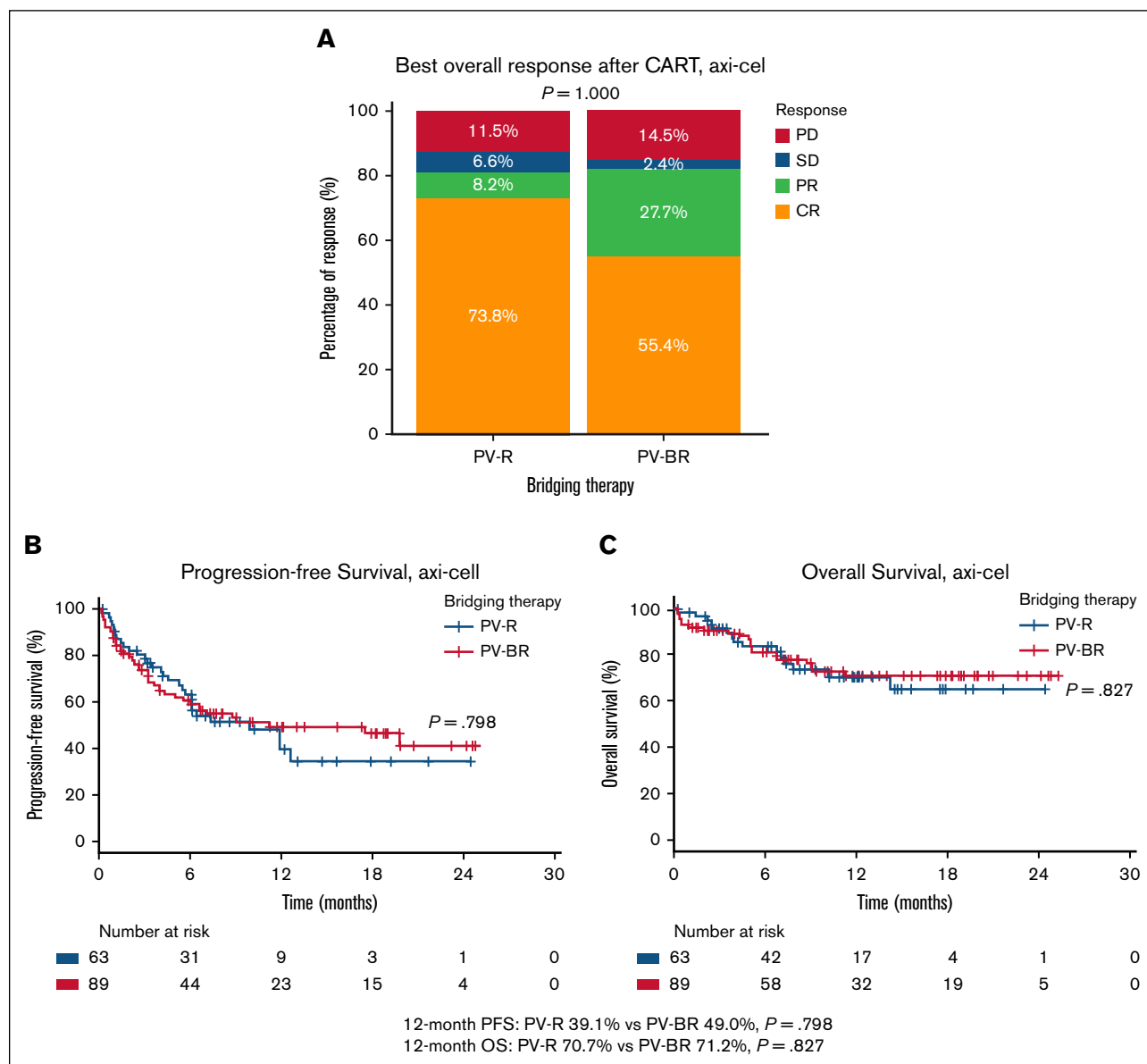


Figure 3. Best ORR and survival after CART stratified by BT in axi-cel recipients. (A) Best ORR after CART stratified by BT, calculated in axi-cel recipients (P value refers to best overall response, CR-PR vs SD-PD). (B-C) Kaplan-Meier curves of PFS (B) and OS (C) stratified by BT, calculated in axi-cel recipients.

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}

PV combined with rituximab as BT was effective in controlling tumor burden before 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%; $P = .018$), primarily hematological toxicities, as well as a higher incidence of ICANS (all-grade event, 31.1% vs 15.4%; $P = .019$).

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; $P = .578$). Interestingly, a higher best CR rate after CART infusion

was achieved with PV-R than PV-BR (72.4% vs 56.5%; $P = .027$), 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 ($P = .556$), exceeding that reported in other studies⁵² 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 patients with LBCL 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

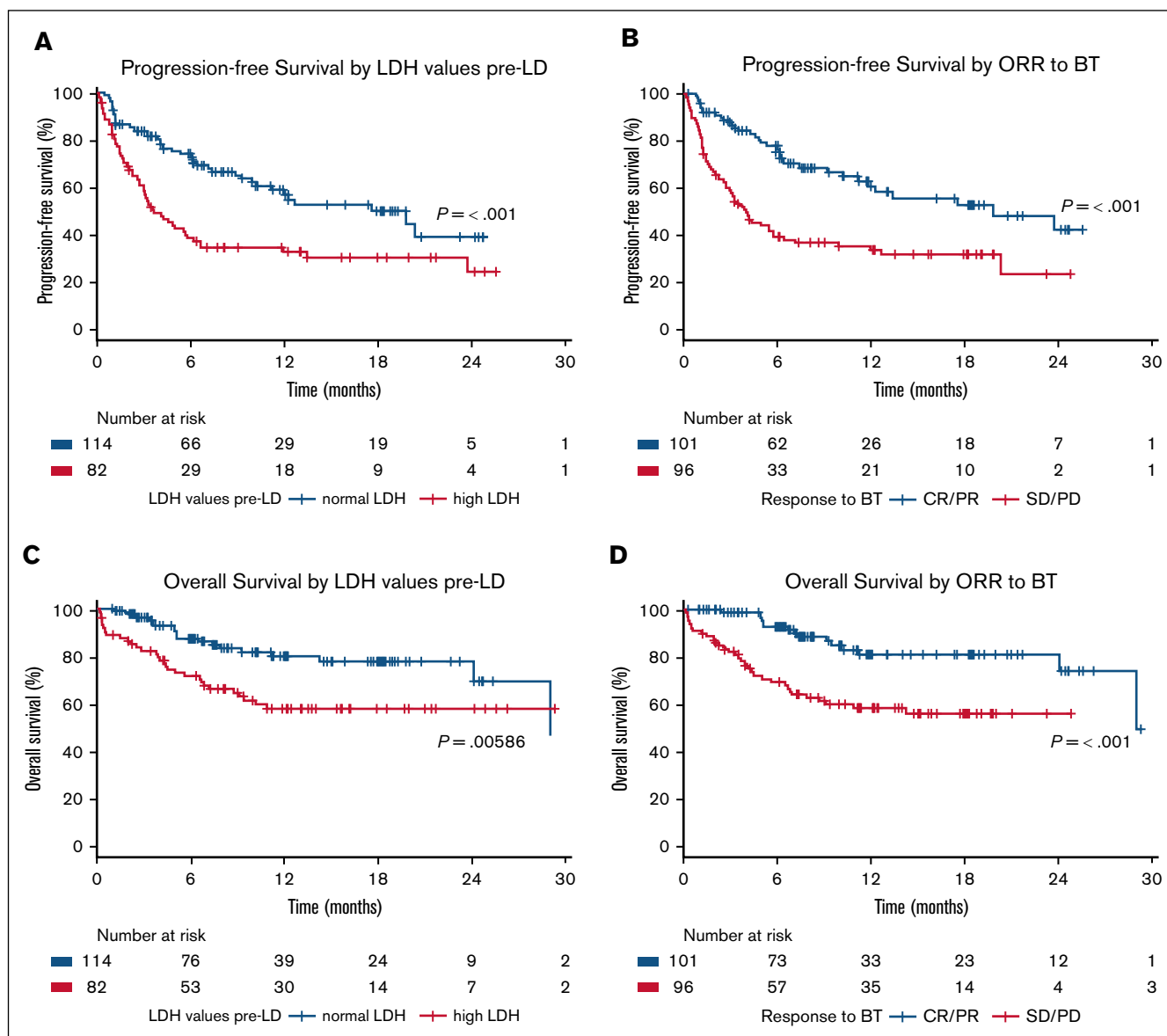


Figure 4. PFS and OS by response to BT and by pre-LD LDH value in all cohorts. (A-B) Kaplan-Meier curves of PFS stratified by LDH values before LD (A) and overall response to BT (B), calculated in all cohorts. (C-D) Kaplan-Meier curves of OS stratified by LDH values before LD (C) and overall response to BT (D), calculated in all cohorts.

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 before CART infusion in patients with LBCL 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 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; $P = .016$), 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 CI (supplemental Table 2).

Table 3. Univariable and multivariable analyses for PFS using Cox proportional hazards model

Variable	Univariable analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex	0.90	0.59-1.37	.633			
Age, continuous	0.99	0.98-1.01	.620			
Diagnosis	0.95	0.88-1.03	.193			
ECOG ≥ 2	0.82	0.30-2.23	.692			
Stage III-IV	1.86	1.01-3.41	.045	1.74	0.85-3.57	.130
Extranodal disease	1.51	1.00-2.30	.049	1.30	0.81-2.09	.276
Bulky disease at BT	1.52	0.99-2.31	.052	1.34	0.84-2.12	.220
Previous lines 3 vs 2	1.44	0.91-2.26	.120			
Prior ASCT	0.62	0.34-1.14	.127			
Primary refractory	0.94	0.55-1.73	.941			
Preleukapheresis LDH, $>ULN$	1.36	0.86-2.17	.190			
Pre-LD LDH, $>ULN$	2.16	1.45-3.21	<.001	1.63	1.06-2.50	.027
CART product	1.22	0.80-1.87	.350			
BT (PV-BR vs PV-R)	0.89	0.60-1.33	.570			
SD/PD after BT	2.46	1.63-3.72	<.001	2.05	1.32-3.18	.001

Variables with at least marginal association with PFS/OS from the univariable analysis ($P < .1$) were included in the multivariable model. Significant P values are set in bold. ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; SD, stable disease; ULN, upper limit normal.

To ensure a more homogeneous cohort, we performed these analyses for the axi-cel subgroup. Baseline characteristics were well balanced between the 2 subgroups, and we confirmed the results obtained in the full cohort (Figure 3; supplemental Table 3; supplemental Figures 3 and 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

Table 4. Univariable and multivariable analyses for OS using Cox proportional hazards model

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex	0.66	0.37-1.19	.174			
Age, continuous	1.01	0.98-1.03	.580			
Diagnosis	0.93	0.84-1.04	.193			
ECOG ≥ 2	0.89	0.22-3.66	.872			
Stage III-IV	1.33	0.82-4.51	.133			
Extranodal disease	1.84	1.02-3.33	.044	2.06	1.07-3.95	.030
Bulky disease at BT	2.26	1.29-3.97	.005	1.74	0.90-3.36	.098
Previous lines 3 vs 2	1.93	1.09-3.44	.025	2.27	1.18-4.41	.014
Prior ASCT	0.58	0.24-1.34	.193			
Primary refractory	0.65	0.26-1.64	.361			
Preleukapheresis LDH, $>ULN$	1.69	0.87-3.25	.120			
Pre-LD LDH, $>ULN$	2.14	1.23-3.73	.007	2.03	1.10-3.77	.024
CART product	1.28	0.71-2.29	.408			
BT (PV-BR vs PV-R)	1.01	0.58-1.77	.954			
SD/PD after BT	3.01	1.65-5.48	<.001	2.10	1.11-3.99	.023

Variables with at least marginal association with PFS/OS from the univariable analysis ($P < .1$) were included in the multivariable model. Significant P values are set in bold. Abbreviations are explained in Table 3.

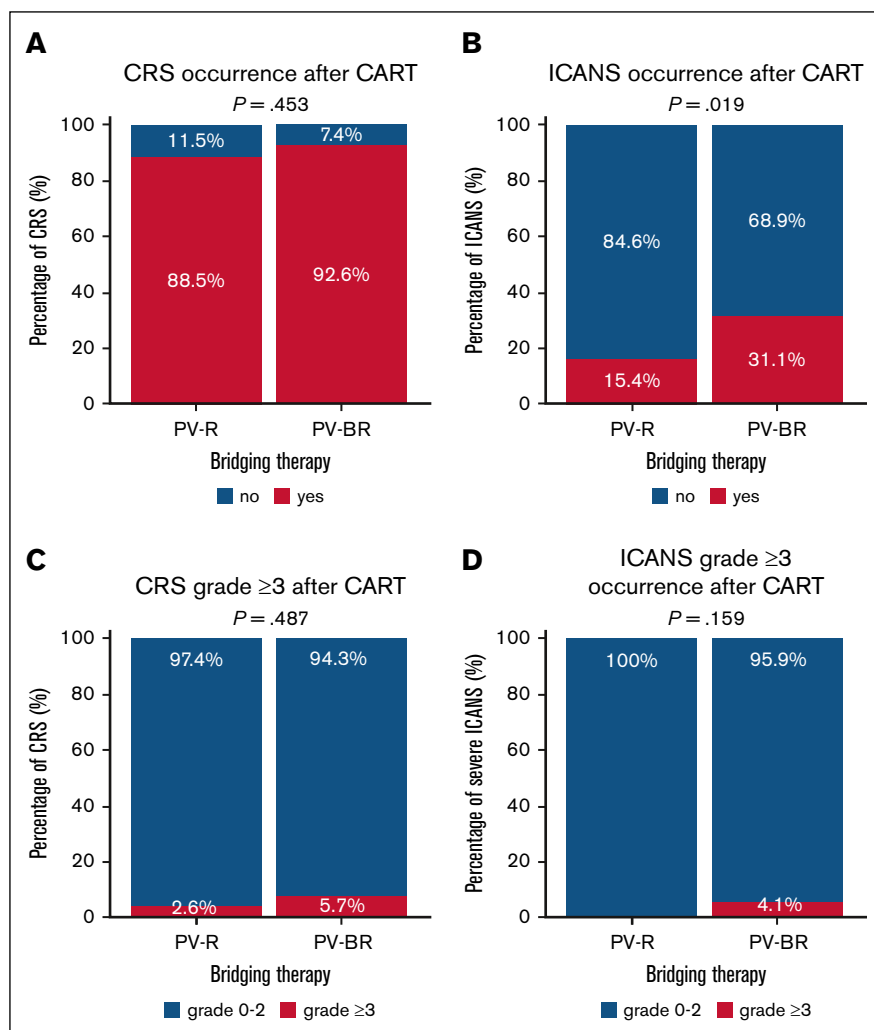


Figure 5. CRS and ICANS occurrence after CART in all cohorts. (A-B) All-grade CRS rate (A) and all-grade ICANS rate (B) after CART, calculated in all cohorts. (C-D) Grade ≥ 3 CRS rate (C) and all-grade ICANS rate (D) after CART, calculated in all cohorts.

hematological 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, although the manufacturing time was similar between the 2 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 affect performance status, increase infection risk, 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-BR³⁵ or PV-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 for direct comparisons.

We acknowledge several limitations of this study, primarily stemming from the retrospective extraction of data for this subanalysis. Although CART-SIE is a prospective, observational study, data for this 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 LBCL⁶⁹ precluded these patients from receiving PV as BT, and they were therefore automatically excluded. Including only patients who received CART infusion prevented evaluation of the dropout rate from leukapheresis, which would be addressed by an intention-to-treat analysis. Furthermore, measuring end points from the time of CART infusion rather than from BT initiation, and consequently, excluding 174 patients enrolled in CART-SIE who did not proceed with CART infusion, among whom there may have been patients with LBCL eligible for PV-based BT, may have limited the identification of potential efficacy or toxicity signals of these regimens.

On the contrary, 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 end points.

To the best of our knowledge, this is the largest cohort of patients with LBCL bridged to anti-CD19 CART using PV-containing regimens. Our findings confirm the poor outcomes of patients who received infusion 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 after 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

Contribution: G. Gabrielli, B.C., and P.L.Z. conceptualized and designed the study and interpreted and discussed results;

G. Gabrielli collected clinical data and performed data analysis and interpretation; L.A. contributed to statistical analysis; G. Gabrielli, B.C., L.A., and P.L.Z. drafted the manuscript; and all authors participated in manuscript writing and review and provided final approval of the manuscript.

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ORCID profiles: G. Gabrielli, [0000-0002-1162-8712](https://orcid.org/0000-0002-1162-8712); A.C., [0000-0002-2977-0098](https://orcid.org/0000-0002-2977-0098); I.C., [0000-0003-3721-0004](https://orcid.org/0000-0003-3721-0004); A.D.R., [0000-0003-0985-9623](https://orcid.org/0000-0003-0985-9623); L.D., [0000-0002-6926-3648](https://orcid.org/0000-0002-6926-3648); M.M., [0000-0002-3987-419X](https://orcid.org/0000-0002-3987-419X); G.P., [0000-0003-1382-7341](https://orcid.org/0000-0003-1382-7341); F.S., [0000-0003-3401-1309](https://orcid.org/0000-0003-3401-1309); C.V., [0000-0003-2863-0883](https://orcid.org/0000-0003-2863-0883); M.K., [0000-0002-7280-2040](https://orcid.org/0000-0002-7280-2040); M.F., [0000-0002-2980-9028](https://orcid.org/0000-0002-2980-9028); B.B., [0000-0002-7299-6770](https://orcid.org/0000-0002-7299-6770); G. Grillo, [0000-0002-9084-9969](https://orcid.org/0000-0002-9084-9969); F.B., [0000-0003-1544-9911](https://orcid.org/0000-0003-1544-9911); P.C., [0000-0002-9186-1353](https://orcid.org/0000-0002-9186-1353); P.L.Z., [0000-0002-2112-2651](https://orcid.org/0000-0002-2112-2651).

Correspondence: Pier Luigi Zinzani, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" and Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Via Massarenti, 9, 40138 Bologna, Italy; email: pierluigi.zinzani@unibo.it.

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