Brentuximab vedotin plus nivolumab as bridging therapy to CAR T-cells in relapsed/refractory primary mediastinal B-cell lymphoma

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare subtype of large B-cell non-Hodgkin lymphoma that occurs predominantly in adolescents and young adults. PMBCL is generally accompanied by a good prognosis but in about 10-30% of patients, first-line treatment is not curative.[1,2] Salvage chemo-immunotherapy followed by autologous stem cell transplantation was historically the standard of care for first-relapse PMBCL, but outcomes were often unsatisfactory, with low complete remission (CR) rates and limited long-term survival.[3,4] The most recent LYSA guidelines now recommend chimeric antigen receptor T-cell (CAR-T) therapy as the preferred second-line option, a change supported by results from the TRANSFORM trial, which included nine patients with PMBCL in the experimental arm.[5,6]

Real-world data on CAR-T therapy in PMBCL are encouraging but highlight the need for further improvements. In an Italian registry of 70 patients treated with axicabtagene ciloleucel (axi-cel), the CR rate was 65%, with 1-year progression-free survival (PFS) and overall survival (OS) rates of 62% and 86%, respectively.[7] Similarly, the CARTHYM study from the French DESCAR-T registry reported a CR rate of 74.5% among 62 axi-cel treated patients, with 2-year PFS and OS rates of 70.4% and 86.9%, respectively.[8]

Evidence of the efficacy of check point inhibitors (CPI) in PMBCL was first observed in the phase I KEYNOTE013 study, which evaluated the efficacy of pembrolizumab as monotherapy in a population of patients with relapsed/refractory (R/R) lymphoma, including PMBCL. The overall response rate (ORR) in the R/R PMBCL subgroup was 48%, with 33% achieving CR. Similar results were observed in the subsequent phase II study, KEYNOTE-170, which reported an ORR of 41.5% and a CR rate of 20.8%.[9,10]

The programmed cell death protein-1 (PD-1) inhibitor nivolumab was used in combination with the anti-CD30 conjugated antibody brentuximab vedotin (BV) in the CheckMate-436 study, which included a cohort of patients with R/R PMBCL.[11] Although BV alone showed an ORR of 13% in R/R PMBCL, the combination therapy resulted in an ORR of 73% (40% CR), with the median duration of response not reached at a median follow-up of 39.6 months, indicating synergy between the CPI-BV combination.[11,12]

In a retrospective study of 33 PMBCL patients treated with CAR T-cells, a sub-analysis evaluated the 19 who also received CPI, either before or after CAR-T infusion, to explore treatment sequencing. No significant differences in response or toxicity were observed.[13]

Notably, in the CARTHYM study, 20 patients received CPI as bridging therapy prior to CAR-T infusion, including nine treated with the BV-nivolumab combination. No significant differences in response rates or PFS were observed between patients who received CPI bridging and those who did not, suggesting no clear impact of prior CPI exposure on clinical outcomes. Additionally, prior CPI exposure was not associated with an increased incidence of grade 3-4 immune-mediated toxicities.[8]

These findings underscore the need for further research on the safety and efficacy of combining BV and nivolumab with CAR-T therapy. Importantly, defining the optimal sequencing of these agents remains critical to improving outcomes in R/R PMBCL.

Given this background, we conducted a retrospective analysis of nine patients with R/R PMBCL who received BV and a PD-1 inhibitor as bridging therapy prior to CAR-T infusion at our institution.

From November 2019 to April 2024, nine patients with R/R

Table 1. Patients' characteristics.

Characteristics	Values
N of patients	9
Male sex, N (%)	5 (55.6)
Age at BV-nivolumab start, years, median (range)	37 (21-75)
Stage at BV-nivolumab start, N (%) I II III IV	 1 (11.1) 2 (22.2) 0 (0) 6 (66.7)
Refractory to last line, N (%)	9 (100)
Time to relapse/progression after 1st line, months, median (range)	9 (3-15)
N of previous lines, median (range)	2 (2-4)
Prior ASCT, N (%)	2 (22.2)
Prior radiotherapy, N (%)	1 (11.1)
CAR-HEMATOTOX score, median (range)	1 (0-4)
N of BV-nivolumab cycles, median (range)	2 (1-3)
Time from diagnosis to CAR-T, months, median (range)	13 (7-35)
Time from leukapheresis to CAR-T infusion (vein-to-vein time), days, median (range)	45 (29-83)

BV: brentuximab vedotin; ASCT: autologous stem cell transplantation; CAR-T: chimeric antigen receptor T-cells.

PMBCL were treated with BV and nivolumab as a bridging regimen to axi-cel in a real-life setting at Humanitas Cancer Center. This study was approved by the ethical committee and conducted in accordance with the Helsinki Declaration.

In this report, we present the outcomes of these patients. The decision to prioritize CAR-T therapy after BV-nivolumab bridging rather than autologous stem cell transplantation was driven by the patients' chemotherapy-refractory disease and aimed at reducing cumulative toxicity through an entirely immunotherapy-based approach.

The patients' characteristics before starting BV-nivolumab are reported in Table 1: their median age was 37 years (range, 21-75). Six patients (66.7%) had stage IV disease, two (22.2%) had stage II, and one (11.1%) had stage I. Most patients received R-CHOP-like regimens as first-line therapy, followed by R-DHAP as second-line treatment. The median lactate dehydrogenase concentration was 375 IU/L (range, 185-3,585, upper limit of normal: 295). The median CAR HEMATOTOX score was 1 (range, 0-4). Prior to CAR-T infusion the median ferritin level was 599 ng/mL (range, 17-3,319, upper limit of normal: 307).

All patients received nivolumab (240 mg) and BV (1.8 mg/kg) once every 3 weeks, with a median of two cycles (range, 1-3) before CAR-T infusion.

Response to bridging therapy was assessed using positron emission tomography.

CR was achieved in 55.6% of the patients, 11.1% had a partial response and 33.3% maintained stable disease. Notably, no disease progressions were observed (Figure 1A). Patients received CAR-T infusion regardless of response to bridging therapy. At day +30 after CAR-T infusion, the ORR was 100%, with 88.9% achieving CR and 11.1% achieving partial remission which converted into CR at day +90, for an overall CR rate of 100% (Figure 1A).

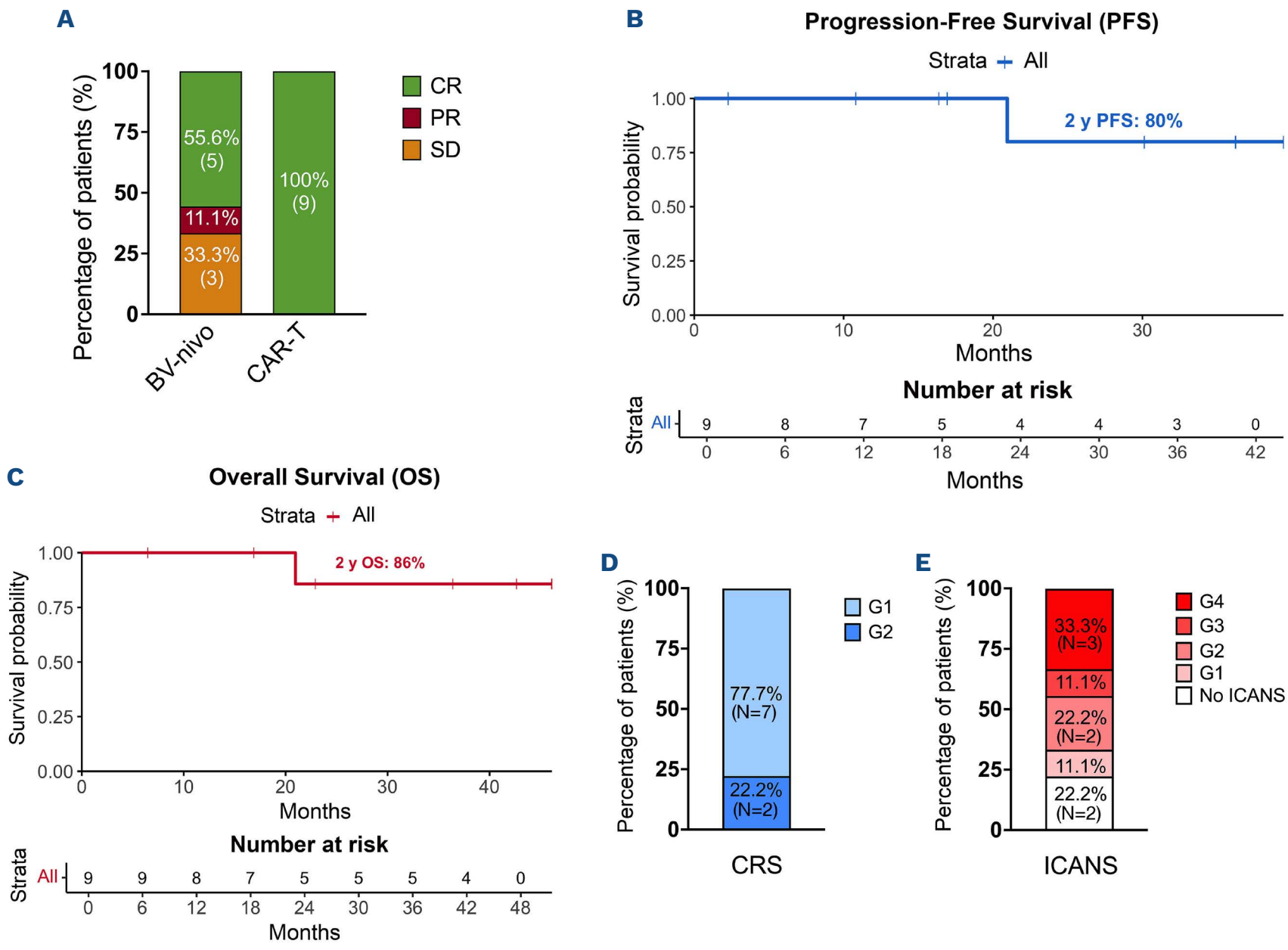

Figure 1. Clinical outcomes and incidence of adverse events following bridging therapy and infusion of chimeric antigen receptor T cells. (A) Bar plot showing the percentage of response categories after bridging therapy and at day +90 after chimeric antigen receptor T-cell (CAR-T) infusion (absolute numbers are shown in brackets). (B, C) Kaplan-Meier curves depicting progression-free survival (B) and overall survival (C). Ticks indicate censored observations. (D) Bar plot illustrating the incidence and severity grades of cytokine release syndrome (N=absolute number). (E) Bar plot illustrating the incidence and severity grades of Immune effector cell-associated neurotoxicity syndrome (N=absolute number). BV: brentuximab vedotin; nivo: nivolumab; CR: complete response; PR: partial response; SD: stable disease; y: year; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

With a median follow-up period of 36 months, PFS and OS at 24 months from CAR-T infusion, estimated using the Kaplan-Meier method, were 80% (95% confidence interval: 51.61%-100%) and 85.71% (95% confidence interval: 63.34%-100%), respectively (Figure 1B, C). The median OS and PFS have not yet been reached.

Of the nine patients, one died of pneumonia 21 months after CAR-T while in CR. Another patient was diagnosed with classical Hodgkin lymphoma 17 months after CAR-T infusion and remains alive at the last follow-up. Unfortunately, it was not possible to perform a histological revision of the baseline biopsy to rule out initial histological misclassification, composite lymphoma, or mediastinal gray zone lymphoma.

Regarding CAR-T-related adverse events, all patients experienced cytokine release syndrome: 77.8% grade 1 and 22.2% grade 2, with no grade 3-4 events reported (according to ASTCT consensus) (Figure 1D). Immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in seven patients (77.8%): one (11.1%) grade 1, two (22.2%) grade 2, one (11.1%) grade 3, and three (33.3%) grade 4 (Figure 1E). All ICANS events were fully reversible, with no long-term neurological sequelae observed at the last follow-up.

We analyzed CAR-T expansion kinetics and found that the number peaked around day 10 after CAR-T infusion, with a mean of 246.61 cells/μL (range, 5.84-956 cells/μL) (Figure 2A). The expansion of $CD8^+$ CAR-T, with an area under the curve from day 1 to day 14 (AUC_{d1-14}) of 929, was greater compared to that of $CD4^+$ CAR-T with an AUC_{d1-14} of 297.3 (Figure 2B).

Additionally, exhaustion markers were analyzed in two patients who achieved further response after CAR-T therapy despite only stable disease after bridging (Figure 2C). At day +10 after infusion, a median of 47% (range, 45-49%) of cells were $LAG3^+$ (44 cells/μL, range, 31.5-57), 45% (range, 34-56%) were $PD1^+$ (45 cells/μL; range, 24-65), and 0% were $TIM3^+$ (0 cells/μL). These characteristics have recently been identified as predictors of better long-term disease control.[14]

Our study is limited by typical challenges of single-center, real-world, retrospective analyses of rare diseases, including a small cohort and variability in treatment cycles. Nevertheless, our findings demonstrate superior response

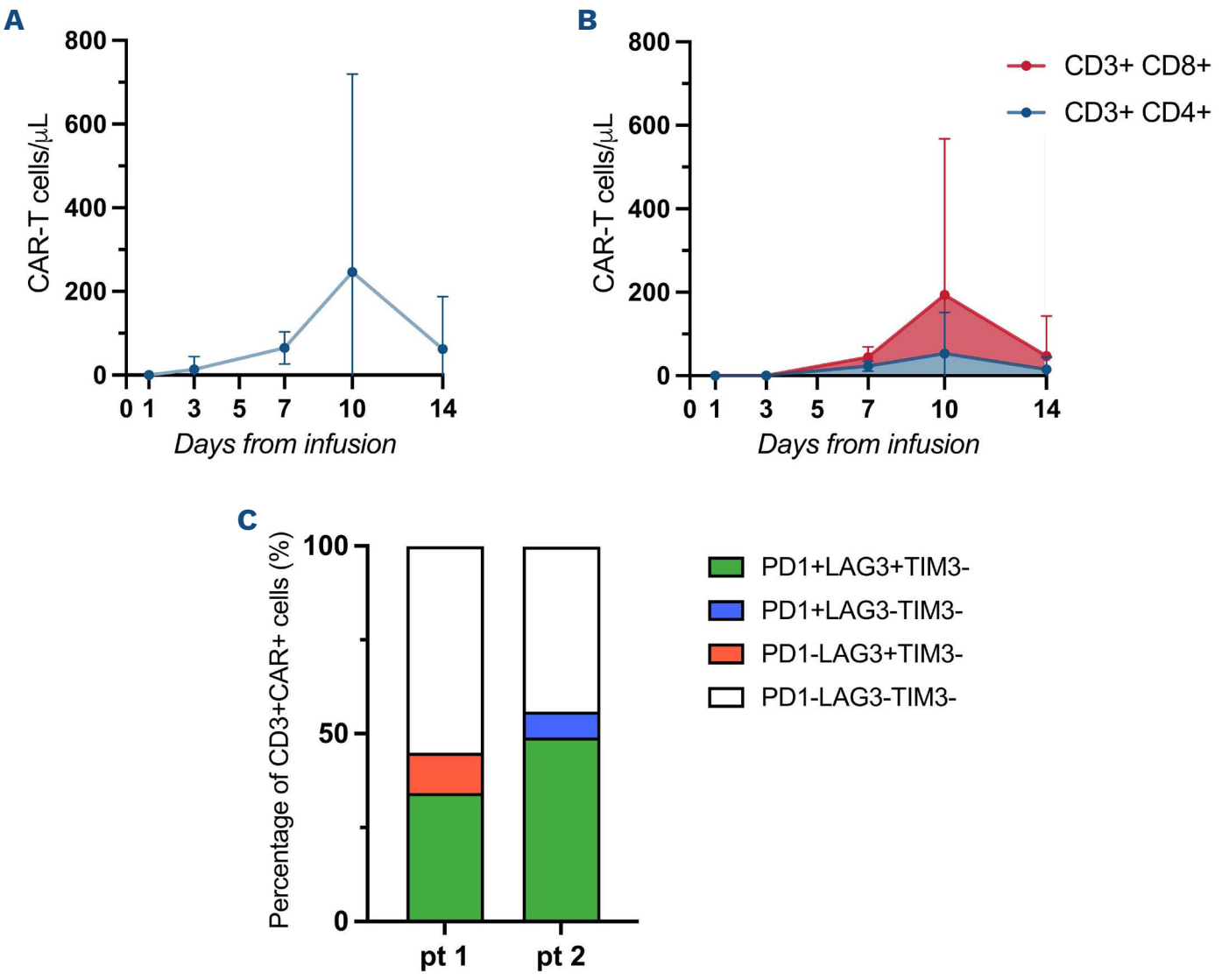

Figure 2. Chimeric antigen receptor T-cell expansion and expression of markers of exhaustion in peripheral blood. (A) Line graph showing $CD3^+$ chimeric antigen receptor (CAR)-positive cells/μL in the peripheral blood by cytofluorometry assessment at different time-points after infusion. (B) Line graph showing expansion kinetics of $CD4^+$ and $CD8^+$ T-cell subsets. (C) Bar plot showing the co-expression of T-cell exhaustion markers (PD1, LAG3, TIM3) at day +10 in the CAR-T cells in the peripheral blood in two patients whose response improved from stable disease after bridging therapy to complete response after CAR-T infusion. Pt: patient; PD1: programmed cell death protein-1; LAG3: lymphocyte-activation gene 3; TIM3: T-cell immunoglobulin and mucin-domain-containing-3.

rates in high-risk, R/R PMBCL patients compared to those in a recent single-center retrospective study by Renaud *et al*., which showed a 60% ORR and a 3-year PFS of 64% with BV-nivolumab, with consolidative mediastinal radiotherapy administered to 50% of the patients.[15]

Compared to the phase II CheckMate 436 study, in which 40% of patients underwent consolidation with hematopoietic stem cell transplantation (20% autologous, 20% allogeneic) after achieving CR or partial remission, our strategy reduces treatment duration by requiring fewer BV-nivolumab cycles.[11] In comparison with the two previously reported studies,[12,15] it offers significant benefits, particularly for younger patients, by minimizing risks related to mediastinal radiotherapy and transplant-associated complications, including late toxicities from high-dose chemotherapy and graft-*versus*-host disease.

Regarding the toxicity profile, our case series suggests that the use of CPI plus BV prior to CAR-T therapy may be associated with increased toxicity, particularly ICANS. However, despite the higher incidence of grade 3-4 ICANS, there was no corresponding increase in mortality.

A direct comparison of our response and toxicity data with those reported by Crombie *et al*. is limited by differences in the CPI administration setting. In our study, CPI were specifically used as immediate bridging therapy preceding CAR-T infusion, whereas in the study by Crombie *et al*. CPI were administered either before or after CAR-T infusion with a longer temporal interval, thus not functioning as bridging therapy *per se*. This divergence in timing and therapeutic context likely affects the observed impact of CPI on efficacy and toxicity profiles, limiting the interpretability of comparisons between studies.[13]

Furthermore, when comparing outcomes and toxicity between our cohort and the CARTHYM patients who received CPI as bridging therapy, certain variables may have influenced efficacy and safety profiles. In particular, the time interval between the last administration of BV-nivolumab and CAR-T infusion, as well as the tumor burden at the time of CAR-T therapy, may have played a critical role in determining patients' outcomes.

In conclusion, these data suggest that integrating BV-nivolumab as a bridging regimen before CAR-T infusion offers a valuable therapeutic strategy, ensuring optimal outcomes for patients in scenarios in which traditional approaches might fail. Further investigation and extended follow-up are warranted to confirm these findings and establish the definitive role of this treatment sequence in the management of R/R PMBCL.

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Contributions

CMI and AS contributed equally to the work. CMI, AS and SB designed the research. CMI and AS analyzed and interpreted data, performed the statistical analyses, and wrote the manuscript. All authors collected and interpreted data, and reviewed the manuscript.

Data-sharing statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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