haematologica
Journal of the Ferrata Storti Foundation

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

by Armando Santoro, Ciro Maria Improta, Barbara Sarina, Daniele Mannina, Chiara De Philippis, Daniela Taurino, Jacopo Mariotti, Monica Balzarotti and Stefania Bramanti

Received: March 15, 2025.
Accepted: September 12, 2025.

Citation: Armando Santoro, Ciro Maria Improta, Barbara Sarina, Daniele Mannina, Chiara De Philippis, Daniela Taurino, Jacopo Mariotti, Monica Balzarotti and Stefania Bramanti. Brentuximab vedotin plus nivolumab as bridging therapy to CAR T-cells in relapsed/refractory primary mediastinal B-cell lymphoma. Haematologica. 2025 Sept 18. doi: 10.3324/haematol.2025.287672 [Epub ahead of print]

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

Armando Santoro[1,2], Ciro Maria Improta[1,2]*, Barbara Sarina[2], Daniele Mannina[2], Chiara De Philippis [2], Daniela Taurino [2], Jacopo Mariotti [2], Monica Balzarotti [2], Stefania Bramanti [2]*

[1] *Department of Biomedical Sciences, Humanitas University,* Pieve Emanuele (MI), Italy

[2] *IRCCS Humanitas Research Hospital, Department of Oncology and Hematology, Rozzano (MI), Italy*

** Contributed equally to this work*

***Contribution**: C.M.I. and A.S. contributed equally to the work. C.M.I., A.S. and S.B designed research. C.M.I. and A.S. analyzed and interpreted data, performed statistical analysis, and wrote the manuscript. All authors collected and interpreted data, and reviewed the manuscript.*

Corresponding Author: Improta Ciro Maria
Address: Via Rita Levi Montalcini 4, 20072. Pieve Emanuele (MI) Italy.
E-mail address: cirimprota@gmail.com
Phone number: +39 3204413912 / +1 (857) 565-6640
https://orcid.org/0009-0008-6221-8271

email addresses co-authors:
A.S. Armando.santoro@cancercenter.humanitas.it
B.S. Barbara.sarina@cancercenter.humanitas.it
D.M. Daniele.mannina@cancercenter.humanitas.it
C.D.P. Chiara.dephilippis@cancercenter.humanitas.it
D.T. Daniela.taurino@cancercenter.humanitas.it
J.M. Jacopo.mariotti@cancercenter.humanitas.it
M.B. Monica.balzarotti@cancercenter.humanitas.it
S.B. Stefania.bramanti@cancercenter.humanitas.it

Short Title: BV- nivolumab as a bridge to CAR-T in r/r PMBCL

Conflict of interest

A.S. reports consulting fees from Incyte and Sanofi; honoraria from AbbVie, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Eisai, Gilead, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sandoz, Servier, and Takeda; and advisory board participation with Bayer, Bristol Myers Squibb, Eisai, Gilead, Merck Sharp & Dohme, Pfizer, and Servier.

S.B. reports speaker bureau participation: Bristol-Myers Squibb, Gilead, Novartis; advisory board participation: Novartis; Travel accommodation: Novartis, Roche.

M.B. reports speakers' bureau participation: Roche, Lilly, Gilead Sciences, SOBI; consulting or advisory role: Roche, Lilly, Gilead Sciences, Abbvie, AstraZeneca; speakers' bureau participation: Roche, Lilly, Gilead Sciences, SOBI

Data-sharing statement:

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

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare subtype of large B-cell non-Hodgkin's 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 (ASCT) 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 CAR-T cell 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 cell 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 1 KEYNOTE013 study, which evaluated the efficacy of pembrolizumab as monotherapy in a population of patients with 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 2 study, KEYNOTE-170, which reported an ORR of 41.5% and a CR of 20.8%. [9,10]
The PD1 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 (DOR) 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, 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 9 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 relapsed/refractory PMBCL.

Given this background, we conducted a retrospective analysis of 9 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 August 2023, 9 patients with R/R 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 ASCT was driven by the patients' chemotherapy-refractory disease and aimed at reducing cumulative toxicity through an entirely immunotherapy-based approach.

Patient characteristics before starting BV-nivolumab are reported in Table 1: the 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 LDH was 375 IU/L (range 185- 3585, ULN 295). The median CAR HEMATOTOX score was 1 (range 0-4). Prior to CAR-T cells infusion the median ferritin was 599 ng/ml (range 17-3319, ULN 307).

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

Response to bridging therapy was assessed using positron emission tomography (PET).
CR was achieved in 55.6% of the patients, 11.1% had a partial response (PR), and 33.3% maintained stable disease (SD). Notably, no disease progressions (PD) were observed (Fig.1A). Patients received CAR-T infusion regardless of response to bridging therapy. At day +30 after CAR-T infusion, the overall response rate was 100%, with 88.9% achieving CR and 11.1% achieving PR converted in CR at day +90, for an overall CR rate of 100% (Fig.1A).
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% (CI 51.61 % - 100 %) and 85.71% (CI 63.34 % - 100 %), respectively (Fig.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 cell infusion while in complete remission. 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 histologic misclassification, composite lymphoma, or mediastinal gray zone lymphoma.

Regarding CAR-T-related adverse events, all patients experienced cytokine release syndrome (CRS): 77.8% grade 1 and 22.2% grade 2, with no grade 3-4 events reported (according to ASTCT consensus, Fig.1D).
Immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in 7 patients (77.8%): 1 (11.1%) grade 1, 2 (22.2%) grade 2, 1 (11.1%) grade 3, and 3 (33.3%) grade 4 (Fig.1E).
All ICANS events were fully reversible, with no long-term neurological sequelae observed at the last follow-up.

We analyzed CAR T-cells expansion kinetic and found that it peaked around day 10 after CAR-T infusion, with a mean of 246.61 cells/µl (range 5.84-956 cells/µl, Fig.2A). The expansion of CD8+ CAR-T cells with an AUC1-14d of 929, was higher compared to CD4+ CAR-T cells with an AUC1-14d of 297.3 (Fig.2B).
Additionally, exhaustion markers were analyzed in two patients who achieved further response post-CAR-T therapy despite only SD after bridging (Fig.2C). At day+10 after infusion, a median of 47% (45-49%) of cells were LAG3+ (44 cells/µl, 31.5 - 57), 45% (34-56%) were PD1+ (45 cells/µl, 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 rates in high-risk, relapsed/refractory PMBCL patients compared to a recent single-center retrospective study by Renaud et al., which reported a 60%

ORR and a 3-year PFS of 64% with BV-nivolumab, with consolidative mediastinal radiotherapy administered in 50% of the patients. [15]

Compared to the Phase II CheckMate 436 study, where 40% of patients underwent consolidation with HSCT (20% autologous, 20% allogeneic) after achieving CR or PR, 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 checkpoint inhibitors 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.

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 cell infusion, whereas in 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 cell infusion, as well as the tumor burden at the time of CAR-T therapy, may have played a critical role in determining patient 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 patient outcomes in scenarios where 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.

References

1. Zinzani PL, Stefoni V, Finolezzi E, et al. Rituximab combined with MACOP-B or VACOP-B and radiation therapy in primary mediastinal large B-cell lymphoma: a retrospective study. Clin Lymphoma Myeloma. 2009;9(5):381-385.
2. Giulino-Roth L, O'Donohue T, Chen Z, et al. Outcomes of Adults and Children with Primary Mediastinal B-Cell Lymphoma Treated with Dose-Adjusted EPOCH-R. Br J Haematol. 2017;179(5):739.
3. Vardhana S, Hamlin PA, Yang J, et al. Outcomes of Relapsed and Refractory Primary Mediastinal (Thymic) Large B Cell Lymphoma Treated with Second-Line Therapy and Intent to Transplant. Biol Blood Marrow Transplant. 2018;24(10):2133-2138.
4. Kuruvilla J, Pintilie M, Tsang R, Nagy T, Keating A, Crump M. Salvage chemotherapy and autologous stem cell transplantation are inferior for relapsed or refractory primary mediastinal large B-cell lymphoma compared with diffuse large B-cell lymphoma. Leuk Lymphoma. 2008;49(7):1329-1336.
5. Renaud L, Donzel M, Decroocq J, et al. Primary mediastinal B-cell lymphoma (PMBCL): The LYSA pragmatic guidelines. Eur J Cancer. 2025;220:115369.
6. Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-1684.
7. Chiappella A, Casadei B, Chiusolo P, et al. Axicabtagene ciloleucel treatment is more effective in primary mediastinal large B-cell lymphomas than in diffuse large B-cell lymphomas: the Italian CART-SIE study. Leukemia. 2024 38:5 2024;38(5):1107-1114.
8. Galtier J, Mesguich C, Sesques P, et al. Outcomes of patients with relapsed or refractory primary mediastinal B-cell lymphoma treated with anti-CD19 CAR-T cells: CARTHYM, a study from the French national DESCAR-T registry. Hemasphere. 2025;9(2):e70091.
9. Kuruvilla J, Armand P, Hamadani M, et al. Pembrolizumab for patients with non-Hodgkin lymphoma: phase 1b KEYNOTE-013 study. Leuk Lymphoma. 2023;64(1):130-139.
10. Zinzani PL, Thieblemont C, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma: final analysis of KEYNOTE-170. Blood. 2023;142(2):141-145.
11. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for R/R primary mediastinal large B-cell lymphoma: a 3-year follow-up. Blood Adv. 2023;7(18):5272-5280.
12. Zinzani PL, Pellegrini C, Chiappella A, et al. Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial. Blood. 2017;129(16):2328-2330.
13. Crombie JL, Nastoupil LJ, Redd R, et al. Real-world outcomes of axicabtagene ciloleucel in adult patients with primary mediastinal B-cell lymphoma. Blood Adv. 2021;5(18):3563-3567.
14. García-Calderón CB, Sierro-Martínez B, García-Guerrero E, et al. Monitoring of kinetics and exhaustion markers of circulating CAR-T cells as early predictive factors in patients with B-cell malignancies. Front Immunol. 2023;14:1152498.
15. Renaud L, Wencel J, Pagès A, et al. Nivolumab combined with brentuximab vedotin with or without mediastinal radiotherapy for relapsed/refractory primary mediastinal large B-cell lymphoma. Haematologica. 2024;109(9):3019-3023.

Tab 1. Patients characteristics	
Number of patients	9
Male sex, n (%)	5 (55.6%)
Age at BV-nivolumab start in years, median (range)	37 (21-75)
Stage at BV-nivolumab start, n (%)	
I	1 (11.1%)
II	2 (22.2%)
III	0 (0%)
IV	6 (66.7%)
Refractory to last line, n (%)	9 (100%)
Median time to relapse/progression after 1st line, (months)	9 (3-15)
Number of previous line, 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)
Number of BV-nivolumab cycles, median (range)	2 (1-3)
Median time from diagnosis to CAR-T (months)	13 (7-35)
Median time from leukapheresis to CAR-T infusion (vein-to-vein time, days)	45 (29-83)

Fig.1 Clinical outcomes and adverse events incidence following bridging therapy and CAR-T cell infusion
A) Bar plot showing the percentage of response categories after bridging therapy and at day +90 after CAR-T cells infusion (n= absolute number).
(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 (CRS, n= absolute number).
(E) Bar plot illustrating the incidence and severity grades of Immune effector cell-associated neurotoxicity syndrome (ICANS, n= absolute number).
Abbreviations: BV, brentuximab vedotin; nivo, nivolumab; CR, complete response; PR, partial response; SD, stable disease; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

Fig.2 CAR-T cell expansion and exhaustion markers expression in peripheral blood
(A) Linegraph showing CD3+ CAR+ cells/µl in the peripheral blood by cytofluorometry assessment at different time-points after infusion. (B) Linegraph showing expansion kinetic in CD4+ and CD8+ T cells subset.
(C) Barplot showing the coexpression of T cells exhaustion markers (PD1, LAG3, TIM3) at D+10 in the CAR-T cells in the peripheral blood in two patients whose response improved from stable disease (SD) post-bridging therapy to complete response (CR) post-CAR-T

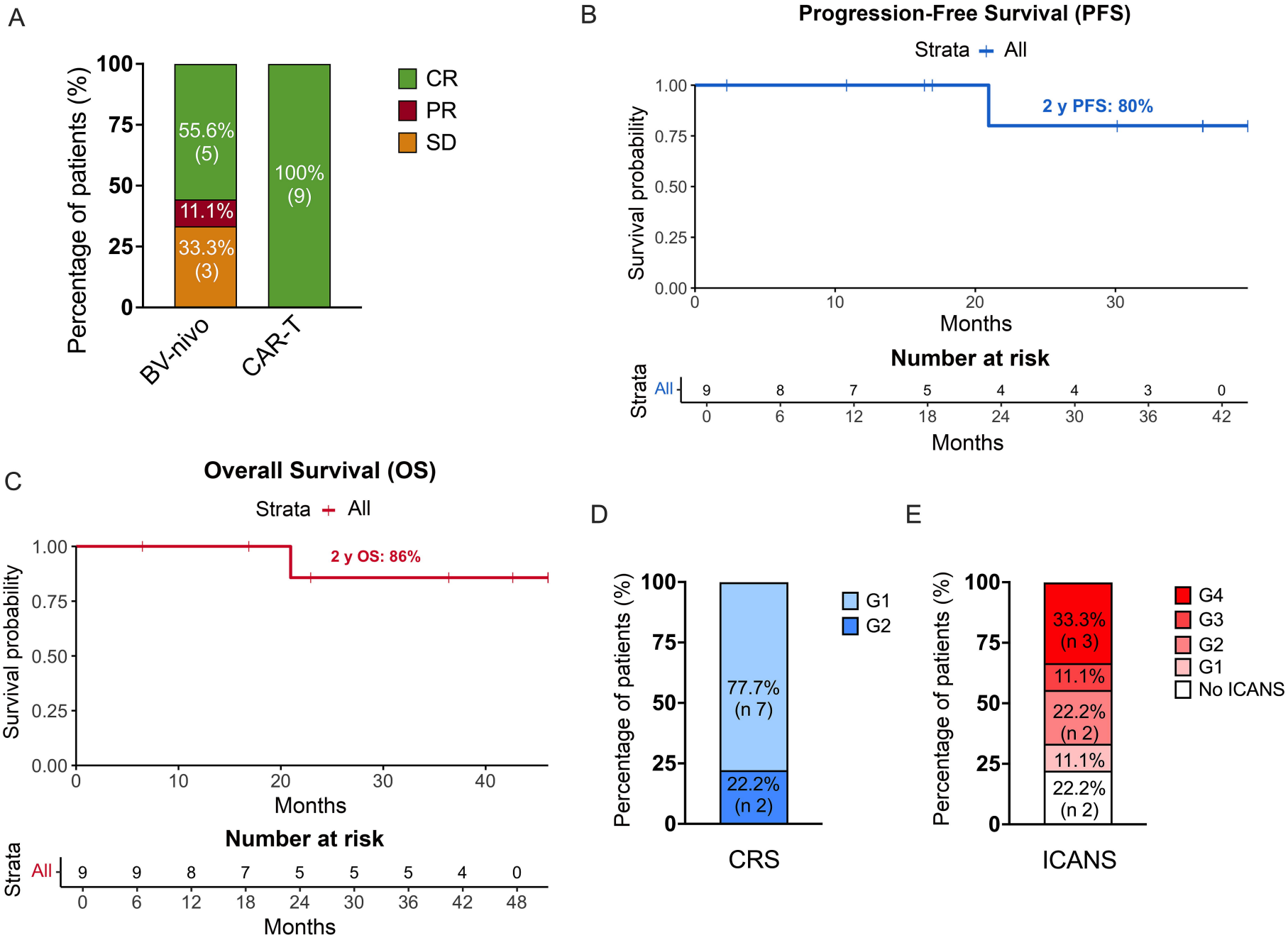
A
Percentage of patients (%)
100
75
50
25
0
55.6%
(5)
11.1%
33.3%
(3)
100%
(9)
CR
PR
SD
BV-nivo
CAR-T
B
Progression-Free Survival (PFS)
Strata All
Survival probability
1.00
0.75
0.50
0.25
0.00
2 y PFS: 80%
0
10
20
30
Months
Number at risk
Strata
All
9
8
7
5
4
4
3
0
0
6
12
18
24
30
36
42
Months
C
Overall Survival (OS)
Strata All
Survival probability
1.00
0.75
0.50
0.25
0.00
2 y OS: 86%
0
10
20
30
40
Months
Number at risk
Strata
All
9
9
8
7
5
5
5
4
0
0
6
12
18
24
30
36
42
48
Months
D
Percentage of patients (%)
100
75
50
25
0
77.7%
(n 7)
22.2%
(n 2)
G1
G2
CRS
E
Percentage of patients (%)
100
75
50
25
0
33.3%
(n 3)
11.1%
22.2%
(n 2)
11.1%
22.2%
(n 2)
G4
G3
G2
G1
No ICANS
ICANS

Fig.2 CAR-T cell expansion and exhaustion markers expression in peripheral blood