



## OPEN ACCESS

EDITED BY  
Anand Rotte,  
Arcellx Inc., United States

REVIEWED BY  
Chengxin Luan,  
The Fourth Division Hospital of Xinjiang  
Production and Construction Corps,  
China  
Bin Xue,  
Tongji University, China

\*CORRESPONDENCE  
Mingfeng Zhao  
✉ [mingfengzhao@sina.com](mailto:mingfengzhao@sina.com)

RECEIVED 13 December 2025  
REVISED 02 February 2026  
ACCEPTED 27 February 2026  
PUBLISHED 19 March 2026

CITATION  
Zhang H, He X, Xiao X, Ly H and Zhao M  
(2026) Efficacy and safety of  
zanubrutinib and camrelizumab  
combined with CD19 chimeric antigen  
receptor T-cell in the treatment of  
relapsed/refractory diffuse large  
B-cell lymphoma.  
*Front. Immunol.* 17:1766905.  
doi: 10.3389/fimmu.2026.1766905

COPYRIGHT  
© 2026 Zhang, He, Xiao, Ly and Zhao.  
This is an open-access article distributed  
under the terms of the [Creative  
Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/).  
The use, distribution or reproduction in  
other forums is permitted, provided the  
original author(s) and the copyright  
owner(s) are credited and that the  
original publication in this journal is  
cited, in accordance with accepted  
academic practice. No use, distribution  
or reproduction is permitted which does  
not comply with these terms.

# Efficacy and safety of zanubrutinib and camrelizumab combined with CD19 chimeric antigen receptor T-cell in the treatment of relapsed/refractory diffuse large B-cell lymphoma

Huan Zhang, Xiaoyuan He, Xia Xiao, Hairong Ly  
and Mingfeng Zhao\*

Department of Hematology, Tianjin First Central Hospital, School of Medicine, Tianjin, China

**Objective:** To retrospectively analyze the efficacy and safety of zanubrutinib and camrelizumab combined with CD19 chimeric antigen receptor T-cell (CD19 CAR T-cell) in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL).

**Methods:** Thirty-six R/R DLBCL patients who received zanubrutinib and camrelizumab combined with CD19 CAR T-cell from January 2022 to June 2024 were selected in the combined group. Twenty R/R DLBCL patients who received only CD19 CART-cell were included in the non-combined group. The efficacy and safety of these two groups were observed and compared.

**Results:** (1) The complete-response (CR) rates of the combined group after 1, 3, and 6 months were 61%, 75%, and 81%, respectively, while those of the non-combined group were 60%, 65%, and 60%, respectively. There were differences in CR rates at months 3 and 6 between the two groups ( $P = 0.043$ ,  $P = 0.006$ ). Of the 10 patients who achieved partial response (PR) in the combined group at month 1, 7 achieved CR at month 6. (2) Median follow-up time was 24 months, and the 2-year progression-free survival (PFS) and overall-survival (OS) rates of the combined group were 64% and 72%, respectively, while those of the non-combined group were respectively 23% and 40%. The differences in 2-year PFS and OS between the two groups were statistically significant ( $P < 0.001$ ,  $P = 0.003$ ). (3) There were no statistically significant differences in adverse events between the two groups. (4) The median expansion time of CAR T-cell in the combined group was 89 days (21-482), significantly longer than that in the non-combined group (42 days, 11-251), and the difference was statistically significant ( $P = 0.015$ ).

**Conclusions:** Zanubrutinib and camrelizumab may enhance the efficacy of CAR T-cell therapy in R/R DLBCL with a manageable safety. The combined therapy prolongs the expansion time of CAR T-cell.

## KEYWORDS

camrelizumab, CD19 chimeric antigen receptor T-cell, diffuse large B-cell lymphoma, efficacy, safety, zanubrutinib

## Introduction

Chimeric antigen receptor T-cell (CAR T-cell) therapy has achieved unprecedented efficacy in the treatment of hematological malignancies. The targeted CD19 chimeric antigen receptor T-cell (CD19 CAR T-cell) therapy has demonstrated remarkable efficacy in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), with a complete response (CR) rate of 39–58% (1–3). However, although CD19 CAR T-cell produce a significant initial response in R/R DLBCL treatment, >50% of patients experience relapse and disease progression during long-term follow-up (2, 4). Achieving CR after 3 months of CAR T-cell treatment is a predictor of long-term remission (5). Tumor microenvironment (TME) is one of the main limitations of CAR T-cell therapy (6–9), which plays a crucial role in lymphoma progression and recurrence, including T cell exhaustion and immunosuppressive cell infiltration (10, 11).

Bruton's tyrosine kinase inhibitors (BTKis) are extensively used to treat lymphomas. Previous clinical trials have demonstrated that the addition of ibrutinib to CD19 CAR T-cell improves the efficacy in patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) (12–14). BTKis change the ratio of CD4<sup>+</sup> to CD8<sup>+</sup> T cells and decrease levels of programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) to regulate the TME, thereby enhancing the efficacy of CAR T-cell (15). Zanubrutinib is a second-generation BTKi with better oral absorption and more-potent targeting capacity than ibrutinib; it also has a superior adverse-reaction profile (16). Zanubrutinib exerts a mild effect on Interleukin-2 inducible tyrosine kinase (ITK), thus having a minimal impact on T cell function, which facilitates the exertion of T cell activity and yields a better synergistic effect with CART therapy. In addition, zanubrutinib shows stronger infiltration into lymphoid tissues and higher targeting ability and activity (17, 18). Combining zanubrutinib with CD19 CAR T-cell has shown significant efficacy in R/R DLBCL treatment (19, 20).

The PD-1/PD-L1 pathway can inactivate CD28 domain signals within CAR T-cell to inhibit the function of these cells (21, 22). Camrelizumab is a humanized PD-1 inhibitor that can effectively block the PD-1/PD-L1 signaling pathway, thereby inhibiting immune evasion of tumor cells, restoring the cytotoxic function of CAR T-cell, and inhibiting CAR T-cell exhaustion (23).

The zanubrutinib combined with CAR T-cell therapy has demonstrated significant efficacy and good tolerance in some clinical series reports on R/R LBCL (17, 18). Combining PD-1 inhibitors with CAR T-cell therapy has shown encouraging results in preclinical studies (21–23). However, how to combine zanubrutinib and camrelizumab with CAR T-cell remains a question worth exploring. Our research aims to investigate the efficacy and safety of this synergistic therapy.

## Material and methods

### Patients

A total of 36 patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) who received combined treatment of zanubrutinib, camrelizumab, and CD19 CAR T-cell in the

Department of Hematology at Tianjin First Central Hospital from January 2022 to June 2024 were included as the combined group. Meanwhile, 20 patients with R/R DLBCL who only received CD19 CAR T-cell treatment during the same period were selected as the non-combined group. The clinical data of both groups were retrospectively analyzed. This study was approved by the Medical Ethics Committee of the Tianjin First Central Hospital (approval no. 2015002X). All patients were enrolled in our clinical trial of CART cells for R/R B-cell non-Hodgkin lymphoma (NHL) (ChiCTR1800019288).

### CAR T-cell preparation, pre-treatment, and reinfusion

Autologous peripheral-blood lymphocytes were harvested from patients. After passing T-cell function tests, they were used by our department's laboratory to prepare CAR T-cell, a process that included the following components: (1) a humanized anti-CD19 antigen-binding domain (a single-chain antibody fragment); (2) a CD8 fusion linker; and (3) a transmembrane domain, i.e. the 4-1BB/CD3 $\zeta$  co-stimulatory-activation domain (Supplementary Figure). Before CAR T-cell reinfusion, patients were pre-treated with fludarabine and cyclophosphamide for lymphocyte depletion. The median dose of infused CAR T-cells was 2.8 $\times$ 10<sup>6</sup>/kg (1.56–4.23 $\times$ 10<sup>6</sup>/kg).

### Use of zanubrutinib and camrelizumab

After 28 days of CAR T-cell infusion, the combined group were started on zanubrutinib (160 mg orally twice daily) and camrelizumab (200 mg intravenously [i.v.] every 21 days) for a maximum 2 years of combination therapy.

### Evaluation of response and adverse events

The Lugano classification and positron emission tomography/computed tomography (PET/CT) were used to evaluate efficacy at 1, 3, 6, and 12 months after CAR T-cell infusion and every 6 months thereafter. The safety evaluation included assessments for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (24). The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to evaluate other adverse events (25).

### Statistical analysis and follow-up

SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. The Kaplan–Meier method was used to plot a survival curve, and the log-rank test was used to compare overall survival (OS) and progression-free survival (PFS) between groups. A difference of  $P < 0.05$  was considered statistically significant.

### CAR T-cell tests

Flow cytometry and quantitative polymerase chain reaction (qPCR) were used to quantify CD19 CAR T-cell. On days 0, 3, 7,

10, 14, 21, 28, 60, 90, 120, 150, and 180 of CAR T-cell infusion, whole-blood samples were collected to extract the percentage of CAR T-cell and genomic deoxyribonucleic acid. Extraction was performed every month during the first 6 months and once every 2 months thereafter until the measured value fell below the lower limit of detection.

## Results

### Patient characteristics

Thirty-three patients (91.7%) were diagnosed with diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS), and three (8.3%) with follicular lymphoma (FL) transformation. Of all 36 patients, 8 patients (22.2%) had germinal center B-cell (GCB) subtype, and 28 patients (77.8%) had non-GCB subtype. In terms of Ann Arbor staging, 33 patients (91.7%) were stage III-IV and 3 patients (8.3%) were stage I-II. Thirty-one patients (86.1%) had International Prognostic Index (IPI) scores of medium-high risk (3–5 points). In addition, 32 patients (88.9%) had extranodal involvement, 7 patients (19.4%) had bulky disease (tumor

diameter, >7.5 cm), and TP53 mutations were detected in 12 patients (33.3%). Twenty-two patients (61.1%) had previously received at least two lines of treatment; five patients (13.9%) of these patients had previously undergone autologous stem cell transplant (ASCT). Seven patients had histories of ibrutinib treatment. No patient had received zanubrutinib and PD-1/PD-L1 inhibitor treatment. The median dose of CD19 CAR T-cells infused was  $2.8 \times 10^6/\text{kg}$  ( $1.56\text{--}4.23 \times 10^6/\text{kg}$ ). The two groups had no statistically significant differences in age, sex, disease type, cell origin, Ann Arbor stage, IPI score, extranodal involvement, bulky disease, lactate dehydrogenase elevation, TP53 mutation, number of past treatment lines, past BTKi or PD-1/PD-L1 inhibitor usage, past ASCT, or median CAR T-cell infusion dose (Table 1).

### Efficacy and survival

Median follow-up time for all patients was 24 months (range, 7–42 months). One month after infusion, the objective-response rate (ORR) of the combined group was 89% (CR rate, 61%; PR rate, 28%), while that of the non-combined group was 85% (CR rate, 60%; PR rate, 25%). There was no statistically significant between-group difference in CR rate ( $P = 0.574$ ; Figure 1). Three months after infusion, the ORR of the combined group was 89% (CR rate,

TABLE 1 Baseline characteristics of all patients.

Characteristic	Non-combined group (n=20, %)	Combined group (n=36, %)	P
Age (median)	67 (50–76)	66 (49–74)	0.982
Sex			0.573
Male	9 (45.0%)	17 (47.2%)	
Female	11 (55.0%)	19 (52.8%)	
Pathologic subtype			0.917
DLBCL	18 (90.0%)	33 (91.7%)	
tFL	2 (10.0%)	3 (8.3%)	
Cell of origin			0.761
GCB	6 (30.0%)	8 (22.2%)	
Non-GCB	14 (70.0%)	28 (77.8%)	
Ann Arbor staging			0.597
I-II	2 (10.0%)	3 (8.3%)	
III-IV	18 (90.0%)	33 (91.7%)	
IPI			0.481
0–2	3 (15.0%)	5 (13.9%)	
3–5	17 (85.0%)	31 (86.1%)	
Extranodal organ involvement	16 (80.0%)	32 (88.9%)	0.642
Tumor mass >7.5 cm	4 (20.0%)	7 (19.4%)	0.892
LDH (>ULN)	19 (95.0%)	34 (94.4%)	0.763
TP53 mutation	6 (30.0%)	12 (33.3%)	0.617
Number of previous lines			0.592
≤2	8 (40.0%)	14 (38.9%)	
>2	12 (60.0%)	22 (61.1%)	
Previous treatment of BTKi	4 (20.0%)	7 (19.4%)	0.869
Previous treatment of PD-1/PD-L1	0 (00.0%)	0 (00.0%)	1.000
ASCT	3 (15.0%)	5 (13.9%)	0.853
Dosage of CD19-CART cells	$2.6 \times 10^6/\text{kg}$	$2.8 \times 10^6/\text{kg}$	0.996

CD19-CART, CD19 chimeric antigen receptor T; DLBCL, diffuse large B-cell lymphoma; tFL, follicular lymphoma transformation; GCB, germinal center B cell-like; IPI, international prognostic index; LDH, lactate dehydrogenase; BTKi, Bruton's tyrosine kinase inhibitor; PD-1/PD-L1, programmed cell death protein-1/programmed cell death 1 ligand 1; ASCT, autologous stem cell transplantation.

75%; PR rate, 14%), while that of the non-combined group was 85% (CR rate, 60%; PR rate, 25%). There was a difference in the CR rate between the two groups ( $P=0.043$ ) (Figure 1). Six months after infusion, the ORR of the combined group was 89% (CR rate, 81%; PR rate, 8%), that of the non-combined group 75% (CR rate, 60%; PR rate, 15%). There were statistically significant differences in CR rate between the two groups ( $P = 0.006$ ). Of the 10 patients who achieved partial response (PR) in the combined group at month 1, 7 achieved CR at month 6 (Figure 1).

The 1-year PFS and OS rates of the combined group were 88% (95% confidence interval [CI], 73–97) and 100%, respectively. These rates were respectively 55% (95% CI, 43–67) and 85% (95% CI, 74–96) for the non-combined group. The 2-year PFS and OS rates of the combined group were 64% (95% CI, 53–75) and 72% (95% CI, 72–84), respectively, while those of the non-combined group were respectively 23% (95% CI, 15–31) and 40% (95% CI, 33–51). The differences in 2-year PFS and OS between the two groups were statistically significant ( $P<0.001$ ,  $P = 0.003$ , respectively). Figures 2 and 3 illustrate the between-group differences in 2-year PFS and OS, respectively.

## Safety

All patients who received the combination therapy of zanubrutinib and camrelizumab, along with CAR T-cell, showed cytokine release syndrome (CRS), among which six patients (16.7%) were grade 3–4 CRS. Additionally, three patients (8.3%) developed grade 1–2 ICANS.

Nineteen patients (52.8%) developed grade 3–4 neutropenia, eight patients (22.2%) developed grade 3–4 anemia, and nine patients (25.0%) developed grade 3–4 thrombocytopenia. Three patients (8.3%) experienced bacterial infections and one patient (2.8%) developed invasive mycosis. Cardiac insufficiency was detected during combination therapy in two patients (5.6%), of whom one had atrial fibrillation and one had premature atrial contraction. Eight patients (22.2%) had abnormal hepatic function, two patients (5.6%) had abnormal renal function, and four patients (11.1%) had coagulopathy abnormalities.

After glucocorticoid, tocilizumab, plasmapheresis, antibiotic, and symptomatic treatment, the adverse events were controlled, and no patient died. There were no statistically significant differences in CRS, ICANS, hematological abnormalities, cardiac insufficiency, hepatic impairment, renal impairment, and coagulopathy abnormalities between the two groups (Table 2).

## CAR T-cell expansion

In the combined group, CAR T-cell peaked at 23.7% (9.2%–57.9%), while in non-combined group they peaked at 21.3% (6.7%–43.1%). There was no statistical difference between the two groups ( $P = 0.628$ ) (Figure 4). In both groups, CAR T-cell attained their peak values 7–14 days after CAR T-cell infusion and gradually decreased thereafter. Notably, the median expansion time of CAR T-cell in the combined group was 89 days (21–482), which was significantly longer than that in the non-combined group at 42 days (11–251;  $P=0.015$ ) (Figure 5).

## Discussion

This study retrospectively analyzed the efficacy and safety of zanubrutinib and camrelizumab combined with CD19 CAR T-cell in the treatment of 36 R/R DLBCL patients. Compared with the non-combined group, the combined group showed better efficacy. Notably, 91.7% of the enrolled patients were Ann Arbor stage III–IV, 86.1% had IPI score of 3–5 points, and 88.9% had extranodal involvement, making this study more clinically significant.

A retrospective study on six R/R DLBCL patients showed that zanubrutinib combined with CD19 CAR T-cell therapy achieved significant efficacy: 1 month after CAR T-cell infusion, three patients achieved CR and three patients achieved PR. After 2 months of zanubrutinib combination therapy, all six patients achieved CR (26). Xu et al. described 17 R/R DLBCL patients who received zanubrutinib and CD19 CAR T-cell therapy, obtained a maximum ORR of 88.2%, a maximum CR rate of 70.5%, an

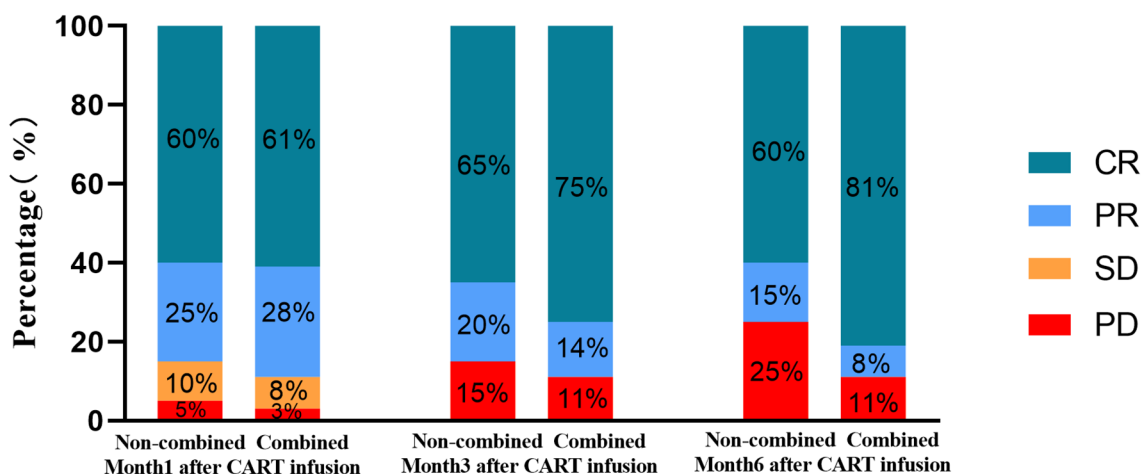


FIGURE 1

Treatment response of patients in the two groups at month 1, month 3, and month 6 after CART infusion.

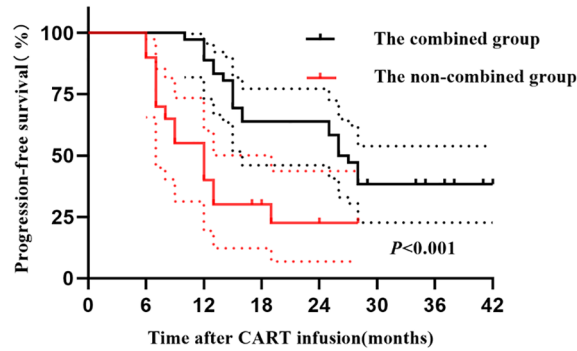


FIGURE 2 PFS of patients in the two groups after CART infusion.

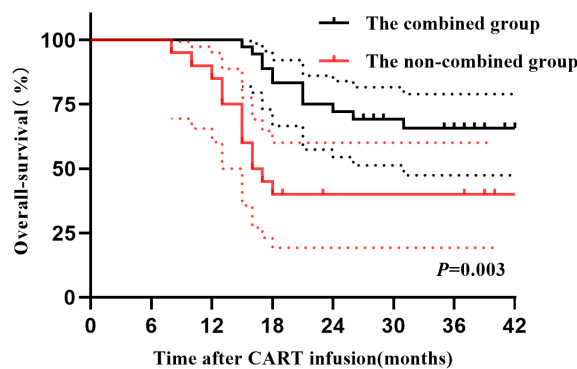


FIGURE 3 OS of patients in the two groups after CART infusion.

expected 2-year PFS rate of 59%, and a 2-year OS rate of 71% (27). PD-1 inhibitor shows superior efficacy in maintenance therapy after CD19/22 CAR T-cell treatment. Xin et al. reported 173 R/R non-Hodgkins' lymphoma patients who received PD-1 inhibitor maintenance therapy after CD19/22 CAR T-cell treatment, the 2-year ORR and CR rates of the maintenance group were 82.9% and 59.8%, respectively, which were significantly higher than those of

the control group (60.0% and 21.3%, respectively) (28). A retrospective study conducted by Ruijin Hospital Affiliated to Shanghai Jiao Tong University confirmed the efficacy and safety of the combination of zanubrutinib and tislelizumab with CD19 CAR T-cell. A total of 54 patients were included, the best ORR and CR rate were 94% and 80% respectively, the 2-year PFS rate was 68%, and the 2-year OS rate was 76% (29). In our study, the highest

TABLE 2 Adverse events.

Adverse event	Non-combined group (n=20, %)	Combined group (n=36, %)	P
CRS			
Grade 1–2	17 (85.0%)	30 (83.3%)	0.635
Grade 3–4	3 (15.0%)	6 (16.7%)	0.318
ICANS			
Grade 1–2	1 (5.0%)	3 (8.3%)	0.683
Grade 3–4	0 (0.0%)	0 (0.0%)	
Hematologic event			
Grade 3–4 leukopenia	12 (60.0%)	19 (52.8%)	0.478
Grade 3–4 anemia	4 (20.0%)	8 (22.2%)	0.721
Grade 3–4 thrombocytopenia	5 (25.0%)	9 (25.0%)	0.974
Heart failure/arrhythmology	7 (35.0%)	13 (36.1%)	0.741
Liver insufficiency	5 (25.0%)	8 (22.2%)	0.673
Renal impairment	1 (5.0%)	2 (5.6%)	0.561
Abnormal clotting function	2 (10.0%)	4 (11.1%)	0.749

CRS, Cytokine release syndrome; ICANS, Immune effector cell associated neurotoxic syndrome.

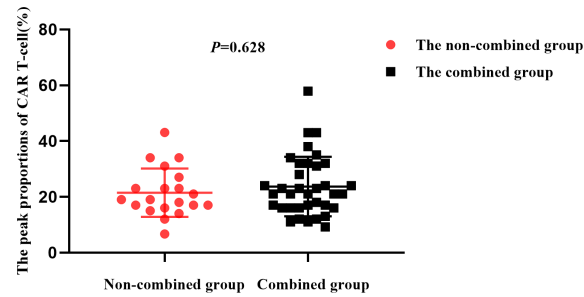


FIGURE 4  
The peak proportions of CAR T-cell in the two groups.

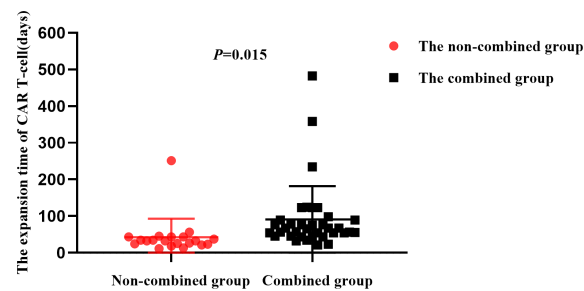


FIGURE 5  
The expansion time of CAR T-cell in the two groups.

ORR and CR rates for combination therapy were 89% and 81%, respectively, and the 2-year PFS and OS rates were 64% and 72%, respectively. Our findings are similar to those of Ruijin Hospital, but better than the ZUMA-1 study and the another study (27). It is worth noting that of our 10 patients who initially achieved PR, 7 patients converted to CR after 6 months of combination therapy. More importantly, no new safety signals occurred during the treatment period, and only six patients had CRS grade 3 or higher. Three patients had grade 1-2 ICANS, but they improved after treatment. The higher CR and 2-year PFS rates observed in our study emphasized the potential of zanubrutinib and camrelizumab in improving the outcome of CAR T-cell therapy.

An immunosuppressive TME decreases the antitumor effects of CAR T-cell (30). After CAR T-cell are activated, PD-1 expression on their surfaces is upregulated, and PD-L1 expression is upregulated on the surfaces of tumor cells. PD-1 on CAR T-cell surfaces binds to PD-L1 on tumor cell surfaces to inhibit the cytotoxic effects of CAR T-cell on tumor cells (31). BTKi maybe downregulate PD-1 expression, thereby enhancing the persistence and function of CAR T-cell (32). PD-1 inhibitors prevent PD-1 from binding to CAR T-cell surfaces and PD-L1 to tumor cell surfaces, thereby inhibiting immune evasion and promoting endocytosis of PD-1 on CAR T-cell surfaces, which may restores

the killing effect of CAR T-cell and inhibits their exhaustion (23). In addition, PD-1 inhibitors can also abolish the “brake” molecules on T cells to reactively inhibit clonal expansion of CD8<sup>+</sup> T cells, thereby producing effective antitumor effects (33). Therefore, we selected zanubrutinib and camrelizumab for use in combination therapy with CAR T-cell. Although the peak levels of CAR T-cell were similar between the two groups, the expansion time of CAR T-cell in the combined group was significantly prolonged, suggesting that the prolonged expansion of CAR T-cell may lead to better clinical benefits for the patients.

In summary, compared with treatment with CAR T-cell alone, the combination of zanubrutinib and camrelizumab with CD19 CAR T-cell for patients with R/R DLBCL not only resulted in better responses and survival, but also did not increase the incidence of adverse events. Although these results are encouraging, some limitations exist in our study. First, due to the small sample size, the conclusion that there is no difference in adverse events between the two groups may be attributed to Type II error caused by low power. Second, randomized, prospective, and comparative studies with larger sample sizes are needed to validate our findings. Third, the patient’s long-term outcomes and quality of life are still being observed, and further studies will be reported in the future.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary files, further inquiries can be directed to the corresponding author/s.

## Ethics statement

The studies involving humans were approved by the Medical Ethics Committee of the Tianjin First Central Hospital (approval no. 2015002X). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

HZ: Writing – original draft. XH: Writing – review & editing, Data curation. XX: Writing – review & editing, Formal analysis. HL: Writing – review & editing, Investigation. MZ: Writing – review & editing.

## Funding

The author(s) declared that financial support was not received for this work and/or its publication.

## References

- Schuster SJ, Tam CS, Borchmann P, Worel N, McGuirk JP, Holte H, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol.* (2021) 22(10):1403–15. doi: 10.1016/s1470-2045(21)00375-2
- Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol.* (2019) 20(1):31–42. doi: 10.1016/s1470-2045(18)30864-7
- Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet.* (2020) 396(10254):839–52. doi: 10.1016/s0140-6736(20)31366-0
- Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *N Engl J Med.* (2017) 377(26):2545–54. doi: 10.1056/NEJMoa1708566
- Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood.* (2023) 141(19):2307–15. doi: 10.1182/blood.2022018893
- Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. *Nat Rev Clin Oncol.* (2018) 15(1):31–46. doi: 10.1038/nrclinonc.2017.128

## Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fimmu.2026.1766905/full#supplementary-material>

- Yoon DH, Osborn MJ, Tolar J, Kim CJ. Incorporation of Immune Checkpoint Blockade into Chimeric Antigen Receptor T Cells (CAR-Ts): Combination or Built-In CAR-T. *Int J Mol Sci.* (2018) 19:340. doi: 10.3390/ijms19020340
- Shah NN, Fry TJ. Mechanisms of resistance to CAR T cell therapy. *Nat Rev Clin Oncol.* (2019) 16(6):372–85. doi: 10.1038/s41571-019-0184-6
- Cherkassky L, Morello A, Villena-Vargas J, Feng Y, Dimitrov DS, Jones DR, et al. Human CAR T cells with cell-intrinsic PD-1 checkpoint blockade resist tumor-mediated inhibition. *J Clin Invest.* (2016) 126(8):3130–44. doi: 10.1172/jci83092
- Scholler N, Perbost R, Locke FL, Jain MD, Turcan S, Danan C, et al. Tumor immune contexture is a determinant of anti-CD19 CAR T cell efficacy in large B cell lymphoma. *Nat Med.* (2022) 28(9):1872–82. doi: 10.1038/s41591-022-01916-x
- Yan ZX, Li L, Wang W, OuYang BS, Cheng S, Wang L, et al. Clinical Efficacy and Tumor Microenvironment Influence in a Dose-Escalation Study of Anti-CD19 Chimeric Antigen Receptor T Cells in Refractory B-Cell Non-Hodgkin's Lymphoma. *Clin Cancer Res.* (2019) 25(23):6995–7003. doi: 10.1158/1078-0432.ccr-19-0101
- Gill S, Vides V, Frey NV, Hexner EO, Metzger S, O'Brien M, et al. Anti-CD19 CAR T cells in combination with ibrutinib for the treatment of chronic lymphocytic leukemia. *Blood Adv.* (2022) 6(21):5774–85. doi: 10.1182/bloodadvances.2022007317
- Wang M, Rossi JM, Munoz J, Goy AH, Locke FL, Reagan PM, et al. Pharmacological Profile and Clinical Outcomes of KTE-X19 By Prior Bruton Tyrosine Kinase Inhibitor (BTKi) Exposure or Mantle Cell Lymphoma (MCL)

- Morphology in Patients With Relapsed/Refractory (R/R) MCL in the ZUMA-2 Trial. *Blood*. (2020) 136(Suppl 1):29. doi: 10.1182/blood-2020-136831
14. Gauthier J, Hirayama AV, Purushe J, Hay KA, Lymp J, Li DH, et al. Feasibility and efficacy of CD19-targeted CAR T cells with concurrent ibrutinib for CLL after ibrutinib failure. *Blood*. (2020) 135(19):1650–60. doi: 10.1182/blood.2019002936
15. Fan F, Yoo HJ, Stock S, Wang L, Liu Y, Schubert ML, et al. Ibrutinib for improved chimeric antigen receptor T-cell production for chronic lymphocytic leukemia patients. *Int J Cancer*. (2021) 148(2):419–28. doi: 10.1002/ijc.33212
16. Hillmen P, Brown JR, Eichhorst BF, Lamanna N, O'Brien SM, Qiu L, et al. ALPINE: zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Future Oncol*. (2020) 16(10):517–23. doi: 10.2217/fon-2019-0844
17. Flinsenbergh TWH, Tromedjo CC, Hu N, Liu Y, Guo Y, Thia KYT, et al. Differential effects of BTK inhibitors ibrutinib and zanubrutinib on NK-cell effector function in patients with mantle cell lymphoma. *Haematologica*. (2020) 105(2):e76–e79. doi: 10.3324/haematol.2019.220590
18. Tam CS, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. (2020) 136(18):2038–50. doi: 10.1182/blood.2020006844
19. Wang L, Yang J, Jin B, Wang B, Zhou L, Zhuo Y, et al. Efficacy and Safety of Chimeric Antigen Receptor T Cells Therapy Combined with Zanubrutinib in the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma. *Blood*. (2023) 142(Suppl 1):4841. doi: 10.1182/blood-2023-186439
20. Lu Y, Liu H, Ye SG, Zhou LL, Luo X, Dang XY, et al. Efficacy and safety analysis of the zanubrutinib-based bridging regimen in chimeric antigen receptor T-cell therapy for relapsed/refractory diffuse large B-cell lymphoma. *Zhonghua Xue Ye Xue Za Zhi*. (2023) 44(10):813–9. doi: 10.3760/cma.j.issn.0253-2727.2023.10.004
21. Zolov SN, Rietberg SP, Bonifant CL. Programmed cell death protein 1 activation preferentially inhibits CD28.CAR-T cells. *Cytotherapy*. (2018) 20(10):1259–66. doi: 10.1016/j.jcyt.2018.07.005
22. Hui E, Cheung J, Zhu J, Su X, Taylor MJ, Wallweber HA, et al. T cell costimulatory receptor CD28 is a primary target for PD-1-mediated inhibition. *Science*. (2017) 355(6332):1428–33. doi: 10.1126/science.aaf1292
23. Chong EA, Alanio C, Svoboda J, Nasta SD, Landsburg DJ, Lacey SF, et al. Pembrolizumab for B-cell lymphomas relapsing after or refractory to CD19-directed CAR T-cell therapy. *Blood*. (2022) 139(7):1026–38. doi: 10.1182/blood.2021012634
24. Lee DW, Santomaso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. (2019) 25(4):625–38. doi: 10.1016/j.bbmt.2018.12.758
25. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. (2014) 124(2):188–95. doi: 10.1182/blood-2014-05-552729
26. Lou Y, Chen C, Long X, Gu J, Xiao M, Wang D, et al. Detection and Quantification of Chimeric Antigen Receptor Transgene Copy Number by Droplet Digital PCR versus Real-Time PCR. *J Mol Diagn*. (2020) 22(5):699–707. doi: 10.1016/j.jmoldx.2020.02.007
27. Xu J, Zhang X, Li Y, Meng F, Zhang Y, Zheng M. Efficacy and safety of zanubrutinib combined with chimeric antigen receptor T-cell therapy targeting CD19 in refractory or relapsed diffuse large B cell lymphoma: A retrospective analysis. *Cancer Treat Res Commun*. (2025) 43:100902. doi: 10.1016/j.ctarc.2025.100902
28. Xin X, Zhu X, Yang Y, Wang N, Wang J, Xu J, et al. Efficacy of programmed cell death 1 inhibitor maintenance after chimeric antigen receptor T cells in patients with relapsed/refractory B-cell non-Hodgkin-lymphoma. *Cell Oncol*. (2024) 47(4):1425–40. doi: 10.1007/s13402-024-00940-y
29. Shen R, Cao WG, Wang L, Sheng LS, Zhang YL, Wu W, et al. Response-adapted zanubrutinib and tislelizumab as a potential strategy to enhance CD19 CAR T-cell therapy in relapsed/refractory large B-cell lymphoma: A retrospective observational study. *Clin Transl Med*. (2025) 15(4):e70310. doi: 10.1002/ctm2.70310
30. Ruella M, Korell F, Porazzi P, Maus MV. Mechanisms of resistance to chimeric antigen receptor-T cells in haematological malignancies. *Nat Rev Drug Discov*. (2023) 22(12):976–95. doi: 10.1038/s41573-023-00807-1
31. Rafiq S, Yeku OO, Jackson HJ, Purdon TJ, van Leeuwen DG, Drakes DJ, et al. Targeted delivery of a PD-1-blocking scFv by CAR-T cells enhances anti-tumor efficacy in vivo. *Nat Biotechnol*. (2018) 36(9):847–56. doi: 10.1038/nbt.4195
32. Luo W, Li C, Wu J, Tang L, Wang X, Zhang Y, et al. Bruton tyrosine kinase inhibitors preserve anti-CD19 chimeric antigen receptor T-cell functionality and reprogram tumor micro-environment in B-cell lymphoma. *Cytotherapy*. (2023) 25(7):739–49. doi: 10.1016/j.jcyt.2023.03.005
33. Chow A, Perica K, Klebanoff CA, Wolchok JD. Clinical implications of T cell exhaustion for cancer immunotherapy. *Nat Rev Clin Oncol*. (2022) 19(12):775–90. doi: 10.1038/s41571-022-00689-z