

Prognostic differences of refractory/relapsed diffuse large B-cell lymphoma with bulky and non-bulky disease in the chimeric antigen receptor T cell therapy era

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Abstract

In the era of chimeric antigen receptor T-cell (CAR-T) therapy, the prognostic impact of bulky disease in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) remains unclear, prompting this study that enrolled 27 patients with bulky disease and 27 with non-bulky disease to compare clinical outcomes. Over the follow-up period, patients with non-bulky disease achieved a higher overall response rate (77.8% vs. 70.4%) and better one-year progression-free survival (PFS) and overall survival (OS), with bulky disease significantly associated with worse OS ($P = 0.040$) and a median OS of 12 months versus 24 months in non-bulky patients. Multivariable Cox regression identified autologous hematopoietic stem cell transplantation combined with CAR-T (ASCT + CAR-T) as an independent variable, and this combination was correlated with superior PFS (HR = 7.363; 95% CI: 2.653–20.437; $P < 0.001$) and OS (HR = 0.208; 95% CI: 0.070–0.615; $P < 0.05$) compared to CAR-T alone, irrespective of bulky disease status. Collectively, these findings indicate that R/R DLBCL patients with bulky disease have worse outcomes after CAR-T therapy than those without, and that ASCT + CAR-T represents a promising alternative for such patients regardless of bulky disease presence.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequently encountered subtype of non-Hodgkin lymphoma, comprising 30% to 40% of incident cases [1]. Despite 5-year survival rates following frontline therapy range from 60% to 70%, up to 50% of patients eventually develop refractory or relapse after treatment. Patients with refractory/relapsed DLBCL, defined as no response to last chemotherapy or relapse ≤ 12 months post-ASCT, exhibit poor overall survival (OS)[2]. In patients with refractory/relapsed DLBCL treated with combination chemotherapy, the presence of bulk disease has consistently been associated with a poorer response rate and a shortened survival [3]. While the definition of tumor bulk has varied, with size thresholds ranging from 5 to 10 cm, findings from the MInT study suggest that in the rituximab era, a cutoff closer to 10 cm is more clinically relevant [4].

Bulky disease has been recognized as a poor prognostic indicator in DLBCL. A retrospective study in Finland addressed that the presence of bulky tumor was associated with inferior prognosis, with 2-year PFS of 53% compared to 90% to those with non-bulky disease[5]. Zelikson V's retrospective study comprises 187 patients including a proportion of patients with bulky disease (17%). They confirmed that those with bulky disease had significantly worse outcomes. Patients with bulky disease had a CRR and ORR of 0% and 16% compared to 16% and 35% in those patients without bulky disease. Specifically, bulky disease was predictive of poor response and inferior PFS and OS [6]. In Gohar S. Manzar's study involving 51 patients with DLBCL, of whom 25.5% presented with bulky disease, the risk of in-field relapse was significantly correlated with bulky disease [7]. Chimeric antigen receptor (CAR) T-cell therapy has reshaped the therapeutic paradigm for relapsed or refractory (R/R) DLBCL, earning approval as a second-line option for primary refractory or early relapsed cases and also in the third-line setting[8–10]. Given that CAR-T therapy has emerged as a promising treatment modality for R/R DLBCL, the prognostic relevance of bulky disease in this novel therapeutic context remains to be established [11, 12].

This retrospective study was performed to evaluate prognostic differences between bulky and non-bulky disease in R/R DLBCL patients treated with CD19 CART therapy, and to investigate prognostic factors in the contemporary CART treatment landscape. The analysis revealed that ASCT combined with CART therapy was independently associated with significantly improved PFS and OS over CART monotherapy, a benefit observed uniformly across subgroups defined by bulky disease.

2. Methods

2.1 Patients

A retrospective analysis was conducted on patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) who received CD19 CART therapy at Changhai Hospital between 2015 and 2023. The DLBCL diagnosis for all enrolled patients was established by expert hematopathologists in accordance with the WHO classification of Tumors of Haematopoietic and Lymphoid Tissue. Mass exceeding 7 cm were considered Bulky disease [13]. The cell of origin was analyzed using the result of immunohistochemistry and Hans algorithm [14]. The CAR used in this trial were manufactured by Shanghai HuaDao Biopharma Limited Corporation. Their design integrated a CD19- specific single-chain variable fragment, along with hinge and transmembrane domains, the 4-1BB costimulatory domain, and the CD3 ζ T-cell activation domain. Prior to therapy initiation, written informed consent was obtained from all participants. The clinical trial, registered under ChiCTR-OIN-15007668, received approval from the Institutional Review Board of Changhai Hospital.

2.2 Treatment response and toxicity assessment

Serial computerized tomography (CT) assessments were conducted at baseline (pre-lymphodepletion) and at months 1, 2, 3, 6, and 12 after CART therapy for response evaluation. Additionally, to confirm the treatment response, positron emission tomography/CT (PET/CT) scans were performed prior to lymphodepletion, and 3 months following CART therapy. Patients underwent bone marrow (BM) aspiration and biopsy before lymphodepletion to determine the presence of BM involvement. Those with confirmed involvement underwent repeat testing post-treatment for response assessment. Finally, treatment outcomes according to the Lugano criteria were categorized as remission, stable, or progression after CD19 CART therapy.

2.3 Statistical analysis

Statistical analyses were analyzed using Statistical software (SPSS 22.0, SPSS Inc., Chicago, IL, USA). Categorical variables were compared between subgroups with Fisher's exact test, while continuous variables were compared using Student's t-tests. PFS was calculated from the treatment initiation to disease progression, and OS was measured from the treatment initiation to death from any cause. Survival probabilities for PFS and OS were estimated using the Kaplan–Meier method, and differences between groups were compared with the log-rank test. Furthermore, log-rank test was employed to evaluate univariate associations between clinical variables and survival outcomes. Variables

demonstrating a significant association ($P < 0.05$) in univariate analysis were subsequently entered into a multivariable Cox proportional hazards regression model.

3. Results

3.1 Patient characteristics

A total of 54 R/R DLBCL were treated with CD19 CART therapy in Changhai Hospital from 2015 to 2023. Patients enrolled in this study were stratified into two groups based on the presence or absence of bulky disease: 27 (50%) patients were R/R DLBCL with bulky disease and 27 (50%) patients were R/R DLBCL with non-bulky disease (Fig. 1). In addition, 29 (53.7%) patients received ASCT combined with CART therapy (ASCT + CART). Among them, 15 patients were R/R DLBCL with bulky disease and 14 patients were R/R DLBCL with non-bulky disease.

Comparative analysis revealed no significant differences in baseline characteristics between patients with bulky and non-bulky disease (Table 1). The overall median age was 48 years (range 19–71), with no significant difference between the bulky (median 47, range 21–71) and non-bulky (median 48, range 19–68) cohorts. Gender distribution was similar between the bulky and non-bulky groups. Most patients had advanced-stage disease (Lugano stage III–IV: 83.3% overall), with 92.6% in the bulky group and 74.1% in the non-bulky group. Elevated pre-lymphodepletion lactate dehydrogenase (LDH) was observed in 59.3% of all patients (bulky: 18 (66.7%), non-bulky: 14 (51.9%)). Additionally, prior lines of therapy were a median of 5 (3–7) for bulky and 4 (3–7) for non-bulky patients. The median CART cell dose infused was $2.83 \times 10^6/\text{kg}$ overall, with no significant difference between bulky and non-bulky patients. The incidence of grade 2–4 CRS did not differ significantly between groups. A similar proportion of patients in each group underwent autologous stem cell transplantation combined with CART (ASCT-CART), and the median infused CD34⁺ cell counts for these patients were comparable. Notably, immune effector cell-associated neurotoxicity syndrome was absent throughout the cohort.

Table 1
Patients baseline clinical characteristics.

Variables	All, N (%)	Bulky, n (%)	Non-bulky, n (%)	P value
Number	54	27 (50)	27 (50)	
Age, y				0.874
Median, range	48 (19–71)	47 (21–71)	48 (19–68)	
Gender				0.106
Male	26 (48.1)	10 (37.0)	16 (59.3)	
Female	28 (51.9)	17 (63.0)	11 (40.7)	
Lugano stage				0.070
I-II	9 (16.7)	2 (7.4)	7 (25.9)	
III-IV	45 (83.3)	25 (92.6)	20 (74.1)	
LDH pre-lymphodepletion				0.277
Normal	22 (40.7)	9 (33.3)	13 (48.1)	
Abnormal	32 (59.3)	18 (66.7)	14 (51.9)	
IPI score				0.285
0–2	28 (51.9)	12 (44.4)	16 (59.3)	
3–5	26 (48.1)	15 (55.6)	11 (40.7)	
Cell of origin				0.785
GCB	21 (38.9)	11 (40.7)	10 (37.0)	
Non-GCB	33 (61.1)	16 (59.3)	17 (63.0)	
Lines of prior therapies, median(range)	5 (3–7)	5 (3–7)	4 (3–7)	0.840
CART cell dose ($\times 10^6$/kg), median (range)	2.83 (0.8–11.76)	2.64 (0.8–8.25)	3.14 (0.35–11.76)	0.256
CRS grade				0.198
0–1	42 (80.8)	19 (70.4)	23 (85.2)	
2–4	12 (19.2)	8 (29.6)	4 (14.8)	
R/R N-DLBCL, refractory/relapsed nodal diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; IPI, international prognostic index; GCB, germinal center B-cell; ASCT, autologous hematopoietic stem cell transplantation; CART, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ASCT-CART, ASCT combined with CART.				

Variables	All, N (%)	Bulky, n (%)	Non-bulky, n (%)	P value
ASCT-CART				0.790
Yes	29 (53.7)	15 (55.6)	14 (51.9)	
No	25 (46.3)	12 (44.4)	13 (48.1)	
The infused CD34⁺ cell numbers for ASCT-CART patients (×10⁶/kg), median (range)	2.98 (0.19-12)	3.01 (0.19-12)	2.48 (1-6.67)	0.359
R/R N-DLBCL, refractory/relapsed nodal diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; IPI, international prognostic index; GCB, germinal center B-cell; ASCT, autologous hematopoietic stem cell transplantation; CART, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ASCT-CART, ASCT combined with CART.				

3.2 Treatment response and survival analysis

Among the 54 patients with R/R DLBCL (Fig. 2A), an overall response rate (ORR) of 74.1% (n = 40) was observed. Complete remission (CR) was attained in 29 of these responders, accounting for 53.7% of the total patients. Furthermore, ORR differed between patient subgroups, which was 70.4% in those with bulky disease and 77.8% in those with non-bulky disease. Among them, 51.9% bulky patients and 55.6% non-bulky patients achieved CR. Meanwhile, stable disease (SD) or progressive disease (PD) was observed in 29.6% of bulky patients and 22.2% of non-bulky patients, respectively. Notably, the incidence of serious CRS (grade 3–4) after CART therapy were 29.6% in bulky patients and 14.8% non-bulky patient (Fig. 2B). Kaplan-Meier survival analysis comparing patients with bulky versus non-bulky disease revealed the PFS and OS of non-bulky patients received superior outcomes than bulky patients throughout the follow-up period (Fig. 3A-B).

3.3 Factors affecting survival in R/R DLBCL treated with CART therapy

To determine the predictors of PFS and OS following CD19 CAR-T therapy in patients with R/R DLBCL, a univariate analysis was initially conducted. Clinical variables assessed included age, gender, International Prognostic Index (IPI) score, presence of bulky disease, LDH level, cell of origin, Lugano stage, number of prior therapy lines, CAR-T cell dose, CRS grade, and combination with ASCT.

The results indicated that the combination of ASCT with CART therapy was significantly associated with both prolonged progression-free survival (PFS) and overall survival (OS) ($P < 0.001$ and $P = 0.003$, respectively) (Table 2). Patients receiving ASCT + CART therapy had a median PFS of 25 months, compared to 2 months for those who only receiving CART therapy. Similarly, their median OS was 25 months in ASCT + CART group versus 9 months in CART group. Furthermore, the presence of bulky disease was significantly associated with worse OS ($P = 0.040$), with a median OS of 12 months for bulky disease patients versus 24 months for non-bulky patients. The number of prior therapy lines also showed a significant association with OS ($P = 0.047$).

Table 2
Factors affecting the PFS and OS of R/R DLBCL by univariate Cox regression analysis.

Variables	PFS, median (range)	P value	OS, median (range)	P value
Age		0.293		0.142
≥ 60	3.5 (0–58)		7.5 (0–58)	
< 60	10.5 (0–59)		18.5 (1–59)	
Gender		0.793		0.866
Male	8.5 (0–58)		18 (1–58)	
Female	9 (0–59)		16.5 (0–59)	
IPI score		0.778		0.470
0–2	15.5 (0–59)		21 (2–59)	
3–5	7 (0–58)		12.5 (0–58)	
Bulky disease		0.147		0.040
Yes	4 (0–54)		12 (0–54)	
No	20 (0–59)		24 (0–59)	
LDH level		0.071		0.236
Normal	17 (0–59)		19.5 (0–59)	
Abnormal	3.5 (0–54)		14 (1–54)	
Cell of origin		0.429		0.683
GCB	18 (0–59)		23 (0–59)	
Non-GCB	7 (0–49)		13 (0–49)	
Lugano stage		0.234		0.540
II–III	20 (0–49)		20 (2–49)	
IV–V	8 (0–59)		17 (0–59)	
Lines of prior therapies		0.082		0.047
≥ 5	5 (0–58)		18 (0–58)	
< 5	9 (0–59)		16 (2–59)	
PFS, progression-free survival; OS, overall survival; LDH, lactate dehydrogenase; IPI, international prognostic index; GCB, germinal center B-cell; CART, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ASCT, autologous hematopoietic stem cell transplantation; ASCT- CART, ASCT combined with CART.				

Variables	PFS, median (range)	<i>P</i> value	OS, median (range)	<i>P</i> value
CART cell dose ($\times 10^6/\text{kg}$)		0.446		0.726
≥ 3	16 (0–59)		21 (0–59)	
< 3	5.5 (0–58)		13 (1–58)	
CRS grade		0.139		0.053
0–1	12.5 (0–59)		18 (1–59)	
2–4	3.5 (0–54)		10.5 (0–54)	
ASCT-CART		<0.001		0.003
Yes	25 (0–59)		25 (2–59)	
No	2 (0–24)		9 (0–32)	
PFS, progression-free survival; OS, overall survival; LDH, lactate dehydrogenase; IPI, international prognostic index; GCB, germinal center B-cell; CART, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ASCT, autologous hematopoietic stem cell transplantation; ASCT- CART, ASCT combined with CART.				

Based on the univariate analysis results, variables including the number of prior therapy lines, LDH level, combination with ASCT, CRS grade, and the presence of bulky disease were included in a subsequent multivariable Cox proportional hazards regression model (Table 3). The model identified ASCT + CART therapy as an independent variable. The combination of ASCT with CART therapy was independently associated with significantly improved PFS (HR = 7.363; 95% CI: 2.653–20.437; $P < 0.001$) and OS (HR = 0.208; 95% CI: 0.070–0.615; $P < 0.05$) compared to CART therapy alone. However, other factors did not retain a statistically significant association with either PFS or OS in the multivariable model.

Table 3
Factors affecting PFS and OS of R/R DLBCL by multivariable Cox regression analysis.

Variables	PFS, Hazard ratio (95%CI)	P value	OS, Hazard ratio (95%CI)	P value
Lines of prior therapies				
≥ 5	Reference		2.182 (0.683–6.976)	0.188
< 5	0.716 (0.270–1.899)	0.502	Reference	
LDH level				
Abnormal	Reference		—	—
Normal	0.685 (0.257–1.825)	0.449		
ASCT-CART				
Yes	Reference	<0.001	0.208 (0.070–0.615)	0.005
No	7.363 (2.653–20.437)		Reference	
CRS grade				
0–1	—	—	0.506 (0.193–1.331)	0.167
2–4			Reference	
Bulky disease				
Yes	—	—	2.310 (0.806–6.615)	0.119
No			Reference	
PFS, progression-free survival; OS, overall survival; LDH, lactate dehydrogenase; CRS, cytokine release syndrome; ASCT, autologous hematopoietic stem cell transplantation; CART, chimeric antigen receptor T cell; ASCT-CART, ASCT combined with CART.				

3.4 The impact of ASCT combined with CART therapy in R/R DLBCL

To further assess the effect of ASCT combined with CART therapy (ASCT + CART) in R/R DLBCL, a subgroup survival analysis was performed. The results demonstrated that ASCT-CART conferred a significant survival benefit. Statistically significant improvements in both PFS and OS were observed with ASCT-CART compared to CART therapy alone, irrespective of bulky disease status (Fig. 4, $P < 0.05$).

Discussion

This retrospective study aimed to compare the clinical outcomes of R/R DLBCL patients following CD19 CART therapy, stratified by the presence or absence of bulky disease. The analysis demonstrated

superior OS in non-bulky patients relative to those with bulky disease, whereas no statistically significant difference in PFS was observed between bulky and non-bulky groups. In addition, to identify prognostic factors influencing survival outcomes in R/R DLBCL, both univariate and multivariable analyses were subsequently performed. The analysis identified ASCT + CART therapy as an independent prognostic factor associated with significantly improved PFS and OS compared to CAR-T therapy alone. Moreover, the subsequent subgroup analysis based on the presence of bulky disease reinforced this benefit, revealing a significant survival advantage of the combined therapy on both PFS and OS irrespective of bulky disease presence.

In recent years, a large number of phase-II trials have addressed ASCT in patients with R/R DLBCL [15]. Our research demonstrated that ORR of R/R DLBCL was 74.1% (n = 40), and CR accounted for 53.7% of the total patients. Bulky disease is a key negative prognostic and predictive factor for both efficacy and safety following CART therapy in R/R DLBCL [16]. Patients with bulky disease tend to have inferior outcomes following treatment failure or relapse[3, 17]. In this study, patients with non-bulky disease achieved higher rates of ORR (77.8% vs. 70.4%) and CR (55.6% vs. 51.9%), along with a lower incidence of SD/PD (22.2% vs. 29.6%), compared to those with bulky disease. In addition, the majority of patients with R/R DLBCL did not develop severe (grade 3–4) CRS following CART therapy, highlighting a manageable safety profile in this regard (Fig. 2). Moreover, PFS and OS of non-bulky patients received superior outcomes than bulky patients. the presence of bulky disease was significantly associated with worse OS (Fig. 3). Consistent with our findings, a retrospective study by Nicholas B. Figura et al. involving 69 patients with R/R large B-cell lymphoma demonstrated that those with any lesion ≥ 5 cm experienced inferior PFS and OS after CART therapy [18]. Mechanistically, bulky disease is highly associated with lower CART efficacy [19, 20]. Despite its recognized prognostic value, the specific mechanisms underlying the adverse prognostic impact of bulky disease remain to be elucidated and merit future study.

Importantly, ASCT + CART therapy conferred a significant and independent survival benefit in terms of both PFS and OS relative to CART alone. This therapeutic advantage was maintained irrespective of bulky disease presence (Fig. 4). Several evidence presented that in patients receiving CAR-T cells, ASCT provided better disease debulking and thereby lead to greater efficacy of subsequent CAR-T cell therapy [21, 22]. Shadman et al. also reported that ASCT treatment with better outcomes compared to CART therapy in patients with DLBCL with partial remission (PR) after salvage therapy [23]. The reason why ASCT combined with CART could improve the outcomes may be associated with lower disease burden assessed before CAR-T cells infusion [24]. However, these results need to be further validated in larger cohorts in the future.

In summary, our study results revealed that ASCT combined with CD19 CART therapy serves as an independent prognostic factor for improved survival in R/R DLBCL. In addition, patients with non-bulky disease exhibited better PFS and OS outcomes than those with bulky disease. Notably, we also found that ASCT combined with CART therapy could significantly improve the PFS and OS of patients with R/R

DLBCL irrespective of bulky disease status, suggesting ASCT + CART therapy as an effective alternative for patients with R/R DLBCL.

Declarations

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. The Institutional Review Board of Changhai Hospital has reviewed and approved this study. Written informed consent of patients was obtained in this study.

Conflict of interest

The authors declare that they have no conflict of interest.

Author Contribution

J. Y., L. G. and Y. W were responsible for designing and guiding study; X. H., D. Z. and G. L. analyzed the data, made the figures, and wrote the manuscript; X. N., L. W., Z. S. provided clinical consultation; G. T., W. Y. and L. C. revised manuscript; J. C. and T. W. provided patients' data.

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Data availability

All data that support the key findings of this study are available from the corresponding authors upon reasonable request.

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Figures

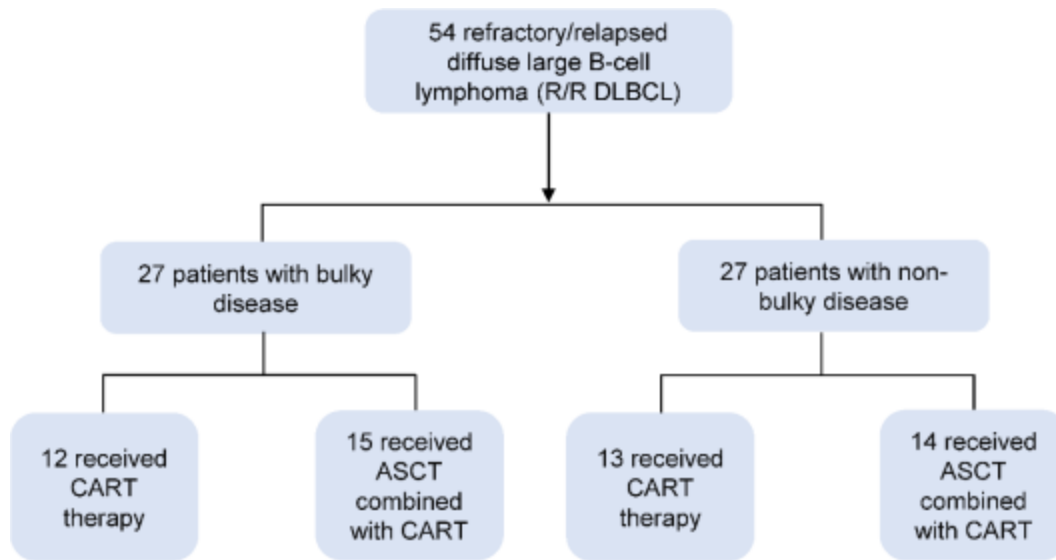


Figure 1

Study design. 54 R/R DLBCL treated with CD19 CART therapy were enrolled in this study: 27 patients were bulky diseases and 27 patients were non-bulky diseases. In addition, 15 and 14 patients received ASCT combined with CART therapy in bulky disease and non-bulky disease, respectively.

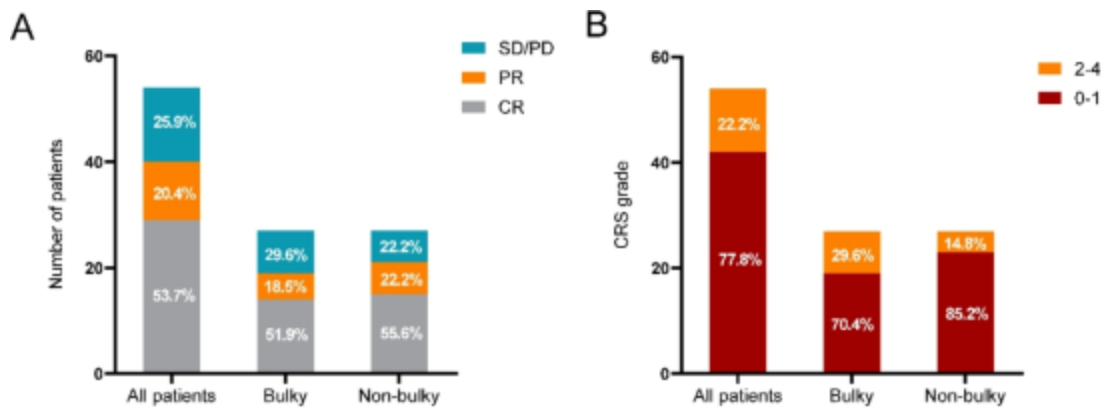


Figure 2

The treatment response (A) and cytokine release syndrome (CRS) grade in refractory/relapsed diffuse large B-cell lymphoma (R/R DLBCL) after CD19 CART therapy.

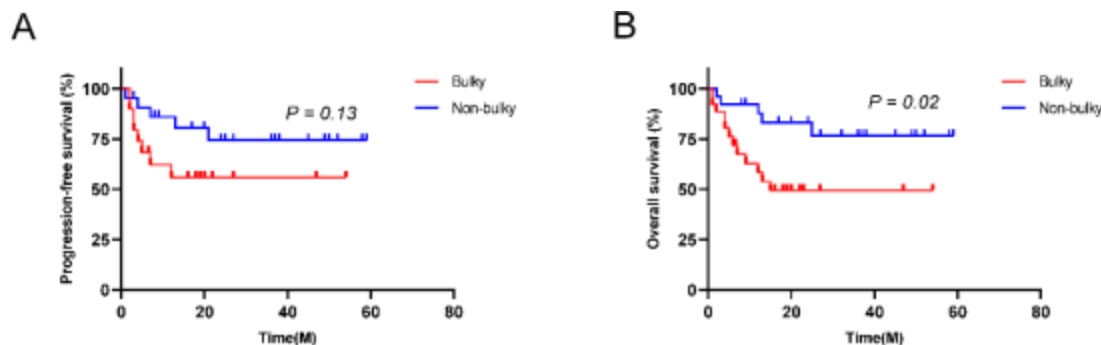


Figure 3

The progression-free survival (PFS) (A) and overall survival (OS) (B) analyses in patients with refractory/relapsed diffuse large B-cell lymphoma with bulky disease (R/R DLBCL) and refractory/relapsed diffuse large B-cell lymphoma with non-bulky disease. R/R DLBCL with bulky disease presented superior PFS and OS compared with R/R DLBCL with non-bulky disease.

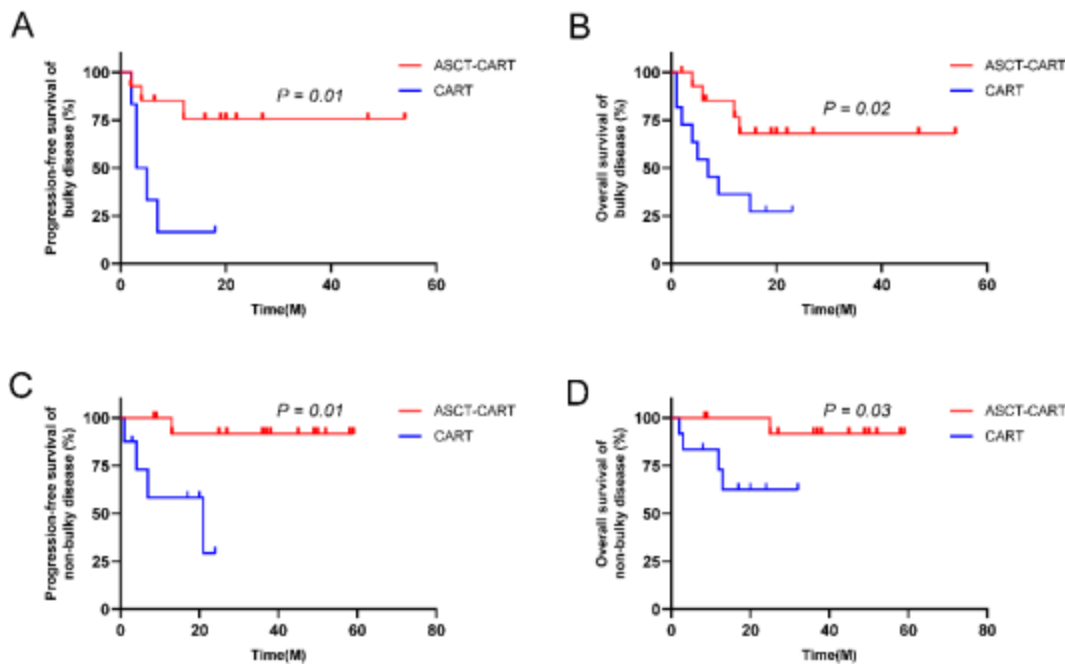


Figure 4

The progression-free survival (PFS) and overall survival (OS) analyses for bulky (A, B) and non-bulky patients (C, D) with or without autologous hematopoietic stem cell transplantation combined with CART (ASCT+CART) therapy. Patients with ASCT+CART therapy presented superior PFS than CART treatment alone.