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ARTICLE

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Chimeric antigen receptor-T cell therapy shows similar efficacy and toxicity in patients with diffuse large B-cell lymphoma aged 70 and older compared to younger patients: A multicenter cohort study

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Abstract

CD19-directed chimeric antigen receptor (CAR)-T cell therapy has become a standard treatment for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). While the benefits of CAR-T cell treatment are clear in the general patient population, there remains a relative scarcity of real-world evidence regarding its efficacy and toxicity in patients (pts) aged ≥70 years with DLBCL. We conducted a multicenter retrospective analysis including 172 r/r DLBCL pts with CAR-T cell treatment, axicabtagene ciloleucel or tisagenlecleucel, between 2019 and 2023 at three tertiary centers. Pts were grouped by age at CAR-T infusion (<70 vs. ≥70 years). Subsequently, descriptive and survival analyses, including propensity score matching, were performed to compare outcomes between both age groups. We identified 109 pts aged <70 and 63 pts aged ≥70 years. Overall response rates for both age groups were comparable (77.7% vs. 78.3%; $p = 0.63$). With a median follow-up of 8.3 months, median progression-free survival was 10.2 months (95% confidence interval [CI]: 6.5–21.8) and 11.1 months (95% CI: 4.9–NR) ($p = 0.93$) for both cohorts. Median overall survival reached 21.8 months (95% CI: 11.8–NR) and 34.4 months (95% CI: 10.1–NR) ($p = 0.97$), respectively. No significant differences in the incidence of cytokine release syndrome ($p = 0.53$) or grade ≥3 neurotoxicity ($p = 0.56$) were observed. Relapse and nonrelapse mortality were not significantly different between both groups. Our findings provide additional support that CAR-T cell therapy is feasible and effective in patients with r/r DLBCL aged 70 years or older, demonstrating outcomes comparable to those observed in younger patients. CAR-T cell therapy should be not withheld for elderly patients with r/r DLBCL.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive lymphoma, typically manifesting with a median age of diagnosis of 66 years.[1] It is noteworthy, however, that approximately 30% of newly diagnosed DLBCL patients are aged 75 years or older.[1] Patient age represents a major determinant for DLBCL outcomes, significantly impacting relapse and disease-related mortality.[2–4] Specifically, the long-term progression-free survival (PFS) is markedly lower in elderly patients aged 60–80 years following anthracycline-based treatment, with a 10-year PFS at ~40%, in contrast to younger high-risk patients with 10-year PFS at ~60%.[5–8] This might be due to a higher prevalence of high-risk disease in older DLBCL patients compared to younger patients.[3] Also, elderly DLBCL patients often prove ineligible for full-dose cytotoxic immunochemotherapy, rendering them more susceptible to treatment discontinuation or compromises due to treatment-related side effects. Consequently, nearly 60% of older DLBCL patients do not achieve a cure following first-line treatment, thus requiring salvage therapies.[4,9]

Until recently, the clinical management of relapsed or refractory (r/r) DLBCL patients largely relied on their eligibility for high-dose therapy and autologous stem cell transplantation (auto-HSCT). Meanwhile, building on the positive results of two randomized prospective studies showing favorable results of CD19-directed chimeric antigen receptor (CAR)-T cells compared to auto-HSCT, r/r DLBCL patients deemed CAR-T cell eligible predominantly receive one of the approved CAR-T cell products: Axi-cel (Axicabtagene ciloleucel) or Liso-cel (Lisocabtagene maraleucel).[10,11] In randomized studies comparing auto-HSCT with CAR-T cells, the overall response rates (ORR) were 50% versus 83% and 49% versus 87%, respectively.[10,11] Notably, CAR-T cell therapy boasts potential major advantages over auto-HSCT, including reduced morbidity and mortality rates and a decreased risk of infections.

Consequently, CAR-T cell therapy potentially represents a curative approach for elderly patients who would have previously received palliative treatment in the pre-CAR-T era. A growing body of literature advocates for CAR-T cells as an effective treatment option for older patients, who are ineligible for auto-HSCT.[12–15] Clinical trials for patients aged 65–70 years and above have reported encouraging post-CAR-T outcomes. In the ZUMA-1 trial, the long-term response rates at 2 years for patients aged 65 years and older were comparable to those of the younger counterparts, both at approximately 40%.[14] More recently, the open-label, phase 2, ALYCANTE study reported on the efficacy and safety of axi-cel as second-line treatment for 40 r/r large B-cell lymphoma (LBCL) patients, who were not candidates for auto-HSCT due to age and/or comorbidities.[16] The study met its primary endpoint with a complete-metabolic remission (CMR) rate of 70% at 3 months, in stark contrast to the expected 12% based on historical controls.[16,17] Median PFS was 11 months, and median OS was not reached. Cytokine release syndrome (CRS) occurred in 90% of patients, including 10% of grade 3–4. Immune cell-associated neurotoxicity syndrome (ICANS) occurred in 55% of patients, including 20% with grade 3–4 severity.

Despite the encouraging data, there is a need to better understand how age and other factors influence survival outcomes among elderly CAR-T patients, particularly those aged 70 years and older, in the real-world scenario. Aiming to fill this gap, we sought to evaluate the efficacy and toxicity profiles of older DLBCL patients (≥70 years) treated with CD19-directed CAR-T cells and compare these results to younger patients (<70 years) undergoing the same treatment.

MATERIALS AND METHODS

Data collection

This retrospective study included 172 consecutive relapsed or refractory DLBCL patients treated with CAR-T cell therapy between January 2019 and May 2023 at the University Hospital Muenster, Germany; University Hospital Goettingen, Germany; and the University Hospital/Inselspital Bern, Switzerland. All patients who received CAR-T cell treatment applied within this period were considered: axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel). Clinical data were retrospectively extracted from the medical records and electronic patient files. The patients included in the analysis were divided into two age groups (<70 vs. ≥70 years) dependent on the age at CAR-T infusion. The study was approved by the local ethics committee, and all patients signed informed consent and/or did not declare refusal to participate. All study procedures were performed in accordance with relevant guidelines, such as the Declaration of Helsinki, as well as local regulations.

Definitions

All patients received lymphodepleting chemotherapy with fludarabine (cumulative dose 75 mg/m^2 i.v. for tisa-cel; 90 mg/m^2 i.v. for axi-cel) and cyclophosphamide (cumulative dose 750 mg/m^2 i.v. for tisa-cel; 1500 mg/m^2 i.v. for axi-cel) before CAR-T cell infusion on Day 0. Grading of CRS and ICANS was performed according to the American Society for Transplantation and Cellular Therapy consensus grading.[18] Response to CAR-T cell therapy was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The ORR was defined as the proportion of patients who achieved CR or PR. Disease status was assessed by individual investigators according to standard criteria. The best response was assessed using radiological criteria based on computed tomography (CT) and/or magnetic resonance imaging (MRI) and/or positron emission tomography (PET-CT) performed after CAR-T cell infusion. Bridging therapy was defined as any treatment between leukapheresis before CAR-T infusion and CAR-T infusion itself, and classified as none, systemic therapy (immunochemotherapy and/or targeted therapies), and radiotherapy. Nonrelapse mortality (NRM) and relapse mortality (RM) were defined as death due to complication (other than relapse) and death due to recurrence or progressive lymphoma following CAR-T cell therapy, respectively. Early NRM was defined as those that occurred within the first 100 days post-CAR-T administration. Late NRM considered patients succumbed from other reasons than relapse/progressive disease beyond 100 days post-CAR-T.

The standard infectious prophylaxis was used irrespective of age at the time of CAR-T cell therapy. Aciclovir (400 mg twice daily) and cotrimoxazole (960 mg twice daily 2 days a week or 960 mg once daily 3 days per week) were mandatory for all CAR-T cell patients. Immunoglobulin replacement therapy (IgRT) was employed in cases where patients exhibited serum IgG levels below 4 g/L and experienced recurrent or severe infections. For those with an absolute neutrophil count (ANC) falling below 1000/mm^3, primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was administered. The guidelines for managing toxicity were consistent across all age groups. Notably, there were no distinctions in the approach to managing CRS and/or ICANS.

Statistical analysis

For descriptive analyses, we calculated means, medians, and standard deviations (SD) for continuous variables, while frequencies and proportions for categorical variables were determined. For categorical data, Fisher's exact test was applied to evaluate differences. The unpaired *t*-test was applied for normally distributed metrical data. In case of not normally distributed metrical data, the Mann–Whitney *U* test was used. All analyses were stratified by age groups (<70 vs. ≥70 years). PFS and overall survival (OS) were calculated using Kaplan–Meier analyses from the date of CAR-T infusion. NRM was defined as death without previous lymphoma relapse, relapse incidence as disease relapse or progression. All outcomes were measured from the day of CAR-T cell infusion. Surviving patients were censored at the time of the last contact. Cumulative incidences for NRM and relapse mortality were calculated using a competing risk model, with death in remission as a competing event for relapse. Differences in PFS and OS across age groups were assessed using the log-rank test, for cumulative incidences the Gray's test was applied.

Univariate and multivariate Cox proportional hazards models were performed to analyze the association between patient and disease characteristics and PFS or OS. Results were shown as hazard ratios (HR) with a 95% confidence interval (CI).

For further analysis, we performed propensity score matching (PSM) in a 1:1 ratio for both age groups with exact matching for the applied CAR-T cell product (axi-cel, tisa-cel) and previous auto-HSCT (yes, no), and nearest neighbor matching for gender, bridging therapy, remission status before CAR-T, and Eastern Cooperative Oncology Group (ECOG) performance score (PS) (0–2, 3). A caliper of 0.25 SD was applied for PSM. All tests were two-sided, and the type I error was fixed at 0.05 for factors associated with time-to-event outcomes. All analyses were performed using R statistical software version 4.2.2 (available online at http://www.R-project.org).

RESULTS

Patient characteristics

The study population consisted of 172 patients who underwent CAR-T cell treatment meeting the inclusion criteria. The median age of all patients at CAR-T treatment was 65 years (range: 19–82 years), 37.2% were female, 9.1% had an ECOG PS 3, and 65.7% received axi-cel and 34.3% tisa-cel treatment. Of these, 109 (63.4%) were aged <70 years and 63 (36.6%) were aged 70 years and older at CAR-T infusion. Patient characteristics are summarized across both age groups (<70 years vs. ≥70 years) in Table 1. The median age was 61 years (range: 19–69) and 74 (range: 70–82) and the median follow-up time post-CAR-T was 8.2 (range: 0.1–44.3) and 8.6 months (range: 0.4–42.3), respectively. We noted similar proportions for both groups for ECOG PS 3 (7.5% vs. 11.9%, $p = 0.40$), axi-cel treatment (68.8% vs. 60.3%, $p = 0.32$), GCB subtype (56.6% vs. 67.6%, $p = 0.37$), de novo DLBCL (72.5% vs. 71.4, $p = 1.0$), and advanced disease stage (III–IV) at diagnosis (74.1% vs. 71.7%, $p = 0.86$) as well as advanced disease stage (III–IV) (64.2% vs. 63.5%, $p = 1.00$) and bulk manifestation (defined as lymphoma manifestation ≥7.5 cm; 11.0% vs. 14.3%, $p = 0.63$) at CAR-T infusion. Additionally, we found no significant differences in the incidence of extranodal manifestations ($p = 0.83$), secondary CNS manifestation (3.7% vs. 4.8%, $p = 0.71$), and elevated LDH levels at CAR-T (60.2% vs. 55.9%, $p = 0.62$). In terms of pre-existing medical conditions, younger patients exhibited significantly lower rates of moderate-severe chronic kidney disease (CKD stage 3–4: 10.1% vs. 28.6%, $p = 0.005$), congestive heart failure (NYHA I–IV: 6.4% vs. 17.5%, $p = 0.04$), atrial fibrillation (7.3% vs. 25.4%, $p = 0.002$), chronic obstructive pulmonary disease (COPD: 0.9% vs. 7.9%, $p = 0.03$), and diabetes mellitus (7.3% vs. 19.0%, $p = 0.03$) (Table 1). However, no significant differences were noted in the proportions of patients with arterial hypertension ($p = 0.52$). Overall, the percentage of patients ≥70 years undergoing CAR-T beyond two lines of prior treatment was higher (<70 years: 86.2% vs. ≥70 years: 76.2%, $p = 0.10$), while previous auto-HSCT was more frequent among younger patients (43.1% vs. 14.3%, $p < 0.001$). The proportion of patients who received bridging therapy, including systemic therapy or radiotherapy, (90.8% vs. 82.5%, $p = 0.15$) as well as the proportion of patients in CR at CAR-T infusion (14.2 vs. 9.5%, $p = 0.28$) was similar among both age groups (Table 1). No differences across age groups for the time between indication and CAR-T infusion were noted (Table 1).

Efficacy and outcomes

The outcomes of CAR-T cell therapy are presented in Tables 2 and 3 and Figures 1–3. The overall response, indicated by achieving a CR or PR as the best response, was 77.7% (<70 years) and 78.3% (≥70 years) for both age groups ($p = 0.63$), respectively. The median time to best response was comparable for both the younger and older groups with 2.3 and 3.0 months, respectively (Table 2). Figure 1 depicts response patterns before and after CAR-T infusion for both age groups. The proportion of patients with PD at CAR-T infusion achieving a response (CR or PR) as the best response after CAR-T was 72.2% (39/54 patients) for the younger group and 77.8% (21/27 patients) for the older group (Figure 1). We noted a relapse incidence at 3 months of 21% (95% CI: 14–29) and 12% (95% CI: 5.1–22); at 1 year 42% (95% CI: 32–52) and 32% (95% CI: 20–45) ($p = 0.23$) for both age groups, respectively (Figure 2, Table 3).

With a median follow-up of 8.3 months (range: 0.07–44.3), estimated median PFS was 10.2 months (95% CI: 6.5–21.8) and 11.1 months (95% CI: 4.9–NR) ($p = 0.93$), and estimated median OS 21.8 months (95% CI: 11.8–NR) and 34.4 months (95% CI: 10.1–NR) ($p = 0.97$) for patients age <70 and ≥70 years, respectively (Figure 3). The 1- and 2-year PFS were 44.7% (95% CI: 35–56.2) and 35.5% (95% CI: 25.6–49.1) in the younger group, while 46.7% (95% CI: 35.1–62.2) and 43.4% (95% CI: 31.5–59.8) in the elderly group ($p = 0.93$), respectively (Table 3). Of note, the rates of PFS were similar in both age groups irrespective of remission status prior to CAR-T (Supporting Information S1: Figure S1). OS rates at 1 and 2 years were 58.3% (95% CI: 49.1–69.4) and 47.4% (95% CI: 37.1–60.4) for patients <70 years, and 57.3% (95% CI: 45.5–72.1) and 51.4% (95% CI: 39–67.6) for those aged 70 years and above ($p = 0.97$). When considering only the elderly group, patients aged 70–74 years (38/63 patients) and those aged 75 and above (25/63 patients) demonstrated similar PFS ($p = 0.66$) and OS rates ($p = 0.75$), as illustrated in Supporting Information S1: Figure S2. Additionally, no differences in terms of PFS and OS for patients aged <60 years and patients 60–69 years were noted ($p = 0.96$; $p = 0.95$) (Supporting Information S1: Figure S2). Comparing axi-cel versus tisa-cel, PFS and OS for patients <70 years were significantly higher for axi-cel with a median PFS of 11.9 months (95% CI: 8.8–NR) versus 3.1 months (95% CI: 1.8–21.8) ($p = 0.02$) and median OS of 29.6 months (95% CI: 14.4–NR) versus 8.1 months (95% CI: 3.7–NR) ($p = 0.04$). For patients ≥70 years, axi-cel was associated with a numerically higher median PFS of 11.4 months (95% CI: 7.6–NR) versus 5.6 months (95% CI: 3.3–NR) ($p = 0.35$), but similar median OS of 34.4 months (95% CI: 6.2–NR) versus 36.5 months (95% CI: 8.1–NR) ($p = 0.88$) (Supporting Information S1: Figure S3).

TABLE 1 Clinical characteristics by age groups. (continued on next page)

	<70 years (*N* = 109)	≥70 years (*N* = 63)	*p*-Value
Age at CAR-T infusion in years			
Median (min, max)	61.0 (19.0, 69.0)	74.0 (70.0, 82.0)	<0.001
Gender			
Male	68 (62.4%)	40 (63.5%)	1.000
Female	41 (37.6%)	23 (36.5%)	
ECOG score			
0–2	98 (92.5%)	52 (88.1%)	0.402
3	8 (7.5%)	7 (11.9%)	
Missing	3	4	
CAR-T product			
Axi-cel	75 (68.8%)	38 (60.3%)	0.317
Tisa-cel	34 (31.2%)	25 (39.7%)	
DLBCL subtype by immunohistochemistry			
Non-GCB	23 (43.4%)	11 (32.4%)	0.370
GCB	30 (56.6%)	23 (67.6%)	
Missing	56	29	
Transformed DLBCL			
No	79 (72.5%)	45 (71.4%)	1.000
Yes	30 (27.5%)	18 (28.6%)	
Pre-existing comorbidities			
Chronic kidney disease (CKD stages)			
Stage 1–2	4 (3.7%)	1 (1.6%)	0.005
Stage 3–4	11 (10.1%)	18 (28.6%)	
Congestive heart failure (NYHA I-IV)	7 (6.4%)	11 (17.5%)	0.036
Arterial hypertension (all grades)	44 (40.4%)	29 (46.0%)	0.523
Atrial fibrillation	8 (7.3%)	16 (25.4%)	0.002
COPD	1 (0.9%)	5 (7.9%)	0.025
Diabetes mellitus	8 (7.3%)	12 (19.0%)	0.027
Ann-Arbor stage at diagnosis			
I/II	28 (25.9%)	17 (28.3%)	0.866
III/IV	80 (74.1%)	43 (71.7%)	
Missing	1	3	
Ann-Arbor stage before CAR-T infusion			
I/II	39 (35.8%)	23 (36.5%)	1.000
III/IV	70 (64.2%)	40 (63.5%)	
Bulk manifestation before CAR-T infusion			
No	97 (89.0%)	54 (85.7%)	0.630
Yes	12 (11.0%)	9 (14.3%)	
Extranodal manifestations before CAR-T infusion			
None	45 (41.3%)	24 (38.1%)	0.829
1 site	35 (32.1%)	23 (36.5%)	
≥2 sites	29 (26.6%)	16 (25.4%)	
Secondary CNS manifestation before CAR-T infusion			
No	105 (96.3%)	60 (95.2%)	0.708
Yes	4 (3.7%)	3 (4.8%)	

TABLE 1 (Continued)

	<70 years (*N* = 109)	≥70 years (*N* = 63)	*p*-Value
LDH > ULN before CAR-T			
No	43 (39.8%)	26 (44.1%)	0.624
Yes	65 (60.2%)	33 (55.9%)	
Missing	1	4	
Treatment lines before CAR-T			
1–2	15 (13.8%)	15 (23.8%)	0.101
≥3	94 (86.2%)	48 (76.2%)	
Treatment lines before CAR-T			
Median (min, max)	3.00 (1.00, 11.0)	3.00 (1.00, 8.00)	0.029
Previous auto-HSCT			
No	62 (56.9%)	54 (85.7%)	<0.001
Yes	47 (43.1%)	9 (14.3%)	
Bridging therapy before CAR-T			
None	10 (9.2%)	11 (17.5%)	0.146
Systemic therapy/radiotherapy	99 (90.8%)	52 (82.5%)	
Remission at CAR-T infusion			
CR	15 (14.2%)	6 (9.5%)	0.275
PR	24 (22.6%)	23 (36.5%)	
SD	13 (12.3%)	7 (11.1%)	
PD	54 (50.9%)	27 (42.9%)	
Missing	3	0	
Days from indication to CAR-T infusion			
Median (min, max)	76.0 (40.0, 265)	76.0 (30.0, 256)	0.872
Follow-up in months post-CAR-T			
Median (min, max)	8.15 (0.1, 44.3)	8.58 (0.4, 42.3)	0.951

Abbreviations: auto-HSCT, high-dose therapy and autologous stem cell transplantation; Axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor-T cells; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; LDH, lactate dehydrogenase; Max., maximal; Min., minimal; NYHA; New York Heart Association; PD, progressive disease; PR, partial remission; SD, stable disease; Tisa-cel, tisagenlecleucel; ULN, upper limit of normal.

Safety and CAR-T-specific toxicities

Table 2 shows the frequency of CRS and ICANS. In total, CRS (of all grades) was recorded for 145 patients (84.3%), accounting for 87.2% in the younger age group and 79.4% in the older group ($p = 0.67$). Both age groups presented with a similar incidence of severe CRS (≥3): 11.9% and 7.9%, accordingly ($p = 0.45$). For all grades ICANS, there was no difference between the younger and the elderly group ($p = 0.11$), in particular for grades ≥3 events (18.4% vs. 22.2%, $p = 0.57$). The proportion of patients requiring tocilizumab treatment was comparable across the two groups (60.6% vs. 66.7%, $p = 0.51$). Similarly, the percentage of patients given steroids was similar (46.8% vs. 54.0%, $p = 0.43$). No significant variances were identified across both age groups concerning mean absolute lymphocyte counts (1.73 vs. 0.89×10^9/L, $p = 0.24$) and mean IgG levels (5.52 vs. 5.99 g/L, $p = 0.26$) in the time period between Days 30–45 post-CAR-T (Table 2). Overall, 49 patients in the younger age group (44.9%) and 28 in the older age group (44.4%) had died at the last follow-up, with disease relapse/progression being the main reason for death accounting for 33 (67.3%) and 14 (50.0%) in both age groups, respectively. Out of all 172 patients, 30 patients (17.4%) experienced NRM with infections and CRS/ICANS being the most frequent reasons in 18/30 patients (60%) and 4/30 patients (13.3%), respectively. Early NRM cases (≤day+ 100 post-CAR-T) comprised 40% (12/30 patients), while late NRM cases (>day+ 100 post-CAR-T) constituted 60% (18/30). Cumulative incidences of NRM, considering relapse/progression as a competing event, were numerically higher in patients aged ≥70 years compared to patients <70 years with 14.7% (95% CI: 7.2–25) versus 8.3% (95% CI: 4.1–15) at 3 months and 23% (95% CI: 13–34) versus 14% (95% CI: 8.0–22) at 12 months (both $p = 0.20$), respectively (Table 3).

The primary causes of NRM in both age groups are outlined in Table 4. Grade 5 infections showed a similar frequency in both cohorts, 9.2% versus 12.7% ($p = 0.61$). The characteristics of 18 patients with NRM due to infection are presented in Supporting Information S1: Table S1. Ten out of 18 infections grade 5 (56%) occurred beyond day 100 post-CAR-T in the whole patient cohort and in 50% (4/8) and 60% (6/10) of elderly and young patients, accordingly. Particularly, three patients (17%) succumbed to COVID-19 while two patients (11%) died from bacterial infection preceding severe pancytopenia post-CAR-T and one more patient (6%) following allogeneic hematopoietic stem cell transplantation due to persisting pancytopenia after CAR-T. Two other patients

TABLE 2 Safety, toxicities, and response to CAR-T therapy by age groups.

	<70 years (*N* = 109)	≥70 years (*N* = 63)	*p*-Value
Cytokine release syndrome (grade)			
No CRS	14 (12.8%)	13 (20.6%)	0.673
1	38 (34.9%)	20 (31.7%)	
2	44 (40.4%)	25 (39.7%)	
3	12 (11.0%)	5 (7.9%)	
4	0 (0%)	0 (0%)	
5	1 (0.9%)	0 (0%)	
ICANS (grade)			
No ICANS	71 (65.1%)	33 (52.4%)	0.108
1	9 (8.3%)	5 (7.9%)	
2	9 (8.3%)	11 (17.5%)	
3	12 (11.0%)	13 (20.6%)	
4	5 (4.6%)	1 (1.6%)	
5	3 (2.8%)	0 (0%)	
Tocilizumab usage			
No	43 (39.4%)	21 (33.3%)	0.513
Yes	66 (60.6%)	42 (66.7%)	
Steroid usage			
No	58 (53.2%)	29 (46.0%)	0.429
Yes	51 (46.8%)	34 (54.0%)	
Absolute lymphocyte count, days 30–45 after CAR-T ($\times 10^9$/L)			
Mean (standard deviation)	1.73 (6.62)	0.89 (0.83)	0.242
Missing	20	8	
IgG levels, days 30–45 after CAR-T [g/L]			
Mean (standard deviation)	5.52 (2.11)	5.99 (2.59)	0.259
Missing	18	10	
Best response after CAR-T			
CR/PR	80 (77.7%)	47 (78.3%)	1
SD/PD	23 (22.3%)	13 (21.7%)	
Missing	6	3	
Time to best response in months			
Median (min, max)	2.30 (0.1, 10.0)	3.00 (0.1, 13.1)	0.572
Missing	8	3	

Abbreviations: CAR-T, chimeric antigen receptor-T cells; CR, complete remission; ICANS, immune cell-associated neurotoxicity syndrome; IgG, immunoglobulin G; Max., maximal; Min., minimal; PD, progressive disease; PR, partial remission; SD, stable disease.

TABLE 3 Univariate outcomes by age groups.

Outcomes	<70 years Probability (95% confidence interval [CI])	≥70 years Probability (95% CI)	*p*-Value
Relapse incidence (months)			0.23[a]
1	6.4% (2.8–12.1)	4.8% (1.3–12.2)	
3	20.8% (13.6–29.0)	11.8% (5.1– 21.5)	
6	27.8% (19.5–36.7)	26.3% (15.6–38.3)	
12	42.2% (32.0–52.0)	32.4% (20.4–45.0)	
24	46.7% (35.2–57.3)	32.4% (20.4–45.0)	
Nonrelapse mortality (months)			0.20[a]
1	4.6% (1.7–9.7)	9.7% (3.9–18.6)	
3	8.3% (4.1–14.5)	14.7% (7.2–24.8)	
6	10.4% (5.5–17.2)	18.4% (9.7– 29.2)	
12	14.1% (8.0–21.8)	22.6% (12.6–34.3)	
24	18.6% (10.5–28.5)	25.8% (14.5–38.6)	
Progression-free survival (months)			0.93
6	61.8% (53.1–71.9)	55.3% (43.8–69.9)	
12	44.7% (35.6–56.2)	46.7% (35.1–62.2)	
24	35.5% (25.6–49.1)	43.4% (31.5–59.8)	
Overall survival (months)			0.97
6	73.7% (65.6–82.8)	71.1% (60.3–83.8)	
12	58.3% (49.1–69.4)	57.3% (45.5–72.1)	
24	47.4% (37.1–60.4)	51.4% (39–67.6)	

[a]Gray's test.

(11%) experienced bacterial infection grade 5 following multiple organ failure of either unknown reason or due to hemophagocytic lymphohistiocytosis post-CAR-T. Among elderly patients, two out of eight patients died from invasive pulmonary mycosis following CAR-T cell therapy. Fatal cases of CRS or ICANS were observed in four patients (3.7%) within the younger group, while no such cases were reported in the older patient group. Furthermore, one patient (0.9%) from the younger group and two patients (3.2%) from the older group succumbed to vascular events ($p = 0.57$). Notably, a single case of secondary malignancy, esophageal cancer, was documented in an elderly patient post-CAR-T therapy.

Regression analysis and PSM

Next, we built univariable and multivariable Cox regression models (Table 5) for PFS and OS. Based on univariate analyses, no significant differences in PFS and OS were noted for age groups, gender, disease stage at diagnosis, GCB subtype, elevated LDH levels prior to CAR-T, transformed DLBCL, previous auto-HSCT, number of treatment lines, remission status at CAR-T infusion, and days from indication and occurrence of CRS (Table 5). For univariable outcomes, we noted lower PFS for patients with ECOG 3 (HR = 2.06 [95% CI: 1.06–3.98], $p = 0.03$), tisa-cel treatment (HR = 1.67 [95% CI: 1.10–2.53], $p = 0.02$), ICANS grade 4–5 (HR = 2.75 [95% CI: 1.19–6.37], $p = 0.02$), as well as lower OS rates for ECOG 3 (HR = 2.80 [95% CI: 1.43–5.47], $p = 0.003$), and ICANS grade 4–5 (HR = 3.77 [95% CI: 1.49–9.57], $p = 0.005$). The multivariate model showed that tisa-cel treatment (HR = 1.59 [95% CI: 1.02–2.49], $p = 0.04$) independently reduced PFS (Table 5). To further adjust for potentially underlying differences across age groups, we performed PSM using CAR-T product (axi-cel, tisa-cel), previous auto-HSCT, gender, bridging therapy, remission status before CAR-T, and ECOG performance as covariables. As a result, we identified two patient groups, each consisting of 51 individuals, who exhibited comparability across all observed covariates and baseline characteristics (Supporting Information S1: Table S2). Nevertheless, chronic kidney disease ($p = 0.048$) and atrial fibrillation ($p = 0.03$) were more frequent among the PSM-elderly-cohort (Supporting Information S1: Table S2). The distribution of toxicities

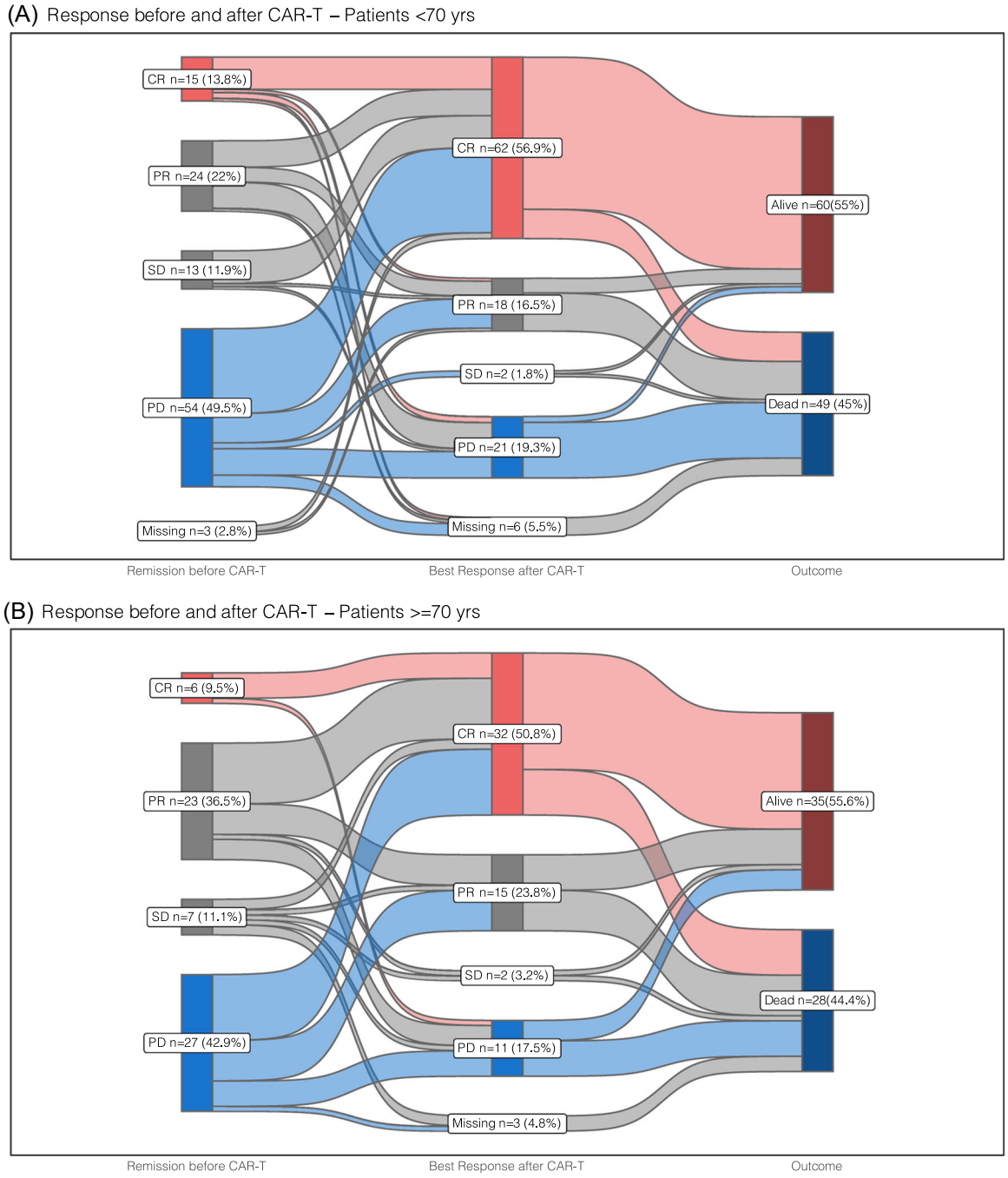

FIGURE 1 Sankey diagrams for patterns of treatment response and outcomes by age groups. Patterns of remission before CAR-T infusion, best response after CAR-T infusion, and survival outcomes at last follow-up for patients aged (A) <70 years and (B) ≥70 years. CAR-T, chimeric antigen receptor-T cells; CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.

and response were comparable after matching and are shown in Supporting Information S1: Table S3. Kaplan–Meier estimates for PFS and OS were also following PSM in both age groups ($p = 0.47$ and $p = 0.48$, respectively). In the PSM-*older*-cohort, PFS at 1 and 2 years were both 45.9% (95% CI: 33.1–63.8), OS at 1 and 2 years were 59.4% (95% CI: 46.3–76.1) and 55.7% (95% CI: 42.1–73.5), respectively. In the PSM-*younger*-cohort, we noted PFS of 39.2% (95% CI: 26.6–57.7) and 33.6% (95% CI: 20.5–54.9) and OS of 55.7% (95% CI: 42.2–73.4) and 40.5% (95% CI: 26.5–61.7) (Supporting Information S1: Figure S4). No significant differences in relapse incidence and NRM were noted for both age groups after PSM ($p = 0.51$ and $p = 0.93$, respectively) (Supporting Information S1: Figure S5).

DISCUSSION

Extensive data on the efficacy and toxicity of CAR-T cell therapy for patients with relapsed/refractory DLBCL are available. However, limited data on the outcomes of CAR-T cell therapies in elderly patients within real-world scenarios emphasize the need for further

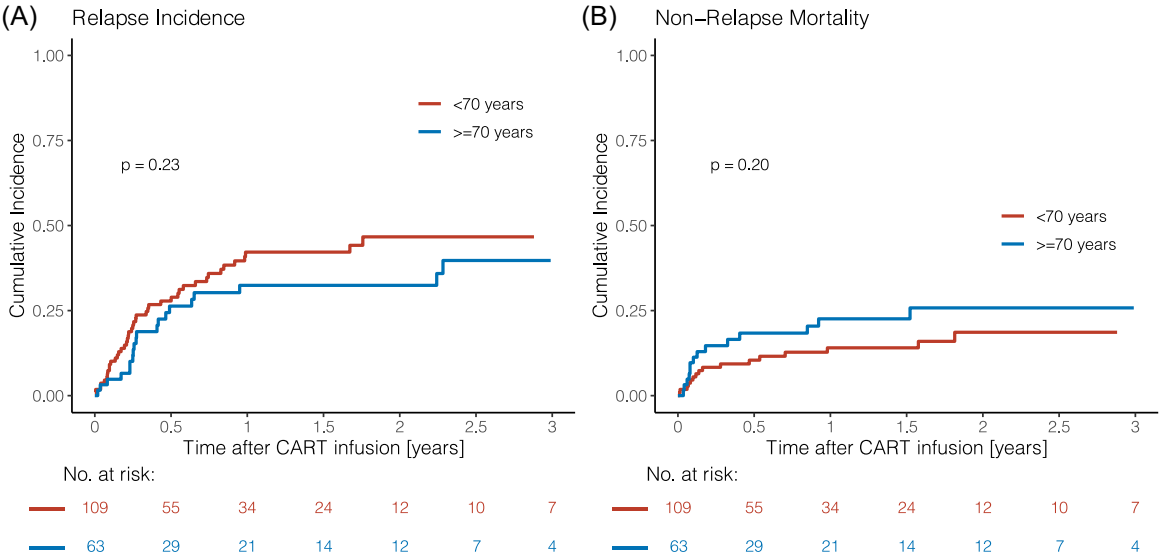

FIGURE 2 Cumulative Incidences of relapse and nonrelapse mortality (NRM) by age groups. Cumulative incidences of relapse (A) and nonrelapse mortality (B) after CAR-T cell therapy by age group. Cumulative incidences are presented as competing risk analysis with relapse/progression and NRM as competing events. CAR-T, chimeric antigen receptor-T cells.

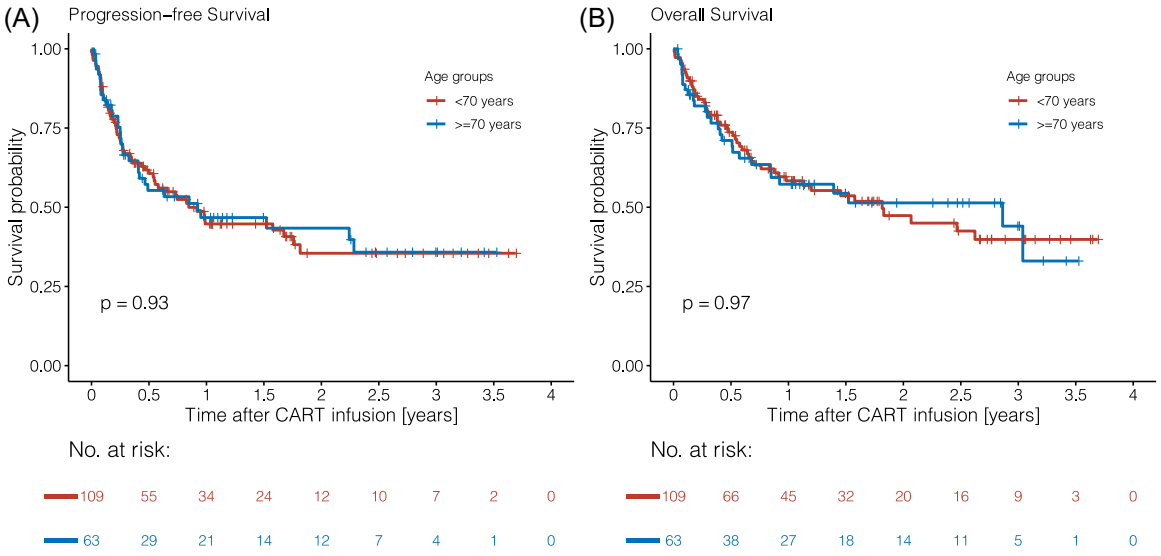

FIGURE 3 Kaplan–Meier estimates by age groups. Progression-free survival (A), overall survival (B) after CAR-T-cell therapy by age group. CAR-T, chimeric antigen receptor-T cells.

focused exploration. This retrospective multicenter study compared the characteristics and outcomes of a real-life r/r DLBCL cohort of 172 patients, including 63 patients aged 70 years or older, undergoing CD19-directed CAR-T cell therapy at three academic centers in Germany and Switzerland.

The efficacy of CAR-T therapy in both age groups within our cohort, primarily treated with axi-cel, demonstrated a comparable ORR exceeding 75%. These results were consistent not only between the age groups (<70 vs. ≥70 years) but also with other large real-world cohorts, especially for elderly patients, as reported in previous studies.[13,19]

With the observed 2-year PFS rate of 43% in the older and 36% in the younger cohort, key outcomes of our real-world results mirrored those of clinical trials, such as the ZUMA-1 trial that showed long-term response rates at 2 years for patients ≥65 years and <65 years both at approximately 40% for both groups.[14] Of note, PSM, as a robust matching method, confirmed that outcomes of CAR-T cell therapy were comparable between both age groups with a cut-off of 70 years in our cohort. We also did not observe any survival differences in patients aged 75 years and above and those aged 70–74 years. Recently, several other real-world analyses showed

TABLE 4 Incidence and reasons of mortality following CAR-T infusion.

	Overall (*N* = 172)	<70 years (*N* = 109)	≥70 years (*N* = 63)	*p*-Value
Deaths	77 (44.8%)	49 (45.0%)	28 (44.4%)	1.000
Relapse	47 (27.4%)	33 (30.3%)	14 (22.2%)	0.490
NRM	30 (17.4%)	16 (14.7%)	14 (22.2%)	0.314
NRM reasons				
Infections Grade 5	18 (10.4%)	10 (9.2%)	8 (12.7%)	0.606
CRS or ICANS Grade 5	4 (2.3%)	4 (3.7%)	0 (0%)	0.298
Embolism	3 (1.7%)	1 (0.9%)	2 (3.2%)	0.556
Other reasons[a]	5 (2.9%)	1 (0.9%)	4 (6.3%)	0.200

Note: *p*-Value: for <70 years vs. ≥70 years.

Abbreviations: CAR-T, chimeric antigen receptor-T cells; CRS, cytokine release syndrome; ICANS, immune cell-associated neurotoxicity syndrome; NRM, non-relapse mortality.

[a]Including cerebral bleeding after trauma (*n* = 1), secondary malignancy (*n* = 1), gastrointestinal perforation (*n* = 1), adhesive small bowel obstruction (*n* = 1), gastrointestinal bleeding (*n* = 1).

similar outcomes with long-term rates of event-free or PFS rates of 32–37% in patients aged 70 years and older.[12,13,20]

Our study found that tisa-cel treatment was associated with an approximately 60% higher risk considering relapse and/or death when compared to axi-cel treatment, which was mainly driven by less favorable survival outcomes with tisa-cel in patients aged younger than 70 years. In this context, some reports showed that axi-cel may offer enhanced effectiveness compared to tisa-cel in patients aged 65 and older, despite higher rates of neurotoxicity.[13,16,19,21] However, two smaller analyses failed to show an increased risk of neurotoxicity associated with axi-cel in older patients.[20,22]

Bridging r/r DLBCL patients to CAR-T cell therapy poses a challenge in real-life scenarios, with elderly patients being particularly vulnerable to non-hematologic and hematologic toxicities associated with bridging therapies before CAR-T. These toxicities have the potential to impact the outcomes of the latter. It is important to note that elderly patients may be more affected by the impact of r/r DLBCL on their performance status compared to younger patients. Of note, two-thirds of our patients with PD at CAR-T infusion could achieve an objective response post-CAR-T treatment irrespective of age. This fact should be considered when deciding about the time point of entering the CAR-T cell treatment to minimize the dropout rate in the phase between indication to and CAR-T cell therapy itself, particularly in elderly patients. Due to steadily decreasing intervals between lymphocyte apheresis and CAR-T cell therapy, the application of CAR-T cell therapies in elderly r/r DLBCL patients will probably increase in the near future.

In terms of CAR-T-associated toxicities, we observed similar rates of 20% for grade ≥3 ICANS in older patients, even after applying PSM to mitigate potential differences in factors with known prognostic relevance. The rates of CRS grade ≥3 were also similar (11.9% <70 vs. 7.9% ≥70 years). Such incidence of severe CRS and ICANS was numerically higher than those reported in a large real-world analysis of over 800 patients by Bachy et al. (approximately 14% ICANS grade ≥3 and 5% CRS grade ≥3 for axi-cel) but remained below the reported 35% ICANS grade ≥3 and 15% CRS grade ≥3 (both axi-cel) in other studies.[21,23] Of note, the incidence of severe neurotoxicity across all ages associated with tisa-cel is reportedly lower with grade ≥3 ICANS at around 5%–7%.[20,21,24] However, importantly, as several real-world analyses as well as our results underline, tisa-cel treatment may be associated with reduced PFS when compared with axi-cel.[13,21,24]

Unexpectedly, we noted comparatively high NRM after CAR-T for both younger and older patients. While several analyses reported 12-month NRM results in a real-world context in the range of 5–9%, and NRM for patients ≥65 treated with axi-cel reached 13%,[13,21,23] the findings for our cohort revealed a NRM of 14% for patients in the younger group and 23% for those aged 70 years or older. In line with previous reports,[19,21] the leading cause of NRM was infections documented among 10% of all patients and occurring also frequently after day 100 post-CAR-T irrespective of age. Notably, eight out of 18 cases (44%) who died from infection in our study experienced either critical COVID-19, severe and long-term pancytopenia, or multiple organ failure of either unknown reason or due to hemophagocytic lymphohistiocytosis post-CAR-T. These conditions can partly explain the high incidence of mortality due to infection in our study. Furthermore, all types of pathogens such as viral, bacterial, and fungal ones were documented among fatal infections. Of note, we observed significantly increased frequencies of co-morbidities such as atrial fibrillation, heart failure, and chronic kidney disease, among elderly patients potentially contributing to NRM. So far, we lack a definitive explanation for the elevated NRM rates when compared to other comprehensive registry analyses. Nevertheless, our data underline the crucial relevance of comprehensive prophylaxis and optimal management of infectious complications in both, early and later follow-up after CAR-T cell therapy.

For the younger patients, we noted an unexpectedly high number (4 of 16 NRM cases) of CRS/ICANS fatalities, all of which were without known CNS manifestations. So far, no patients in our study have undergone CD-19-directed CAR-T cell therapy with the approved product liso-cel. With the increasing availability of the latter, decreasing rates of severe CRS and ICANS can be expected in the future including also those aged 70 and above.[25]

At present, several study groups aim at optimizing the assessment of comorbidities with respect to the outcome of CAR-T cell therapies.[26–29] Despite being associated with reduced PFS as highlighted in the present study and also shown by other analyses,[27,28] functional scores such as ECOG performance score do not capture comorbidities, and good performance scores are usually part of CAR-T eligibility criteria in several countries.[2,28] Thus, given the already comparable outcomes for elderly patients, effective and easy-to-use assessment tools are needed to further optimize patient selection, particularly among older patients to further reduce toxicities.

This study has several limitations. Despite being a multi-center study, our sample size was limited. Furthermore, patients underwent different treatments prior to CAR-T cell therapy and the study had a retrospective design. While we cannot entirely exclude that outcome data for a small subset of our cohort might have been included in a national registry-based analysis from Germany up to April 2021,[13] potentially affecting less than 13% of our cohort, our analysis surpasses such registries in data depth. We believe that this potential limitation is outweighed by the extensive information on outcomes and clinical variables in the present analysis that goes beyond the nature of such registry-based analyses. Additionally, sample size, especially for patients aged 70 years and older, may affect our ability to detect differences in NRM and other outcomes despite numerical variations. Therefore, the present data may not allow definitive conclusions for this age group, and future (prospective) studies with larger cohorts are recommended to further explore age-related outcomes after CAR-T cell treatment. Patients with comorbidities may have exhibited a preference for tisa-cel over axi-cel in their assignment, thereby introducing a potential confounding factor in data interpretation. While we have incorporated CAR-T product selection as a covariate for PSM, the extent to which pre-existing conditions influenced physicians'

TABLE 5 Univariate and multivariate Cox proportional hazards models of post-CAR-T outcomes.

Variable	Category	Progression-free survival		Overall survival	
		HR (univariable)	HR (multivariable)	HR (univariable)	HR (multivariable)
Age at CAR-T infusion in years (continuous)	Mean (standard deviation)	1.00 (0.99–1.02, $p = 0.622$)	-	1.01 (0.99–1.03, $p = 0.523$)	-
Age group	<70 years	-	-	-	-
	≥70 years	0.98 (0.64–1.51, $p = 0.935$)	1.02 (0.65–1.59, $p = 0.942$)	1.01 (0.63–1.61, $p = 0.971$)	1.09 (0.67–1.78, $p = 0.730$)
Gender	Male	-	-	-	-
	Female	0.76 (0.49–1.19, $p = 0.233$)	0.79 (0.50–1.24, $p = 0.304$)	0.74 (0.45–1.20, $p = 0.220$)	0.77 (0.47–1.27, $p = 0.306$)
ECOG score	0–2	-	-	-	-
	3	**2.06 (1.06–3.98, $p = 0.032$)**	1.77 (0.90–3.49, $p = 0.098$)	**2.80 (1.43–5.47, $p = 0.003$)**	**2.69 (1.35–5.35, $p = 0.005$)**
CAR-T product	Axi-cel	-	-	-	-
	Tisa-cel	**1.67 (1.10–2.53, $p = 0.015$)**	**1.59 (1.02–2.49, $p = 0.040$)**	1.37 (0.87–2.15, $p = 0.173$)	1.24 (0.76–2.02, $p = 0.388$)
Disease stage at diagnosis	I/II	-	-	-	-
	III/IV	1.28 (0.79–2.08, $p = 0.307$)	1.21 (0.74–1.97, $p = 0.444$)	1.58 (0.91–2.74, $p = 0.104$)	1.58 (0.90–2.76, $p = 0.109$)
CNS manifestation at CAR-T infusion	No	-	-	-	-
	Yes	0.64 (0.20–2.04, $p = 0.454$)	0.90 (0.27–2.96, $p = 0.864$)	0.69 (0.22–2.20, $p = 0.531$)	0.88 (0.27–2.90, $p = 0.836$)
DLBCL Subtype	Non-GCB	-	-	-	-
	GCB	0.86 (0.50–1.48, $p = 0.578$)	-	0.73 (0.40–1.33, $p = 0.303$)	-
High LDH before CART	No	-	-	-	-
	Yes	1.05 (0.69–1.60, $p = 0.815$)	-	1.25 (0.79–1.99, $p = 0.338$)	-
Transformed DLBCL	No	-	-	-	-
	Yes	0.81 (0.51–1.29, $p = 0.375$)	-	0.73 (0.44–1.22, $p = 0.233$)	-
Previous auto-HSCT	No	-	-	-	-
	Yes	1.13 (0.74–1.73, $p = 0.564$)	-	0.85 (0.53–1.37, $p = 0.505$)	-
Bridging Therapy before CAR-T	None	-	-	-	-
	Systemic therapy/ radiotherapy	0.72 (0.41–1.27, $p = 0.260$)	-	0.94 (0.48–1.82, $p = 0.844$)	-
Treatment lines before CAR-T	1–2	-	-	-	-
	≥3	1.92 (0.93–3.97, $p = 0.079$)	1.83 (0.84–3.97, $p = 0.127$)	1.50 (0.69–3.27, $p = 0.310$)	1.45 (0.62–3.37, $p = 0.390$)
Remission at CAR-T infusion	CR	-	-	-	-
	PR	1.03 (0.52–2.01, $p = 0.936$)	-	1.21 (0.56–2.63, $p = 0.631$)	-
	SD	0.63 (0.26–1.52, $p = 0.300$)	-	0.68 (0.24–1.92, $p = 0.467$)	-
	PD	1.13 (0.61–2.11, $p = 0.694$)	-	1.32 (0.64–2.72, $p = 0.461$)	-
Days from indication to CAR-T infusion (continuous)	Mean (standard deviation)	1.00 (1.00–1.01, $p = 0.396$)	-	1.00 (1.00–1.01, $p = 0.411$)	-
CRS	No	-	-	-	-
	Yes	0.98 (0.65–1.48, $p = 0.938$)	-	1.09 (0.70–1.70, $p = 0.712$)	-
ICANS	0–3	-	-	-	-
	4–5	**2.75 (1.19–6.37, $p = 0.018$)**	**2.53 (0.99–6.42, $p = 0.052$)**	**3.77 (1.49–9.57, $p = 0.005$)**	**3.06 (1.07–8.73, $p = 0.037$)**

Abbreviations: auto-HSCT, high-dose therapy and autologous stem cell transplantation; Axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor-T cells; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; HR, hazard ratio; ICANS, immune cell-associated neurotoxicity syndrome; LDH, lactate dehydrogenase; Tisa-cel, tisagenlecleucel; ULN, upper limit of normal.

referral to either product cannot be entirely addressed in the present retrospective approach. The analysis of hematologic toxicity was not available for our study cohort. Finally, the follow-up time was relatively limited, thereby reducing the capability to draw long-term conclusions about the safety and efficacy of CAR-T cell therapy in older patients.

Despite these limitations, results from our study and other analyses provide support in terms of the application of CAR-T cells in

elderly patients (70 years and older) with r/r DLBCL. Additionally, our study underlines the fact that enhanced vigilance is required in terms of infection complications and NRM post-CAR-T cell treatment, particularly in elderly patients. Future studies with longer follow-ups are necessary to further evaluate the long-term safety and efficacy in older DLBCL patients undergoing CAR-T cell therapy. To sum up, CAR-T cell therapy should be not withheld for elderly patients with relapsed/refractory DLBCL.

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AUTHOR CONTRIBUTIONS

Philipp Berning: Conceptualization; methodology; software; investigation; data curation; writing—original draft preparation. **Evgenii Shumilov**: Conceptualization; methodology; investigation; data curation; writing—original draft preparation. **Markus Maulhardt**: Investigation; data curation. **Hristo Boyadzhiev**: Investigation; data curation. **Andrea Kerkhoff**: Validation. **Simon Call**: Validation. **Christian Reicherts**: Validation. **Anna O. Saidy**: Validation. **Enver Aydilek**: Validation. **Michèle Hoffmann**: Writing—review and editing. **Urban Novak**: Writing—review and editing. **Michael Daskalakis**: Writing—review and editing. **Norbert Schmitz**: Writing—review and editing. **Matthias Stelljes**: Writing—review and editing. **Gerald Wulf**: Writing—review and editing. **Ulrike Bacher**: Conceptualization; writing—review and editing. **Georg Lenz**: Conceptualization; writing—review and editing. **Thomas Pabst**: Conceptualization; writing—review and editing. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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