haematologica
Journal of the Ferrata Storti Foundation

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Received: January 15, 2026.
Accepted: July 24, 2026.

Citation: Vanderson Rocha, Jarl E. Mooyaart, Ron Ram, Katherine Clesham, Michael Daskalakis, Anne Huynh, Victoria Potter, Sridhar Chaganti, Ludovic Gabellier, Eleni Tholouli, Matthew Collin, Emma Nicholson, Rachel Protheroe, Jacob Passweg, Francis Ayuk, Dominik Schneidawind, Mi Kwon, Lucia Lopez Corral, Robert Zeiser, Christof Scheid, Ibrahim Yakoub-Agha, Peter Dreger, Friedrich Stolzel, Jorinde Hoogenboom, Maiana Hamdan Melo Coelho, Ana Alarcon Tomas, Florent Malard, Jürgen Kuball, Anna Sureda, Ali Barzabachi and Annalisa Ruggeri. Improved progression free survival after axicabtagene ciloleucel compared to tisagenlecleucel, in patients aged >70 years with large B-cell lymphoma. Haematologica. 2026 Aug 13. doi: 10.3324/haematol.2026.300508 [Epub ahead of print]

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Short title: Axi-cel vs Tisa-cel in Patients ≥70 Years With LBCL

Author contributions

VR and AR designed the study. VR and AR wrote the manuscript. JM performed the statistical analysis.RR, KC, MD, AH, VP, FK, LG, ET, MC, EM, RP, JP, FA, DS, MK, LLC, RZ, CS, IYA, PD, FS provided cases for the study, JH and MHMC helped with data preparation, AAT, FM, JK, AS, AB critically reviewed the manuscript. All authors edited and approved the manuscript.

Data availability statement

Data cannot be shared unless a specific request is sent to the EBMT.

Conflict of Interest Statement

VR reports lecture honoraria from Kite/Gilead, Sanofi, Amgen, Takeda, Astellas, Abbvie, J&J.FM reports lecture honoraria from Therakos/Mallinckrodt, BMS, MSD, Sanofi, Novartis, Astra Zeneca and JAZZ Pharmaceuticals, all outside the submitted work.FA reports Honoraria: AbbVie, BMS, Kite/Gilead, Janssen, Therakos, Miltenyi Biomedicine, Novartis, Takeda, Medac, NeoviiResearch funding: Therakos, Neovii. AR reports lecture honoraria from Kite/Gilead. The other authors do not report conflict of interest.

Artificial Intelligence Statement:

Generative artificial intelligence was used exclusively for language editing to improve English grammar, clarity, and readability. No AI tool was used for data analysis, interpretation, or scientific writing. All scientific content, data interpretation, statistical analyses, and manuscript revisions were performed by the authors, who take full responsibility for the content of the manuscript.

Abstract

Chimeric antigen receptor(CAR) T-cell therapy is effective in relapsed/refractory large B-cell lymphoma(LBCL), but evidence in elderly patients(≥70y) is limited. We compared outcomes of tisagenlecleucel(tisa-cel) and axicabtagene ciloleucel(axi-cel) and assessed prognostic factors.

We analyzed 1,191 patients(aged ≥70y) reported to the EBMT(tisa-cel n=402; axi-cel n=789). Median follow-up was 22.7 months. Outcomes included cytokine release syndrome(CRS), immune effector cell–associated neurotoxicity syndrome(ICANS), overall survival(OS), progression-free survival(PFS), relapse incidence(RI), and non-relapse mortality(NRM). Multivariable models adjusted for age, sex, ECOG, disease status, prior transplantation, and year of infusion.

Median age at infusion was 74y; 65.6% were aged 70–75y. Progressive disease at infusion was 59% vs 53% for tisa-cel and axi-cel(p=0.04). Tisa-cel patients were older(74.0 vs 73.7y, p=0.019). At day-30, CRS(any grade) occurred in 62% vs 77%(p<0.001) and ICANS(any grade) in 22% vs 47%(p<0.001) for tisa-cel vs axi-cel. Kaplan-Meier(KM) and Cumulative incidence (CI) estimates for 1-year OS, PFS, RI, and NRM were 57%, 37%, 59%, and 4% with tisa-cel vs 63%, 50%, 41%, and 9% with axi-cel. Outcomes were similar across age groups(70–74, 75–79, ≥80y). In multivariable analyses, axi-cel was associated with improved PFS(HR 0.72, p<0.001) and lower RI(HR 0.59, p<0.001), but higher NRM(HR 1.75, p=0.01), ICANS(HR 2.25, p<0.001), and CRS(HR 1.29, p=0.009). There was a statistical trend of improved OS using axi-cel in univariate analyses(p=0.076), however it was not in multivariable analyses(HR=0.86, p=0.12)

In patients(≥70y), axi-cel achieved superior disease control and potentially better survival but at greater toxicity. Adverse prognostic factors included ECOG≥2, advanced disease before infusion, and earlier treatment year, while age itself did not influence outcomes.

Key Points

- In patients ≥70 years with LBCL, axi-cel was associated with superior PFS and lower relapse risk compared with tisa-cel, at the cost of higher CRS, ICANS and NRM.
- ECOG status and disease burden at infusion and earlier treatment year were independent predictors of outcome, while chronological age (70–74 vs 75-79 vs ≥80) did not impact outcomes.
- Frailty assessment may improve patient selection and optimize outcomes for older adults undergoing CAR-T therapy.

Introduction

Large B-cell lymphoma (LBCL) is the most common subtype of aggressive non-Hodgkin lymphoma, accounting for approximately 30% to 40% of adult cases worldwide.[1] The median age at diagnosis is 66 years, and nearly one-third of patients are aged ≥75 years at presentation.[2] This demographic distribution underscores the importance of optimizing therapies for older adults, who frequently have comorbidities and impaired performance status that limit the feasibility of intensive treatments.

Chimeric antigen receptor (CAR) T-cell therapy has transformed the management of relapsed or refractory (R/R) LBCL. Phase 1, 2, and 3 trials have demonstrated high response rates and durable remissions with CD19-directed CAR-T products, including axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel).[3–9] These pivotal studies established CAR-T therapy as the standard of care after ≥2 prior lines of therapy and, more recently, in the second-line setting. However, these trials predominantly enrolled younger and fitter patients, with limited representation of individuals aged ≥70 years, raising uncertainty regarding the generalizability of trial results to elderly populations.

Real-world evidence (RWE) has begun to address this gap. Data from the US Lymphoma CAR-T Consortium and the Center for International Blood and Marrow Transplant Research (CIBMTR) have confirmed the feasibility of CAR-T therapy in older adults, while also demonstrating inferior outcomes among patients with greater comorbidity or frailty.[10–12] In a CIBMTR analysis of 551 patients aged ≥65 years, 12-month event-free survival declined with increasing age (52% for 65–69 years, 43% for 70–74 years, and 34% for ≥75 years; $P = .002$), although overall survival did not differ significantly.[13] Importantly, this study did not stratify outcomes by CAR-T product or comprehensively evaluate early toxicities.

In a more recent CIBMTR analysis including approximately 840 patients aged >64 years, overall survival, progression-free survival, and cytokine release syndrome rates were comparable across age groups; however, increasing age was associated with a higher risk of immune effector cell–associated neurotoxicity syndrome (ICANS).[14] Notably, this cohort was treated during the early commercial CAR-T era (2018–2020), when toxicity recognition and management strategies were still evolving, and outcomes were not analyzed separately for axi-cel and tisa-cel.

Several studies have identified predictors of poor outcomes after CAR-T therapy, including high tumor burden, elevated lactate dehydrogenase levels, poor performance status, and comorbidity.[15–18] Comorbidity indices such as the Hematopoietic Cell Transplantation–Comorbidity Index, the Cumulative Illness Rating Scale, and a CAR-T–specific comorbidity index derived from CIBMTR data have been associated with survival and nonrelapse mortality.[19–21] In older adults, comprehensive geriatric assessments incorporating comorbidity, functional status, and activities of daily living further predict outcomes and may help guide treatment eligibility.[22]

In Europe, axi-cel and tisa-cel were approved in 2018, followed by liso-cel in 2022.[23] Despite widespread adoption of CAR-T therapy, comparative evidence to guide product selection in elderly patients remains limited. National registry analyses from France and Germany suggest differences in efficacy and toxicity between products, but few studies have focused specifically on patients aged ≥70 years.[24],[25]

Given the aging population and the increasing use of CAR-T therapy in elderly patients, large registry-based analyses are needed. Using the European Society for Blood and Marrow Transplantation (EBMT) registry, we conducted the largest study to date comparing axi-cel and tisa-cel in patients aged ≥70 years with LBCL. We evaluated differences in survival, relapse, and toxicity outcomes and performed a prognostic factor analysis to identify modifiable risk factors that may influence outcomes in this vulnerable population.

Methods

Study Design and Data Source

This retrospective registry-based study was conducted within the Cellular Therapy & Immunobiology Working Party of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT registry prospectively collects data from more than 600 transplant and cellular therapy centers worldwide, with standardized data reporting and regular audits to ensure data quality and completeness.[26]

Ethics Approval

All patients provided written informed consent for data collection and analysis in accordance with the Declaration of Helsinki. The study was approved through the EBMT scientific review process.

Eligibility Criteria

We included adult patients aged ≥70 years with a diagnosis of large B-cell lymphoma (LBCL), most frequently diffuse large B-cell lymphoma, who received commercial CAR-T therapy with either tisagenlecleucel (tisa-cel) or axicabtagene ciloleucel (axi-cel) between January 2019 and December 2024. Patients treated with lisocabtagene maraleucel (liso-cel) were excluded because of limited numbers (n=59). All data were reported by EBMT-affiliated centers. Only the first CAR-T infusion was considered for each patient.

Endpoints and Definitions

The primary endpoints were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from CAR-T infusion to death from any cause, and PFS as the time from infusion to relapse, progression, or death, whichever occurred first. Secondary endpoints included the cumulative incidence of relapse or progression (RI), nonrelapse mortality (NRM), and the incidence and severity of early toxicities, including cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS).

Some centers reported grading according to Common Terminology Criteria for Adverse Events, developed by NCI (CTCAE) and few centers used other systems. CRS/ICANS were reported by most participating centers within the EBMT registry, following publication of the ASTCT consensus criteria in 2019. [27] Some centers reported grading according to Common Terminology Criteria for Adverse Events, developed by NCI (CTCAE) and few centers used other systems. Most CRS/ICANS events (76%) were reported using ASTCT criteria, while 15% were graded according to CTCAE (Common Terminology Criteria for Adverse Events, developed by NCI) and 9% using other systems; grading system was missing in 63 cases.

Best response at day 100 among surviving patients was defined according to institutional assessment, primarily based on PET/CT imaging when available, and classified according to the Lugano response criteria where possible.[28]

Statistical Analysis

Statistical analyses followed the recommendations of the EBMT Statistical Committee. Survival outcomes (OS and PFS) were estimated using the Kaplan–Meier method, with comparisons performed using the log-rank test. Cumulative incidences of CRS, ICANS, relapse or progression, and NRM were estimated using competing-risk methods, with death treated as a competing event for RI, CRS, and ICANS, and relapse or progression as a competing event for NRM.[29] Gray's test was used for univariate comparisons of cumulative incidence functions.

Multivariable analyses were performed using Cox proportional hazards regression models. The primary variables of interest were CAR-T product (tisa-cel vs axi-cel) and patient age. Models were adjusted for clinically relevant baseline covariates, including year of infusion, disease status at infusion, ECOG performance status, and sex. A shared frailty term was included to account for center-level variation. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. All statistical tests were two-sided, and $P < .05$ was considered statistically significant.

Although missing data were present, sensitivity analyses using multiple imputation yielded results consistent with the primary analyses, supporting the robustness of the findings. Missing covariate data were handled using multiple imputation by chained equations with substantive model–compatible fully conditional specification (SMC-FCS), a missing imputation approach that is compatible with Cox proportional hazards models. All variables included in the analysis models were incorporated in the imputation procedure, along with survival time and event indicators to preserve associations with outcomes. For competing risk analyses, the event type indicator was also included as an auxiliary variable.

Fifty imputed datasets were generated with 50 iterations each. Estimates were combined using Rubin's rules to obtain pooled hazard ratios and 95% confidence intervals.

The results of the multiple imputation analyses were consistent with the complete-case analyses. For example, hazard ratios for axi-cel versus tisa-cel were 0.88 for OS and 0.74 for PFS, compared with 0.86 and 0.72, respectively, in the complete-case analysis. These findings indicate that missing data did not materially influence the results.

Results

Patient characteristics

A total of 1,191 patients aged ≥70 years with LBCL who received commercial CAR-T therapy between 2019 and 2024 were included from 159 centers in 20 countries. Of these, 402 received tisagenlecleucel (tisa-cel) and 789 received axicabtagene ciloleucel (axi-cel).

The median age at infusion was 73.8 years (range, 70–88), and the median age at diagnosis was 71.4 years. Overall, 65% of patients were male, and 91% had an ECOG performance status of 0–1. Refractory or progressive disease at infusion was present in 54% of patients. Baseline characteristics by product are summarized in Table 1.

Median age at diagnosis was similar between cohorts (71.5 vs 71.4 years; p=0.40), but tisa-cel recipients were older at infusion (74.0 vs 73.7 years; p=0.019). Age distribution differed, with more axi-cel patients aged 70–75 years (68% vs 62%) and more tisa-cel patients aged ≥80 years (8.0% vs 3.4%; p=0.001). Sex distribution and ECOG status were not statistically difference (male, 62% vs 61%; ECOG 0–1, 90% vs 92%).

Year of infusion differed significantly (p<0.001). Tisa-cel was more often infused in 2019–2021 (64% vs 32%), while axi-cel predominated in 2022–2024 (74% vs 38%). Disease status before infusion also varied (p=0.043): relapse/progression was more frequent with tisa-cel (59% vs 53%), whereas partial response or stable disease was more common with axi-cel.

Prior autologous HSCT rates were similar (13% vs 12%; p=0.40). Median time from apheresis to infusion was shorter with axi-cel (39 vs 49 days; p<0.001). Lymphodepletion was uniform, with >97% receiving cyclophosphamide plus fludarabine.

The median follow-up of survivors was 22.7 months (IQR 11.5–36.0): 24.7 months (11.7–47.8) for tisa-cel and 17.0 months (11.4–33.4) for axi-cel.

Univariate analysis comparing products

Early Toxicities

Among patients experiencing CRS, most events were low grade, with grade 1 and 2 accounting for 42% and 48% of cases, respectively, while grade ≥3 events were uncommon (9.3%). CRS incidence increased over time. Moderate between-center variability was observed in CRS reporting (frailty variance $\theta \approx 0.2$, p<0.001).

At day +30, the cumulative incidence of cytokine release syndrome (CRS, any grade) was 62% (95% CI, 57–67%) after tisa-cel and 77% (74–81%) after axi-cel (p<0.001). Grade ≥3 CRS occurred in 9% and 6%, respectively. Among patients with CRS, grade 4 events were reported in 2 tisa-cel and 9 axi-cel recipients, and 1 patient in the axi-cel group experienced grade 5 CRS. Immune effector cell–associated neurotoxicity syndrome (ICANS) occurred in 22% (18–27%) after tisa-cel and 47% (44–51%) after axi-cel (p<0.001). Grade ≥3 ICANS was reported in 8 % and 21%, respectively. Grade 4 or 5 ICANS occurred in 2 patients treated with tisa-cel and 11 with axi-cel (Figures 1).

Best Response at Day 100

The best response achieved for survivors by day 100 showed that complete remission (CR) rate was substantially higher after axi-cel compared with tisa-cel (69% vs 53%. Progression was more frequent with tisa-cel (22% vs 10%). Data were missing in 32 tisa-cel and 52 axi-cel patients. Accounting for death as a competing risk, the cumulative incidence of CR/PR was 65% (95% CI: 62–68) at day 100 and 76% (95% CI: 73–78) at 6 months. For tisa-cel the numbers are 57% (95% CI: 52-62) at 100 days 66% (95% CI: 61-70) at 6 months, whereas for axi-cel patients this is 69% (95% CI: 66-73) at 100 days 81% (95% CI: 78-84) at 6 months.

Relapse and Non-Relapse Mortality

At 1-year, the cumulative incidence of relapse/progression was 59% (54–64%) for tisa-cel and 41% (38–45%) for axi-cel (p<0.001). Corresponding 1-year non-relapse mortality (NRM) was 4% (2–6%) vs 9% (7–11%), respectively (p<0.001) (Figure 2).

Overall and Progression Free-Survival

At 1-year, overall survival (OS) was 62% (58–65%) for patients aged 70–74 years, 61% (55–66%) for those aged 75–79 years, and 59% (45–72%) for patients ≥80 years (p=0.40). Progression-free survival (PFS) was 44% (40–48%), 48% (48% (43–54%), and 49% (35–62%), respectively (p=0.40). By product, OS was higher after axi-cel compared with tisa-cel (63% [60–67%] vs 57% [52–63%], p<0.08), albeit not significant. Similarly, PFS was superior with axi-cel (50% [46–54%]).

Causes of Death

Patterns of causes of mortality differed across time points. Within 30 days, deaths after axi-cel were more often cellular therapy–related (47% vs 30% with tisa-cel), whereas relapse/progression accounted for a higher proportion of early deaths with tisa-cel (40% vs 22%). Between days 30–100, relapse/progression was the main cause in both groups (72% tisa-cel, 56% axi-cel), though therapy-related deaths remained frequent after both therapies (15% vs 13%). Beyond 100 days, relapse/progression again predominated (65% in tisa-cel vs 58% in axi-cel). Cellular therapy–related mortality decreased over time but persisted (5.5% in tisa-cel vs 7.1% in axi-cel). Secondary malignancy–related deaths were rare but slightly more frequent after axi-cel (3.8% vs 0.7%). Unknown or other causes accounted for 30% of late deaths with tisa-cel and 29% with axi-cel. Unfortunately, detailed causes of death were not available.

In addition, we evaluated whether the association between CAR-T product and NRM varied over time. The proportional hazards assumption was not violated, indicating no evidence of a time-dependent effect.

Multivariable Analysis: adjustments for comparisons

In multivariable analyses (age, sex, ECOG, year of infusion, disease status, prior transplantation), axi-cel was associated with improved PFS (HR 0.72, 95% CI 0.60–0.86; p<0.001) and reduced risk of progression (HR 0.59, 95% CI 0.49–0.72; p<0.001). A trend toward improved OS did not reach significance (HR 0.86, 95% CI 0.72–1.04; p=0.12). Conversely, axi-cel was associated to higher NRM (HR 1.75, 95% CI 1.14–2.69; p=0.010) and increased toxicity, with greater CRS (HR 1.29, 95% CI 1.07–1.57; p=0.009) and markedly higher ICANS (any grade HR 2.25, 95% CI 1.71–2.96; p<0.001; grade ≥3 HR 2.39, 95% CI 1.55–3.67; p<0.001). (Table 2).

Prognostic Factors in the Elderly Cohort

Results of the univariate analysis of prognostic factors for the entire cohort are presented in the supplementary tables 1 and 2. In the multivariable analysis (see footnote of Table 2), ECOG ≥2 was associated with worse OS (HR 1.93) and PFS (HR 1.59), as well as higher relapse risk (HR 1.57) and increased risk of CRS grade ≥3 (HR 3.22) and ICANS (HR 1.57) and ICANS grade ≥3 (HR 1.72). Similarly, patients infused with relapse or disease progression had inferior OS (HR 1.41), PFS (HR 1.43), and higher relapse incidence (HR 1.61), and were more likely to develop CRS (HR 1.22) and ICANS (HR 1.25). In contrast, long term outcomes were not impacted by chronological age. OS and PFS by age group (70–75, 75–80, >80 years) are shown in Supplementary Figures 1a and 1b. The year of infusion also independently influenced outcomes, suggesting a learning-curve effect. Later treatment years were associated with lower non-relapse mortality (NRM;

HR 0.85, 95% CI 0.74–0.98; p=0.021). Toxicity increased with increasing rates of CRS (HR 1.14 per earlier year; p<0.001) and ICANS (HR 1.12 per earlier year; p=0.005), which is likely due to improved detection methods of these complications. Moreover, higher grade (≥3) CRS and ICANS did not show an increase over the years (Supplementary Figure 2).

Discussion

In this large registry-based analysis of 1,191 patients ≥70 years with R/R LBCL treated with commercial CAR-T cell products across 159 centers reporting to EBMT, we demonstrate that CAR-T therapy is feasible in the elderly, yielding clinically meaningful survival. Importantly, we observed clear differences between products: axi-cel was associated with higher overall response, lower relapse incidence improved PFS, while tisa-cel was associated with lower NRM and reduced rates of CRS and ICANS.

Our findings extend evidence from pivotal CAR-T trials, including ZUMA-1, JULIET, BELINDA, TRANSFORM, and ZUMA-7, which established the efficacy of CD19-directed CAR-T therapy but largely excluded patients aged ≥70 years.[4–9] Real-world studies have begun to address this gap. The US Lymphoma CAR-T Consortium demonstrated comparable efficacy of axi-cel to ZUMA-1 in broader populations but reported higher neurotoxicity rates.[10] CIBMTR analyses showed that advanced age alone was not associated with inferior survival, although older patients had an increased risk of ICANS; however, these studies were conducted during the early CAR-T era (2018–2020) and did not perform product-specific comparisons.[13],[14] Our study addresses this unmet need by directly comparing axi-cel and tisa-cel in a large cohort exclusively composed of elderly patients. Consistent with French and German national registry analyses, axi-cel demonstrated higher efficacy but greater toxicity than tisa-cel.[24],[25] These differences are biologically plausible, reflecting distinct CAR constructs: axi-cel incorporates a CD28 costimulatory domain associated with rapid expansion and potent cytotoxicity, whereas tisa-cel contains a 4-1BB domain linked to slower expansion and potentially improved tolerability.[11] This mechanistic distinction likely underlies the observed trade-off between efficacy and toxicity.

CRS/ICANS grading was predominantly based on ASTCT criteria, although heterogeneity across centers persisted, particularly for lower-grade events, as reflected by moderate inter-center variability, which should be considered when interpreting toxicity comparisons. Nonetheless, CRS and ICANS remain the most clinically relevant acute toxicities of CAR-T therapy. In our cohort, axi-cel was associated with significantly higher rates of both, although 1-year NRM remained below 10%, reflecting improvements in supportive care and standardized toxicity management.[12] Notably, year of infusion was independently associated with reduced NRM, underscoring the impact of increasing center experience, earlier intervention, and improved prophylactic strategies. NRM causes showed temporal heterogeneity, with early deaths predominantly related to cellular therapy and later deaths more diverse causes. However, the association between CAR-T product and NRM was not found to change over time.

Patient-related factors had a strong and consistent impact on outcomes. ECOG performance status ≥2 and refractory disease or high tumor burden were independently associated with inferior PFS, consistent with prior registry analyses.[15–17] Although exploratory analyses revealed a possible greater PFS benefit with axi-cel in older patients and those with preserved performance status, this could not be confirmed in the analyses as the interaction terms were not significant. In particular, the ≥80-year subgroup likely reflects a selected population, and

conclusions in this group remain limited. Across both products, ECOG performance status remained a key determinant of outcome.

Recent studies highlight the prognostic value of frailty indices and comprehensive geriatric assessments, which may improve risk stratification and guide supportive care strategies in older adults.[30–31]

From a clinical perspective, our findings suggest that axi-cel may be preferred in fit elderly patients when maximal disease control is the priority, acknowledging the higher risk of neurotoxicity. In contrast, tisa-cel represents a reasonable option for frailer patients or those with significant comorbidities, given its more favorable toxicity profile but higher relapse risk. Treatment decisions should therefore be individualized, incorporating disease burden, functional status, and patient preferences.

This study has limitations inherent to its retrospective design. CAR-T product selection was not randomized and likely influenced by national approvals and center practices, and detailed comorbidity data were unavailable. Missing data were present, but sensitivity analyses using multiple imputation yielded results consistent with the primary analyses, supporting the robustness of our findings. Although multivariable adjustment and center-level frailty modeling were applied, residual confounding cannot be excluded. **Consequently, some findings should be interpreted with caution, particularly when considering their application to individual patient management. Continued efforts to improve completeness of data capture within large international registries are essential to enhance the clinical utility of future real-world studies."**

Nevertheless, the strengths of this analysis include its large sample size, pan-European representation, and exclusive focus on elderly patients—an underrepresented population in CAR-T trials.

Other limitation of our study was that key prognostic variables such as LDH, IPI, tumor burden, and disease biology were not systematically captured, introducing potential residual confounding. Comorbidity data (HCT-CI/comorbidity index), available for approximately 69% of patients, were included in exploratory analyses and were associated with increased NRM but not with survival outcomes. In contrast, ECOG performance status was consistently associated with survival endpoints. While these findings suggest that HCT-CI may capture risk of treatment-related mortality in this population, its prognostic role should be interpreted with caution given missing data. Inclusion of HCT-CI did not materially alter effect estimates, supporting the robustness of the findings, although residual confounding cannot be excluded.

Unfortunately, detailed data on CRS management, including use of tocilizumab, corticosteroids, or ICU admission, were not consistently captured in the EBMT registry and therefore could not be reliably analyzed. The higher incidence of any-grade CRS with axi-cel, in the context of similar rates of severe CRS, may partly reflect differences in reporting practices, increased recognition of low-grade events over time, and inter-center variability. The predominance of grade 1–2 CRS, the temporal increase in reporting, and the observed center-level heterogeneity support this interpretation, although the lack of detailed management data limits further assessment. **Although detailed infection data were unavailable, infectious complications are recognized as major contributors to NRM following CAR T-cell therapy, particularly in older adults who may experience delayed immune reconstitution. Future registry studies**

incorporating systematic assessment of infections, immunoglobulin recovery, and immune reconstitution parameters may help clarify the mechanisms underlying non-relapse mortality in this population.

With the recent availability of liso-cel in Europe, future analyses may further refine the balance between efficacy and toxicity in elderly patients. Two recent real-world studies reported broadly comparable outcomes between axi-cel and liso-cel, although results were influenced by differences in patient age.[32,33] These findings underscore the need for larger, elderly-focused comparative studies to define the optimal CAR-T strategy in this vulnerable population.

In conclusion, our study demonstrates a clear efficacy–toxicity trade-off between axi-cel and tisa-cel in patients aged ≥70 years with LBCL. Both CAR-T product selection and patient-related factors—particularly performance status and disease burden—remain critical determinants of outcome. Incorporation of geriatric assessments and continued refinement of toxicity management strategies are essential to optimize CAR-T therapy in the growing elderly population.

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Table 1. Baseline characteristics of elderly patients with LBCL given Tisa-cel or Axi-cel

Characteristics	Tisa-cel (N = 402,%)	Axi-cel (N = 789,%)	All patients (N = 1191,%)	*p*
Median age at diagnosis, y	71.5 (69.4–74.2)	71.4 (69.3–73.7)	71.4 (69.3–74.0)	.40
Median age at infusion, y	74.0 (71.9–76.6)	73.7 (71.7–75.8)	73.8 (71.8–76.1)	.019
Age group at infusion, y				.001
70–75	246 (62)	535 (68)	781 (66)	
75–80	124 (31)	227 (29)	351 (30)	
≥80	32 (8)	27 (3)	59 (5)	
ECOG performance status				.46
0–1	347 (90)	679 (92)	1026 (91)	
≥2	37 (10)	60 (8)	97 (9)	
Missing	18	50	68	
Year of infusion				<.001
2019	43 (11)	36 (5)	79 (7)	
2020	104 (26)	82 (11)	186 (16)	
2021	105 (27)	121 (16)	226 (19)	
2022	85 (22)	155 (21)	240 (20)	
2023	52 (13)	268 (36)	320 (27)	
2024§	13 (3)	127 (17)	140 (12)	
Grouped disease status				.043
Progression/relapse	228 (59)	385 (53)	613 (54)	
CR + PR + SD	157 (41)	346 (47)	503 (45)	
Missing	17	58	75	
Prior auto-HSCT	53 (13)	91 (12)	144 (12)	.40
Prior therapy lines				.004
1	63 (33)	202 (43)	265 (39)	
2	38 (20)	103 (22)	141 (21)	

Characteristics	Tisa-cel (N = 402,%)	Axi-cel (N = 789,%)	All patients (N = 1191,%)	*p*
3	56 (29)	91 (19)	147 (22)	
≥4	45 (24)	76 (16)	121 (18)	
Missing	200	317	517	

Data are median (Q1–Q3) or n (%). Percentages exclude missing values. P values from Wilcoxon rank-sum, χ^2, or Fisher's exact tests as appropriate.

§ 2024 data collection ongoing. Abbreviations: CR, complete response; PR, partial response; HSCT, hematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; Cy, cyclophosphamide; Flu, fludarabine.

Table 2. Multivariable outcomes in elderly patients comparing Axi-cel versus Tisa-cel

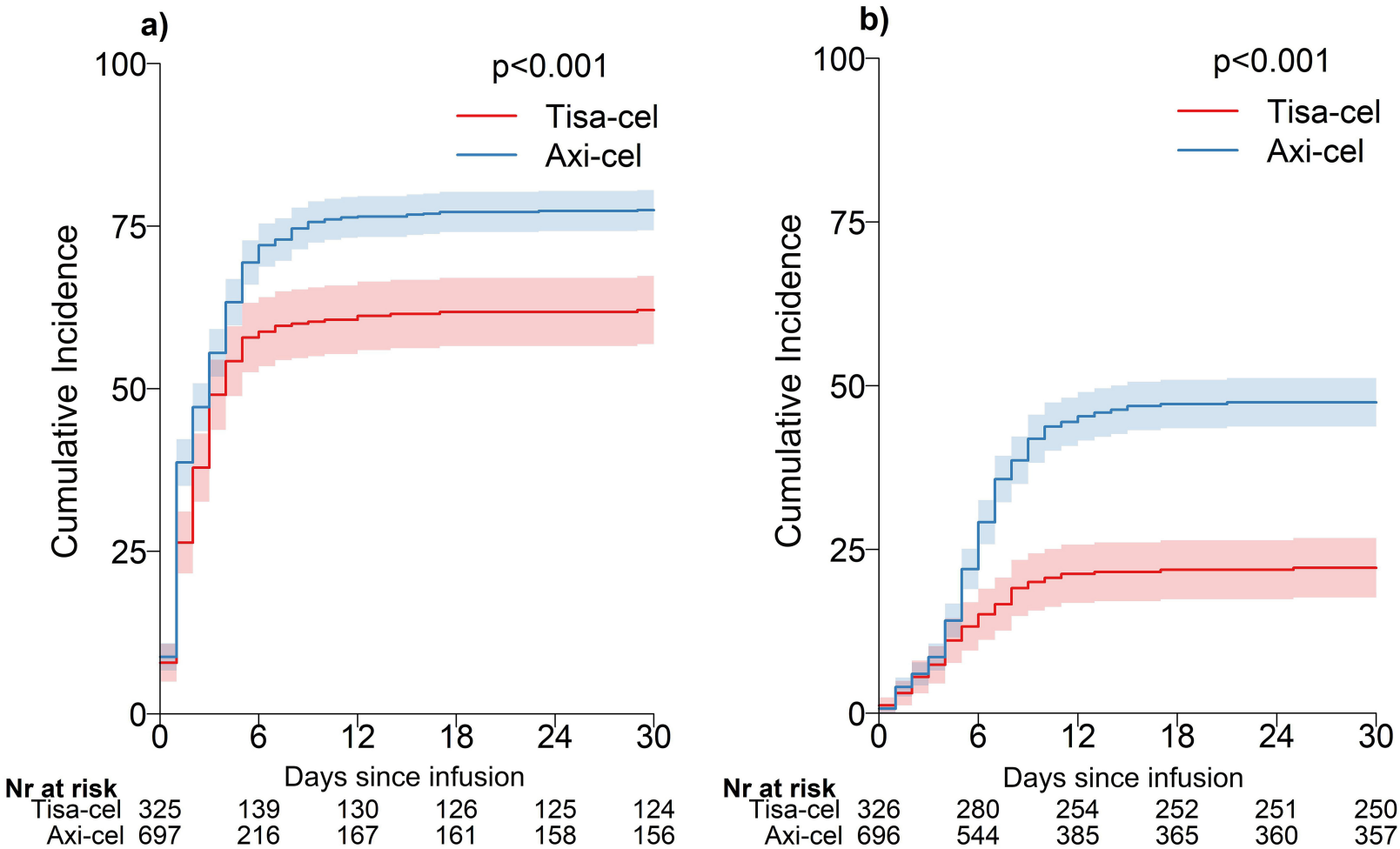
Outcome	N	HR (95% CI)	p-value
Overall Survival	1079	0.86 (0.72–1.04)	0.124
Progression-Free Survival	1045	0.72 (0.60–0.86)	<0.001**
Progression incidence	1045	0.59 (0.49–0.72)	<0.001**
Non-relapse mortality (NRM)	1045	1.75 (1.14–2.69)	0.010*
CRS (any grade)	943	1.29 (1.07–1.57)	0.009**
CRS grade ≥3	930	0.74 (0.42–1.30)	0.301
ICANS (any grade)	932	2.25 (1.71–2.96)	<0.001**
ICANS grade ≥3	932	2.39 (1.55–3.67)	<0.001**

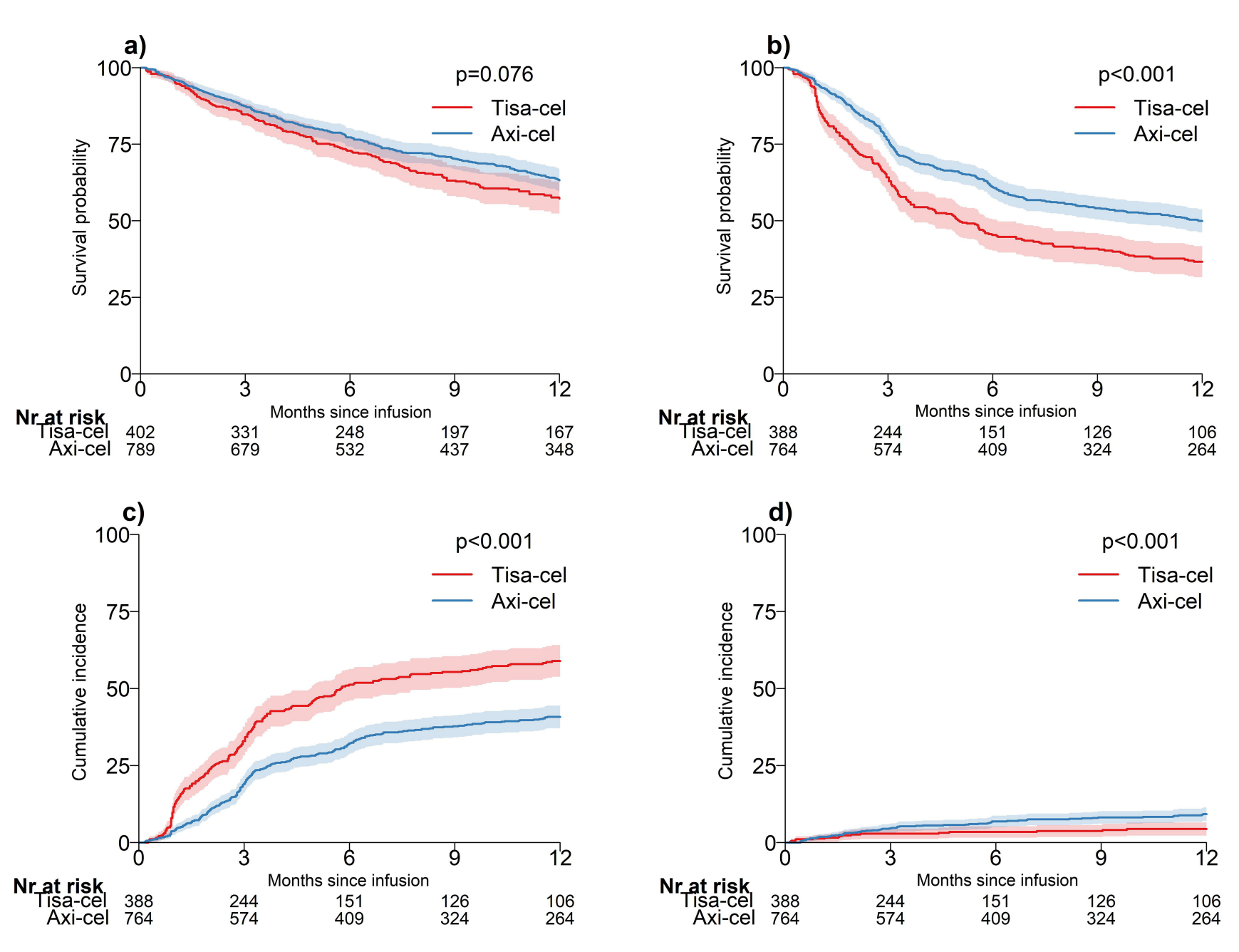
Footnote: In multivariable analyses, several patient-related variables influenced outcomes independently of CAR-T product. For overall survival (N=1079), both disease stage at infusion (relapse/progression vs CR/PR/Stable; HR 1.41, 95% CI 1.18–1.69, $p < 0.001$) and ECOG performance status (ECOG ≥2 vs 0–1; HR 1.93, 95% CI 1.47–2.53, $p < 0.001$) were significant predictors. For progression-free survival (N=1045), disease stage (HR 1.43, 95% CI 1.22–1.69, $p < 0.001$) and ECOG status (HR 1.59, 95% CI 1.22–2.08, $p < 0.001$) remained significant. For progression incidence (N=1045), both disease stage (HR 1.61, 95% CI 1.34–1.94, $p < 0.001$) and ECOG (HR 1.57, 95% CI 1.17–2.12, $p = 0.003$) were independent predictors. For non-relapse mortality (N=1045), year of therapy was protective (HR 0.85, 95% CI 0.74–0.98, $p = 0.023$). For CRS incidence (any grade, N=943), later year of therapy (HR 1.16, 95% CI 1.09–1.23, $p < 0.001$) and advanced disease stage (HR 1.21, 95% CI 1.03–1.42, $p = 0.024$) were associated with higher risk. For CRS grade ≥3 (N=930), male sex (HR 1.81, 95% CI 1.03–3.18, $p = 0.038$) and ECOG ≥2 (HR 3.25, 95% CI 1.71–6.18, $p < 0.001$) increased the odds of severe CRS. For ICANS incidence (any grade, N=932), older age (HR 1.05 per year, 95% CI 1.01–1.08, $p = 0.006$), later year of therapy (HR 1.12, 95% CI 1.04–1.21, $p = 0.005$), advanced disease stage (HR 1.25, 95% CI 1.02–1.54, $p = 0.033$), and ECOG ≥2 (HR 1.57, 95% CI 1.12–2.20, $p = 0.010$) were associated with higher risk. Finally, for ICANS grade ≥3 (N=932), ECOG ≥2 remained a significant predictor (HR 1.72, 95% CI 1.03–2.87, $p = 0.039$).

Figure legend:

Figure 1: Early toxicities at 30 days after CAR T cell therapy in elderly population given Tisa-cel or Axi-cel: CRS (1a) and ICANS (1b)

Figure 2: Main outcomes at 1 year after CAR T cell therapy in elderly population given Tisa-cel or Axi-cel: OS (2a), PFS (2b), RI (2c) and NRM (2d)


a)
p<0.001
Tisa-cel
Axi-cel
Cumulative Incidence
100
75
50
25
0
0
6
12
18
24
30
Days since infusion
Nr at risk
Tisa-cel 325 139 130 126 125 124
Axi-cel 697 216 167 161 158 156
b)
p<0.001
Tisa-cel
Axi-cel
Cumulative Incidence
100
75
50
25
0
0
6
12
18
24
30
Days since infusion
Nr at risk
Tisa-cel 326 280 254 252 251 250
Axi-cel 696 544 385 365 360 357


a)
p=0.076
Tisa-cel
Axi-cel
Survival probability
100
75
50
25
0
0
3
6
9
12
Months since infusion
Nr at risk
Tisa-cel 402 331 248 197 167
Axi-cel 789 679 532 437 348
b)
p<0.001
Tisa-cel
Axi-cel
Survival probability
Months since infusion
Nr at risk
Tisa-cel 388 244 151 126 106
Axi-cel 764 574 409 324 264
c)
p<0.001
Tisa-cel
Axi-cel
Cumulative incidence
Months since infusion
Nr at risk
Tisa-cel 388 244 151 126 106
Axi-cel 764 574 409 324 264
d)
p<0.001
Tisa-cel
Axi-cel
Cumulative incidence
Months since infusion
Nr at risk
Tisa-cel 388 244 151 126 106
Axi-cel 764 574 409 324 264

Supplementary Tables and Figures

Supplementary Table 1- KM and CI analyses for acute toxicities at 30 days (95% CI)

Group	Total N	CRS any	p-value	CRS ≥3	p-value	ICANS any	p-value	ICANS ≥3	p-value
Tisa-cel	330-324	62% (57–67)		6% (4–8)		22% (18–27)		8% (5–11)	
Axi-cel	706-698	77% (74–81)		9% (6–12)		47% (44–51)		21% (18–14)	
p-value (Tisa vs Axi)			<0.001		0.30		<0.001		<0.001
Age 70–75	675–665	73% (70–76)	0.3	7% (5–9)	0.14	38% (34–41)	0.2	16% (13–19	0.4
Age 75–80	313–311	73% (68–78)		5% (3–8)		42% (37–48)		18% (14–22)	
Age ≥80	48–46	62% (49–76)		13% (3–23)		47% (33–61)		21% (10–33)	
ECOG 0–1	901–888	73% (70–76)	0.12	6% (4–7)	<0.001	39% (35–42)	0.012	16% (14–19)	0.05
ECOG ≥2	79-78	82% (74–91)		19% (10–28)		52% (41–63)		25% (16–35)	
CR/PR/Stable	449–448	70% (66–74)	0.024	6% (3–8)	0.09	36% (32–41)	0.18	15% (12–19)	0.5
Relapse/Progression	587–577	76% (73–80)		8% (6–11)		42% (38–46)		18% (15–21)	

Abbreviations: CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; ECOG = Eastern Cooperative Oncology Group. Cumulative incidence with 95% CI. p-values from Gray's test.

Supplementary Table: 2 KM and CI analyses for main outcomes at 1 year (95%CI)

Group	Total N	1-y OS	p-value	1-y PFS	p-value	1-y RI	p-value	1-y NRM	p-value
Tisa-cel	402-388	57% (52–31)		37% (32–42)		59% (54–64)		4% (2–6)	
Axi-cel	789-764	63% (60–67)		50% (46–54)		41% (37–44)		9% (7–11)	
p-value (Tisa vs Axi)			0.08		<0.001		<0.001		<0.01
Age 70–75	781-759	62% (58–65)	0.4	44% (40–48)	0.4	48% (45–52)	0.5	8% (6–10)	0.7
Age 75–80	351-335	61% (55–66)		48% (43–54)		44% (38–49)		8% (5–11)	
Age ≥80	59-58	59% (45–72)		49% (35–62)		46% (33–59)		5% (0–11)	
ECOG 0–1	1026-996	63% (59–66)	<0.001	46% (43–50)	<0.001	46% (43–50)	0.003	7% (6–9)	0.3
ECOG ≥2	97-91	45% (34–55)		30% (20–41)		59% (49–70)		10% (4–17)	
CR/PR/Stable	503-485	68% (64–73)	<0.001	54% (49–59)	<0.001	38% (34-43)	<0.001	7% (5–10)	0.07
R/P	613-596	56% (52–60)		38% (34–42)		54% (50-58)		8% (5–10)	

Abbreviations: OS = overall survival; PFS = progression-free survival; RI = relapse incidence; NRM = non-relapse mortality; ECOG = Eastern Cooperative Oncology Group. Estimates from Kaplan–Meier or competing-risk methods with 95% CI. p-values from log-rank or Gray's test.

Supplementary Figure 1 Survival differences between different age group for a) Overall Survival and b) Progression-free survival

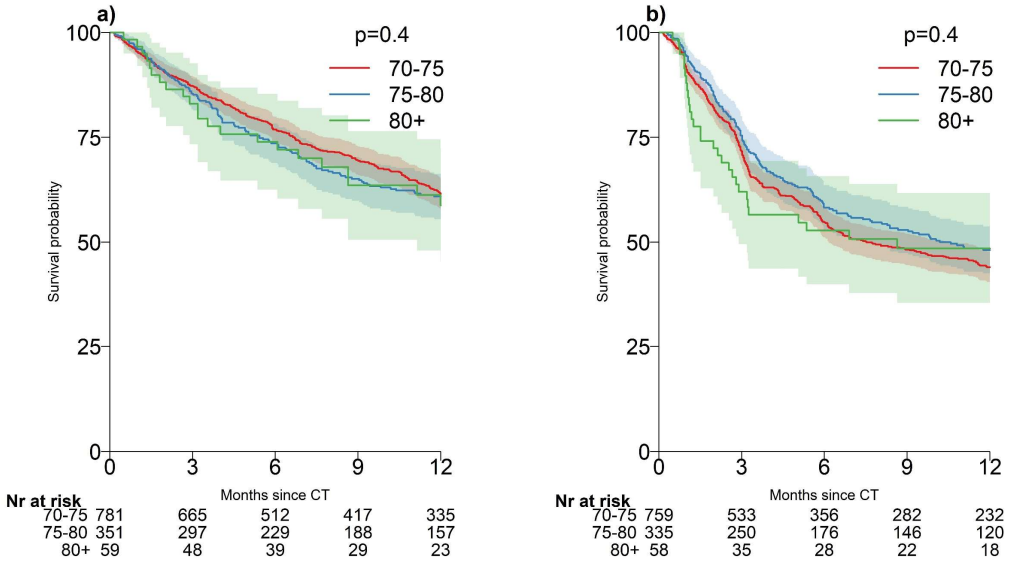


Figure S2. Temporal trends in non-relapse mortality (NRM), cytokine release syndrome (CRS), and immune effector cell–associated neurotoxicity syndrome (ICANS) according to year of CAR-T infusion.