Frequency of secondary T-cell lymphoma in chimeric antigen receptor T-cell naïve B-cell lymphoid-lineage cancers is higher than that reported on chimeric antigen receptor T-cell therapy

Chimeric antigen receptor (CAR) T-cell therapies improve clinical outcomes for diffuse large B-cell lymphoma (DLBCL) and other B-cell lymphoid lineage cancers (B-LC).[1-3] Today, more than 27,000 CAR T-cell doses have been administered in the US.[4] A recent case series identified 22 patients developing T-cell lymphoma (TCL) after CAR T-cell therapy. The Food and Drug Administration (FDA) has issued a warning on all six approved CAR T-cell products based on these findings. For now, the benefits of CAR T-cell therapies seem to outweigh this risk. First reported in a CAR T-cell treated case-series, three of the 22 US CAR T-cell-associated TCL cases demonstrated evidence of clonal similarity to the CAR T-cell product, while another large center reports no clonal relationship between the DLBCL and secondary TCL.[5] Further, the crude rate of T-cell malignancies was only 0.1% in FAERS data[6] and 0.1% to 0.2% in two single-center studies.[5,7] However, such rates typically underestimate the cumulative incidence without accounting for effects of follow-up time, competing risks, frontline chemoimmunotherapy, and increased likelihood of performing new biopsies in this patient population. As such, data on the background risk of TCL among CAR T-cell naïve patients with relapsed or refractory (R/R) DLBCL or other primary B-LC diagnoses are warranted.

In this study, we investigated the cumulative incidence of TCL for CAR T-cell naïve patients with a diagnosis of DLBCL, mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM); four B-LC approved for CAR T-cell therapies by the FDA. Additionally, we assessed the cumulative incidence of TCL in patients with R/R DLBCL considered eligible for CAR T-cell therapy. All data were retrieved from the Danish Lymphoid Cancer Research (DALY-CARE) data resource.[8] We included all Danish patients registered with a diagnosis of DLBCL, MCL, CLL, and MM between January 2002 and February 2023 for whom pathology notes were available until May 2023. To exclude concomitant B-LC and TCL diagnoses, patients were first considered at risk 3 month after B-LC diagnosis and followed until TCL, death, or end of follow-up, whichever came first. From January 2005, patients with R/R DLBCL after frontline therapy and younger than 70 years were retrospectively considered eligible for CAR T-cell therapy. CAR T-cell therapy was first approved by the Danish Medicines Council in September 2023 for patients with early R/R DLBCL younger than 70 years, and all patients in this study are thus CAR T-cell therapy naïve. The study was approved by the Danish Health Data Authority and National Ethics Committee (approvals P-2020-561 and 1804410, respectively).

We included 10,805 patients with DLBCL (C83.3), 1,515 with MCL (C83.1), 13,773 with CLL/SLL (C83.0 and C91.1), and 10,994 with MM (C90.0). After a median follow-up of 8.5 years (interquartile range [IQR], 4.6-13.5) from time of diagnosis (Table 1), we identified 127 patients with a sec-

Table 1. Baseline characteristics at time of diagnosis.

Variable	DLBCL N=10,805	MCL N=1,515	CLL N=13,773	MM N=10,994	Total N=37,087
Median age in years (IQR)	69.3 (59.4-77.3)	70.4 (62.3-77.9)	71.5 (63.4-78.7)	71.7 (63.5-78.7)	71 (62.3-78.3)
Sex: F/M, N (%)	4,728 (43.8)/ 6,077 (56.2)	483 (31.9)/ 1,032 (68.1)	5,714 (41.5)/ 8,059 (58.5)	4,840 (44.0)/ 6,154 (56.0)	15,765 (42.5)/ 21,322 (57.5)
IPI*, N (%)					
Low	519 (7.1)	185 (15.9)	1,887 (53.2)	1,809 (26.6)	4,400 (23.3)
Intermediate	3,385 (46.1)	378 (32.5)	1,006 (28.4)	4,241 (62.4)	9,010 (47.8)
High	3,444 (46.9)	600 (51.6)	526 (14.8)	751 (11.0)	5,321 (28.2)
Very high	0 (0.0)	0 (0.0)	128 (3.6)	0 (0.0)	128 (0.7)
Missing	3,457	352	10,226	4,193	18,228

*International Prognostic Index (IPI) represents Revised-IPI in diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma IPI (MIPI) in mantel cell lymphoma (MCL), chronic lymphocytic leukemia IPI (CLL-IPI), and Revised International Staging System for multiple myeloma (MM). IQR: interquartile range.

ondary biopsy-verified TCL: 36 (28%) with peripheral TCL not otherwise specified (C84.4), 28 (22%) with anaplastic large cell lymphoma (C84.6), 27 (22%) with angioimmunoblastic TCL (C86.5), 18 (14%) with mycosis fungoides (C84.0), eight (6.3%) with cutaneous TCL not otherwise specified (C84.8), and ten with other TCL. The overall 1-, 2-, and 5-year cumulative incidence of TCL was 0.11%, 0.17%, and 0.28%, respectively. Stratified on disease, the 5-year cumulative incidence of TCL was 0.56% (N=55), 0.30% (N=4), 0.23% (N=29), and 0.07% (N=7) in patients with DLBCL, MCL, CLL, and MM, respectively (Figure 1A). In a subset of 1,051 patients younger than 70 years with R/R DLBCL after frontline therapy, who today could be considered CAR T-cell treatment eligible in Denmark, the 1-year cumulative incidence of TCL from time of relapse was 0.77% (N=8) and plateaued during 5 years of follow-up (Figure 1B). On the other hand, the median overall survival (OS) from time of DLBCL relapse was only 3.8 years (95% confidence interval [CI]: 3.0-4.7 years), despite significantly improved OS in recent years (Figure 2; *P*=0.035). Of note, only 319 (30.4%) RR DLBCL patients received high-dose therapy followed by an autologous stem cell transplant.

In these population-based, CAR T-cell naïve cohorts, the 5-year incidence of TCL from diagnosis of DLBCL was low, but higher than for patients with CLL or MM. For the patients younger than 70 years at time of R/R DLBCL, who

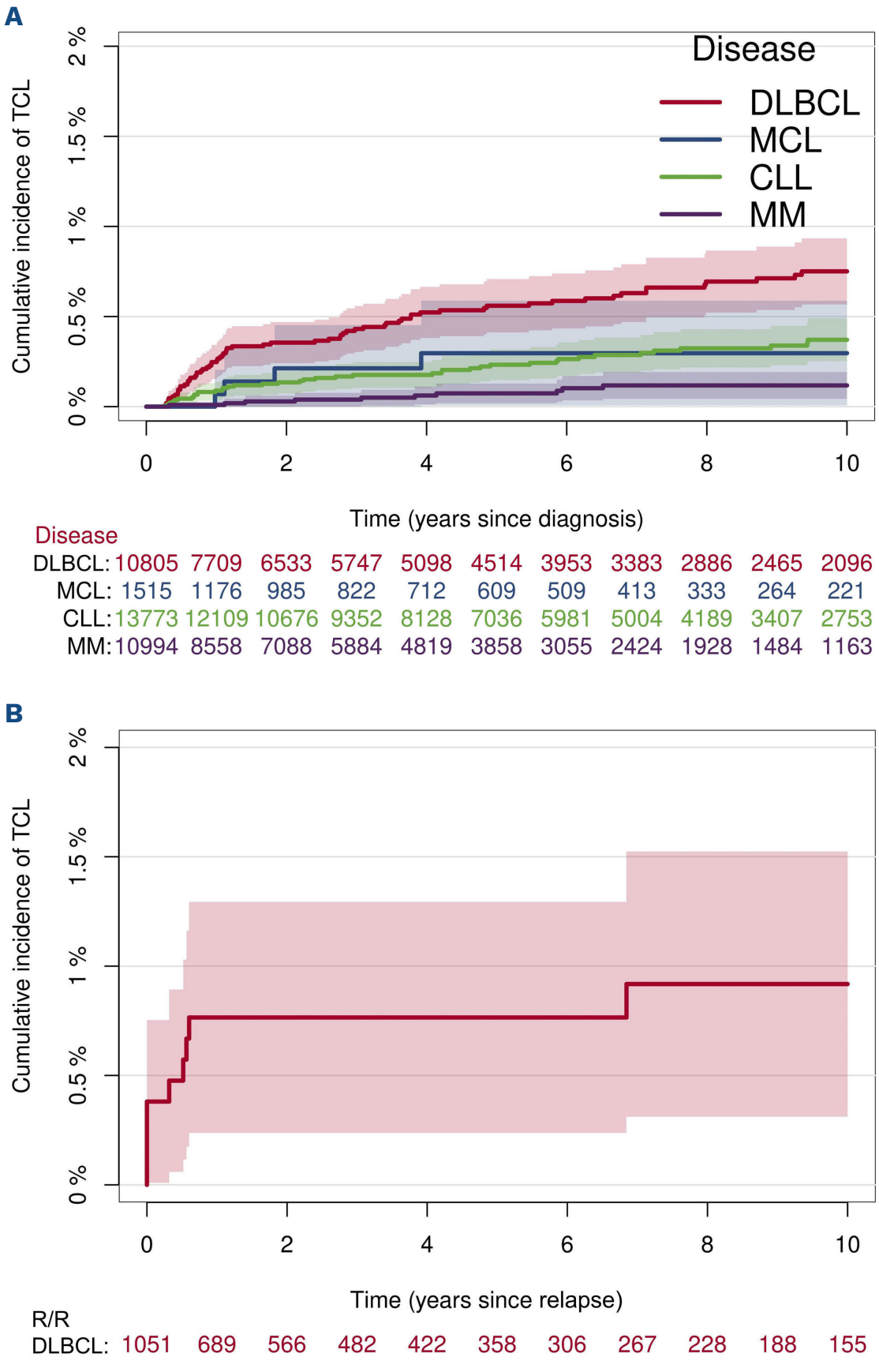

Figure 1. Cumulative incidence of secondary T-cell lymphoma. (A) Cumulative incidence with 95% confidence intervals in patients followed from time of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM), and (B) from time of relapsed/refractory (R/R) DLBCL in patients younger than 70 years. Note that the Y-axis is limited to 2%; TCL: T-cell lymphoma.

would be considered eligible for CAR T-cell therapy today, the cumulative incidence of TCL was 0.77% after 1 year of follow-up. This is higher than reported in US patients having undergone CAR T-cell therapy (0.14% or 17 cases per 12,394 patients). The crude rate of TCL after CAR T-cell therapy in the US was thus lower compared to the cumulative incidence after just 14 months from time of diagnosis (overall x-intercept for 0.14%) and to the cumulative incidence after 7.5 months from DLBCL diagnosis (Figure 1A; DLBCL x-intercept for 0.14%). Importantly, two large single-center studies have each reported a single clonally unrelated TCL case among 724 (0.14%) and 449 (0.22%) T-cell therapy recipients, which support a very low incidence of secondary TCL after CAR T-cell therapies.[5,7] Our study is limited by the retrospective design and the fact that risk of a second primary malignancy is associated with chemotherapy exposure,[9] while shorter survival in the CAR T-cell naïve R/R DLBCL population reduces the time at risk of a secondary malignancy.[10] However, developing TCL after a diagnosis of DLBCL, CLL, and MM rarely occurs in CAR T-cell-treated[6] and naïve patients, whereas CAR T-cell-treated children do not develop TCL at all.[11] Among R/R DLBCL patients considered eligible for CAR T-cell treatment, the cumulative incidence of secondary TCL was markedly higher than what has been reported for patients upon CAR T-cell therapy.[6] Although reporting TCL as an adverse event in the case

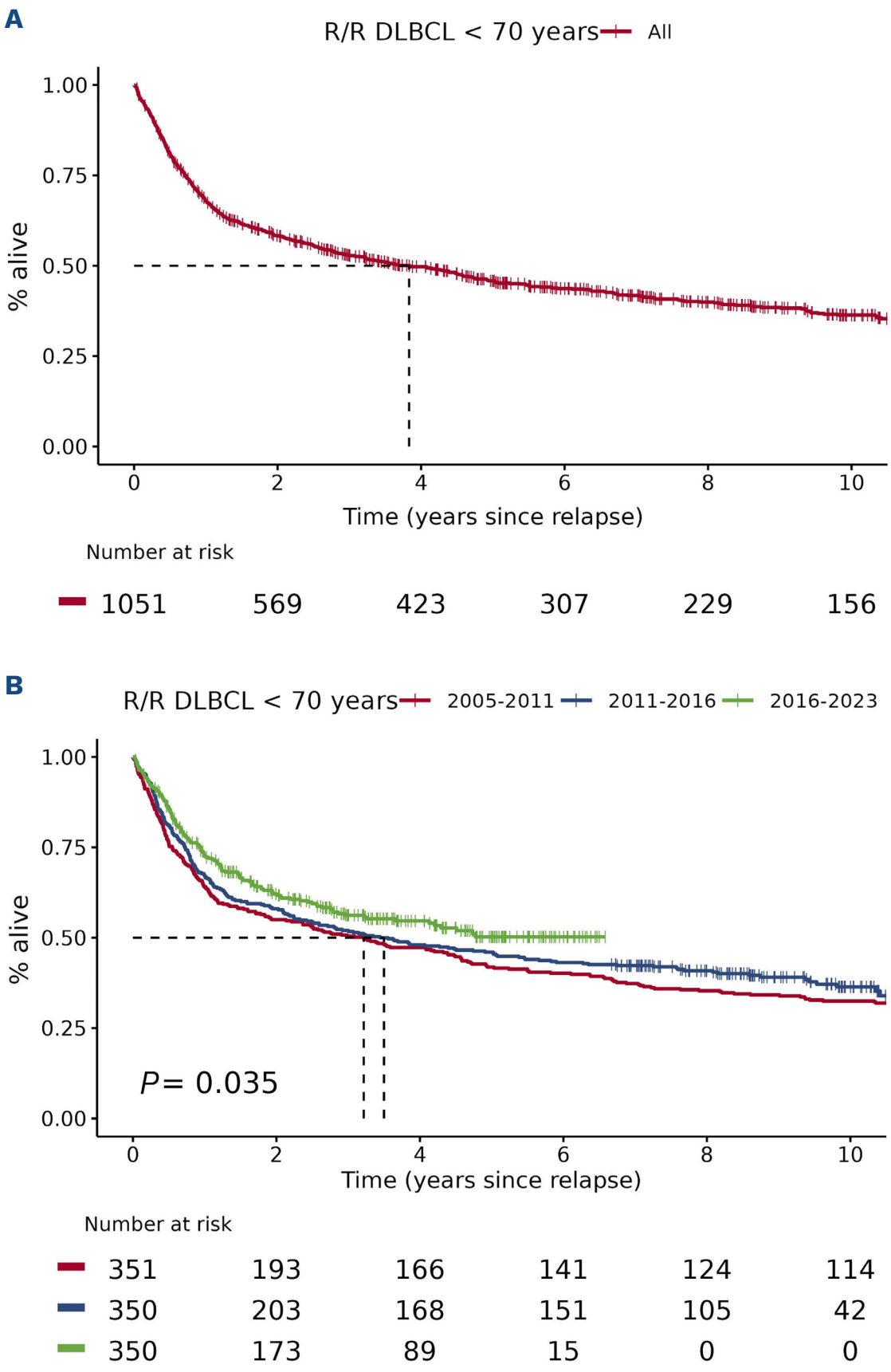

Figure 2. Overall survival from time of diffuse large B-cell lymphoma relapse. (A) Overall survival (OS) in younger patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) from time of relapse. (B) Stratifying patients into three time-periods based on tertile of relapse (i.e., July 11, 2005 to July 11, 2011 *vs*. July 21, 2011 to June 28, 2016 *vs*. July 11, 2016 to January, 26 2023), OS improved significantly in recent years.

studies from CAR T-cell-treated cohorts may occur, the here reported population-based data on the background risk of TCL in comparable patient populations emphasize that the benefits of CAR T-cell therapies greatly outweighs the risk of CAR T-cell-derived TCL. Despite improved survival for patients with R/R DLBCL in recent years as a likely result of better patient selection, supportive care and bispecific therapy in clinical trials,[12] we underscore the urgent need for improved therapy in this patient population.

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Contributions

CB and CUN conceived the study, gathered the data, and wrote the draft manuscript. CB performed the analyses. CB, CUN, SLP and PB interpreted the data. All authors contributed to and approved the final manuscript.

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Data-sharing statement

Data may be shared on the Danish Lymphoid Cancer Research (DALY-CARE) data resource on a collaborative basis. Data may not be shared publicly.

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