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Chimeric Antigen Receptor T-Cell Therapy for Richter Transformation: A CIBMTR Analysis

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A B S T R A C T

Relapsed and/or refractory Richter transformation (RT) is generally associated with poor response to available therapies and a short survival time. As RT patients were excluded from participating in the pivotal studies of chimeric antigen receptor T cell therapy (CAR-T) for large B-cell lymphoma, there is a paucity of information about the efficacy of CAR-T in RT. Therefore, through the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, we analyzed data from 140 RT patients who received anti-CD19 CAR-T between 2018 and 2023. Patients had received a median of 3 lines of therapy for RT (range: 1 to 8), with nearly 43% being exposed to a Bruton's tyrosine kinase inhibitor and/or venetoclax. Axicabtagene ciloleucel (axi-cel) (65%) and tisagenlecleucel (tisa-cel) (28%) were the most commonly prescribed products. Grade ≥3 cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome occurred in 9.4% and 20%, respectively. After a median follow-up of 25 months (range: 1.8 to 61.5) from CAR-T infusion, 2-year progression-free and overall survival were 32.5% (95% CI, 24 to 41) and 46.6% (95% CI, 38 to 58), respectively. The 2-year cumulative incidence of relapse and non-relapse mortality were 58.8% (95% CI, 50 to 67), and 8.7% (95% CI, 4% to 14%), respectively. Poor performance status and refractory disease before CAR-T infusion were predictive of inferior survival and disease progression. Our results show that anti-CD19 CAR-T can function as an effective treatment modality for a proportion of RT patients.

INTRODUCTION

Richter transformation (RT) represents an evolution of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), commonly to a diffuse large B-cell lymphoma (DLBCL) histology, occurring in ~ 3% to 10% of patients with CLL, with an observed overall incidence of up to 1% per year [1–4].

The clinical course of RT is typically aggressive, driven by the presence of high-risk genetic markers, previous treatment history, clonal relationship with CLL and patient-specific factors. Standard treatment of RT is usually modeled after *de novo* DLBCL management guidelines, with anthracycline-based multi-agent chemoimmunotherapy (CIT) generally being employed as the first line therapy in fit patients. Further, consolidation with hematopoietic cell transplantation (HCT), particularly allogeneic, has been shown to provide durable remissions in a proportion of transplant eligible patients who have achieved complete response (CR) [3,5]. However, RT patients are often ineligible for intensive CIT or HCT attributed to frailty [6]. Moreover, due to the preponderance of high-risk genetic markers, and inherent resistance to therapy, response rates to RT-directed CIT are often low and short-lived [5–8]. Therefore, median overall survival (OS) is poor, approximately 12 months, in high-risk RT patients [1,9–11]. Although the advent of venetoclax and Bruton's tyrosine kinase inhibitors (BTKi) has expanded treatment options for RT, short duration of response remains a clinical challenge [12]. RT progressing after failure of venetoclax and BTKi has an even worse anticipated median OS of ~4 to 6 months illustrating the critical need for developing newer treatment strategies for these patients [6,13–15].

The development of anti-CD19 chimeric antigen receptor T-cell therapy (CAR-T) has provided a significant breakthrough for the treatment of various relapsed or refractory (R/R) non-Hodgkin B-cell malignancies. Despite questions regarding constitutional T-cell dysfunction and exhaustion in CLL, a few early studies showed potential efficacy of anti-CD19 CAR-T in CLL and RT [16–20]. In spite of these encouraging data, patients with RT were still excluded from participating in the pivotal registrational trials that led to approval of anti-CD19 CAR-T for the treatment of R/R DLBCL by the US Food and Drug Administration (FDA) [21,22]. Although the prospective TRANSCEND-NHL-001 trial of lisocabtagene maraleucel (liso-cel) allowed enrollment of patients with DLBCL transformed from any indolent non-Hodgkin lymphoma (iNHL), only 5 patients with RT were included in that study [23]. Similarly, the TRASN-CEND- CLL-004 study of liso-cel also excluded patients with RT [24].

Nevertheless, due to limited treatment options, off-label use of anti-CD19 CAR-T has been well adopted into clinical practice for the treatment of RT under the indication of DLBCL, and thus, the

gap in evidence supporting the clinical efficacy of CAR-T for RT has been largely addressed by retrospective studies [25,26].

Adding to the existing data and experience, here, we report results from a CIBMTR analysis of patients with DLBCL type RT who received commercially approved anti-CD19 CAR-T.

METHODS

Data Source

This is a retrospective registry-based study. The CIBMTR is a working group comprised of over 380 transplantation centers worldwide that provide data regarding cellular therapies to a statistical center at the Medical College of Wisconsin (MCW). Data quality is augmented through computerized affirmation of discrepancies, physicians' review of submitted data, and on-site audits of participating centers. Observational studies are conducted by the CIBMTR in compliance with all pertinent federal regulations regarding the protection of human research participants. All patients included in this analysis have provided written consent for research. The Institutional Review Board of MCW has approved this study.

Patients

Adult patients ($\geq$ 18 years) with a diagnostic indication of DLBCL type RT from pre-existing CLL who had received one of the commercially approved anti-CD19 CAR-T products, namely axicel, tisa-cel or liso-cel, between 2018 and 2023 and had data reported to the CIBMTR registry were included in this analysis.

Definitions and Endpoints

OS was the primary study endpoint. Secondary endpoints included progression-free survival (PFS), cumulative incidence of progression/relapse (CIP/R), nonrelapse mortality (NRM), incidence of cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). Death from any cause was considered an event for OS analysis. For PFS, progression/relapse or death from any cause were considered events. NRM was defined as death without evidence of prior lymphoma progression/relapse, where relapse was considered a competing risk. Bridging was defined as any therapy, including radiation, administered between apheresis and lymphodepletion (LD), or a patient's last line of treatment before CAR-T if it was continued after apheresis. Disease response to the last line of therapy before CAR-T was defined using the Lugano Classification [27]. American Society for Transplantation and Cellular Therapy (ASTCT) criteria were used to grade the severity of CRS and ICANS [28].

Statistical Analysis

Baseline characteristics of the study population were described. Kaplan-Meier estimates were used for OS and PFS. Cumulative incidence was calculated for progression/relapse and NRM to handle competing risks. Forest plots were created to present hazard ratios (HR) and their 95% confidence intervals (95% CI) based on the univariable Cox model for OS and the univariable proportional cause-specific hazards model for relapse. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.4 (Vienna, Austria).

RESULTS

Patient Characteristics

One hundred and forty patients from 66 centers met inclusion criteria, of which 93 patients were found to have de novo RT. Table 1 shows relevant demographic, baseline disease, and treatment-related characteristics of the study population. The median age of patients at the time of CAR-T infusion was 66.5 years (range: 30 to 83). Most patients were male (62.1) and Caucasian (77.1%), while Blacks were 7.1%, Asians 5.7% and Hispanics 5.7%. Fifty-three (37.9%) patients had an HCT comorbidity index (HCT-CI) $\geq$3 and over half the patients (n = 75, 54.3%) had a Karnofsky performance status (KPS) $<$90 at the time of CAR-T infusion.

At the time of RT diagnosis, extra nodal disease was present in 74 (52.9%) patients and deletion of chromosome 17p was reported in 53 (37.9%) patients. Treatment information only since the diagnosis of RT was available and analyzed here. CLL treatment data were not available for this analysis. The median number of lines of therapy prescribed for RT treatment before the CAR-T infusion was 3 (range: 1 to 8). A total of 18.6% of patients with clinical evidence of RT received venetoclax, 24.3% received BTKi, and 6.4% both agents, before CAR-T. A total of 27 patients (19.3%) had previously received an allogeneic (n = 16, 11.4%) or an autologous (n = 11, 7.9%) HCT for RT. Sixty-seven patients (47.9%) received some form of bridging therapy. Of this, notably, 27 (19.3%) patients received multi-agent CIT, 11 (7.9%) got single agent chemotherapy, 6 (4.3%) single agent monoclonal antibody, 8 (5.7%) received a BTKi or an immunomodulatory agent, and 8 (5.7%) received radiation therapy.

Table 1
Baseline Characteristics of RT Patients Who Received Anti-CD 19 CAR-T between 2018 and 2023

Characteristic	N = 140 (%)
Age in years at CAR-T, median (min-max)	66.5 (range, 31-83)
≥60 years	104 (74.3)
Female sex	53 (37.9)
Race	
White	108 (77.1)
Black or African American	10 (7.1)
Asian	8 (5.7)
Other/Not reported	14 (10)
Ethnicity	
Not Hispanic or Latino	117 (83.6)
Hispanic or Latino	8 (5.7)
Nonresident of the U.S	9 (6.4)
Unknown	6 (4.3)
Karnofsky performance status prior to CAR-T	
90-100	51 (36.4)
<90	76 (54.3)
Not reported	13 (9.3)
Hematopoietic cell transplantation—comorbidity index	
0	31 (22.1)
1-2	50 (35.7)
3+	53 (37.9)
Not reported	6 (4.3)
No. of prior lines of therapy for RT—median (min-max)	3 (1-8)
Prior allogeneic transplant	16 (11.4)
Prior autologous transplant	11 (7.9)
Bridging therapy	
Yes	67 (47.9)
No	51 (36.4)
Not reported	22 (15.7)
Disease status prior to CAR-T	
CR	13 (9.3)
PR	34 (24.3)
Resistant	87 (62.1)
Untreated	2 (1.4)
Unknown	4 (2.9)
Bulky disease	
≥5 cm	19 (13.6)
5 cm	75 (53.6)
Not reported	46 (32.9)
Time from diagnosis to CAR-T, months—median (min-max)	10.7 (1.7-276.3)
Lymphodepletion regimen	
Bendamustine based	10 (7.1)
Cyclophosphamide + fludarabine	130 (92.9)
CAR-T product	
Axicabtagene ciloleucel	91 (65)
Tisagenlecleucel	39 (27.9)
Lisocabtagene maraleucel	10 (7.1)

Response assessment was available and reported for the DLBCL component. The modality of assessment varied per treating center's discretion and consisted of either a positron emission tomography and computed tomography (PET-CT); n = 122, or a plain CT. At the time of the last disease restaging prior to administering lymphodepleting (LD) chemotherapy, the majority of the patients had resistant disease (n = 87, 62.1%) with 19 (13.6%) having residual bulky disease (> 5cm). Only a small fraction of patients had achieved CR (n = 13, 9.3%), while partial response (PR) was obtained in 34 (24.3%) patients. The median time between diagnosis of RT and CAR-T infusion was 10.7 months (range: 1.7 to 282). Nearly all patients (93%) received cyclophosphamide plus fludarabine as the LD regimen except for 10 (7%) patients who received bendamustine-based LD. Axi-cel was the most prescribed CAR-T product (65%).

Safety and Toxicity

CRS of any grade was reported in 73% of patients. Grade 1 CRS was reported in 39.3% and grade ≥ 3 CRS in 13 (9.4%). The incidence of ICANS of any grade was 35.7%, and grade ≥3 ICANS was reported in 28 (20%) patients. The median times to onset of CRS and ICANS were 3 days (range: 1 to 31) and 5 days (range: 1 to 18), respectively. Grade 5 CRS and /or ICANS was reported in 5 patients in total (3.6%) (Supplemental Table 1). Most of the high grade ICANS were contributed by axi-cel as it was the most predominantly used product. A breakdown and comparison of the rates of CRS and ICANS per product type are provided in Supplemental Table 2.

The leading cause of death was disease recurrence/progression (66.2%), followed by infections (9.6%) and second primary malignancies (5.4%) (Supplemental Table 3). Notably, the coronavirus disease of 2019 (COVID-19) was the predominant cause among infections (n = 4, 5.5%). Further information about the specific second primary malignancies were not available.

Efficacy

Among 128 evaluable patients, the overall response rate (ORR) following CAR-T infusion was 71% (92/128). The CR rate was 57% (73/128). After a median follow-up of 25 months (range: 1.8 to 61.5) from CAR-T infusion, 2-year PFS and OS were 32.5% (95% CI, 24.2 to 41.4) and 46.6% (95% CI, 37.7 to 55.7), respectively. The 2-year CIP/R and NRM were 58.8% (95% CI, 49.8 to 67.6) and 8.7% (95% CI, 4.2 to 14.6), respectively (Figure 1).

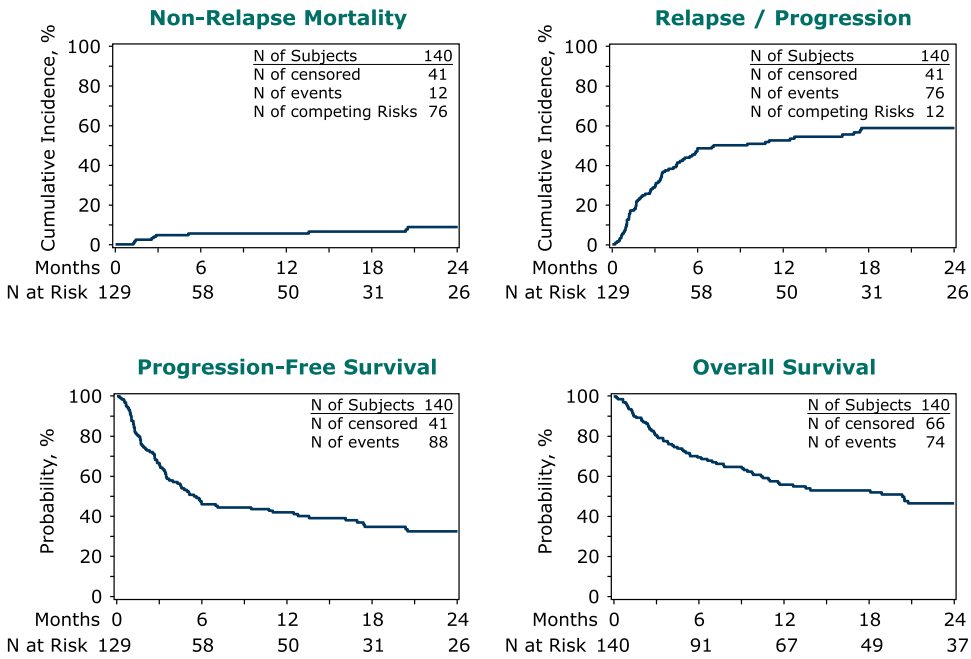

Figure 1. NRM, CIR/P, PFS, and OS of patients with RT treated with anti CD19 CAR-T therapy from the CIBMTR registry.

Outcomes for the exclusive liso-cel cohort are shown in Supplemental Table 4.

Poor Karnofsky performance status, (HR = 1.76, 95% CI, 1.05 to 2.93), and refractory disease pre-LD, (HR = 2.30, 95% CI, 1.33 to 3.99) were significantly associated with shorter OS, while only refractory disease was found to be significantly associated with shorter PFS (HR = 1.97, 95% CI, 1.21 to 3.20) (Figure 2A,B). Refractory disease was also associated with higher relapse risk (HR = 1.84, 95% CI, 1.10 to 3.06) (Supplemental Figure 1). Receipt of bridging therapy showed a significant association with shorter PFS (HR = 1.83, 95% CI, 1.13 to 2.94) and higher relapses (HR = 1.93, 95% CI, 1.15 to 3.26) while having no impact on OS. Also, unexpectedly, we found that exposure to ≥3 lines of therapy for RT pre-CAR-T was associated with a favorable OS

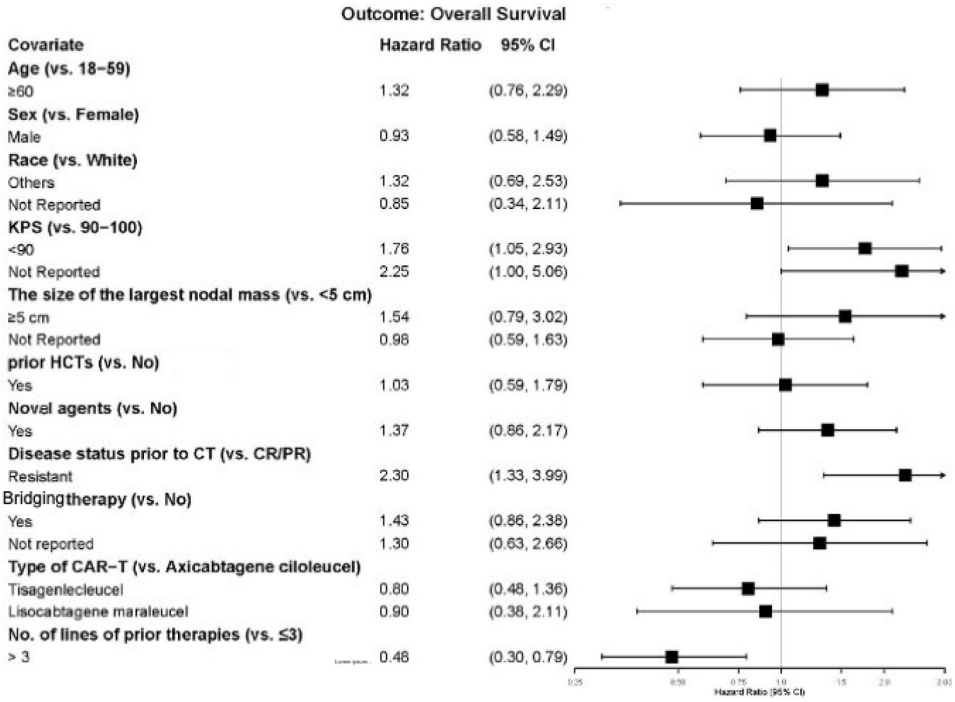

Figure 2. (A) Forest plot of variables associated with overall survival identified with the univariable Cox model. (B) Forest plot of variables associated with progression-free survival identified with the univariable Cox model.

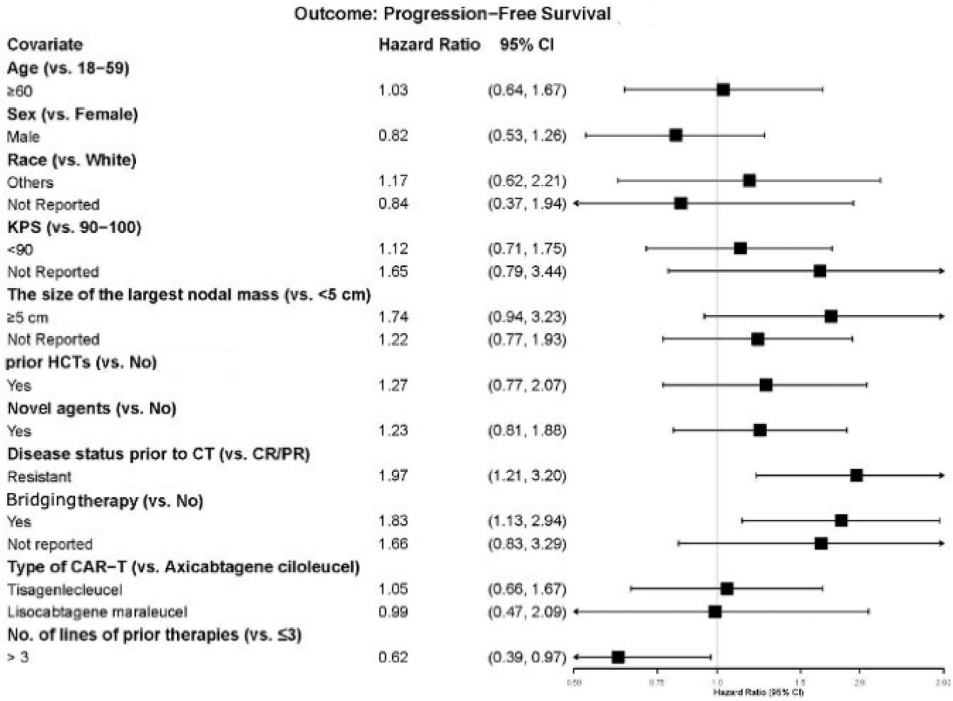

Figure 2. Continued.

(HR = 0.48, 95% CI, 0.30 to 0.79), and PFS (HR = 0.62, 95% CI, 0.39 to 0.97). Eight patients have undergone subsequent allogeneic HCT. However, long-term survival data pertaining to this specific cohort are not available for reporting at the time of this analysis.

We separately analyzed the outcomes of patients with early treatment failure as defined by the Zuma-1 study criteria [29]. The early treatment failure group includes those with primary refractory disease. There was no statistical difference between the groups, in 2-year PFS (40.4% [95% CI, 22.1 to 60.1] vs. 30.6 [95% CI, 21.5 to 40.6], P = .257) and 2-year OS (53.3% [95% CI, 34.5 to 71.7] vs. 44.5% [95% CI, 934.5 to 54.8], P = .477); Supplemental Table 5).

DISCUSSION

In this relatively large registry study, we found that anti-CD19 CAR-T therapy demonstrated clinical activity in a subset of heavily treated and high-risk RT patients—with a significant number of patients having refractory disease (62%) at pre-LD restaging, and 42.9% having had prior exposure to BTKi and/or venetoclax. Two-year PFS and OS were 32.5% and 46.6%, respectively. These results are encouraging, especially when compared to the historical data that suggest an anticipated median survival of approximately 6 months after failing to respond to or progress on venetoclax and BTKi [6,12–14]. Our results complement the cumulative experience of smaller prospective [18,23,30] and observational studies [25,26,31–33], showing anti-CD19 CAR-T as a potentially effective treatment modality for RT.

Although the ORR and CR achieved in this high-risk population—71% and 57%, respectively—are encouraging, the non-enduring responses, evidenced by a CIP/R of 58.8% at 2 years, remain a major hurdle to be addressed in future studies.

The observed incidence of grade ≥3 CRS and ICANS incidence (9.4% and 20%, respectively) in our cohort was in-line with data reported in the pivotal trials of CAR-T for R/R DLBCL [21,22]. These results are somehow reassuring given concerns about the possibility that concurrent marrow involvement with CLL, particularly if present in high burden, could contribute to increased toxicity [24,33–35].

While acknowledging the limited statistical power, we did not find any significant differences in outcomes by the type of CAR-T product used (Figure 2A,B). While limited evidence exists regarding variation in efficacy or toxicity rates among the commercially available anti-CD19 CAR-T products specifically in RT or transformed iNHL, one recent study suggested that axi-cel might yield higher CR rates, albeit at the expense of higher toxicity [36]. These findings need confirmation in larger studies. Of note, a higher rate of

ICANS was observed in the axi-cel cohort in this study, which is attributed to the likely predominant use of the product.

In our study, unsurprisingly, lower physical performance scores and disease refractoriness at the time of LD correlated with inferior survival. It is possible that sub-optimal performance could be just a surrogate for an aggressive disease biology and/or heavy treatment exposure. Other CAR-T studies in RT have identified higher Ki-67 proliferation index, elevated C-reactive protein, an above-normal lactate dehydrogenase level, and presence of bulky adenopathy and refractory disease at the time of LD as predictive markers for relapse and shorter PFS [25,37]. Collectively, these findings underscore the importance of attaining better disease control prior to CAR-T. Development of therapeutic agents with novel modes of action and higher efficacy is critically needed in RT and several trials are currently underway [38–43]. One such promising effort was the recently published results from the RT subgroup of the open-label phase $^{1}/_{2}$ BRUIN study which showed favorable responses with selective noncovalent BTKi pirtobrutinib in R/R RT, even after previous exposure to covalent BTKi [44].

As previously discussed, consolidative autologous or allogeneic HCT has demonstrated the capability of producing prolonged remissions in a proportion of RT patients who have achieved CR with prior therapies [5]. It is, therefore, conceivable that an allogeneic HCT consolidation following CAR-T be given an important consideration to induce sustained responses in eligible patients. This would be even more crucial if longer follow-up of our cohort shows relapses over time in those who achieved post-CAR-T remissions.

Additional barriers to achieving wider success of anti-CD19 CAR-T therapy in CLL and RT are related to the inherent problem of T-cell exhaustion and inadequate expansion [19,20].

Insights gained from extensive pre-clinical studies and clinical trials showed that concurrent BTKi with CAR-T infusion could mitigate some of the challenges posed by T-cell exhaustion. A few prospective clinical trials have already demonstrated that combining anti-CD19 CAR-T and ibrutinib is feasible, and could result in higher response rates that are durable even after prior BTKi exposure, without increasing toxicities [18,37,45]. Similar efforts are ongoing to augment CAR-T function and improve responses by combining it with BTKi and/or checkpoint inhibitors for CLL, RT and in other NHL, some of which have reported positive preliminary results [45–48].

We acknowledge that our study has inherent limitations. Prominently, details pertaining to treatment history and the status of CLL at the time of CAR-T infusion and at disease relapse, were not immediately available. This limited our understanding of the true treatment exposure and its impact on the outcomes in our population. Information about post-CAR-T management with and without relapse of RT, subsequent treatments, and how these could have affected the long-term outcomes were also not available. Due to these constraints, we were unable to perform more detailed analyses on outcomes. The clonal association of RT with CLL was also not known.

In conclusion, the collective results from our study along with other published reports support the role of CAR-T in RT. We recognize the limitations of CAR-T, and therefore, enrolling RT patients in various ongoing clinical trials for CAR-T and other novel cellular therapies is paramount and must be prioritized. Future trials could focus on determining the optimal combinations, timing and placement of CAR-T and HSCT in the RT treatment algorithm. Our observations warrant investigation of CAR-T as an earlier line of therapy in RT when the disease burden is lower.

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SUPPLEMENTARY MATERIALS

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