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Outcomes associated with CD3xCD20 bispecific antibody therapies in relapsed/refractory transformed indolent lymphoma

Pierre Stephan[1,2,3,*], Karan L. Chohan[4,*], Robert A. Redd[2], Wendy Dixon[2], Aaron Zou[2], Sairah Ahmed[4], Christopher R. Flowers[4], Ayushi Chauhan[4], Amy A. Ayers[4], Geoffrey Shouse[5], Swetha Kambhampati Thiruvengadam[5], Alex F. Herrera[5], Allison M. Bock[6], Narendranath Epperla[6], Matthew A Lunning[7], Gilles Salles[8], Lorenzo Falchi[8], Yazeed Sawalha[9], Sonia Godbole[9], Andrew P. Jallouk[10], Shakthi T. Bhaskar[10], Ajay Major[11], Steven M. Bair[11], Scott J. Rodig[1,2], Philippe Armand[2], Reid W. Merryman[2] , Alexey V. Danilov[5,#], Jennifer L. Crombie[2,#].

[1]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

[2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA.

[3]Department of Hemato-Oncology, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris, Paris, France.

[4]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

[5]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, CA, USA.

[6]Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA.

[7]Fred and Pamela Buffett Cancer Center at the University of Nebraska Medical Center, Omaha, NE, USA.

[8]Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

[9]Department of Internal Medicine, Division of Hematology, Arthur G. James Comprehensive Cancer Center, The Ohio State University Wexner Medical Center, Columbus, OH, USA.

[10]Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

[11]University of Colorado Cancer Center, Aurora, CO, USA.

[*]Equal contribution as co-first authors

[#] Equal contribution as co-last authors

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Running head: Outcomes of CD3xCD20 BsAbs in R/R tiNHL

Corresponding author:

Pierre Stephan, Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02115; e-mail: pierre_stephan@dfci.harvard.edu

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Abstract

Transformed indolent non-Hodgkin lymphoma (tiNHL) has historically been associated with poor outcomes, particularly for patients with relapsed or refractory (R/R) disease. Although chimeric antigen receptor (CAR) T-cell therapy has improved prognosis, many patients lack access or experience relapse following treatment, highlighting the need for additional therapeutic strategies. CD3×CD20 bispecific antibodies (BsAbs) are active in R/R large B-cell lymphoma (LBCL), though data in tiNHL are limited. Here, we report the efficacy and safety of epcoritamab and glofitamab in patients with R/R tiNHL (N = 74) compared with those of patients with R/R *de novo* diffuse LBCL (DLBCL; N = 166) from 9 academic centers in the Collaborative US Bispecifics Consortium (CUBIC). With a median follow-up of 11.5 months, best overall response rate (ORR) and complete response rate (CRR) were comparable in tiNHL (50%/31%) vs *de novo* DLBCL (51%/34%). 12-month progression-free survival was 25% (95% confidence interval [CI], 15-39) for tiNHL vs 34% (95% CI, 27-43) for *de novo* DLBCL (HR, 1.15 [95% CI, 0.83-1.61]) and 12-month overall survival was 38% (95% CI, 26-55) for tiNHL vs 47% (95% CI, 39-56) for *de novo* DLBCL (HR, 1.08 [95% CI, 0.73-1.60]). No differences in toxicity were observed. Similar findings were found via a 1:1 propensity score matching statistical approach. In conclusion, our study revealed comparable efficacy and toxicity of BsAbs for patients with R/R tiNHL vs patients with R/R *de novo* DLBCL, supporting their use in this patient population.

Introduction

Histological transformation of indolent non-Hodgkin lymphoma (NHL) to large B-cell lymphoma (LBCL) constitutes a pivotal adverse event with substantial implications for patient survival[1–5]. In the 2022 World Health Organization (WHO) classification, transformed indolent non-Hodgkin lymphoma (tiNHL) is designated as a distinct clinicopathological entity within the broader category of LBCL[6]. tiNHL has historically been associated with an aggressive clinical course and poor outcomes, particularly in patients with relapsed or refractory (R/R) disease, and remains the principal cause of disease-related mortality in follicular lymphoma (FL)[2,7–12]. More importantly, management of tiNHL differs markedly from that of indolent B-cell lymphoma; therefore, accurate identification and documentation of transformation are critical, as they have important implications for alternative therapeutic strategies.

Recent studies in tiNHL have demonstrated improvements in outcome. In particular, anti-CD19 chimeric antigen receptor (CAR) T-cell therapy has been associated with favorable outcomes with potentially improved responses as compared to *de novo* LBCL[13–16]. Most patients receiving CAR T-cell therapy, however, will ultimately relapse and furthermore, accessibility remains a challenge[17,18]. CD3xCD20 T-cell-engaging bispecific antibodies (BsAbs) have demonstrated efficacy in R/R LBCL[19,20]. The NP30179 and EPCORE NHL-1 pivotal studies led to approval of glofitamab and epcoritamab for R/R LBCL after at least two prior lines of therapy, respectively. While patients with tiNHL were enrolled on these trials, they made up a small percentage of the study population, 18% (n=27) in NP30179 and 25% (n=40) in EPCORE NHL-1, and thus information on the activity of BsAbs in tiNHL remains limited.

The goal of our study was to assess the clinical efficacy and safety of BsAbs in patients with R/R tiNHL, in comparison with those with R/R *de novo* diffuse LBCL (DLBCL) not otherwise specified (NOS). We conducted a multicenter, retrospective study of patients from the Collaborative US Bispecifics Consortium (CUBIC) treated with standard of care epcoritamab or glofitamab, balancing covariate distribution known to be involved in prognosis in the two cohorts via adapted propensity score matching (PSM) analysis.

Methods

Study Design and Patients

We conducted a multicenter, retrospective study across 9 academic centers that are part of the CUBIC (Table S1).

The study included adults (≥18 years old) with R/R tiNHL or R/R *de novo* DLBCL NOS treated with standard of care CD3xCD20 BsAbs epcoritamab or glofitamab outside of clinical trials from May 2023 to September 2025. We defined tiNHL as LBCL transformed from FL, marginal zone lymphoma (MZL), Waldenstrom's macroglobulinemia

(WM)/lymphoplasmacytic lymphoma (LPL), Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL) or low-grade B-cell lymphoma, NOS. Patients with Richter's syndrome and those receiving BsAbs as bridging therapy prior to CAR T-cell infusion were excluded. Study data were collected by the participating sites by chart review and managed using REDCap electronic data capture tools hosted at MD Anderson Cancer Center. The study was approved by the Institutional Review Board at each site, and the study was undertaken in accordance with the Declaration of Helsinki.

Objectives

The primary objective was to evaluate the efficacy of CD3xCD20 BsAbs therapy in R/R tiNHL compared with *de novo* DLBCL as measured by best overall response rate (ORR) and complete response rate (CRR). Response was assessed by local investigators according to Lugano 2014 criteria[21]. Secondary objectives included progression-free survival (PFS), overall survival (OS), duration of response (DOR) and safety, specifically rates of cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and infection. CRS and ICANS were graded according to the consensus criteria from American Society for Transplantation and Cellular Therapy (ASTCT) criteria[22]. PFS was defined from the date of BsAbs initiation to the date of first documented relapse, progressive disease, date of last follow-up, or death from any cause, whichever came first. OS was defined from the date of BsAbs initiation to the date of death from any cause or the date of last follow-up.

Subgroup analyses

Four subgroup analyses within the tiNHL cohort were originally planned: (1) evaluation of outcomes according to the BsAbs product used (epcoritamab *vs.* glofitamab); (2) comparison of outcomes between patients with exposure to prior CAR T-cell therapy and those without; (3) analysis of outcomes specifically within the tFL subgroup, including by time to transformation; and (4) analysis of outcomes in patients with a high-grade B-cell lymphoma (HGBL) diagnosis at time of BsAbs initiation.

Statistical Considerations

Demographic and disease characteristics were summarized using median (range) for continuous variables and count (percentage) for categorical variables. ORR, CRR, and toxicity rates were compared using Fisher’s exact test, with 95% confidence intervals (CI) estimated by the Clopper–Pearson exact method. Survival distributions were estimated using the Kaplan–Meier method and compared using the log-rank test; 95% CI for survival estimates were calculated using Greenwood’s formula with log-log transformation. Univariable Cox regression results were reported as hazard ratios (HR) with 95% CI and Wald p-values. A 2-sided $P<0.05$ was considered significant, without adjustment for multiple testing.

To balance baseline characteristics between the tiNHL and de novo DLBCL cohorts, PSM was performed using logistic regression including prespecified baseline clinical characteristics at BsAbs initiation known to impact outcomes in aggressive B-cell lymphomas (Table S2). Patients were matched 1:1 using nearest-neighbor matching without replacement. Covariate balance before and after matching was assessed using standardized mean differences. In the matched cohort, PFS and OS were further compared using stratified Cox regression with robust standard errors clustered by matched pairs. Statistical analyses were performed using R version 4.4.2 and knitr v1.50.

Results

Patient characteristic, disease response and survival in the original cohort

A total of 74 patients with tiNHL and 166 patients with *de novo* DLBCL were treated with either epcoritamab or glofitamab. Patient characteristics are presented in Table 1. Among tiNHL and *de novo* DLBCL cohorts, respectively, 41% (n=30) vs 52% (n=86) received epcoritamab while 59% (n=44) vs 48% (n=80) received glofitamab. Aside from the use of obinutuzumab with glofitamab, the majority of patients did not receive any concomitant treatment (Table S3). A minority of patients received therapy before BsAbs initiation for disease control (2 tiNHL, 7 de novo DLBCL) or concomitant systemic treatment, mainly gemcitabine-oxaliplatin (GemOx) (10 tiNHL, 6 *de novo* DLBCL) according to STARGLO[23].

Among the tiNHLs, 77% (n=57) arose from FL, 11% (n=8) from MZL, 3% (n=2) from WM/LPL, 4% (n=3) from NLPHL, and 5% (n=4) from a low-grade B-cell lymphoma, NOS (Table 2). At treatment initiation, 77% (n=57) of tiNHL had DLBCL, NOS, 20% (n=15) HGBL, 3% (n=2) T-cell/histiocyte-rich LBCL (Table 2). Thirty percent of patients (n=22) experienced transformation within one year following the diagnosis of indolent disease. All patients in the *de novo* DLBCL cohort had a diagnosis of DLBCL, NOS.

With a best ORR of 50% (95% CI, 38-62) and CRR of 31% (95% CI, 21-43) for patients with tiNHL and best ORR of 51% (95% CI, 43-58) and CRR of 34% (95% CI, 27-42) for patients with *de novo* DLBCL, no significant difference was observed between the two cohorts (best ORR, $p > 0.99$; best CRR, $p = 0.66$; Figure 1A and Table 3).

The 12-month DOR was 38% (95% CI, 22-68) in the tiNHL cohort vs 60% (95% CI, 48-74) in the *de novo* DLBCL (HR, 1.24 [95% CI, 0.67-2.29]; $p = 0.49$; Figure 1B and Table 3). The 12-month duration of CR (DOCR) was 58% (95% CI, 35-95) in the tiNHL cohort vs 76% (95% CI, 62-92) in the *de novo* DLBCL (hazard ratio [HR], 1.62 [95% CI, 0.59-4.47]; $p = 0.35$; Figure 1C).

With a median follow-up of 11.5 months (range: 0.1-27.4), the median PFS was 3 months (95% CI, 2-6) in the tiNHL cohort and 4 months (95% CI, 3-5) in the *de novo* DLBCL cohort, with 12-month PFS of 25% (95% CI, 15-39) vs 34% (95% CI, 27-43), respectively (HR, 1.15 [95% CI, 0.83-1.61]; $p = 0.40$; Figure 1D and Table 3).

The median OS was 9 months (95% CI, 6-NR) in tiNHL cohort and 11 months (95% CI, 8-NR) in *de novo* DLBCL cohort, with 12-month OS of 38% (95% CI, 26-55) vs 47% (95% CI, 39-56; HR, 1.08 [95% CI, 0.73-1.60]; p = 0.71), respectively (Figure 1E and Table 3).

Patient characteristics, disease response and survival in the PSM cohort

To confirm our results and ensure the comparability of the two cohorts, we performed a PSM with 1:1 matching. After PSM incorporating variables in Table S2, the matched population (n = 148) included 74 patients in each cohort. Patient characteristics were comparable between the two cohorts (Table 1) with absolute values of the standardized mean differences (SMDs) <0.1 for majority of variables, and <0.25 for all of them (Table S2). Regarding the previous treatment lines, we considered all of them whether they were used for the indolent form or the transformed form. After matching, the main previous treatment lines were similar in both groups (Table S4).

With a best ORR (50%, [95% CI, 38-62] vs 55%, [95% CI, 43-67], p = 0.62) and a best CRR (31%, [95% CI, 21-43] vs 39%, [95% CI, 28-51], p = 0.39) in tiNHL and *de novo* DLBCL respectively, no significant difference was observed between the two cohorts, confirming the results of the original cohort (Figure 2A and Table 3).

The 12-month DOR was 38% (95% CI, 22-68) in the tiNHL cohort vs 53% (95% CI, 35-81) in the *de novo* DLBCL cohort (HR, 1.00 [95% CI, 0.29-3.45]; p > 0.99; Figure 2B and Table 3). The 12-month DOCR was 58% (95% CI, 35-95) in the tiNHL cohort vs 67% (95% CI, 45-99) in the *de novo* DLBCL (HR, 1.27 [95% CI, 0.43-3.80]; p = 0.66; estimated using an unstratified Cox regression with cluster-robust standard errors; Figure 2C).

With a median follow-up of 10.3 months in the matched population, the median PFS was 3 months (95% CI, 2-6) in the tiNHL cohort and 4 months (95% CI, 2-13) in the *de novo* DLBCL cohort, with a 12-month PFS of 25% (95% CI, 15-39) vs 35% (95% CI, 24-50), respectively (HR, 1.10 [95% CI, 0.67-1.82]; p = 0.70; Figure 2D and Table 3).

The median OS was 9 months (95% CI, 6-NR) in tiNHL cohort and 11 months (95% CI, 8-NR) in *de novo* DLBCL cohort, with a 12-month OS of 38% (95% CI, 26-55) vs 47% (95% CI, 35-63), respectively (HR, 1.11 [95% CI, 0.59-2.06]; p = 0.75; Figure 2E and Table 3).

Safety

In the original cohort (N = 240; tiNHL n = 74, *de novo* DLBCL n = 166), there was no significant difference in terms of CRS, ICANS, or infections. Twenty-six (35%) and 59 (36%) patients in the tiNHL and *de novo* DLBCL cohorts, respectively, experienced CRS of any grade (p > 0.99), and 2 (3%) and 7 (4%) patients, respectively, experienced grade ≥3 CRS, including 1 grade 5 CRS event in the *de novo* DLBCL cohort (Table 4).

Six (8%) and 20 (12%) patients in the tiNHL and *de novo* DLBCL cohorts, respectively, experienced ICANS of any grade (p = 0.50). No grade ≥3 ICANS was observed in tiNHL cohort while two patients each experienced a grade 3 and grade 4 ICANS event in the *de novo* DLBCL cohort (Table 4).

Twenty-eight (38%) patients from the tiNHL cohort and 52 (31%) from de novo DLBCL cohort experienced infections (p = 0.29). Finally, 7 (9%) and 24 (14%) patients in the tiNHL and *de novo* DLBCL cohorts, respectively, required hospitalization in an intensive care unit (p = 0.40; Table 4).

The safety profiles were also comparable in the PSM matched cohorts (Table 4).

Subgroup analyses in tiNHL cohort

Epcoritamab vs glofitamab

Within the tiNHL cohort, four separate subgroup analyses were performed. First, outcomes were evaluated according to BsAbs product: epcoritamab (n=30) vs glofitamab (n=44). No significant difference was observed in term of best ORR (50%, [95% CI, 31-69] vs 50%, [95% CI, 35-65] p > 0.99) and CRR (27%, [95% CI, 12-46] vs 34%, [95% CI, 20-50]; p = 0.61) in epcoritamab vs glofitamab cohorts, respectively (Figure S1A). Responders demonstrated similar DOR regardless of the BsAbs product (Figure S1B, C). No significant difference was observed for either PFS (12-month PFS, 27%, [95% CI, 14-50] vs 23%, [95% CI, 12-47]; HR, 1.19, [95% CI, 0.68-2.08]; p = 0.54) or OS (12-month OS, 34%, [95% CI, 18-61] vs 46%, [95% CI, 30-69]; HR, 1.06, [95% CI, 0.54-2.09]; p=0.86) as well between epcoritamab and glofitamab respectively (Figure S1D, E).

Rates of any-grade CRS were similar regardless of the BsAbs product, 40% (12/30) with epcoritamab vs 32% (14/44) with glofitamab, with 1 patient experiencing grade 3 in each group. No ICANS was observed in the epcoritamab subgroup, whereas 6 patients (14%) receiving glofitamab experienced grade 1-2 ICANS.

Exposure to prior CAR T-cell therapy

Second, we evaluated outcomes according to receipt of prior CAR T-cell therapy. Thirty-seven patients had received CAR T-cell (n=37; 50%) with a median interval of 134 days between CAR T-cell infusion and BsAbs initiation (range, 37–1111 days). No significant difference was observed in terms of ORR (54%, [95% CI, 37-71] vs 46%, [95% CI, 29-63] p = 0.64) and CRR (30%, [95% CI, 16-47] vs 32%, [95% CI, 18-50]; p > 0.99) between CAR T-cell therapy recipients and non-recipients, respectively (Figure S2A). DOR was similar regardless of prior CAR T-cell (Figure S2B, C). In addition, no significant difference was observed for either PFS (12-month PFS, 27%, [95% CI, 15-47] vs 17%, [95% CI, 6-51]; HR, 0.92 [95% CI, 0.53-1.59]; p = 0.75) or OS (12-month OS, 35%, [95% CI, 21-58] vs 40%, [95% CI, 21-76]; HR, 1.37 [95% CI,0.69-2.70]; p = 0.37) among those who

received CAR T-cells versus not, respectively (Figure S2D, E). Similarly, no difference in BsAbs-related adverse events was observed between patients with prior CAR T-cell therapy and those without.

tFL subgroup

Thirdly, we analyzed efficacy outcomes and survival specifically in tiNHL arising from FL (n = 57). ORR/CRR were 51% (95% CI, 37-64)/32% (95% CI, 20-45) (Figure S3A). In responders, the 12-month DOR was 50% (95% CI, 32–80). The 12-month DOCR was 77% (95% CI, 57–100). The 12-month PFS and OS were 26% (95% CI, 16–43) and 31% (95% CI, 18–52), respectively.

Thirty percent of patients (n = 17) experienced transformation within one year of FL diagnosis (early transformation), while 67% (n = 38) developed transformation more than one year after FL diagnosis (late transformation); time to transformation was missing for 2 patients. Among the 17 patients with early transformation, 7 achieved a response, including 4 CR and 3 PR. Of the 38 patients with late transformation, 21 achieved a response, including 13 CR and 8 PR. The best ORR and CRR were 41% (95% CI, 18–67) and 24% (95% CI, 7–50), respectively, in the early transformation group, compared with 55% (95% CI, 38–71) and 34% (95% CI, 20–51), respectively, in patients with late transformation (Figure S3A) (best ORR, p = 0.39; best CRR, p = 0.54). Responders showed comparable DOR regardless of time to transformation (Figure S3B, C). In addition, no significant difference was observed for either PFS (12-month PFS, 19%, [95% CI, 6-57] vs 28%, [95% CI, 16-51]; HR, 0.57 [95% CI, 0.29-1.13]; p = 0.11) or OS (12-month OS, 12%, [95% CI, 2-71] vs 38%, [95% CI, 22-65]; HR, 0.61 [95% CI,0.28-1.30]; p = 0.20) in case of early transformation vs late transformation (Figure S3D, E).

HGBL subgroup

Finally, among the tiNHL cohort, 15 patients had HGBL at BsAbs initiation, including 3 classified as HGBL, NOS, and 12 as HGBL with MYC and BCL2 and/or BCL6 rearrangements. ORR/CRR were 60% (95% CI, 32–84)/33% (95% CI, 12–62). Among responders, the 12-month DOR was 28% (95% CI, 9–87). The 12-month DOCR was 53% (95% CI, 21–100). The 12-month PFS and OS were 16% (95% CI, 5–55) and 38% (95% CI, 18–79), respectively.

Discussion

In this large, off-trial multicenter study through the CUBIC Consortium, we found that response and survival outcomes, in context of CD3xCD20 T-cell-engaging BsAbs, were comparable in R/R tiNHL vs R/R *de novo* DLBCL.

Seventy-four patients with tiNHL and 166 patients with *de novo* DLBCL treated with BsAbs, either epcoritamab or glofitamab were included. After a median follow-up of 11.5

months, with best ORR of 50% for tiNHL and 51% for *de novo* DLBCL and best CRR of 31% for tiNHL and 34% for *de novo* DLBCL, efficacy was comparable across cohorts. In the same way, there was no statistically significant difference in DOR (12-month DOR, 38% vs 60%), PFS (12-month PFS, 25% vs 34%) or OS (38% vs 47%) between tiNHL vs *de novo* DLBCL. After adjustment for known and measurable confounding factors influencing treatment efficacy and outcomes in LBCL, the post-PSM cohort confirmed our findings, demonstrating that BsAbs are comparable in tiNHL and *de novo* DLBCL cohorts. Although numerical differences were observed for some time-to-event endpoints, no statistically significant difference was observed before or after matching, and the overlapping 95% confidence intervals, together with the consistency of the results across analyses, support comparable outcomes between the 2 cohorts.

Our results were in keeping with clinical trial data. The best CRR/ORR (31%/50% for tiNHL and 34%/51% *de novo* DLBCL) were similar to those reported in the pivotal clinical trial NP30179 (CRR/ORR = 39%/52%) and EPCORE NHL-1 (CRR/ORR = 38.9%/63%). As observed in clinical trials, the majority (79% in tiNHL and 84% in *de novo* DLBCL) of CR were ongoing at 6 months. Furthermore, with a 12-month PFS of 25% (95% CI, 15-39) for tiNHL and 34% (95% CI, 27-43) for *de novo* DLBCL, these results were similar to those observed with epcoritamab [39.9% (95% CI, 31.8-47.8)] and glofitamab [37% (95% CI, 28-46)] in their respective phase II clinical trials[19,20,24].

In most pivotal BsAbs trials, transformed indolent non-Hodgkin lymphomas (tiNHL) have been underrepresented, and subgroup-specific outcomes have not been reported, limiting the ability to evaluate this high-risk population separately[19,20]. To our knowledge, our study is the first to specifically assess the efficacy of BsAbs in tiNHL. While recent real-world studies have reported encouraging outcomes with other immune-based therapies as CAR T-cell therapy in tiNHL, a significant proportion of patients either relapse or lack access[13–16]. These challenges underscore a persistent unmet need, particularly among patients who are ineligible for intensive therapies. In this context, BsAbs represent an attractive therapeutic option, offering an off-the-shelf, readily deliverable approach with a manageable safety profile that may enhance accessibility in routine practice[19,20,25,26]. By specifically evaluating this high-risk population, our study helps address an important gap in literature and provides preliminary evidence to inform clinical decision-making.

Importantly, BsAbs were active in tiNHL, but outcomes were comparable to those observed in *de novo* DLBCL. This contrasts prior CAR T-cell series, in which tiNHL has been associated with particularly favorable outcomes relative to *de novo* DLBCL. These observations are not necessarily discordant, as BsAbs and CAR T-cell therapy are distinct therapeutic platforms with different mechanisms of action and different dependence on the host immune milieu. In addition, tiNHL is biologically heterogeneous, and emerging data suggest that transformation is accompanied by remodeling of the tumor microenvironment, which may modulate sensitivity to T-cell-engaging therapies[27,28]. Our

findings should also be interpreted in the context of a heavily pretreated and selected population, as many patients had received multiple prior lines of therapy and half had prior CAR T-cell exposure. Together, these findings support BsAbs as an active option in tiNHL, though not necessarily more active than seen in *de novo* DLBCL.

With respect to safety, there was no difference in the percentage of patients experiencing ICANS and CRS of any grade and grade ≥3 among the two cohorts. The incidence of ICANS of any grade (8% for tiNHL vs 12% for *de novo* DLBCL) was low and in accordance with observations from clinical trials, 6.4% with epcoritamab and 8% with glofitamab[19,20,25]. The rate of CRS of any grade was slightly lower in both the tiNHL (35%) and *de novo* DLBCL (36%) cohorts compared with clinical trials, where rates were 49.7% with epcoritamab and 63% with glofitamab, potentially reflecting changes in CRS prophylaxis or reporting. Grade ≥3 CRS, 3% for tiNHL and 4% for de novo DLBCL, were low, consistent with clinical trials (2.5 % with epcoritamab and 4% with glofitamab)[19,20,25]. Our study confirms a favorable safety profile of BsAbs in this high-risk population, supporting their ease of use in practice[29].

Although our subgroup analyses within the tiNHL cohort involved smaller sample sizes, they provide additional preliminary and valuable insights that should be confirmed in larger cohorts. In our initial subgroup analysis comparing patients with tiNHL treated with epcoritamab vs glofitamab, no significant differences were observed in efficacy or survival outcomes according to the type of BsAbs. These findings are consistent with recent data in LBCL demonstrating comparable outcomes between epcoritamab and glofitamab[30].

In our second subgroup analysis, comparing patients with tiNHL previously treated with CAR T-cell therapy to those without prior exposure, response rates and outcomes were comparable between groups suggesting similar activity of BsAbs regardless of prior CAR T-cell therapy. These findings are consistent with prior reports showing BsAbs activity after CAR T-cell therapy [31,32]. However, the number of patients with tiNHL who received BsAbs following CAR T-cell therapy was limited (n = 37) and recent real-world data indicate that relapse after CAR T-cell therapy remains associated with poor outcomes in LBCL, despite frequent use of BsAb-based salvage therapy[33]. In addition, the time to relapse after CAR T-cell infusion was not available in our cohort. Recent studies have demonstrated that clinical outcomes in patients treated with BsAbs after CAR T-cell relapses are influenced by the interval between CAR T-cell infusion and disease progression, with particularly poor prognosis observed in cases of early relapse[31,34]. While further studies are needed to define the optimal sequencing of BsAbs and CAR T-cell therapy, these preliminary data support the potential activity of BsAbs after CAR T-cell failure in R/R tiNHL.

Thirdly, in tFL, the best ORR/CRR did not differ significantly between patients with early versus late transformation, suggesting that the time from FL diagnosis to transformation

might not affect response to BsAbs. However, the number of patients with early transformation (n=17) was small, and these preliminary findings warrant further investigation to clarify the impact of time to transformation on outcomes after BsAbs, particularly given that shorter time to transformation has been associated with inferior outcomes in studies conducted prior to the BsAbs era[4,5,12,35,36]. Moreover, outcomes in tFL appeared inferior to those reported in FL treated with BsAbs, further underscoring the importance of repeat biopsy at relapse or progression to identify histologic transformation and guide appropriate DLBCL-directed management [37,38].

Finally, in the exploratory subgroup of patients with a diagnosis of HGBL within the tiNHL cohort, BsAbs retained activity, although survival outcomes remained limited, consistent with the high-risk biology of this population. However, this subgroup was very small (n = 15), and these findings should therefore be interpreted with caution.

Although our study constitutes the first off-trial cohort to assess the effectiveness of BsAbs in tiNHL patients, it is subject to several limitations. The primary limitation lies in the retrospective design of this study, which we attempted to mitigate by using a rigorous comparative method, PSM, balancing all potential prognostic covariables, to validate the results comparing tiNHL vs *de novo* DLBCL from the same database. Although central pathology and response review were not performed, all participating sites were expert lymphoma centers applying contemporary international recommendations, and data collection was standardized across institutions using a common REDCap-based case report form[21,39]. The rarity of transformed indolent NHL also resulted in a limited sample size with heterogeneous histologies, which may have reduced the power of some subgroup and survival analyses. Nevertheless, this study provides one of the largest real-world comparative datasets in this setting. Finally, the median follow-up of our cohort is relatively short (11.5 months), though response rates and clinical outcomes are able to be compared to pivotal clinical trials[19,20].

In conclusion, the safety and efficacy of the CD3xCD20 T-cell-engaging BsAbs epcoritamab and glofitamab in R/R tiNHL appear comparable to those in *de novo* DLBCL and suggest that BsAbs provide an important salvage option in this challenging-to-treat population.

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	Before matching		After matching	
	tiNHL	***De novo* DLBCL**	**tiNHL**	***De novo* DLBCL**
	N = 74	N = 166	N = 74	n = 74
Age				
Median	71	71	71	71
Min; max	27; 91	23; 91	27; 91	32; 91
Sex, n (%)				
Male	47 (64)	110 (66)	47 (64)	44 (59)
Female	27 (36)	56 (34)	27 (36)	30 (41)
Race, n (%)				
Asian	4 (5)	15 (9)	4 (5)	5 (7)
Black or African American	4 (5)	10 (6)	4 (5)	4 (5)
White	57 (77)	137 (83)	57 (77)	62 (84)
Other	3 (4)	3 (2)	3 (4)	2 (3)
Missing	6 (8)	1 (1)	6 (8)	1 (1)
Ethnicity, n (%)				
Hispanic	12 (16)	20 (12)	12 (16)	12 (16)
Non-Hispanic	61 (82)	143 (86)	61 (82)	61 (82)
Missing	1 (1)	3 (2)	1 (1)	1 (1)
Bispecific product, n (%)				
Epcoritamab	30 (41)	86 (52)	30 (41)	26 (35)
Glofitamab	44 (59)	80 (48)	44 (59)	48 (65)
LDH, n (%)				
Normal	28 (38)	67 (40)	28 (38)	32 (43)
More than the upper limit	46 (62)	96 (58)	46 (62)	42 (57)
Missing	0 (0)	3 (2)	0 (0)	0 (0)
ECOG PS, n (%)				
0-1	53 (72)	101 (61)	53 (72)	54 (73)
≥ 2	12 (16)	46 (28)	12 (16)	13 (18)
Missing	9 (12)	19 (11)	9 (12)	7 (9)
B symptoms, n (%)				
No	58 (78)	128 (77)	58 (78)	61 (82)
Yes	6 (8)	17 (10)	6 (8)	6 (8)
Missing	10 (14)	21 (13)	10 (14)	7 (9)
Ann Arbor stage, n (%)				
Localized (I-II)	7 (9)	20 (12)	7 (9)	6 (8)
Disseminated (III-IV)	54 (73)	124 (75)	54 (73)	59 (80)
Missing	13 (18)	22 (13)	13 (18)	9 (12)
More than 1 extranodal site, n (%)				
No	29 (39)	67 (40)	29 (39)	29 (39)
Yes	33 (45)	74 (45)	33 (45)	36 (49)
Missing	12 (16)	25 (15)	12 (16)	9 (12)
CNS involvement, n (%)				
No	69 (93)	151 (91)	69 (93)	65 (88)
Yes	5 (7)	15 (9)	5 (7)	9 (12)
CD20 expression, n (%)				
Positive	66 (89)	148 (89)	66 (89)	70 (95)
Negative	6 (8)	3 (2)	6 (8)	1 (1)
Missing	2 (3)	15 (9)	2 (3)	3 (4)
Number of previous lines of treatment, n (%)				
Median	3	3	3	3

Min; max	1; 9	1; 9	1; 9	1; 9
1-2	26 (35)	70 (42)	26 (35)	29 (39)
3-4	26 (35)	70 (42)	26 (35)	27 (36)
> 4	22 (30)	26 (16)	22 (30)	18 (24)
Prior treatment by CAR T-cells, n (%)				
No	37 (50)	70 (42)	37 (50)	35 (47)
Yes	37 (50)	96 (58)	37 (50)	39 (53)
Prior ASCT, n (%)				
No	67 (91)	153 (92)	67 (91)	69 (93)
Yes	7 (9)	13 (8)	7 (9)	5 (7)

Table 1. Patient characteristics at bispecific initiation before and after PSM.

ASCT, Autologous Stem Cell Transplant; CAR, Chimeric Antigen Receptor; CNS, Central nervous system; DLBCL, Diffuse Large B-Cell Lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; PSM, Propensity Score Matching; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

TiNHL histology (N=74)	
Prior indolent, n (%)	
Follicular Lymphoma	57 (77)
Marginal Zone Lymphoma	8 (11)
Waldenstrom Macroglobulinemia/ Lymphoplasmacytic Lymphoma	2 (3)
Nodular Lymphocyte-Predominant Hodgkin Lymphoma	3 (4)
Low grade B-cell Lymphoma NOS	4 (5)
Diagnosis at bispecific initiation	
DLBCL NOS	57 (77)
High-grade B-cell Lymphoma	15 (20)
T-cell/Histiocyte rich LBCL	2 (3)

Table 2. tiNHL cohort histology.

DLBCL, Diffuse Large B-Cell Lymphoma; LBCL, Large B-Cell Lymphoma; NOS, Not Otherwise Specified; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

	Before matching			After matching		
	tiNHL	***De novo* DLBCL**	***P* value**	**tiNHL**	***De novo* DLBCL**	***P* value**
	N = 74	N = 166		N = 74	n = 74	
Response						
ORR (95% CI), %	50 (38-62)	51 (43-58)	> 0.99	50 (38-62)	55 (43-67)	0.62
CRR (95% CI), %	31 (21-43)	34 (27-42)	0.66	31 (21-43)	39 (28-51)	0.39
DOR at 12 months (95% CI), %	38 (22-68)	60 (48-74)	0.49	38 (22-68)	53 (35-81)	> 0.99
HR (95% CI)	1.24 (0.67-2.29)	1 (reference)		1.00 (0.29-3.45)	1 (reference)	
Survival						
PFS at 12 months (95% CI), %	25 (15-39)	34 (27-43)	0.40	25 (15-39)	35 (24-50)	0.70
HR (95% CI)	1.15 (0.83-1.61)	1 (reference)		1.10 (0.67-1.82)	1 (reference)	
OS at 12 months (95% CI), %	38 (26-55)	47 (39-56)	0.71	38 (26-55)	47 (35-63)	0.75
HR (95% CI)	1.08 (0.73-1.60)	1 (reference)		1.11 (0.59-2.06)	1 (reference)	

Table 3. Response outcomes and survival according to the histology before and after PSM.

CI, confidence interval; CRR, Complete Response Rate; DLBCL, Diffuse Large B-Cell Lymphoma; DOR, Duration Of Response; HR, Hazard Ratio; ORR, Overall Response Rate; OS, Overall Survival; PFS, Progression Free Survival; PSM, Propensity Score Matching; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

	Before matching			After matching		
	tiNHL	***De novo* DLBCL**	***P* value**	**tiNHL**	***De novo* DLBCL**	***P* value**
	N = 74	N = 166		N = 74	n = 74	
CRS, n (%)						
Any grade	26 (35)	59 (36)	> 0.99	26 (35)	30 (41)	0.61
Grade 1	14 (19)	38 (23)	0.71	14 (19)	20 (27)	0.40
Grade 2	10 (14)	14 (8)		10 (14)	6 (8)	
Grade 3	2 (3)	5 (3)		2 (3)	2 (3)	
Grade 4	0	1 (1)		0	1 (1)	
Grade 5	0	1 (1)		0	1 (1)	
ICANS, n (%)						
Any grade	6 (8)	20 (12)	0.50	6 (8)	9 (12)	0.59
Grade 1	3 (4)	9 (5)	> 0.99	3 (4)	5 (7)	0.08
Grade 2	3 (4)	6 (4)		3 (4)	0	
Grade 3	0	2 (1)		0	2 (3)	
Grade 4	0	2 (1)		0	2 (3)	
Grade 5	0	0		0	0	
Grade missing	0	1		0	0	
Any infections, n (%)	28 (38)	52 (31)	0.29	28 (38)	19 (26)	0.08
Any ICU stay, n (%)	7 (9)	24 (14)	0.40	7 (9)	10 (14)	0.61

Table 4. Toxicities after Bispecific before and after PSM.

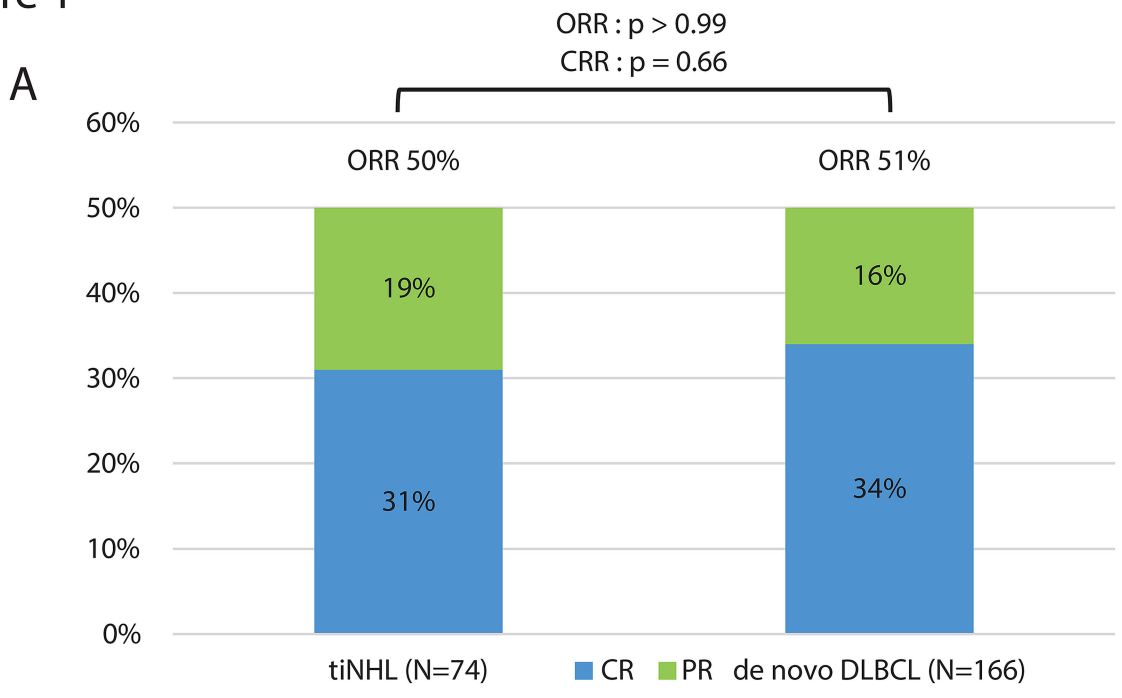
Toxicities were graded according to the consensus grading from the American Society for Transplantation and Cellular Therapy for CRS and ICANS. Missing data by cohort and toxicity ranged from 0% to 9%. CTCAE, Common Terminology Criteria for Adverse Events; CRS, Cytokine Release Syndrome; DLBCL, Diffuse Large B-Cell Lymphoma; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome; ICU, Intensive Care Unit; PSM, Propensity Score Matching; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

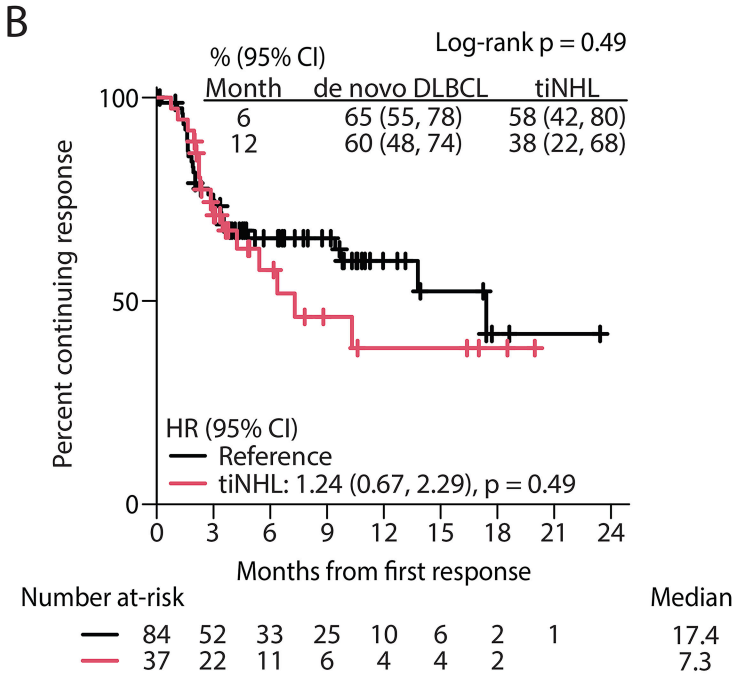
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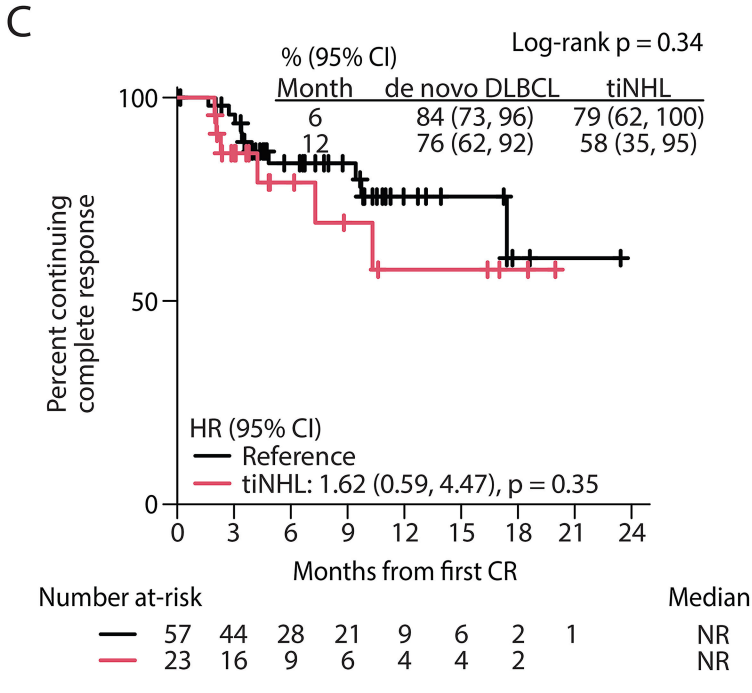
Figure 1. Efficacy and outcomes in the original cohort according to histology. (A) Best response rate. (B) Duration of overall response. (C) Duration of complete response. (D) Progression-free survival. (E) Overall survival. BsAbs, Bispecific Antibodies; CR, Complete Response; CRR, Complete Response Rate; DLBCL, Diffuse Large B-Cell Lymphoma; HR, Hazard Ratio; ORR, Overall Response Rate; PR, Partial Response; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

Figure 2. Efficacy and outcomes in the 1:1 post-PSM cohort according to histology. (A) Best response rate. (B) Duration of overall response. (C) Duration of complete response. (D) Progression-free survival. (E) Overall survival. For panel C, HR for duration of complete response was estimated using an unstratified Cox regression with cluster-robust standard errors. BsAbs, Bispecific Antibodies; CR, Complete Response; CRR, Complete Response Rate; DLBCL, Diffuse Large B-Cell Lymphoma; HR, Hazard Ratio; ORR, Overall Response Rate; PR, Partial Response; PSM, Propensity Score Matching; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

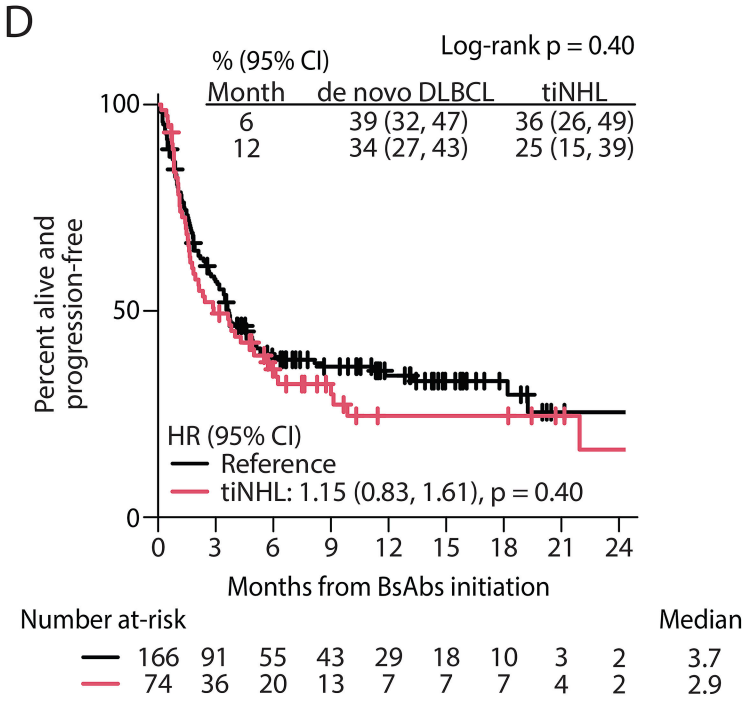
Figure 1


A
ORR : p > 0.99
CRR : p = 0.66
60%
50%
40%
30%
20%
10%
0%
ORR 50%
ORR 51%
19%
31%
16%
34%
tiNHL (N=74)
CR
PR
de novo DLBCL (N=166)


B
Log-rank p = 0.49
% (95% CI)
Month de novo DLBCL tiNHL
6 65 (55, 78) 58 (42, 80)
12 60 (48, 74) 38 (22, 68)
Percent continuing response
100
50
0
HR (95% CI)
Reference
tiNHL: 1.24 (0.67, 2.29), p = 0.49
0 3 6 9 12 15 18 21 24
Months from first response
Number at-risk
84 52 33 25 10 6 2 1
37 22 11 6 4 4 2
Median
17.4
7.3


C
Log-rank p = 0.34
% (95% CI)
Month de novo DLBCL tiNHL
6 84 (73, 96) 79 (62, 100)
12 76 (62, 92) 58 (35, 95)
Percent continuing complete response
100
50
0
HR (95% CI)
Reference
tiNHL: 1.62 (0.59, 4.47), p = 0.35
0 3 6 9 12 15 18 21 24
Months from first CR
Number at-risk
57 44 28 21 9 6 2 1
23 16 9 6 4 4 2
Median
NR
NR


de novo DLBCL
tiNHL


D
Log-rank p = 0.40
% (95% CI)
Month de novo DLBCL tiNHL
6 39 (32, 47) 36 (26, 49)
12 34 (27, 43) 25 (15, 39)
Percent alive and progression-free
100
50
0
HR (95% CI)
Reference
tiNHL: 1.15 (0.83, 1.61), p = 0.40
0 3 6 9 12 15 18 21 24
Months from BsAbs initiation
Number at-risk
166 91 55 43 29 18 10 3 2
74 36 20 13 7 7 7 4 2
Median
3.7
2.9

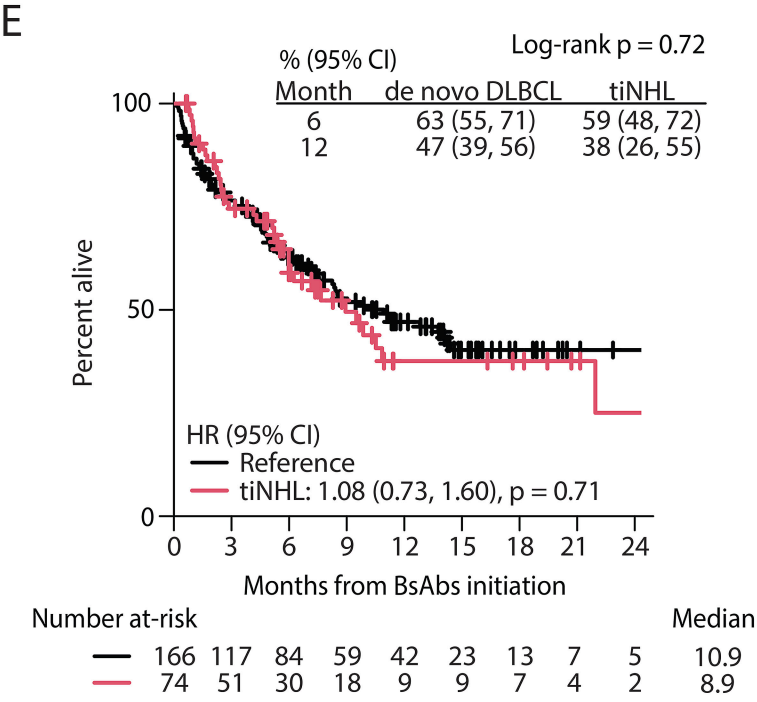
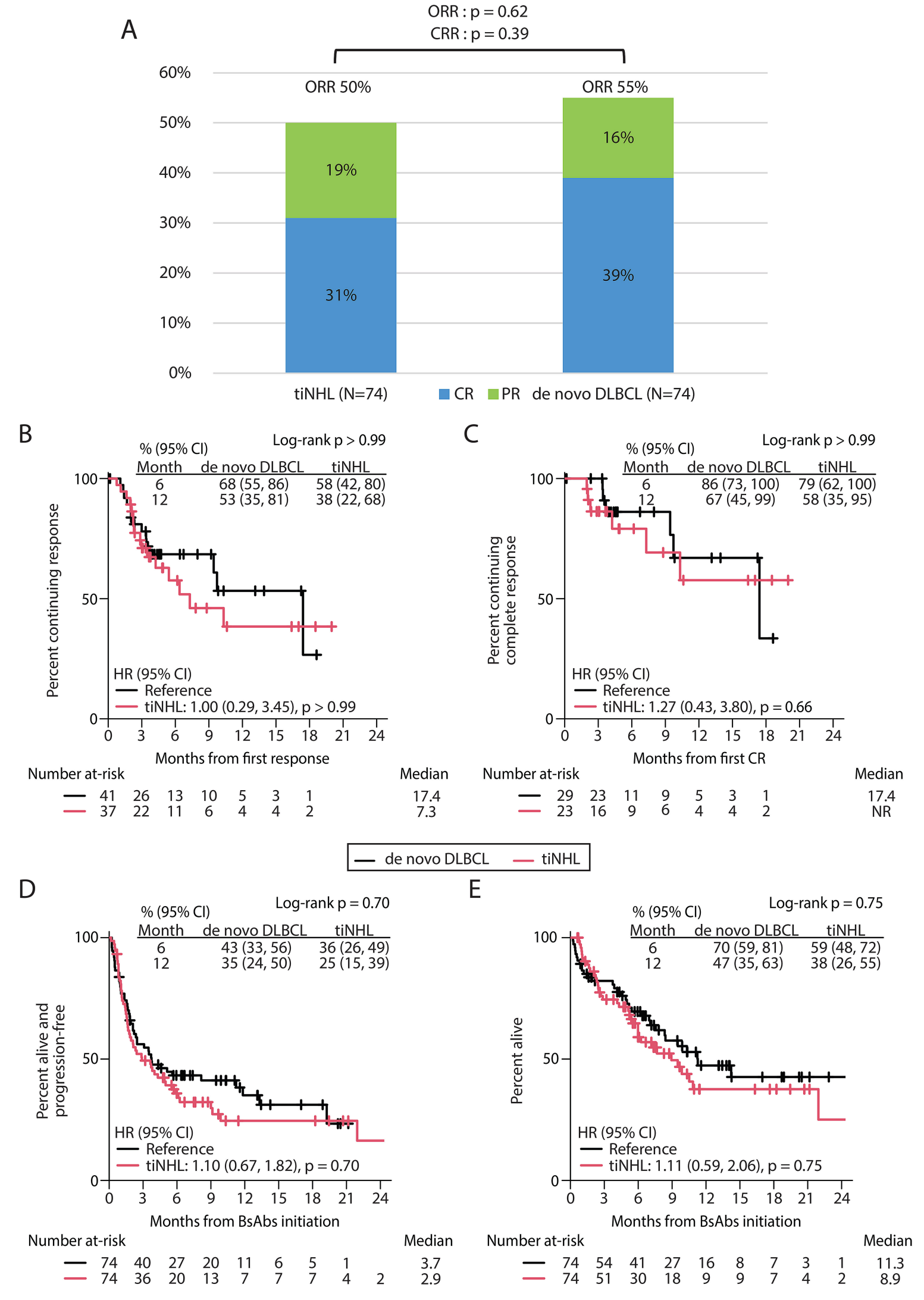

E
Log-rank p = 0.72
% (95% CI)
Month de novo DLBCL tiNHL
6 63 (55, 71) 59 (48, 72)
12 47 (39, 56) 38 (26, 55)
Percent alive
100
50
0
HR (95% CI)
Reference
tiNHL: 1.08 (0.73, 1.60), p = 0.71
0 3 6 9 12 15 18 21 24
Months from BsAbs initiation
Number at-risk
166 117 84 59 42 23 13 7 5
74 51 30 18 9 9 7 4 2
Median
10.9
8.9

Figure 2


A
ORR : p = 0.62
CRR : p = 0.39
60%
50%
40%
30%
20%
10%
0%
ORR 50%
ORR 55%
19%
31%
16%
39%
tiNHL (N=74)
CR
PR
de novo DLBCL (N=74)
B
Log-rank p > 0.99
% (95% CI)
Month de novo DLBCL tiNHL
6 68 (55, 86) 58 (42, 80)
12 53 (35, 81) 38 (22, 68)
Percent continuing response
HR (95% CI)
Reference
tiNHL: 1.00 (0.29, 3.45), p > 0.99
Months from first response
Number at-risk
41 26 13 10 5 3 1
37 22 11 6 4 4 2
Median
17.4
7.3
C
Log-rank p > 0.99
% (95% CI)
Month de novo DLBCL tiNHL
6 86 (73, 100) 79 (62, 100)
12 67 (45, 99) 58 (35, 95)
Percent continuing complete response
HR (95% CI)
Reference
tiNHL: 1.27 (0.43, 3.80), p = 0.66
Months from first CR
Number at-risk
29 23 11 9 5 3 1
23 16 9 6 4 4 2
Median
17.4
NR
de novo DLBCL
tiNHL
D
Log-rank p = 0.70
% (95% CI)
Month de novo DLBCL tiNHL
6 43 (33, 56) 36 (26, 49)
12 35 (24, 50) 25 (15, 39)
Percent alive and progression-free
HR (95% CI)
Reference
tiNHL: 1.10 (0.67, 1.82), p = 0.70
Months from BsAbs initiation
Number at-risk
74 40 27 20 11 6 5 1
74 36 20 13 7 7 7 4 2
Median
3.7
2.9
E
Log-rank p = 0.75
% (95% CI)
Month de novo DLBCL tiNHL
6 70 (59, 81) 59 (48, 72)
12 47 (35, 63) 38 (26, 55)
Percent alive
HR (95% CI)
Reference
tiNHL: 1.11 (0.59, 2.06), p = 0.75
Months from BsAbs initiation
Number at-risk
74 54 41 27 16 8 7 3 1
74 51 30 18 9 9 7 4 2
Median
11.3
8.9

Participating center
Dana-Farber Cancer Institute, Boston, MA, USA
MD Anderson Cancer Center, Houston, TX, USA
City of Hope, Duarte, CA, USA
Huntsman Cancer Institute, Salt Lake City, UT, USA
Fred and Pamela Buffett Cancer Center at the University of Nebraska Medical Center, Omaha, NE, USA
Memorial Sloan Kettering Cancer Center, New York, NY, USA
Ohio State University Wexner Medical Center, Columbus, OH, USA
Vanderbilt University Medical Center, Nashville, TN, USA
University of Colorado Cancer Center, Aurora, CO, USA

Supplemental table 1. CUBIC academic centers participating in the retrospective study.

Variable at time of BsAbs initiation	Unmatched	Matched
Age (continuous)	0.088	0.055
Sex (categorical)		
Sex female	0.057	-0.084
Sex male	-0.057	0.084
Race (categorical)		
Asian	-0.161	-0.060
Black or African American	-0.027	0.000
White	-0.131	-0.161
Other	0.114	0.069
NA	0.275	0.248
Ethnicity (categorical)		
Hispanic	0.113	0.000
Non-Hispanic	-0.098	0.000
NA	-0.039	0.000
Number of prior lines* (continuous)	0.310	0.184
Prior treatment by CAR T-cells (categorical)		
No	0.157	0.054
Yes	-0.157	-0.054
Prior ASCT (categorical)		
No	-0.056	-0.092
Yes	0.056	0.092
PS ECOG (categorical)		
0-1	0.239	-0.030
≥ 2	-0.312	-0.037
NA	0.022	0.083
B symptoms (categorical)		
No	0.031	-0.098
Yes	-0.078	0.000
NA	0.025	0.119
Ann Arbor stage (categorical)		
I-II	-0.088	0.046
III-IV	-0.039	-0.152
NA	0.113	0.142
CNS involvement (categorical)		
No	0.091	0.215
Yes	-0.091	-0.215
More than 1 extranodal site (categorical)		
No	-0.024	0.000
Yes	0.000	-0.082
NA	0.031	0.110
LDH (categorical)		
Normal	-0.052	-0.111
More than the upper limit	0.089	0.111
NA	-0.163	0.000
Bispecific product (categorical)		
Epcoritamab	-0.229	0.110
Glofitamab	0.229	-0.110
Year of Bispecific treatment initiation (categorical)		
2023	-0.193	0.059
2024	-0.109	-0.217
2025	0.326	0.186

**For tiNHL cohort number of prior line included both for treatment of indolent and transformed disease.*

Supplemental table 2. SMD before matching and after matching for the variable used for PSM.

ASCT, Autologous Stem Cell Transplant; CAR, Chimeric Antigen Receptor; CNS, Central Nervous System; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase; NA, Not Available; PS, Performance Status; PSM, Propensity Score Matching; SMD, Standardized Mean Difference.

		tiNHL (n)	*De novo* DLBCL (n)
Pre-BsAbs bridging therapy (1–2 cycles)	CHOP Like regimen	1	1
	Platinum-based regimen +/- Rituximab	1	1
	Polatuzumab +/- Rituximab		2
	High-dose cytarabine-based regimen +/- Rituximab		2
	Other chemotherapy regimen		1
Association to BsAbs	Lenalidomide	2	2
	GemOx (according to STARGLO)	10	6
	Acalabrutinib	1	5
	Pembrolizumab	1	1
	Polatuzumab	1	1
	Single dose of rituximab during BsAbs (for elevated EBV)		1
	Single dose of loncastuximab tesirine during BsAbs		1

Supplemental table 3. Systemic Therapies Administered Before, Concurrently With, or After BsAbs Treatment (Excluding Obinutuzumab with Glofitamab) in the original cohort.

BsAbs, Bispecific Antibodies; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL, Diffuse Large B-Cell Lymphoma; EBV, Epstein-Barr Virus; GemOx, gemcitabine and oxaliplatin; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

	tiNHL n=74	*De novo* DLBCL n=74
RITUXIMAB or OBINUTUZUMAB, n (%)		
Never used	0	0
Used in at least 1 line	74 (100)	74 (100)
Major chemotherapy systemic regimen, n (%)		
CHOP Like regimen		
Never used	4 (5)	0
Used for at least 1 line	70 (95)	74 (100)
Platinum-based regimen		
Never used	46 (62)	42 (57)
Used for at least 1 line	28 (38)	32 (43)
Platinum + cytarabine-based regimen		
Never used	71 (96)	67 (91)
Used for at least 1 line	3 (4)	7 (9)
Cytarabine-based regimen		
Never used	67 (91)	62 (84)
Used for at least 1 line	7 (9)	12 (16)
Bendamustine-based regimen		
Never used	50 (68)	61 (82)
Used for at least 1 line	24 (32)	13 (18)
Lenalidomide, n (%)		
Never used	61 (82)	62 (84)
Used for at least 1 line	13 (18)	12 (16)
Polatuzumab, n (%)		
Never used	46 (62)	37 (50)
Used for at least 1 line	28 (38)	37 (50)
Tafasitamab, n (%)		
Never used	67 (91)	64 (86)
Used for at least 1 line	7 (9)	10 (14)
Radiotherapy, n (%)		
Never used	45 (61)	40 (54)
Used for at least 1 line	29 (39)	34 (46)
Prior Autologous stem cells transplantation, n (%)		
No	67 (91)	69 (93)
Yes	7 (9)	5 (7)
Prior CAR T-cells therapy, n (%)		
No	37 (50)	35 (47)
Yes	37 (50)	39 (53)
CAR T-cells products, n (%)		
Axicabtagene ciloleucel	16 (43)	16 (41)
Lisocabtagene maraleucel	13 (35)	17 (44)
Tisagenlecleucel	3 (8)	1 (3)
CAR product on clinical trial	5 (14)	5 (13)

Missing data for treatment regimen by cohort and line of therapy ranged from 0% to 5%.
Percentages for CAR T-cell products were calculated among patients who received prior CAR T-cells therapy.

Supplemental table 4. Main prior treatment exposure after matching.

BsAbs, Bispecific Antibodies; CAR, Chimeric Antigen Receptor; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL, Diffuse Large B-Cell Lymphoma; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

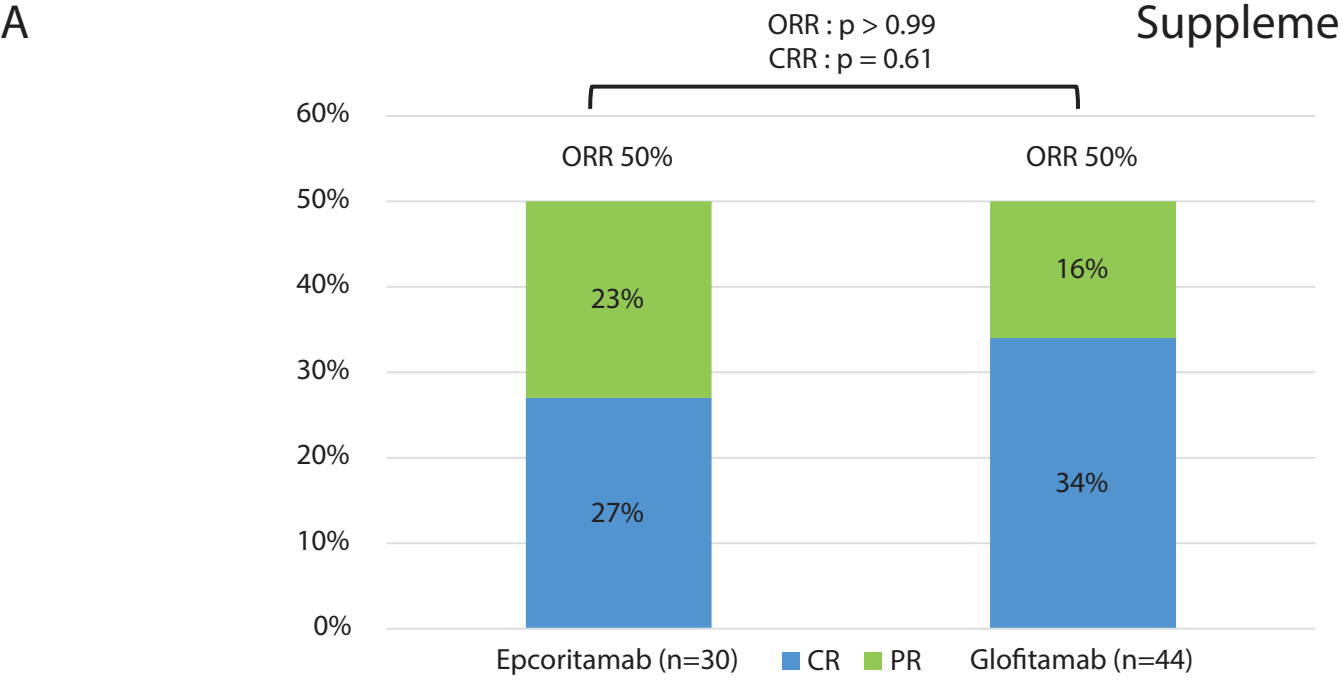
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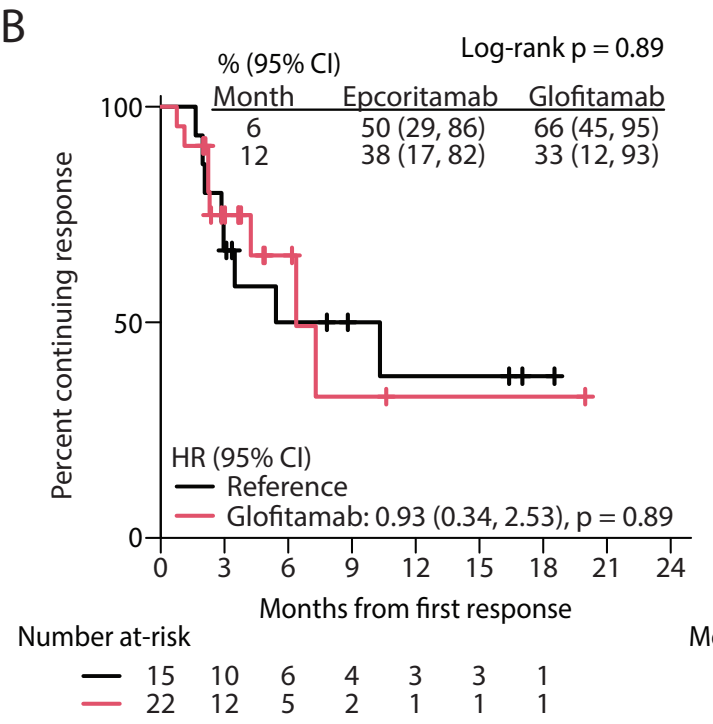
Supplemental figure 1. Efficacy and outcomes in tiNHL cohort according to BsAb product. (A) Best response rate. (B) Duration of overall response. (C) Duration of complete response. (D) Progression free survival. (E) Overall survival. BsAbs, Bispecific Antibodies; CR, Complete Response; CRR, Complete Response Rate; HR, Hazard Ratio; ORR, Overall Response Rate; PR, Partial Response; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

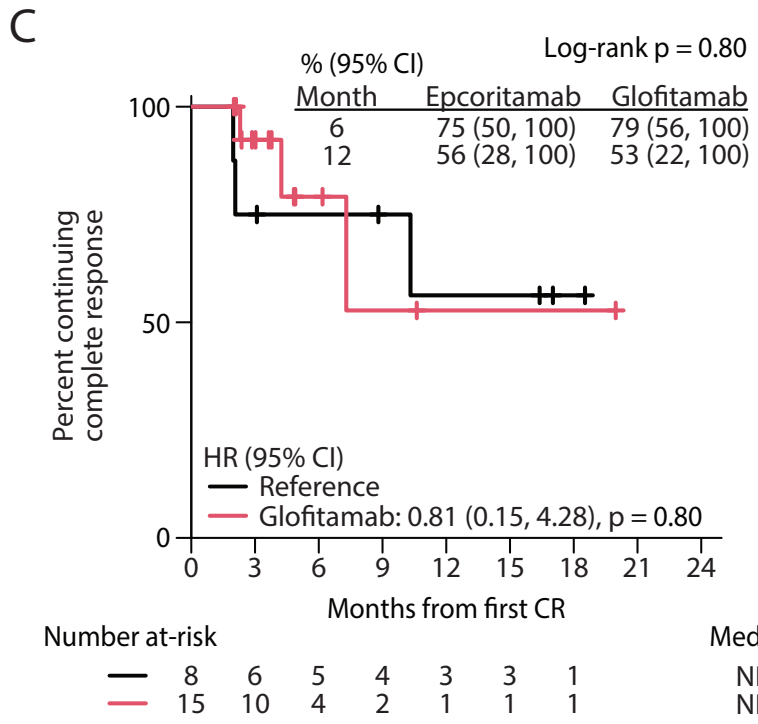
Supplemental figure 2. Efficacy and outcomes in tiNHL cohort according to prior CAR T-cell therapy. (A) Best response rate. (B) Duration of overall response. (C) Duration of complete response. (D) Progression free survival. (E) Overall survival. BsAbs, Bispecific Antibodies; CAR, Chimeric Antigen Receptor; CR, Complete Response; CRR, Complete Response Rate; HR, Hazard Ratio; ORR, Overall Response Rate; PR, Partial Response; tiNHL, Transformed Indolent Non-Hodgkin Lymphoma.

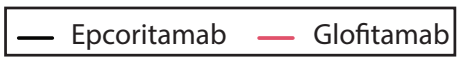
Supplemental figure 3. Efficacy and outcomes in tFL cohort according to time to transformation. (A) Best response rate. (B) Duration of overall response. (C) Duration of complete response. (D) Progression free survival. (E) Overall survival. BsAbs, Bispecific Antibodies; CR, Complete Response; CRR, Complete Response Rate; HR, Hazard Ratio; ORR, Overall Response Rate; PR, Partial Response; tFL, Transformed Follicular Lymphoma.

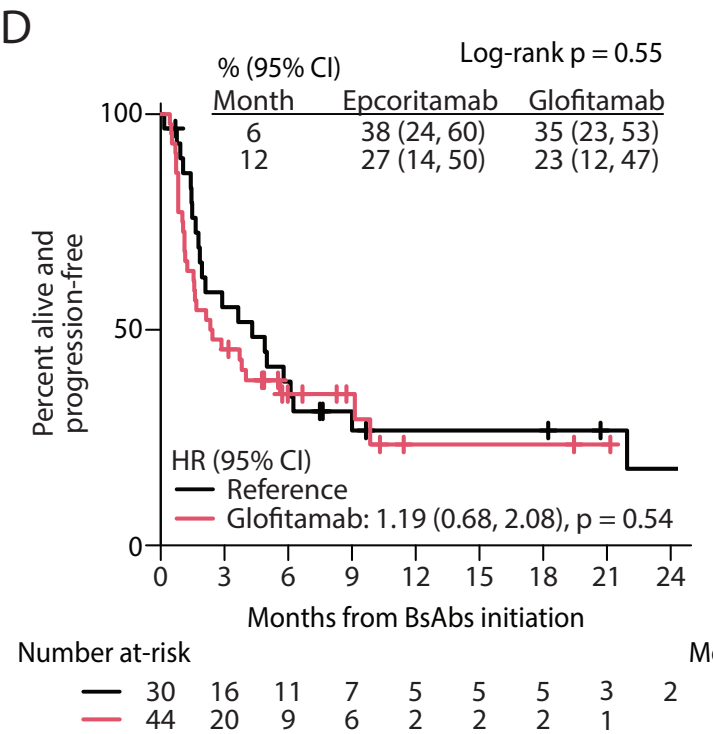
Supplemental Figure 1

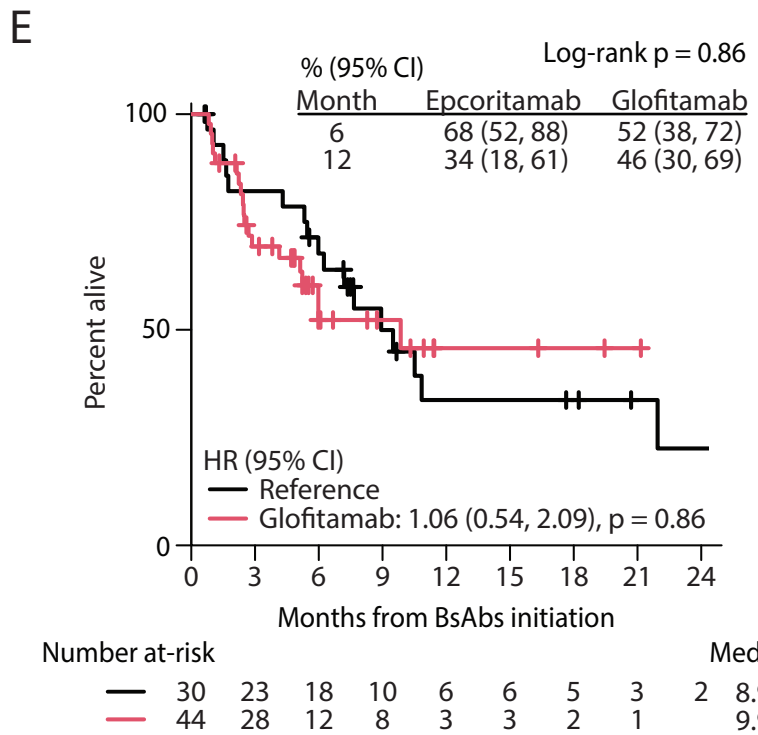




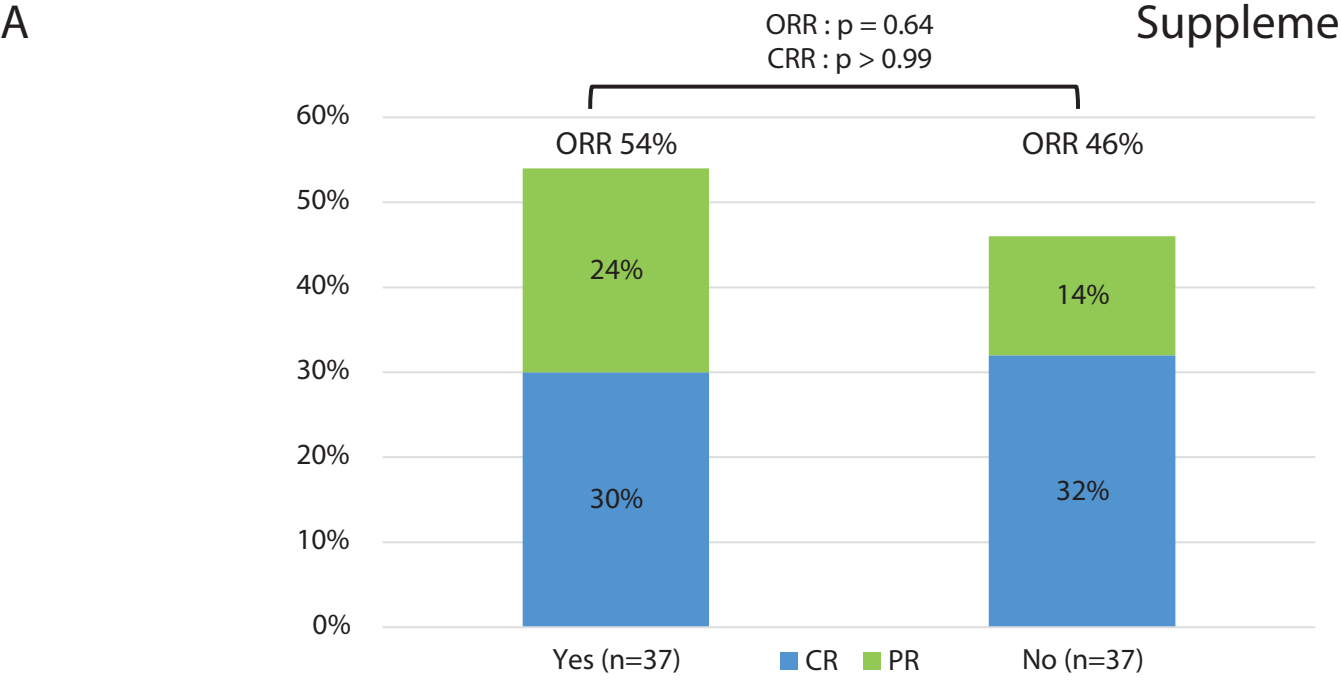


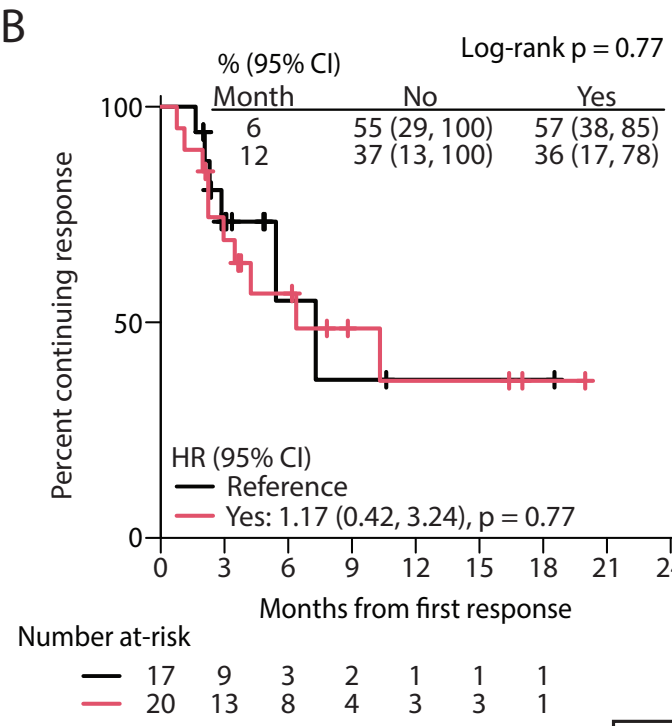


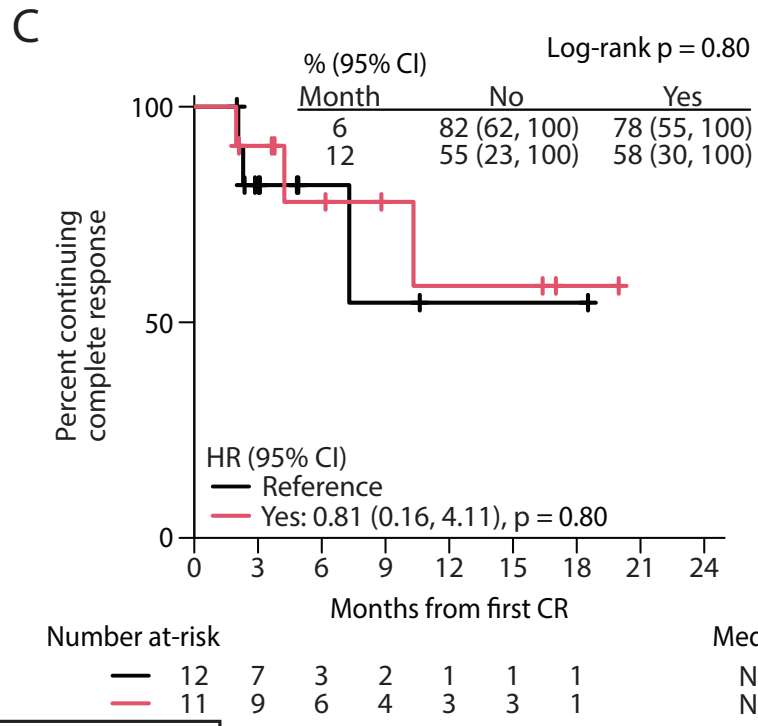


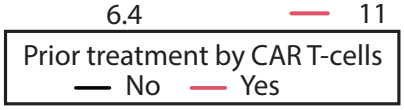


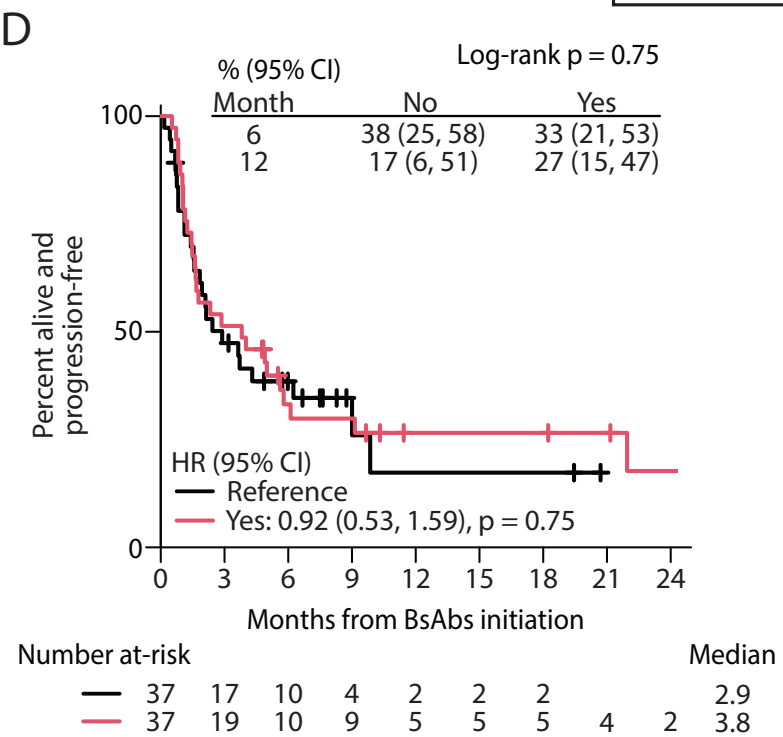
Supplemental Figure 2

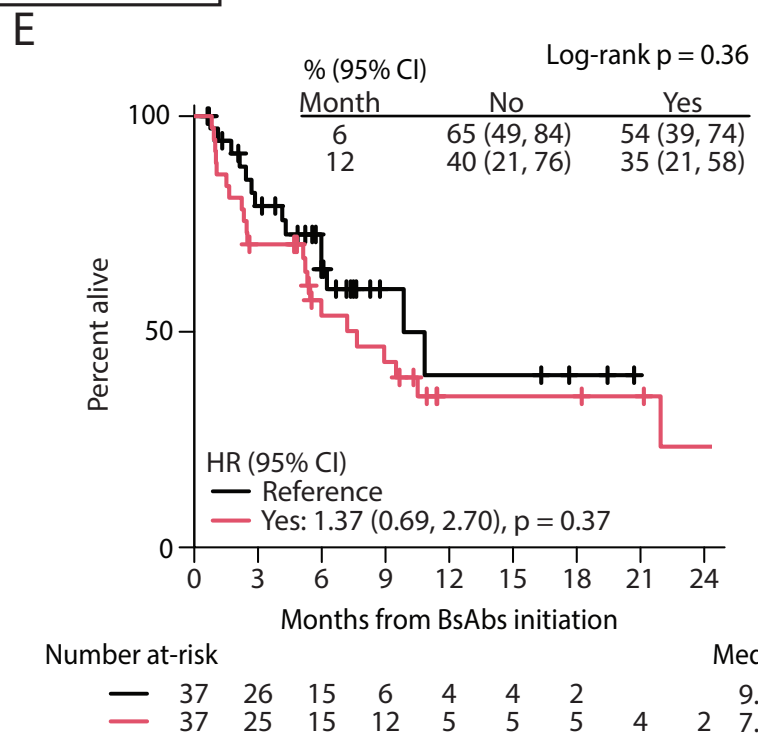












Supplemental Figure 3

