REGULAR ARTICLE

blood advances

Allogeneic HCT as consolidation in B-cell lymphomas after exposure to bispecific antibodies: a GETH-TC study

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Key Points

- BsAb exposure does not compromise the safety or efficacy of alloHCT in patients with R/R B-NHL.
- BsAb use before alloHCT is associated with fewer relapses, possibly because of deeper pretransplant response.

Bispecific antibodies (BsAb) targeting CD20 and CD3 have shown efficacy for relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL), but their impact on outcomes following allogeneic hematopoietic cell transplantation (alloHCT) remains unclear. In this international, retrospective study, we compared outcomes of adult patients with R/R B-NHL undergoing first alloHCT after BsAb exposure (n = 47) versus a historical BsAb-naïve cohort (n = 101). Baseline imbalances were addressed using inverse probability of treatment weighting (IPTW) and propensity score matching (PSM). The primary end point was nonrelapse mortality (NRM); secondary end points included overall survival (OS), progression-free survival (PFS), cumulative incidence of relapse (CIR), graft-versus-host disease (GVHD), engraftment, and GVHD/relapse-free survival (GRFS). In the overall cohort, 2-year NRM did not differ significantly between BsAb-exposed and BsAb-naïve groups (IPTW: 29.1% vs 31.4%, $P = 0.80$; PSM: 35.8% vs. 27.9%, $P = 0.43$). CIR was significantly lower in BsAb-exposed patients after IPTW (7.4% vs 20.0%, $P = 0.01$), but not in PSM (9.5% vs 23.4%, $P = 0.06$). OS, GVHD, GRFS, and engraftment were comparable. In a

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The data sets generated and/or analyzed during the current study are available from the corresponding author, Alberto Mussetti (amussetti@iconcologia.net), on reasonable request.

The full-text version of this article contains a data supplement.

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prespecified subanalysis limited to large B-cell lymphomas, CIR differences were consistent across IPTW (6.1% vs 21.1%, $P = 0.01$) and PSM (9.2% vs 33.3%, $P = 0.03$), reinforcing a potential benefit of prior BsAb therapy. A significant improvement in PFS was observed in this subgroup with IPTW (55.5% vs 36.6%; $P = 0.04$), but not in PSM ($P = 0.20$). Prior BsAb exposure does not adversely impact alloHCT safety and may be associated with improved disease control. Prospective studies are warranted to define optimal sequencing in this high-risk population.

Introduction

The advent of immunotherapies has revolutionized the therapeutic landscape for B-cell non-Hodgkin lymphomas (B-NHL), providing innovative strategies to improve outcomes in patients with relapsed or refractory (R/R) disease. Bispecific antibodies (BsAbs), which simultaneously target tumor-associated antigens (eg, CD20) and T-cell activation markers (eg, CD3), represent an emerging modality in immunotherapy,[1-5] particularly following failure of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy. These off-the-shelf therapies offer rapid availability and are therefore particularly suitable for patients with high-risk or rapidly progressive disease. BsAbs have demonstrated remarkable single-agent activity by inducing T-cell mediated cytotoxicity against malignant B cells while maintaining a manageable safety profile.[6] Characteristic toxicities include cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome; however, these typically present with low-grade severity. Despite promising responses rates, 60% to 80% of patients who are treated with BsAbs ultimately relapse, highlighting the need for consolidation strategies to improve the long-term outcomes.[7]

Historically, allogeneic hematopoietic cell transplantation (alloHCT) has been reserved for patients with R/R B-NHL as the last and only potentially curative option, largely because of its intrinsic high risk for nonrelapse mortality (NRM).[8,9] The use of immunotherapies before alloHCT already has been shown to impact the transplant outcomes in other settings as demonstrated with checkpoint inhibitors in Hodgkin lymphoma.[10] However, whether BsAbs affect the transplant outcomes remains unknown, because no robust clinical data are currently available on their use before alloHCT.

This study aimed to evaluate the clinical outcomes of alloHCT in patients who were treated with BsAbs with a focus on transplant-related toxicities, response durability, and survival.

Methods

We conducted a retrospective, international, multicenter study on adult patients (≥18 years old) who were diagnosed with R/R B-NHL and who underwent a first alloHCT after exposure to CD3-CD20 BsAbs (BsAb-exposed group), either in monotherapy or in combination, between January 2018 and July 2023. A historic cohort of patients with B-NHL who were allografted between February 2016 and October 2020 and who were not previously exposed to BsAbs before alloHCT (BsAb-naïve group) from the Grupo Español de Trasplante Hematopoyético y Terapia Celular (GETH-TC) registry was used as control group. The study was coordinated by the GETH-TC collaborative group.

Objectives and end points definition

The primary outcome was NRM, defined as death from any cause without previous disease relapse or progression. Secondary outcomes included overall survival (OS), defined as the time from alloHCT infusion to death from any cause; progression-free survival (PFS), defined as the time from alloHCT infusion to either disease relapse, progression, or death from any cause; and cumulative incidence of relapse (CIR), defined as the occurrence of disease relapse or progression after alloHCT. Additional secondary end points included the incidence of acute and chronic graft-versus-host disease (GVHD), defined according to established criteria for acute GVHD[11] and chronic GVHD.[12] Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count of $\geq 0.5 \times 10^9$/L, and platelet engraftment was defined as the first of 3 consecutive days with a platelet count of $\geq 20 \times 10^9$/L without platelet transfusion for 7 consecutive days. For neutrophil and platelet recovery, death without the event was considered a competing risk. GVHD-free/relapse-free survival (GRFS) was also evaluated as a composite end point and was defined as the time from alloHCT to the first event of grade 3 to 4 acute GVHD, moderate-to-severe chronic GVHD, disease relapse, or death from any cause.[13]

Statistical analysis

A descriptive analysis was conducted to characterize the baseline variables in both the BsAb-exposed and the BsAb-naïve alloHCT cohorts. Categorical variables related to patient demographics, disease characteristics, and transplant details were reported as frequencies and percentages. Continuous variables were described using medians, ranges, and interquartile ranges. Group comparisons at baseline were performed using the Pearson χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The median follow-up time was estimated using the reverse Kaplan-Meier method, censoring patients at their last known follow-up date if alive.

The OS, PFS, and GVHD/relapse-free survival (GRFS) rates were estimated using the Kaplan-Meier curves and compared between groups using the long-rank test. Hazard ratios were calculated using Cox proportional hazards models.

For outcomes subject to competing risks, such as NRM, CIR, and acute and chronic GVHD, cumulative incidence functions were used. In this context, a competing risk was defined as an event that precluded the occurrence of the event of interest. For example, in the analysis of CIR, death without relapse was treated as a

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competing event. In the analysis of NRM, relapse was considered a competing risk. In the GVHD analyses, both relapse and death were treated as competing events. Comparisons of the cumulative incidence curves between groups were performed using the Fine and Gray subdistribution hazard model, which enable the direct modeling of covariate effects on the cumulative incidence function while accounting for competing risks.

To account for potential baseline imbalances between the BsAb-exposed and BsAb-naïve cohorts, 2 adjustments strategies were applied. First, inverse probability of treatment weighting (IPTW) was implemented using the average treatment effect on the treated approach to derive weights. Second, 1:1 propensity score matching (PSM) was conducted as a sensitivity analysis (supplemental Table 1).[14,15] Both methods adjusted for key prognostic covariates, including age, sex, number of previous therapy lines, disease status, conditioning intensity, HCT-specific comorbidity index, donor type, and Eastern Cooperative Oncology Group performance status. Although neither method achieved a perfect balance, IPTW reduced the most absolute standardized mean differences to below the conventional threshold of 0.1, indicating adequate covariate adjustment. PSM also improved the balance when compared with the unadjusted analysis; however, some residual imbalances persisted (supplemental Figure 1). Therefore, the results from both adjusted analyses are presented to provide robust and complementary estimates of the treatment effect. These methods were preferred over conventional multivariable models to ensure covariate balance before outcome analysis. Missing data for variables included in the IPTW model were assumed to be missing completely at random and were imputed using the multivariate imputation by chained equations method. This approach enabled the inclusion of all available cases and reduced potential bias from complete case analysis.[16] All statistical analyses were conducted using R software, version 4.2.2.

The study was approved by the ethics committee of the Bellvitge University Hospital (EOM035/22) and conducted in accordance with the Declaration of Helsinki.

Results

Clinical characteristics of the patient population

A total of 148 patients with B-NHL who underwent their first alloHCT were included in this study. The baseline characteristics for all infused patients are summarized in Table 1. Patients were categorized into 2 groups, namely the BsAb-exposed cohort (n = 47; 31.8%) and the BsAb-naïve cohort (n = 101; 68.2%).

Patients in the BsAb-exposed cohort were older (median age, 59 vs 52 years; $P < .001$), had a higher prevalence of certain lymphoma subtypes, particularly follicular lymphoma (FL; 30% vs 0%; $P < .001$), and were more likely to present with advanced stage disease at diagnosis (stage III-IV: 91% vs 74%; $P = .013$) when compared with the BsAb-naïve group. A greater proportion of BsAb-exposed patients had received more than 4 lines of therapy before alloHCT (45% vs 15%; $P < .001$), had a poorer performance status at the time of the transplant (Eastern Cooperative Oncology Group status $\geq$1: 55.3% vs 31.7%; $P = .007$), and were less likely to have undergone a previous autologous stem cell transplantation (25.5% vs 64.4%; $P < .001$). Notably, BsAb therapy was the last line of therapy in 85% of BsAb-exposed patients; the remaining 15% received additional therapy before alloHCT. Moreover, none of the BsAb-naïve patients had previously received CAR T-cell therapy, whereas 43% of those in the BsAb-exposed cohort had. The pretransplant remission status differed between the cohorts with a higher proportion of patients in complete response (CR) at alloHCT in the BsAb-exposed group (78.7%) than in the BsAb-naïve group (63.4%), whereas partial response was more frequent among the controls (28.7% vs 14.9%).

Most patients in both groups received reduced-intensity conditioning regimens. However, BsAb-exposed patients were more likely to receive grafts from matched unrelated donors, whereas matched related donors were more common in the BsAb-naïve group. Posttransplant cyclophosphamide (PTCy) for GVHD prophylaxis was also more frequently used in the BsAb-exposed group (72.3% vs 42.6%; $P < .001$). In the BsAb-exposed cohort, the median interval from the last dose of BsAb to alloHCT was 42 days (range, 13-421) with a median of 12 doses administered (range, 4-24). Additional characteristics related to the BsAb therapy are summarized in Table 2. In the overall cohort, the median follow-up among survivors was 36.1 months (95% confidence interval [CI], 25.2-49.6). Specifically, the median follow-up was 22.3 months (95% CI, 11.3-33.0) for the BsAb-exposed group and 42.0 months (32.8-53.5) for the BsAb-naïve group ($P < .001$).

NRM and CIR

At 2 years, no significant differences in NRM were observed between the unadjusted BsAb-exposed and BsAb-naïve groups (35.8%; 95% CI, 21.3%-50.5% vs 28.9%; 95% CI, 20.3%-38.0%; $P = .51$; Figure 1A; Table 3). Consistent results were observed in the IPTW-adjusted cohort (29.1% vs 31.4%; $P = .80$) and the PSM-adjusted cohort (35.8% vs 27.9%; $P = .43$).

In the unadjusted analysis, the BsAb-exposed patients showed a numerically lower 2-year CIR than the BsAb-naïve patients, although this difference was not statistically significant (9.5%; 95% CI, 2.9%-20.8% vs 18.9%; 95% CI, 11.9%-27.2%; $P = .13$; Figure 1B; Table 3). Following IPTW adjustment, the CIR was significantly lower in the BsAb-exposed cohort (7.4%; 95% CI, 0.0%-14.1% vs 20.0%; 95% CI, 12.4%-27.7%; $P = .01$), suggesting a potential protective effect associated with previous BsAb therapy. A similar trend was observed in the PSM analysis (9.5%; 95% CI, 2.9%-20.8% vs 23.4%; 95% CI, 12.4%-36.4%), although the difference remained nonsignificant ($P = .06$).

OS and PFS

Of the 18 patients in the BsAb-exposed group who died during follow-up, the causes of death were relapse in 2 cases (11.1%) and transplant-related toxicities in 16 cases (88.9%). Among the toxicity-related deaths, infections accounted for 9 (56.3%), followed by GVHD-related complications in 4 cases (25.0%), cerebrovascular disease in 1 case (6.3%), secondary neoplasm in 1 case (6.3%), and unknown cause in 1 (6.3%). Among the 9 infection-related deaths in the BsAb cohort, 2 (22%) were attributed to COVID-19, corresponding to 12.5% of all NRM deaths.

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Table 1. Patient characteristics

	Overall N = 148	BsAb-exposed n = 47	BsAb-naïve n = 101	*P* value
Median age (range), y	54 (20-73)	59 (23-73)	52 (20-70)	<.001
Sex, n (%)				
Male	84 (56.8)	30 (63.8)	54 (53.5)	
Female	64 (43.2)	17 (36.2)	47 (46.5)	.300
Diagnosis, n (%)				
DLBCL NOS	72 (48.6)	18 (38.3)	54 (53.4)	
HGBCL	11 (7.4)	1 (2.1)	10 (9.9)	
DHTHBCL	3 (2.0)	1 (2.1)	2 (2.0)	
PMBCL	5 (3.4)	0	5 (5.0)	
tFL	39 (26.3)	9 (19.0)	30 (29.7)	
FL	14 (9.5)	14 (30.0)	0	
MCL	3 (2.0)	3 (6.4)	0	
Other*	1 (0.7)	1 (2.1)	0	<.001
Ann Arbor stage, n (%)				
I-II	21 (15.0)	12 (26.0)	9 (9.3)	
III-IV	123 (85.0)	35 (74.0)	88 (90.7)	
Missing	4	0	4	.013
Primary refractory, n (%)	61 (41.5)	28 (59.6)	33 (33.3)	
Missing	2	0	2	.004
Median number of lines at alloHCT, n (range)	4 (2-11)	4 (3-11)	3 (2-7)	<.001
CAR T-cell therapy before BsAb, n (%)	20 (14.0)	20 (43.0)	0	<.001
Previous ASCT, n (%)	77 (52.0)	12 (25.5)	65 (64.5)	<.001
Disease status at alloHCT, n (%)				
CR	101 (68.2)	37 (78.7)	64 (63.4)	
PR	36 (24.3)	7 (14.9)	29 (28.7)	
SD	4 (2.7)	2 (4.3)	2 (2.0)	
PD	7 (4.8)	1 (2.1)	6 (5.9)	.140
HCT-CI, n (%)				
0	44 (30.1)		31 (31.3)	
1-2	49 (33.6)	13 (27.7)	33 (33.3)	
≥3	53 (36.3)	16 (34.0)	35 (35.4)	
Missing	2	18 (38.3)	2	.800
ECOG pre-alloHCT, n (%)				
0	90 (60.8)	21 (44.7)	69 (68.3)	
≥1	58 (39.2)	26 (55.3)	32 (31.7)	.007
Donor, n (%)				
MRD	55 (37.4)	10 (21.3)	45 (45.0)	
MUD	50 (34.0)	22 (46.8)	28 (28.0)	
Haploidentical	42 (28.6)	15 (31.9)	27 (27.0)	
Missing	1	0	1	.014
HLA match, n (%)				
10/10	36 (24.3)	26 (55.3)	56 (55.5)	
9/10	97 (65.5)	6 (12.8)	16 (15.8)	
8/10	1	0	1 (1)	

ASCT, autologous stem cell transplantation; BM, bone marrow; Bu, busulfan; Bu2, 2-days busulfan; 3Bu, 3-days busulfan; CsA, cyclosporine A; Cy, cyclophosphamide; DHTHBCL, double hit/triple hit B-cell lymphoma; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; Flu, fludarabine; HCT-CI, hematopoietic cell transplant comorbidity index; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate-dehydrogenase; MAC, myeloablative conditioning; Mel, melphalan; MIPI, Mantle Cell Lymphoma International Prognostic Index; MRD, matched related donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cells; PD, progressive disease; PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; R-IPI, Revised International Prognostic Index; RIC, reduced intensity conditioning; SD, stable disease; Siro, sirolimus; Tacro, tacrolimus; TBI, total body irradiation; tFL, transformed follicular lymphoma.

*One patient categorized as "other" had a diagnosis of Richter transformation arising from chronic lymphocytic leukemia.

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Table 1 (continued)

	Overall N = 148	BsAb-exposed n = 47	BsAb-naïve n = 101	*P* value
Haploidentical	15 (10.1)	15 (31.9)	27 (26.7)	
Missing	1	0	1 (1)	<.001
Stem cell source, n (%)				
PBSC	147 (99.3)	46 (97.9)	101 (100)	
BM	1 (0.7)	1 (2.1)	0	.300
Conditioning intensity, n (%)				
RIC	134 (90.5)	43 (91.5)	91 (90.1)	
MAC	14 (9.5)	4 (8.5)	10 (9.9)	>.9
Conditioning type, n (%)				
FluMel	16 (10.8)	2 (4.3)	14 (13.9)	
FluBu	40 (27.0)	11 (23.4)	29 (28.7)	
FluCyTBI	18 (12.2)	15 (31.9)	3 (3.0)	
TBF (Bu2)	15 (10.1)	9 (19.1)	6 (5.9)	
TBF (Bu3)	59 (39.9)	10 (21.3)	49 (48.5)	<.001
GVHD prophylaxis, n (%)				
CsA	20 (13.5)	3 (6.4)	17 (16.9)	
Tacro/Siro	21 (14.2)	0	21 (20.7)	
PTCy based	77 (52.0)	34 (72.3)	43 (42.6)	
Other	30 (20.3)	10 (21.3)	20 (19.8)	<.001
Median alloHCT year (Q1-Q3)	2019 (2017-2020)	2021 (2020-2022)	2018 (2017-2019)	<.001
Median follow-up (range), mo	36.1 (25.17-49.63)	27.7 (9.4-33.8)	42.0 (38.7-50.5)	<.001

ASCT, autologous stem cell transplantation; BM, bone marrow; Bu, busulfan; Bu2, 2-days busulfan; 3Bu, 3-days busulfan; CsA, cyclosporine A; Cy, cyclophosphamide; DHTHBCL, double hit/triple hit B-cell lymphoma; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; Flu, fludarabine; HCT-CI, hematopoietic cell transplant comorbidity index; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate-dehydrogenase; MAC, myeloablative conditioning; Mel, melphalan; MIPI, Mantle Cell Lymphoma International Prognostic Index; MRD, matched related donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cells; PD, progressive disease; PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; R-IPI, Revised International Prognostic Index; RIC, reduced intensity conditioning; SD, stable disease; Siro, sirolimus; Tacro, tacrolimus; TBI, total body irradiation; tFL, transformed follicular lymphoma.

*One patient categorized as "other" had a diagnosis of Richter transformation arising from chronic lymphocytic leukemia.

No significant differences in OS were observed between the groups across all analyses. In the unadjusted cohort, the 2-year OS was 58.4% (95% CI, 44.8%-76.3%) for BsAb-exposed patients and 58.1% (95% CI, 49.2%-68.7%) for BsAb-naïve patients (P = .76; Figure 1C; Table 3). Similar results were observed after IPTW (66.4% vs 54.1%; P = .19) and PMS (58.4% vs 53.0%; P = .54).

The 2-year PFS did not differ statistically between the groups in the unadjusted cohort (54.7%; 95% CI, 41.3%-72.5% vs 52.2%; 95% CI, 43.2%-62.9%; P = .65; Figure 1D; Table 3). Similar findings were observed in the IPTW-adjusted cohort (P = .18) and the matched cohort (P = .52).

GVHD

The cumulative incidence of grade 2 to 4 acute GVHD by day +100 was comparable between the groups across all analyses (Figure 2A; Table 3). In the unadjusted analysis, it occurred in 21.3% (95% CI, 10.9%-34.0%) of the BsAb-exposed patients and in 24.8% (95% CI, 16.8%-33.5%) of the BsAb-naïve patients (P = .51). These findings remained consistent across the IPTW-adjusted (24.3% vs 25.3%; P = .98) and PSM analyses (21.3% vs 23.4%; P = .45).

Similarly, no statistically significant differences were observed in the cumulative incidence of grade 3 to 4 acute GVHD by day +100 (Figure 2B; Table 3). In the unadjusted analysis, the incidence was 14.9% (95% CI, 6.5%-26.6%) in BsAb-exposed patients and 9.9% (95% CI, 5.0%-16.7%) in BsAb-naïve group (P = .26). In the IPTW-adjusted cohort, the corresponding incidences were 19.1% vs 11.4% (P = .39), whereas in the PSM cohort, they were 14.9% vs 10.6% (P = .58).

The 2-year cumulative incidence of moderate-to-severe chronic GVHD was higher in the BsAb-exposed patients in the unadjusted analysis (21.7%; 95% CI, 10.3%-35.7% vs 7.0%; 95% CI, 3.1%-13.2%; P = .11), although the difference did not reach statistical significance (Figure 2C; Table 2). This finding remained nonsignificant after IPTW adjustment (16.1% vs 6.0%; P = .12) and in the PSM cohort (21.7% vs 4.3%; P = .12).

GRFS

At 2 years, GRFS did not differ significantly between the BsAb-exposed and BsAb-naïve patients (31.5%; 95% CI, 19.9%-49.8% vs 40.7%; 95% CI, 31.8%-2.0%, respectively; P = .39; Figure 2D; Table 3). Consistent results were observed in the IPTW-adjusted cohort (30.3% vs 38.0%; P = .76) and in the PSM cohort (31.5% vs 40.8%; P = .51).

Engraftment

Neutrophil engraftment by day +30 was achieved in 91.5% (95% CI, 77.9%-96.9%) of patients in the unadjusted

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Table 2. Characteristics of patients who received BsAb therapy

	BsAb-exposed n = 47
CAR-T before BsAbs, n (%)	20 (42.6)
CAR-T as a previous line of therapy, n (%)	
Axi-cel	15 (75)
Tisa-cel	3 (15.0)
Allogeneic CAR-T	1 (5.0)
Missing type	1 (5.0)
BsAb therapy, n (%)	
Monotherapy	34 (72.3)
Combination	13 (27.7)
BsAb type, n (%)	
Epcoritamab in monotherapy	9 (19.1)
Epcoritamab in combination*	2 (4.3)
Glofitamab in monotherapy	11 (23.4)
Glofitamab in combination†	11 (23.4)
Mosunetuzumab in monotherapy	1 (2.1)
Odronextamab in monotherapy	13 (27.7)
BsAb as last line, n (%)	40 (85)
Number of BsAb's administered doses, median (range)	12 (4-24)
Time from diagnosis to alloHCT, median (range), mo	44.7 (9.4 - 208.2)
Time from BsAb's last dose to alloHCT, median (range), d	42 (13 - 421)

Axi-Cel, axicabtagene ciloleucel; Tisa-cel, tisagenlecleucel.
*Epcoritamab in combination (n = 2) with rituximab and lenalidomide.
†Glofitamab in combination (n = 11) with polatuzumab in 3 patients, atezolizumab in 2 patients, and englumafusp in 6 patients.

BsAb-exposed group and in 87.5% (95% CI, 78.8%-92.8%) in the BsAb-naïve group (P = .093), indicating comparable rates between the cohorts. Similarly, platelet engraftment by day +30 occurred in 66.0% (95% CI, 50.2%-77.8%) of BsAb-exposed patients and in 68.4% (95% CI, 57.9%-76.8%) of BsAb-naïve patients (P = .99). These findings remained consistent after adjustments using the IPTW and PSM methods (Table 3).

Subanalysis that excluded patients with FL and MCL

Given the clinical and biologic distinctiveness of FL and mantle cell lymphoma (MCL) and the absence thereof in the BsAb-naïve cohort, a subanalysis that excluded these histologies from the BsAb-exposed group (n = 30) was conducted to assess their potential impact on transplantation outcomes (supplemental Table 2).

In this restricted analysis, the 2-year CIR was significantly lower in the BsAb-exposed group than in the BsAb-naïve group, both after IPTW adjustment (6.1%; 95% CI, 0%-14.6% vs 21.1%; 95% CI, 12.9%-29.3%; P = .01) and after PSM (9.2%; 95% CI, 1.5%-26.1% vs 33.3%; 95% CI, 17.1%-50.4%; P = .03). PFS at 2 years was significantly higher in the BsAb-exposed group in the IPTW analysis (55.5%; 95% CI, 38.6%-79.8% vs 36.6%; 95% CI, 25.0%-53.5%; P = .04), although this difference was not confirmed after PSM (55.5%; 95% CI, 38.6%-79.8% vs 40.0%; 95% CI, 25.8%-62.0%; P = .20). OS also showed a trend that favored BsAb exposure in the IPTW-adjusted model (P = .07) but remained comparable across groups in the matched and unadjusted analyses. No significant differences were observed in NRM, acute or chronic GVHD, GRFS, or the engraftment rates (Table 4; supplemental Figure 2).

Discussion

As BsAbs become increasingly integrated into the treatment landscape for R/R B-NHL, their potential influence on subsequent transplant outcomes remains poorly defined. In particular, it is unclear whether patients who achieve a response after BsAb therapy should proceed to alloHCT for consolidation or continue on maintenance strategies. Given the limited long-term data on the curative potential of BsAbs alone, consolidative alloHCT may represent a rational approach for selected high-risk patients. In pivotal BsAb studies, only a minority of patients underwent consolidative alloHCT, and no survival outcomes were reported in that context.[1-5] Our study aimed to clarify the potential impact of previous BsAb exposure on alloHCT outcomes by analyzing a multicenter cohort of 47 BsAb-exposed patients and comparing them with a BsAb-naïve group.

The primary outcome of this study was NRM based on concerns that previous BsAb therapy could predispose patients to alloHCT-related toxicity. This hypothesis stems from the potential BsAb-mediated redirection and prolonged activation of donor T cells, which may lead to T-cell dysfunction or exhaustion, thereby increasing the risk for infections (particularly viral and fungal) and GVHD. However, NRM was comparable between BsAb-exposed and BsAb-naïve groups across both unadjusted and adjusted analyses, suggesting that previous BsAb therapy does not increase transplant-related mortality. Although we previously reported a high burden of infections in BsAb-exposed alloHCT recipients,[17] this concern was not confirmed in the present comparative analysis. Although detailed cause-of-death data were only available for BsAb-exposed patients, the similarity in NRM between the groups suggests that infection-related mortality was unlikely to differ substantially.

The rates of acute GVHD (grade 2-4 and 3-4) were also comparable between the groups across all models. Interestingly, the cumulative incidence of moderate-to-severe chronic GVHD at 2 years was numerically higher in the BsAb-exposed patients (21% vs 7%), but the difference did not reach statistical significance. However, given the limited size of the BsAb cohort and the magnitude of the numerical difference observed, the study may be underpowered to detect clinically relevant differences in this outcome, and therefore, these findings should be interpreted with caution. Notably, 32% of patients in the BsAb-exposed group received haploidentical alloHCT, a setting known to carry an increased incidence of chronic GVHD risk despite PTCy prophylaxis. Real-world data report moderate chronic GVHD rates of 25% to 30% at 1 year after haploidentical transplants.[18] The incidence observed in our cohort is consistent with published data and considered clinically acceptable. The observed chronic GVHD incidence is also consistent with the use of PTCy, the most prevalent GVHD prophylaxis strategy in the BsAb-exposed group, in the HLA-matched donor settings, supporting the clinical plausibility of these findings.[19]

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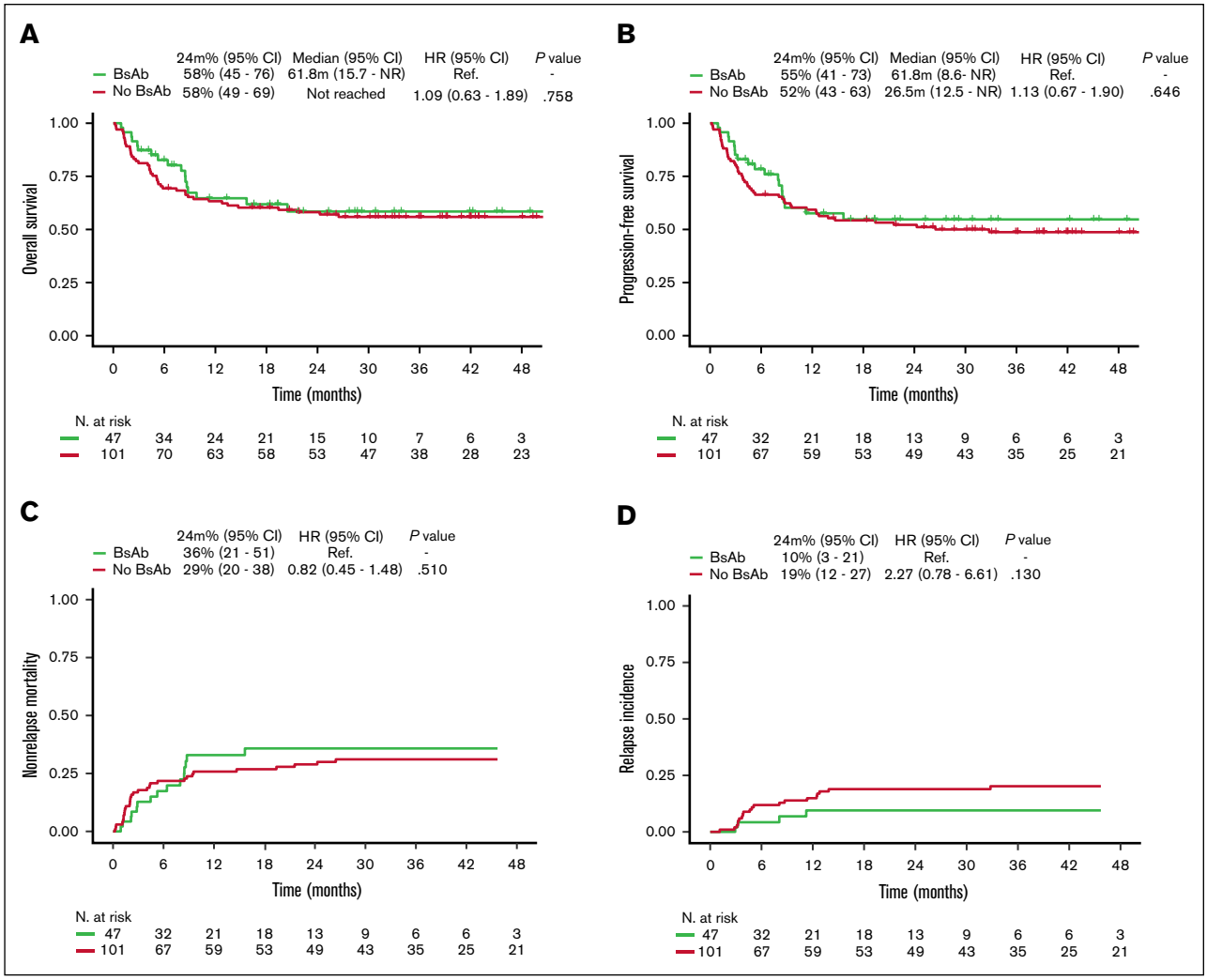

Figure 1. Outcomes after alloHCT according to previous exposure to BsAbs. Kaplan-Meier curves showing the (A) CIR, (B) NRM, (C) PFS, and (D) OS in patients with previous BsAb exposure (n = 47) vs no previous BsAb exposure (n = 101). HR, hazard ratio; NR, not reached.

Regarding disease control, the 2-year CIR was numerically lower among the BsAb-exposed patients than among the BsAb-naïve controls in the overall cohort, but this difference was not statistically significant in the unadjusted (9.5% vs 18.9%; $P = .13$) or matched analyses (9.5% vs 23.4%; $P = .06$). However, after IPTW adjustment, CIR was significantly lower in the BsAb-exposed group (7.4% vs 20.0%; $P = .01$). A higher proportion of BsAb-exposed patients proceeded to alloHCT in CR when compared with the BsAb-naïve controls. This likely represents a major advantage of incorporating BsAbs before alloHCT, because achieving a deeper disease response before transplant consistently has been associated with improved posttransplant outcomes.[20,21] The lower relapse risk observed in the BsAb cohort may therefore be, at least partly, explained by this higher CR rate at the time of transplantation. We acknowledge that ~15% of BsAb-exposed patients did not receive BsAb as the immediate line of therapy before alloHCT. The outcomes of these patients may be less directly attributable to BsAb exposure, and their inclusion could introduce some heterogeneity in the BsAb cohort. Nevertheless, this proportion was small, and most patients underwent alloHCT shortly after BsAb, which we believe better reflects the potential role of BsAbs as an effective bridging strategy.

Given that the tumor microenvironment of FL is particularly sensitive to immunotherapy and considering the clinical distinctiveness of both FL and MCL, we conducted a prespecified subanalysis that excluded these histologies to minimize disease-specific bias. In this refined cohort, the reduction in CIR among BsAb-exposed patients was confirmed across both the IPTW (6.1% vs 21.1%; $P = .01$) and PSM (9.2% vs 33.3%; $P = .03$) models, reinforcing the consistency of this finding. Although a statistically significant improvement in 2-year PFS was also observed in the IPTW analysis (55.5% vs 36.6%; $P = .04$), this result was not confirmed in the matched cohort ($P = .20$) and should therefore be interpreted cautiously. A nonsignificant trend toward improved OS was observed in the BsAb-exposed group in the IPTW model, but this was not confirmed in the PSM analysis. Together, these results support the

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Table 3. Clinical outcomes in BsAb-exposed and BsAb-naïve patients, across unadjusted, IPTW-adjusted, and PSM analyses

	Unbalanced			Balanced IPTW			Balanced matching		
	BsAb-exposed	BsAb-naïve		BsAb-exposed	BsAb-naïve		BsAb-exposed	BsAb-naïve	
	% (95% CI)	% (95% CI)	*P* value	% (95% CI)	% (95% CI)	*P* value	% (95% CI)	% (95% CI)	*P* value
2-year NRM	35.8 (21.3-50.5)	28.9 (20.3-38.0)	.51	29.1 (14.7-43.6)	31.4 (21.5-41.3)	.80	35.8 (21.3-50.5)	27.9 (15.8-41.3)	.43
2-year CIR	9.5 (2.9-20.8)	18.9 (11.9-27.2)	.13	7.4 (0.0-14.1)	20.0 (12.4-27.7)	**.01**	9.5 (2.9-20.8)	23.4 (12.4-36.4)	.06
2-year OS	58.4 (44.8-76.3)	58.1 (49.2-68.7)	.76	66.4 (51.1-86.3)	54.1 (44.5-65.7)	.19	58.4 (44.8-76.3)	53.0 (40.5-69.5)	.54
2-year PFS	54.7 (41.3-72.5)	52.2 (43.2-62.9)	.65	61.5 (45.7-82.7)	48.5 (39.1-60.1)	.18	54.7 (41.3-72.5)	48.7 (36.2-65.4)	.52
Grade 2-4 acute GVHD at 100 days	21.3 (10.9-34.0)	24.8 (16.8-33.5)	.51	24.3 (7.3-41.3)	25.3 (16.3-34.4)	.98	21.3 (10.9-34.0)	23.4 (12.5-36.3)	.45
Grade 3-4 acute GVHD at 100 days	14.9 (6.5-26.6)	9.9 (5.0-16.7)	.26	19.1 (2.8-35.3)	11.4 (4.5-18.3)	.39	14.9 (6.5-26.6)	10.6 (3.8-21.4)	.58
2-year moderate-severe chronic GVHD	21.7 (10.3-35.7)	7.0 (3.1-13.2)	.11	16.1 (4.1-28.1)	6.0 (1.7-10.4)	.12	21.7 (10.3-35.7)	4.3 (0.8-13.2)	.12
2-year GRFS	31.5 (19.9-49.8)	40.7 (31.8-52.0)	.39	30.3 (16.9-54.5)	38.0 (29.0-49.8)	.76	31.5 (19.9-49.8)	40.8 (28.6-58.3)	.51
Neutrophil engraftment at 30 days	91.5 (77.9-96.9)	87.5 (78.8-92.8)	.09	88.9 (74.7-100)	85.6 (78.6-92.6)	.68	91.5 (77.9-96.9)	88.9 (74.3-95.4)	.11
Platelet engraftment at 30 days	66.0 (50.2-77.8)	68.4 (57.9-76.8)	.99	59.5 (43.7-75.3)	67.2 (57.8-76.6)	.41	66.0 (50.2-77.8)	65.9 (49.6-78.1)	.54

Outcomes include 2-year NRM, incidence of relapse or progression of disease, OS, PFS, acute and chronic GVHD, GVHD-free/relapse-free survival, and hematologic recovery. Estimates are presented as percentages with 95% CIs. Comparisons between groups were evaluated using unadjusted, IPTW, and 1:1 PSM. Bolded *P* values highlight statistically significant differences (defined as $P < .05$).

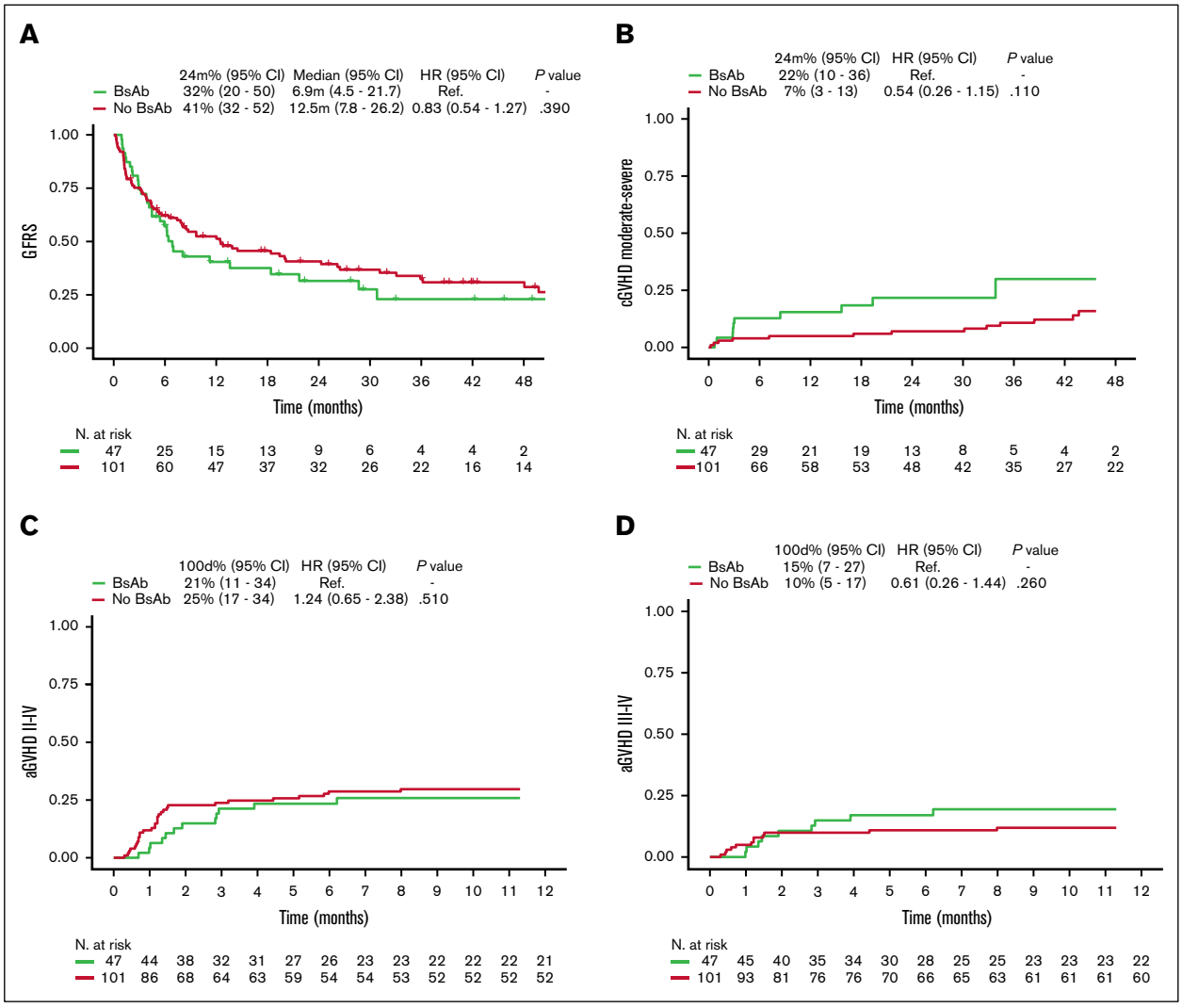

Figure 2. Incidence of GVHD and GRFS according to previous BsAb exposure. The cumulative incidence curves for (A) aGVHD grade 2 to 4, (B) aGVHD grade 3 to 4, (C) moderate-to-severe cGVHD, and (D) GRFS in patients with (n = 47) and those without (n = 101) previous BsAb exposure. aGVHD, acute GVHD; cGVHD, chronic GVHD.

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Table 4. Clinical outcomes in BsAb-exposed and BsAb-naïve patients, excluding those with FL and MCL, across unadjusted, IPTW-adjusted, and PSM analyses

	Unbalanced			Balanced IPTW			Balanced matching		
	BsAb-exposed	BsAb-naïve		BsAb-exposed	BsAb-naïve		BsAb-exposed	BsAb-naïve	
	% (95% CI)	% (95% CI)	*P* value	% (95% CI)	% (95% CI)	*P* value	% (95% CI)	% (95% CI)	*P* value
2-year NRM	35.3 (16.9-54.3)	28.9 (20.3-38.0)	.90	28.4 (8.9-47.9)	30.6 (21.1-40.2)	.68	35.3 (16.9-54.3)	26.7 (12.3-43.4)	.70
2-year CIR	9.2 (1.5-26.1)	18.9 (11.9-27.2)	.20	6.1 (0-14.6)	21.1 (12.9-29.3)	**.01**	9.2 (1.5-26.1)	33.3 (17.1-50.4)	**.03**
2-year OS	59.3 (42.2-83.4)	58.1 (49.2-68.7)	.50	59.3 (42.2-83.4)	42.4 (29.6-60.7)	.07	59.3 (42.2-83.4)	49.8 (34.7-71.4)	.30
2-year PFS	55.5 (38.6-79.8)	52.2 (43.2-62.9)	.40	55.5 (38.6-79.8)	36.6 (25.0-53.5)	**.04**	55.5 (38.6-79.8)	40.0 (25.8-62.0)	.20
Grade 2-4 acute GVHD at 100 days	16.7 (5.9-32.1)	24.8 (16.8-33.5)	.30	19.9 (3.3-36.5)	23.7 (15.4-32.1)	.49	16.7 (5.9-32.1)	26.7 (12.4-43.4)	.50
Grade 3-4 acute GVHD at 100 days	13.3 (4.1-28.1)	9.9 (5.0-16.7)	.50	14.1 (0-29.4)	10.35 (4.4-16.3)	.57	13.3 (4.1-28.1)	13.3 (4.1-28.1)	.21
2-year moderate-severe chronic GVHD	11.4 (2.7-27.3)	7.0 (3.1-13.2)	.80	15.4 (0-32.5)	6.3 (1.8-10.8)	.32	11.4 (2.7-27.3)	6.7 (1.1-19.5)	.07
2-year GRFS	34.3 (19.9-59.0)	40.7 (31.8-52.0)	.80	34.3 (19.9-59.0)	29.3 (18.9-45.3)	.40	34.3 (19.9-59.9)	32.7 (18.9-56.5)	>.90
Neutrophil engraftment at 30 days	93.3 (72.9-98.5)	87.5 (78.8-92.8)	.20	84.7 (69.6-99.7)	86.1 (79.1-93.1)	.87	93.3 (72.9-98.5)	82.8 (62.0-92.8)	.80
Platelet engraftment at 30 days	73.3 (52.8-86)	68.4 (57.9-76.8)	.50	66.8 (47.6-86.0)	66.0 (56.3-75.7)	.98	73.3 (52.8-86.0)	64.3 (43.0-79.3)	.20

This table summarizes the clinical outcomes at 2 years among patients with R/R B-NHL who underwent alloHCT, excluding those with FL and MCL. The outcomes include NRM, incidence of relapse or progression of disease, OS, PFS, acute and chronic GVHD, GRFS, and hematologic recovery (neutrophil and platelet engraftment at day +30). Results are shown for the unadjusted cohort, as well as after IPTW and 1:1 PSM. Values are expressed as percentages with 95% CIs. *P* values reflect comparisons between the BsAb-exposed and BsAb-naïve groups for each method. Statistically significant differences ($P < .05$) are highlighted in bold.

hypothesis that BsAb therapy may contribute to deeper or more sustained remissions when entering the transplant phase, a factor known to correlate with improved posttransplant outcomes. Although speculative, previous BsAb exposure could also influence the subsequent immune dynamics after alloHCT. BsAbs induce transient, yet profound, T-cell activation, which might modulate the immune milieu before transplantation and indirectly affect graft-versus-lymphoma (GVL) activity. Alternatively, differences in donor composition, such as the higher proportion of unrelated donors in the BsAb cohort, could have contributed to a more pronounced GVL effect. Similar immunologic effects have been described with immune checkpoint inhibitors when used before alloHCT.[10,22] Further research is warranted to elucidate whether BsAb therapy acts synergistically with alloHCT and to define the optimal sequence of these treatment modalities.

Despite these promising signals, this study has several limitations that should be acknowledged. First, the retrospective design and the inherent heterogeneity of the patient population may introduce risks of bias and residual confounding. To mitigate this, we used robust statistical methods, including IPTW and PSM methods, which allowed for improved covariate balance when compared with conventional regression models. These techniques adjust for confounders before the outcome analysis, thereby improving comparability. This is particularly relevant in observational studies with moderate sample sizes or substantial baseline heterogeneity in which case traditional multivariate models may yield unstable or biased estimates. Although these methods improved the baseline balance across most covariates, not all standardized mean differences reached the conventional threshold of <0.1, suggesting the possibility of residual imbalance. Second, the relatively small sample size of the BsAb-exposed group (n = 47) limited the power to detect differences between the groups. Although the study was not powered to detect small differences, effect estimates were close to unity with narrow CIs, indicating that any potential impact of previous BsAb exposure on posttransplant risk is likely minimal. Nevertheless, the implementation of prespecified sensitivity analyses, such as the exclusion of patients with FL and MCL, strengthened the consistency of our findings by addressing disease-specific variability. Third, none of the patients in the BsAb-naïve group had previously received CAR-T therapy, whereas several patients in the BsAb-exposed cohort had failed CAR-T therapy before alloHCT. Given the poor prognosis typically associated with post–CAR-T relapse, this imbalance in treatment history may introduce bias and complicate the comparability between groups. Cause-of-death data were available only for BsAb-exposed patients, thereby precluding direct comparisons with the BsAb-naïve cohort. This limitation prevents detailed attribution of NRM causes across groups; however, the overall NRM rates remained comparable. Finally, the use of a historic control group introduces potential biases related to temporal changes in transplant practices. Although both cohorts underwent alloHCT within a comparable contemporary therapeutic era, we acknowledge that transplant practices and supportive care continued to evolve during this timeframe, which may have introduced subtle temporal confounding. Broader adoption of PTCy and increasing availability of ruxolitinib and extracorporeal photopheresis for GVHD management, as well as advances in systemic therapies for R/R NHL, may have contributed to the outcome variability. These aspects should be considered when interpreting the results of this retrospective study. Nonetheless, the study period partially overlapped with the COVID-19 pandemic, which may have differentially affected the BsAb-exposed and BsAb-naïve cohorts. Among the 9 infection-related deaths in the BsAb group, 2 were attributed to COVID-19, corresponding to 12.5% of all NRM deaths. This finding is consistent with recent reports that showed that COVID-19 was a relevant contributor to NRM among patients treated with anti-CD20 × CD3 BsAbs.[23] Because the BsAb cohort (2018-2023) coincided with phases of vaccine rollout and evolving infection-prevention strategies and the BsAb-naïve group (2016-2020) preceded most of the pandemic, these temporal differences may have influenced the outcomes. Furthermore, because only patients who survived to undergo alloHCT were included, COVID-19–related deaths that occurred before transplantation could not

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be captured, thereby potentially underestimating the overall impact of the pandemic on BsAb-exposed patients.

In conclusion, this study provides, to our knowledge, the first comparative evidence that suggests that alloHCT following BsAb exposure is both feasible and safe with no increase in transplant-related toxicities. Moreover, the observed reduction in relapse risk warrants further investigation into potential synergies between BsAb and GVL effects. These results support the consideration of alloHCT as a consolidative strategy in high-risk patients who achieve a response to BsAb therapy. Prospective studies with larger cohorts and longer follow-up are needed to confirm these findings and refine the optimal sequencing of BsAbs and alloHCT in patients with R/R B-NHL within modern treatment algorithms.

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Authorship

Contribution: M. Peña and A.M. were responsible for the overall research questions and design of the study; V. Navarro conducted the statistical analyses; M. Peña, G.L., and A.M. wrote the original draft of the manuscript; and all authors reviewed and revised the manuscript, and read and approved the final manuscript.

Conflict-of-interest disclosure: D.A.Q. reports serving in a consulting or advisory role for ADC Therapeutics, Genmab, and Kite Pharma. The remaining authors declare no competing financial interests.

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