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Short title: Follow-up of post-transplant blinatumomab in B-ALL

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Patients with B-lineage acute lymphoblastic leukemia (ALL) are at high-risk for relapse after allogeneic hematopoietic cell transplantation (HCT). Measurable residual disease (MRD) and adverse cytogenetic or molecular features are key prognostic indicators of relapse and survival.[1-5] The management of ALL patients who relapse after allogeneic HCT is challenging with poor survival outcomes; therefore, it is essential to reduce the risk of relapse after transplantation.[6,7] Beyond tyrosine kinase inhibitor (TKI) maintenance for Ph+ ALL, few maintenance options exist. Donor lymphocyte infusion (DLI) may help in early relapse but yields remission rates under 10% and increases graft-versus-host disease (GVHD) risk.[8-9] Effective strategies to prevent relapse in high-risk ALL remain an unmet need.

Blinatumomab is a bispecific T-cell engager (BiTE) that links CD19 on B-ALL blasts with CD3ζ on T cells, resulting in T-cell activation and subsequent perforin-dependent cytotoxicity directed toward CD19-expressing target cells. Studies have demonstrated a clinical benefit of blinatumomab in MRD-positive ALL patients in morphologic complete response (CR), with 80% achieving conversion to MRD negativity.[10] Blinatumomab has also demonstrated clinical benefit in relapsed or refractory (R/R) ALL, showing meaningful response rates and survival outcomes in both adult and pediatric populations, including post–allogeneic HCT settings, as evidenced by multiple phase 2 and 3 studies.[11-13]

We have previously reported the results of a single-center phase 2 study evaluating blinatumomab administration after HCT for relapse prevention in high-risk ALL. At a median follow-up of 14.3 months, the 1-year OS, PFS, and NRM were 85%, 71%, and 0%, respectively.[14] The cumulative incidence of acute GVHD grades 2–4 and 3–4 was 33% and 5%, respectively, and chronic GVHD occurred in 2 mild cases (10%) and 1 moderate case (5%). Herein, we present updated ten-year follow-up data to further characterize long-term outcomes.

Patients received blinatumomab as continuous IV infusion on days 1 through 28 of each cycle. Dosing and administration followed the standard FDA guidelines for children and adults. The first cycle was given within the first 3 months after allogeneic HCT. The transplant preparative regimen, GVHD prophylaxis, graft source, and graft allotype were determined by the treating physician and not prescribed by this protocol. For patients with Ph+ ALL, post-transplant tyrosine kinase inhibitor (TKI) therapy was permitted. One patient in the treatment cohort received TKI maintenance, compared with six patients in the control cohort. The study was conducted after the protocol was reviewed and approved by MD Anderson Cancer Center’s Institutional Review Board. Patients provided informed consent prior to enrollment in the clinical study in accordance with the Declaration of Helsinki. This phase 2 clinical trial was registered at ClinicalTrials.gov (NCT02807883).

Twenty-three patients signed consent, and 21 patients who received at least 1 cycle of blinatumomab therapy post HCT were included in the analysis. Two patients never received therapy due to GVHD that required treatment. We compared our results to a contemporary cohort control that included information for 128 patients. Using a 2:1 (control:treated) ratio, the matched analysis dataset included information for 57 (36:21) patients. The matched comparator cohort was identical to that used in our original report and was retained to allow consistent longitudinal comparison across follow-up periods.

In the blinatumomab group, 81% of the patients were male, 62% were Caucasian, with a median age at start of blinatumomab therapy of 30 years (range, 17 to 66 years), and 90% (18 of 20) had a high-risk cytogenetic or molecular profile at diagnosis (Patient and treatment characteristics are shown in Table 1). About half of the patients were in CR1, and 80% (16 of 20) had no detectable MRD at the time of HCT. The Karnosky performance score was ≥80% in 94% of 16 patients, and the median HCT comorbidity index was 3 (range, 0 to 8). Regarding donor relations, 33% were matched siblings, 48% matched unrelated donors, and 19% had haploidentical family donors. Approximately half of the patients received a reduced-intensity conditioning regimen and nearly half of the patients received post transplant cyclophosphamide, tacrolimus, and mycophenolate mofetil for GVHD prophylaxis. Two patients had >1 HCT prior to blinatumomab therapy. Seventy-six percent of patients were exposed to blinatumomab prior to allogeneic HCT. The median days from transplant to the first day of cycle 1 of blinatumomab was 78 (range, 44 to 105 days), and MRD was detected prior to the start of blinatumomab in 2 patients. The median number of blinatumomab cycles received was 4 (range, 1 to 4). Fifty-seven percent of patients (12 of 21) completed all 4 cycles of therapy. Three patients could not complete treatment due to GVHD, and the remaining patients (n = 6) relapsed before they could complete all 4 intended cycles. All patients were on tacrolimus during cycle 1 of blinatumomab. No significant associations were observed between progression and either the first tacrolimus dose (odds ratio [95% confidence interval] 1.02 [0.68-1.52]; p=0.93) or the average tacrolimus dose (0.89 [0.56-1.42]; p=0.63). Except for gender and transplant conditioning intensity, all key characteristics were similar between the study and control groups (Table 1). Of note, there was no significant association between conditioning regimen and relapse. Furthermore, there was no significant difference in the treatment groups when conditioning intensity was included in the model or significant interaction (data not shown).

Sixteen of the 21 (76%) patients receiving blinatumomab were alive at last follow-up, and the median follow-up time for all patients was 60.8 months (range, 7.5 to 100.5 months). The median follow-up for the matched comparator cohort was 51.7 months (range, 3.4 to 124.2 months). Seven patients progressed, including the 4 patients who had MRD positivity prior to the start of blinatumomab therapy, for a cumulative incidence

of relapse of 33% (Figure 1A). Importantly, cumulative incidence of relapse was comparable between the blinatumomab-treated patients and the matched comparator cohort (28%), suggesting that long-term disease control was similar between groups. Progression-free survival (PFS) and overall survival (OS) at the final assessment were 67% and 76%, respectively, compared with 52% and 53% in the matched control group (Figure 1B, C). There were no regimen-related deaths. Although PFS and OS rates were higher in the blinatumomab cohort, relapse incidence was similar between groups, and survival differences were primarily driven by non-relapse mortality (NRM), which was 0% in the blinatumomab cohort compared with 20% in matched controls (Figure 1D). These findings should be interpreted cautiously, as the comparator cohort was only matched on disease status at HCT, cytogenetic risk, and MRD prior to HCT, therefore, differences in conditioning intensity, donor type, GVHD, and transplant era may have contributed to the observed NRM disparity.

Blinatumomab was well-tolerated post transplantation, with the most common severe adverse events being limited to hematologic cytopenias, including leukopenia (19% G3) and neutropenia (19% G4). Diarrhea occurred in 7 (33%) patients and was mostly grade 1 (5 patients) and not GVHD-related. Importantly, only 1 patient developed grade 1 CRS, and 1 patient developed grade 2 neurotoxicity in the form of confusion that resolved with a temporary hold of the blinatumomab infusion. Acute GVHD grades 2–4 at 100 days in patients receiving blinatumomab was 33%, compared with 56% in controls (p=0.07; Figure 2E), while 2-year chronic GVHD was observed in 29% of patients in both the blinatumomab and control groups (p=0.57; Figure 2F).The higher incidence of acute GVHD and non-relapse mortality observed in the comparator cohort may reflect differences in transplant-related practices, including a greater proportion of myeloablative conditioning rather than a protective effect of blinatumomab exposure. Importantly, it must be remembered that patients who receive maintenance therapy have the inherent bias that they must be well enough to be eligible for therapy, i.e. they cannot have GVHD, infection, etc.

This extended follow-up of a phase 2 study demonstrated that blinatumomab maintenance following allogeneic transplantation was feasible and associated with a favorable long-term safety profile without an apparent increase in acute or chronic graft-versus-host disease. Of note, a recent mini-dose blinatumomab approach reported markedly reduced post-transplant relapse compared with controls, with 1-year cumulative relapse rates of 0.0% versus 39.5% (p=0.009).[15] In our cohort, relapse rates remained similar to a matched comparator group with longer follow-up. Differences between studies likely reflect the impact of different treatment schedules, and the use of non-randomized comparator cohorts, and should be interpreted cautiously.

Immunophenotypic analyses from the original study identified “responders” and “nonresponders” based on distinct T-cell profiles, with responders showing higher

effector memory CD8 T-cell proportions and nonresponders demonstrating relative T-cell deficiency and increased inhibitory checkpoint expression, including TIM3. These findings suggest that benefit from blinatumomab post-allogeneic HCT depends on the immune milieu at treatment initiation. Extended long-term immune reconstitution analyses were not performed in this follow-up.

Future strategies to optimize immunomodulation approaches for maintenance post transplant should include consideration of drug timing, commencing maintenance once there has been adequate immune recovery post HCT but not too late to impact disease relapse. Furthermore, utilizing strategies such as immune checkpoint inhibition may lead to more robust responses. Finally, large, prospective, randomized studies with integrated longitudinal immune profiling, are needed to conclusively define patients most likely to benefit from maintenance.

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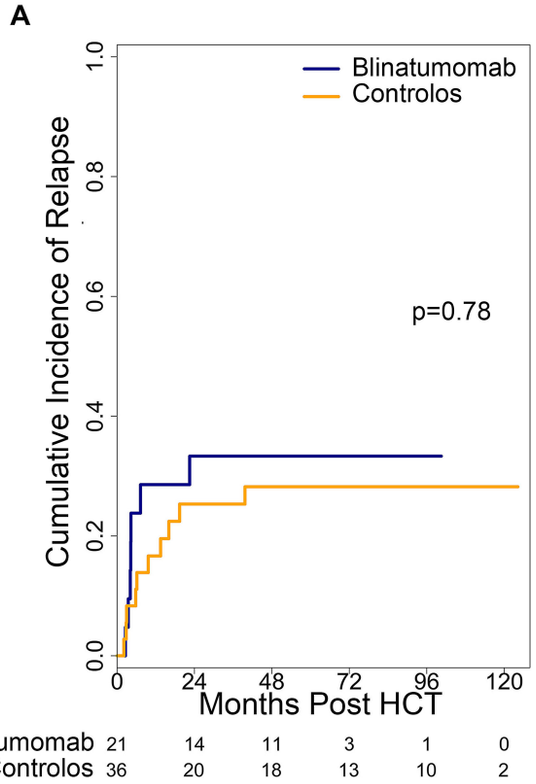
Measure	All (N=57)	Blinatumomab (N=21)	Controls (N=36)	p-value
Gender, n (%)				
Male	33 (58)	17 (81)	16 (44)	0.012
Female	24 (42)	4 (19)	20 (56)	
Age at alloHCT (years), median (range)	38.0 (16.0 - 66.0)	29.0 (16.0 - 65.0)	41.0 (19.0 - 66.0)	0.26
Race/ethnicity, n (%)				
Caucasian	36 (65)	13 (62)	23 (68)	0.13
Hispanic	15 (27)	8 (38)	7 (21)	
Other	4 (7)	0	4 (12)	
Months from diagnosis to alloHCT, median (range)	7.8 (2.9 - 107.7)	8.8 (3.2 - 107.7)	7.0 (2.9 - 99.8)	0.25
Disease status at alloHCT, n (%)				
CR 1	38 (67)	11 (52)	27 (75)	0.16
CR 2	12 (21)	7 (33)	5 (14)	
CR 3+	5 (9)	3 (14)	2 (6)	
Marrow CR	1 (2)	0	1 (3)	
No response	1 (2)	0	1 (3)	
MRD prior alloHCT, n (%)				
Not detected	46 (82)	16 (80)	30 (83)	0.73
Detected	10 (18)	4 (20)	6 (17)	
Total prior lines of therapy, median (range)	1.0 (1.0 - 6.0)	2.0 (1.0 - 3.0)	1.0 (1.0 - 6.0)	0.47
Karnofsky performance score, n (%)				
< 80	5 (10)	1 (6)	4 (13)	0.65
≥ 80	43 (90)	15 (94)	28 (88)	
HCT-CI, median (range)	3.0 (0.0 - 8.0)	3.0 (0.0 - 8.0)	2.5 (0.0 - 8.0)	0.98
Ph+, n (%)	9 (16)	1 (5)	8 (22)	0.13
Cytogenetic risk, n (%)				
Intermediate	6 (11)	2 (10)	4 (11)	1.00
High	49 (89)	18 (90)	31 (89)	
Donor type, n (%)				
Matched siblings	22 (39)	7 (33)	15 (42)	0.48
Matched unrelated donor	21 (37)	10 (48)	11 (31)	
Haploidentical donor	14 (25)	4 (19)	10 (28)	
Cell source, n (%)				
HPC-A	29 (51)	10 (48)	19 (53)	0.79
HPC-M	28 (49)	11 (52)	17 (47)	
Conditioning regimen, n (%)				
MAC	25 (44)	4 (19)	21 (58)	0.010
MAC/TBI	8 (14)	5 (24)	3 (8)	
RIC	24 (42)	12 (57)	12 (33)	
GVHD prophylaxis, n (%)				
PTCy/Tac/MMF	26 (46)	10 (48)	16 (44)	1.00
Tac/MTX	31 (54)	11 (52)	20 (56)	
Follow-up (months) (a*ll patients)*, median (range)	55.7 (3.4 - 124.2)	60.8 (7.5 - 100.5)	51.7 (3.4 - 124.2)	0.82
Follow-up (months) *(survivors)*, number of patients median (range)	36 68.6 (11.1 - 124.2)	16 62.4 (32.5 - 100.5)	20 95.2 (11.1 - 124.2)	0.030

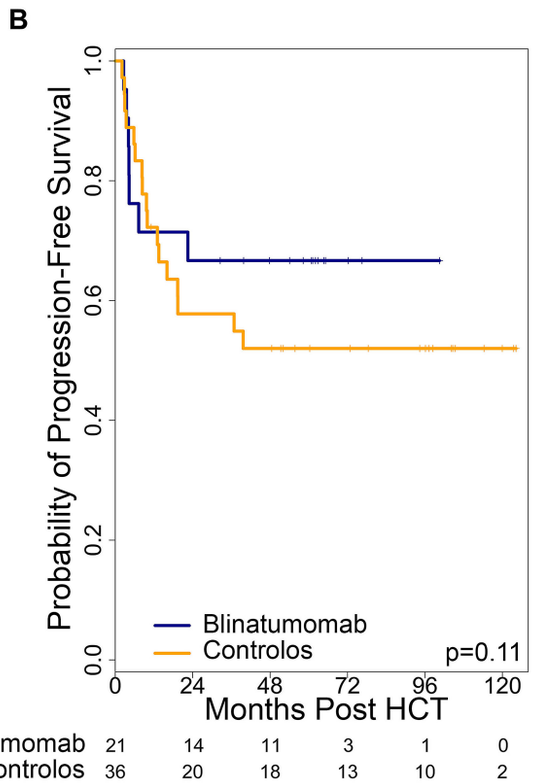
Legend Table 1:

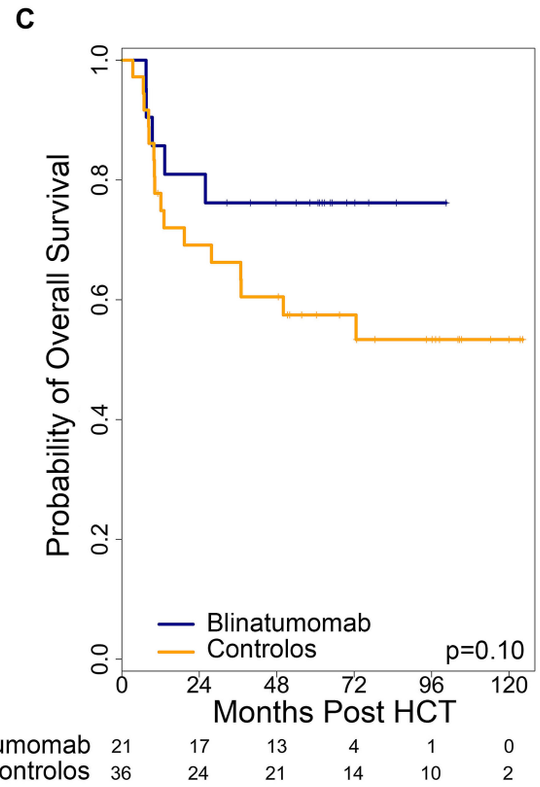
Table 1. Summary of patient and clinical characteristics for all treated and matched patients. alloHCT: allogeneic hematopoietic cell transplantation; CR: complete response; GVHD: graft-versus-host disease; HCT-CI: hematopoietic cell transplantation comorbidity index; HPC-A: hematopoietic progenitor cells - apheresis; HPC-M: hematopoietic progenitor cells - marrow; MAC: myeloablative conditioning; MMF: mycophenolate mofetil; MRD: measurable residual disease; MTX: methotrexate; Ph+: Philadelphia positive; PTCy: post-transplant cyclophosphamide; RIC: reduced intensity conditioning; Tac: tacrolimus; TBI: total body irradiation.

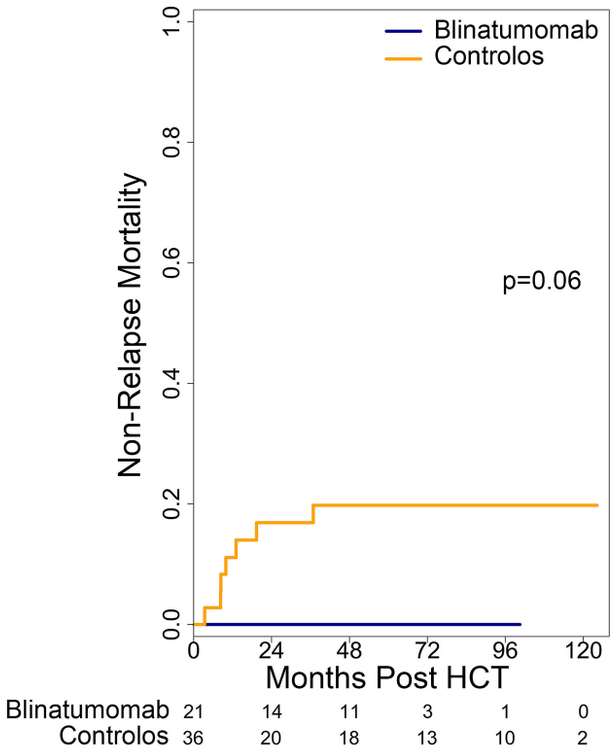
Legend Figure 1:

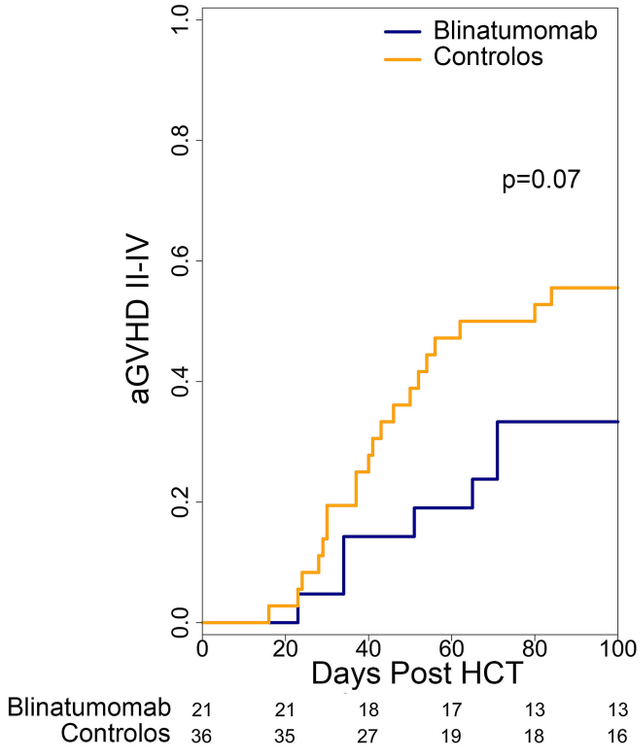
Figure 1. Kaplan-Meier and cumulative incidence analyses of survival, relapse, and GVHD after HCT in blinatumomab versus control cohorts. Cumulative Incidence of Relapse (A), Progression-Free Survival (B), Overall Survival (C), Non-Relapse Mortality (D), acute graft-versus-host-disease (aGVHD) II-IV (E), and chronic-graft-versus-host-disease (cGVHD) (F).


A
Blinatumomab
Controlos
Cumulative Incidence of Relapse
p=0.78
Months Post HCT
Blinatumomab 21 14 11 3 1 0
Controlos 36 20 18 13 10 2


B
Blinatumomab
Controlos
Probability of Progression-Free Survival
p=0.11
Months Post HCT
Blinatumomab 21 14 11 3 1 0
Controlos 36 20 18 13 10 2


C
Blinatumomab
Controlos
Probability of Overall Survival
p=0.10
Months Post HCT
Blinatumomab 21 17 13 4 1 0
Controlos 36 24 21 14 10 2


Blinatumomab
Controlos
Non-Relapse Mortality
p=0.06
Months Post HCT
Blinatumomab 21 14 11 3 1 0
Controlos 36 20 18 13 10 2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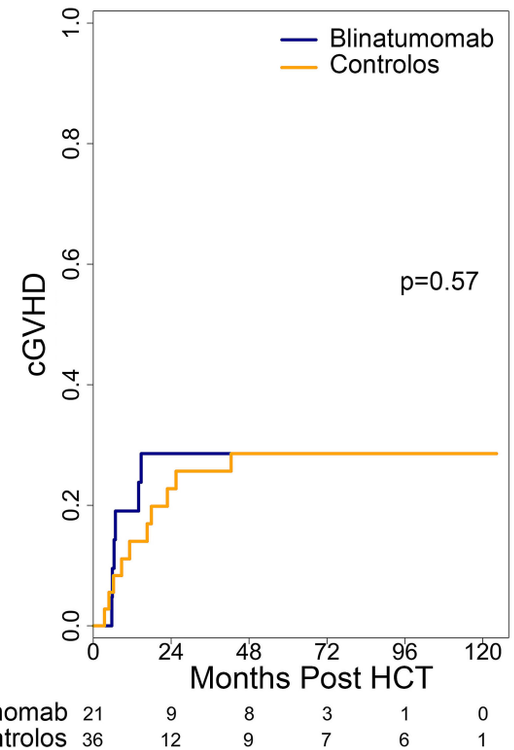
Controlos
aGVHD II-IV
p=0.07
Days Post HCT
Blinatumomab 21 21 18 17 13 13
Controlos 36 35 27 19 18 16


Blinatumomab
Controlos
cGVHD
p=0.57
Months Post HCT
Blinatumomab 21 9 8 3 1 0
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