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Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia

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ABSTRACT

Minimal residual disease (MRD) is the strongest predictor of relapse in B-cell precursor acute lymphoblastic leukemia (BCP-ALL). In BLAST study (NCT01207388), adults with BCP-ALL in remission with MRD after chemotherapy received blinatumomab, a CD19 BiTE[®] immuno-oncology, 15 µg/m²/day for up to four 6-week cycles (4 weeks continuous infusion, 2 weeks off). Survival was evaluated for 110 patients, including 74 who received HSCT in continuous complete remission. With a median follow-up of 59.8 months, median survival (months) was 36.5 (95% CI: 22.0–not reached [NR]). Median survival was NR (29.5–NR) for complete MRD responders (*n* = 84) and 14.4 (3.8–32.3) for MRD non-responders (*n* = 23; *p* = 0.002); after blinatumomab and HSCT, median survival was NR (25.7–NR) (*n* = 61) and 16.5 (1.1–NR) (*n* = 10; *p* = 0.065), respectively. This final analysis suggests complete MRD response during blinatumomab treatment is curative. Post-hoc analysis of study data suggests while post blinatumomab HSCT may be beneficial in appropriate patients, long-term survival without HSCT is also possible.

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Introduction


Up to 90% of adults with B-cell precursor acute lymphoblastic leukemia (BCP-ALL) achieve hematologic complete remission (CR) after induction chemotherapy, and overall survival (OS) rates are 30–70%, mainly depending on age [1–4]. Despite most patients achieving hematologic CR, after the initial treatment phase, 30–50% have persistent measurable minimal residual disease (MRD), defined as the presence of leukemic cells by detection methods with a sensitivity of $\geq 10^{-4}$ in patients with a blast count in the bone marrow below 5% by microscopy [5–11]. MRD is the strongest predictor of relapse in BCP-ALL, regardless of treatment regimen [12,13].

Historically, the best treatment regimen with curative potential for adult patients with MRD was

allogeneic hematopoietic stem cell transplantation (HSCT). Transplantation may offer an advantage for patients with detectable MRD, but results are sub-optimal [10]. Furthermore, not all patients are candidates for HSCT because of treatment-related morbidity and mortality, particularly in older patients [14].

Blinatumomab, an immunotherapy based on the bispecific T-cell engager (BiTE[®]) immuno-oncology platform, redirects CD3⁺ T cells to kill CD19⁺ target cells [15]. Our multi-national single-arm clinical trial (MT103-203; NCT01207388; “BLAST”) investigated the safety and efficacy of blinatumomab administered by continuous infusion in 6-week cycles (4 weeks on treatment, 2 weeks off treatment) in adults with Philadelphia chromosome (Ph)[−]negative BCP-ALL in hematologic CR with relapsed or persistent MRD after intensive chemotherapy. In the updated primary

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 Supplemental data for this article can be accessed [here](#).

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analysis, we observed a complete MRD response in 77% of evaluable patients (87/113) after 1 cycle of blinatumomab treatment; 1 patient was reclassified as a non-responder. Grade 3 or 4 adverse events during blinatumomab treatment included neurologic events (13%) or cytokine release syndrome (2%). After a minimum patient follow-up of 18 months, median OS was 36.5 months (95% CI: 19.8–not reached [NR]) [16]. In this report, we examine long-term outcomes by the final study visit, after a minimum patient follow-up of 5 years.

Methods

Trial design

A detailed description of the trial design was provided previously for this international, multi-centre, single-arm, open-label, phase 2 trial [16]. Eligible study participants were adults ≥ 18 years of age with BCP-ALL in hematologic CR ($< 5\%$ blasts in the bone marrow) and measurable MRD (10^{-3} or greater ≥ 2 weeks after last chemotherapy) after ≥ 3 blocks of intensive chemotherapy. The trial was approved by the relevant institutional review boards or ethics committees, and all participants gave written informed consent.

Blinatumomab was administered in 6-week cycles: 4 weeks of blinatumomab $15 \mu\text{g}/\text{m}^2$ per day by continuous intravenous infusion, followed by a 2-week treatment-free period. Enrolled patients received blinatumomab for up to 4 cycles: after 1 cycle of induction, patients could receive up to 3 additional cycles of consolidation. Patients could also undergo allogeneic HSCT, at the investigator's discretion, any time after cycle 1. Prophylaxis for central nervous system ALL was recommended before cycle 1 and after cycles 2 and 4. Corticosteroid pretreatment for prophylaxis of neurologic events and cytokine release syndrome was required before each cycle. Concurrent anti-leukemic therapy other than corticosteroid pretreatment was prohibited.

A central reference laboratory performed MRD assessments at baseline, at the end of each treatment cycle and during efficacy follow-up using real-time quantitative polymerase chain reaction for detecting clonal immunoglobulin or T-cell receptor gene rearrangements [6]. Complete MRD response was defined as no target amplification with a minimum sensitivity of 10^{-4} after blinatumomab induction [17].

Statistical methods

Kaplan-Meier analyses of OS were performed, including sub-group analyses by complete MRD response,

by the line of therapy (i.e. MRD-positive patients in first or second remission at baseline) and by the combination (i.e. by MRD response within each line of therapy). Analyses by complete MRD response started at day 45, after the MRD response assessment at the end of cycle 1.

For recipients of HSCT in continuous CR, baseline characteristics (age, prior relapses and genetic abnormalities) and on-study characteristics (complete MRD response, HSCT donor type and HSCT conditioning regimen) were summarized. The degree of donor matching was listed for the patients in each trial who received HSCT from an unrelated mismatched donor. Patient outcomes were summarized for patients with or without HSCT in continuous CR in 3 categories: alive without relapse, died without relapse and relapsed (including either alive or died after relapse). Kaplan-Meier analyses of OS were conducted separately for patients who received HSCT in continuous CR (starting at the day of HSCT) and for patients who did not receive HSCT in continuous CR (starting at day 45); each was stratified by complete MRD response status in cycle 1. In all outcome analyses, HSCT was not censored.

For each Kaplan-Meier analysis, the medians and 95% confidence intervals (CI) were calculated. For Kaplan-Meier analyses with sub-groups, the p -value was determined by log-rank test between or across the sub-groups. Overall, the statistical analyses were not adjusted for multiplicity and p -values should be considered descriptive.

Adverse event data were not collected during the long-term survival follow-up period. Adverse event-related data were previously described [16].

Results

Patient characteristics

The primary analysis described baseline characteristics and adverse events associated with treatment for all 116 patients who received blinatumomab. In that population, the median age at baseline was 45 years (range, 18–76); 54 (47%) patients had MRD $\geq 10^{-2}$; and 41 (35%) were in second or later remission [16].

The final analysis includes data through January 2019, when the last patient completed the final 5-year assessment. Of the 116 patients who received blinatumomab, 110 were considered evaluable for OS. Five patients with Ph-positive disease and 1 with $> 10\%$ blasts at screening were excluded from the survival analyses; all 6 of the excluded patients were in second or later remission at baseline (Figure 1).

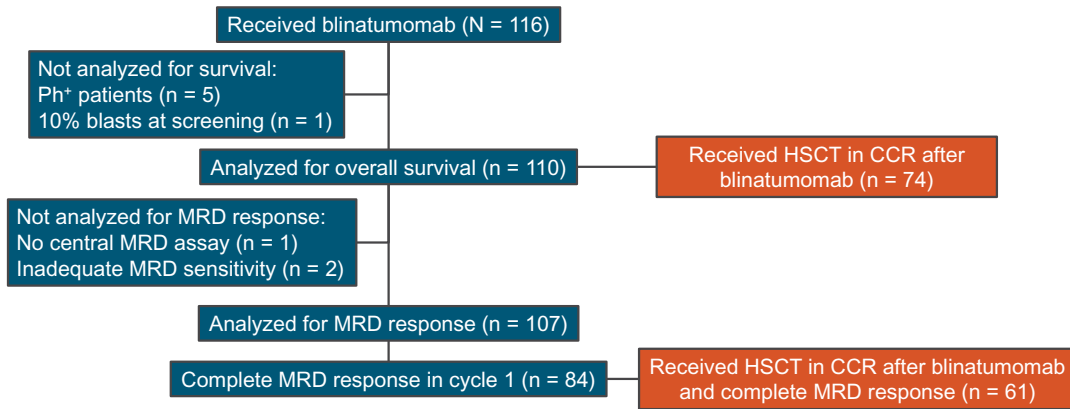


Figure 1. Patient disposition, use of HSCT and complete MRD responses after blinatumomab. CCR, continuous complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; Ph⁺, Philadelphia chromosome-positive.

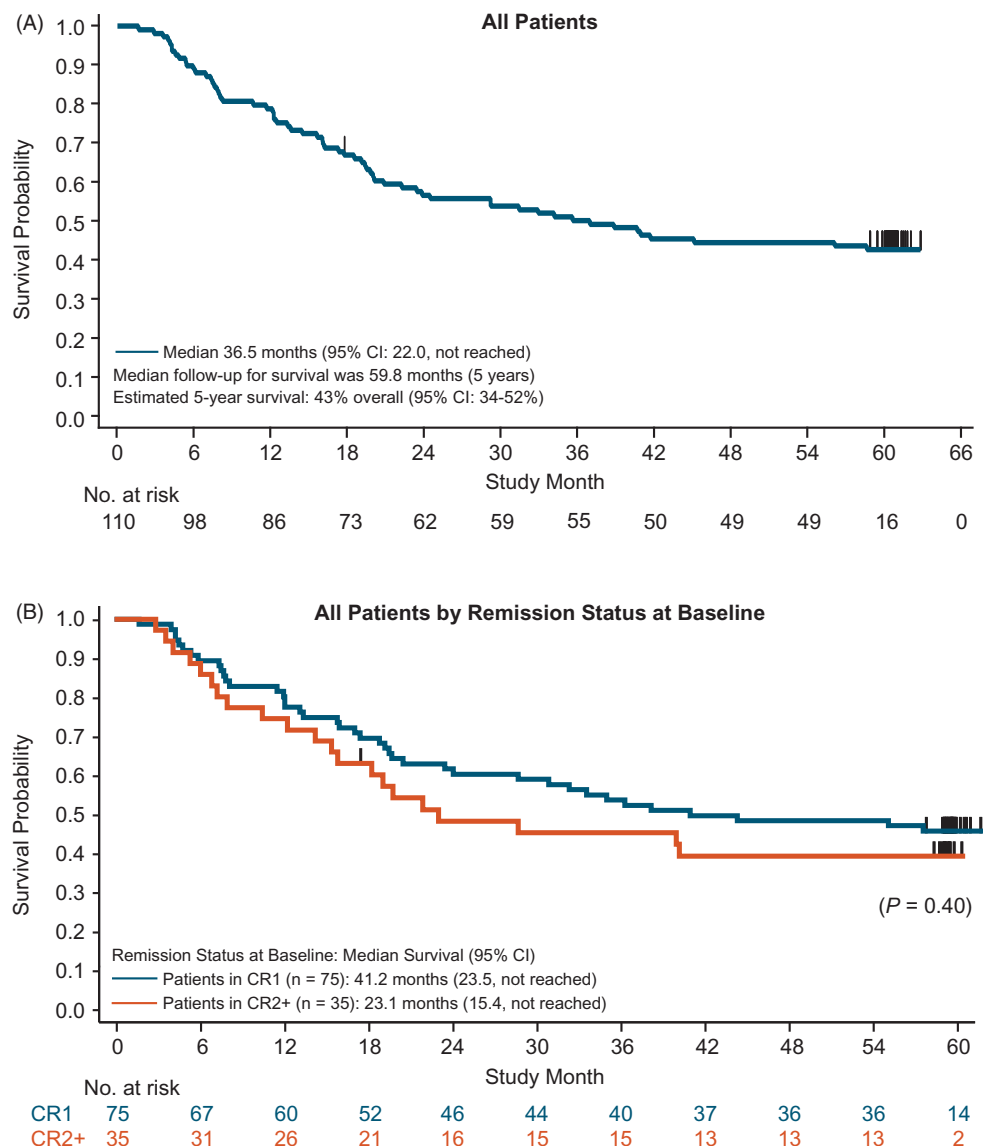


Figure 2. Kaplan-Meier analyses of overall survival in adults with minimal residual disease at baseline. (A) Overall survival among all evaluable patients with Philadelphia chromosome-negative disease and <5% blasts at baseline. (B) Overall survival by use of blinatumomab in CR1 or CR2+ (i.e. after salvage chemotherapy). CI, confidence interval; CR1, first complete remission; CR2+, later complete remission.

Long-term survival after blinatumomab treatment

With a median follow-up of 59.8 months, median OS was 36.5 months (95% CI: 22.0–NR; [Figure 2\(A\)](#)). Estimated 5-year survival was 43% overall (95% CI: 34–52%). Median OS by salvage status was 41.2 months (95% CI: 23.5–NR) ($n=75$) for blinatumomab use in the first remission and 23.1 months (15.4–NR) ($n=35$) for blinatumomab use in second or later remission (log-rank $p=0.40$; [Figure 2\(B\)](#)).

Long-term survival by complete MRD response

In this final analysis, 107 patients were evaluable for MRD response after 1 cycle of blinatumomab. Median OS by complete MRD response was NR (95% CI: 29.5 months–NR) among 84 patients with a complete MRD response and 14.4 months (3.8–32.3) among 23 patients without a complete MRD response (log-rank $p=0.002$; [Figure 3\(A\)](#)). Estimated 5-year survival for complete MRD responders was 50% (95% CI: 39–60%).

For blinatumomab use in the first remission, median OS was NR (95% CI: 29.5 months–NR) ($n=60$) for patients with a complete MRD response in cycle 1 and 10.6 months (2.7–39.7) ($n=13$) for those without a complete MRD response (log-rank $p=0.008$; [Figure 3\(B\)](#)). For blinatumomab use in second or later remission, median OS was 38.8 months (95% CI: 13.9–NR) ($n=24$) for patients with a complete MRD response and 16.0 months (2.0–NR) ($n=10$) for those without a complete MRD response (log-rank $p=0.14$; [Figure 3\(C\)](#)).

At the end of cycle 1 of blinatumomab treatment, most of the patients without a complete MRD response had shifts to a lower level of MRD compared with baseline ([Table 1](#)).

Long-term survival after blinatumomab and HSCT

Allogeneic HSCT was performed in 74 patients in continuous CR after blinatumomab, with a median age of 42 years at baseline ([Table 2](#)). Of these patients, 74% had received blinatumomab in the first remission and 26% had received blinatumomab in the second remission. The median time from blinatumomab treatment to HSCT in continuous CR was 3 months.

Most of the HSCT recipients (82%) had achieved a complete MRD response during blinatumomab treatment before they received HSCT. The HSCT conditioning regimen was myeloablative for 74% of patients with available data. The donor was a matched sibling for 23% of patients, an unrelated matched donor for 27% and a mismatched donor for 34%; donor information was missing for 16%. Most of the mismatched

donors had 1 mismatch with various approaches for donor matching ([Supplemental Table I](#)). Cord blood transplantations were performed in 6% of patients. Of the 36 patients who did not receive HSCT in continuous CR after blinatumomab, 12 (33%) received HSCT after a subsequent relapse and additional salvage therapy.

At the end of follow-up, 30/74 (40.5%) and 7/36 (19.4%) patients with or without HSCT in continuous CR, respectively, were alive in remission. Furthermore, 37% (27/74) with and 8% (3/36) without HSCT in continuous CR, respectively, died without relapse ([Figure 4\(A\)](#)). All 7 patients who were alive in remission without HSCT had achieved a complete MRD response during blinatumomab treatment. Six of them had received blinatumomab only; one patient received further treatment (i.e. cytarabine, dexamethasone, methotrexate and vincristine) after the study ended. When the analysis was limited to patients with a complete MRD response, 46% ($n=28/61$) patients with HSCT and 30% ($n=7/23$) without HSCT in continuous CR were alive in remission. Moreover, among these responders, 33% ($n=20/61$) with HSCT and 9% ($n=2/23$) without HSCT in continuous CR died without relapse ([Figure 4\(B\)](#)).

Median OS by HSCT use was as follows among patients with vs without complete MRD response: with HSCT in continuous CR, NR vs 16.5 months (log-rank $p=0.065$; [Figure 4\(C\)](#)); without HSCT in continuous CR, 56.4 vs 6.2 months (log-rank $p=0.043$; [Figure 4\(D\)](#)). Outcomes for individual patients are provided in [Supplemental Table II](#) (HSCT in continuous CR), [Supplemental Table III](#) (relapse after blinatumomab and subsequent HSCT) and [Supplemental Table IV](#) (no HSCT). The most frequently reported cause of long-term non-relapse mortality after HSCT was infection. One patient died of veno-occlusive disease after HSCT.

Discussion

In this final analysis of adults with BCP-ALL and MRD treated with blinatumomab, the median OS of 3 years compares favorably with previous evidence that median OS after chemotherapy for adult ALL with MRD is about 2 years [13].

Survival was even longer among patients who received blinatumomab in the first remission compared with those who received blinatumomab in second or later remission with MRD, although the difference was not statistically significant. Among 107 patients who were evaluable for MRD response after

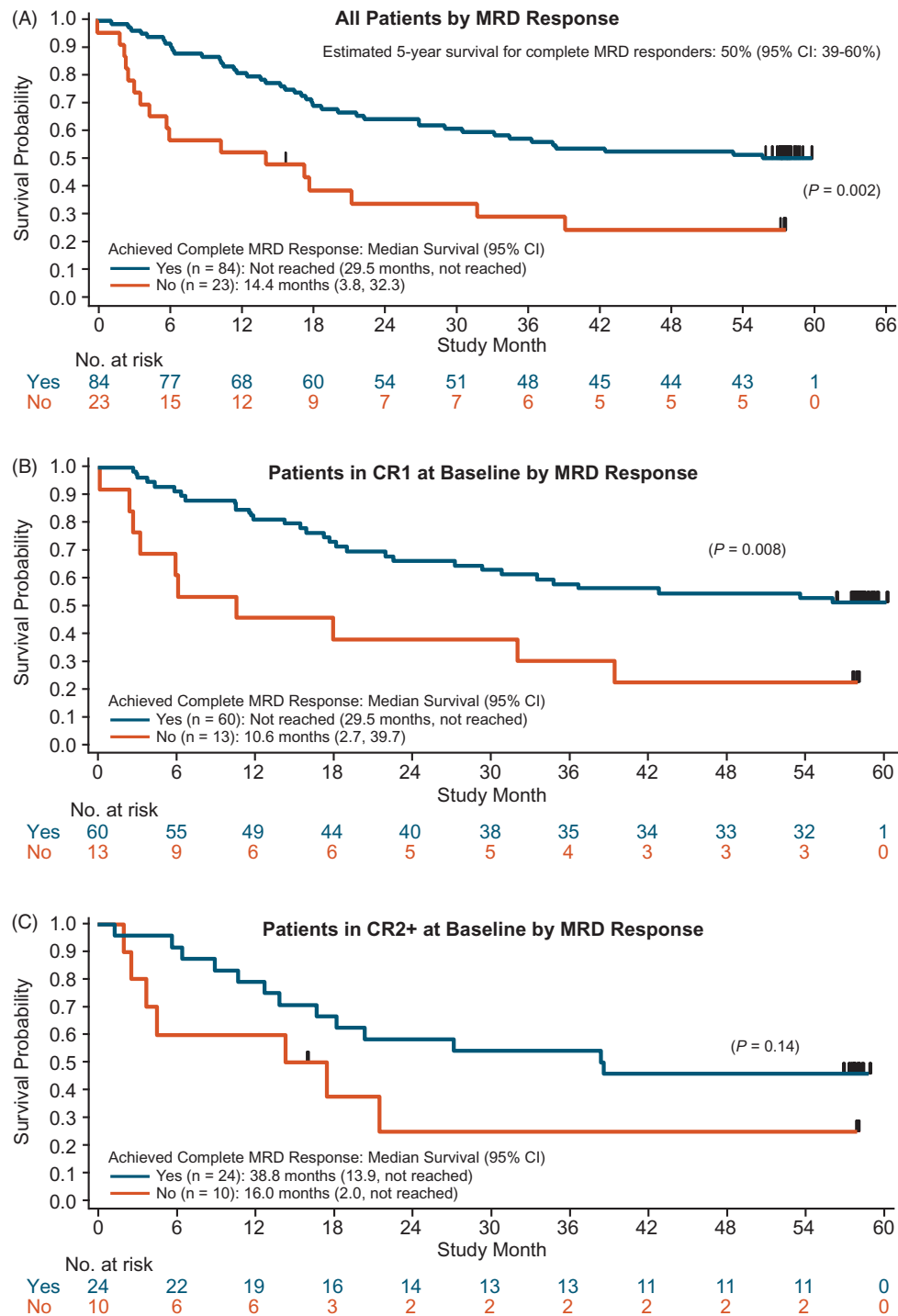


Figure 3. Kaplan-Meier analyses of overall survival in adults with MRD at baseline by complete MRD response after blinatumomab treatment. (A) Overall survival, starting at day 45 (after MRD assessment), by complete MRD response among evaluable patients with adequate MRD response assessment at cycle 1. (B) Overall survival, starting at day 45, by complete MRD response among patients in CR1 at baseline. (C) Overall survival, starting at day 45, by complete MRD response among patients in CR2+ at baseline. CI, confidence interval; CR1, first complete remission; CR2+, later complete remission; MRD, minimal residual disease.

the first cycle of blinatumomab treatment, 84 achieved a complete MRD response. Many of the patients who did not achieve a complete MRD response experienced an improvement in MRD from baseline to the end of the first cycle of blinatumomab.

A clear survival benefit was observed in patients with a complete MRD response for whom the median OS was NR after 5 years of follow-up, compared with 14.4 months in the 23 patients who did not achieve a complete MRD response. These results suggest that

Table 1. Change in MRD level from baseline to the end of cycle 1 in patients not achieving a complete MRD response ($n = 23$).

Baseline MRD ^a	Cycle 1 MRD ^b value						Total
	-5	-4	-3	-2	-1	NA	
NA	0	1	0	0	0	0	1
-5	0	0	0	0	0	0	0
-4	0	1	0	0	0	0	1
-3	1	6	2	0	1	0	10
-2	0	5	2	0	1	0	8
-1	1	0	0	0	0	2	3
Total	2	13	4	0	2	2	23

MRD: minimal residual disease; NA: not applicable.

^aIf multiple MRD measurements were taken at baseline visit, the latest one prior to blinatumomab infusion was used.

^bIf multiple MRD measurements were taken during cycle 1, the non-missing minimum MRD result was used.

long-term survival and cure are possible after a complete MRD response during blinatumomab treatment. Of particular interest is the 5-year remission achieved by 7 of 36 patients after blinatumomab but without HSCT; all 7 patients had a complete MRD response with blinatumomab and meet the generally accepted criteria for cure.

The significant difference in survival between patients with or without a complete MRD response was even greater when blinatumomab was used in the first remission with MRD. Patients who received blinatumomab in the first remission were also more likely to achieve a complete MRD response compared with those in second or later remission. Although these findings support the early use of blinatumomab in the first remission with MRD, benefit was also observed when blinatumomab was used in second or later remission with MRD.

In this analysis, we also provide a detailed examination of long-term outcomes after blinatumomab treatment followed by HSCT. Here, we report a 5-year survival of 43% overall and 50% for complete MRD responders regardless of the HSCT status. Blinatumomab improved long-term survival, even though this study had a relatively high rate of mismatched donors and relatively high median age of the patients who received HSCT, variables that normally result in worse outcomes. Previous investigations of outcomes for HSCT after chemotherapy salvage reported a 5-year survival of 16–23% for a highly selected sub-group that received HSCT from a matched donor after the first chemotherapy salvage [18]. Among patients who received HSCT after the second salvage regardless of matching or remission status, 1-year survival was only 18% [19].

The potential benefits of allogeneic HSCT in BCP-ALL must be compared with the potential risks. In this

Table 2. Characteristics of adults with BCP-ALL and MRD who received HSCT in CCR after blinatumomab treatment.

Characteristic	Received HSCT ($n = 74$)
Baseline characteristics	
Age, years	
≤35	26 (35)
>35 to ≤55	29 (39)
>55	19 (26)
Median (range)	42 (18–67)
Prior relapses	
0 (first remission)	55 (74)
1 (second remission)	19 (26)
≥2	0 (0)
Genetic abnormalities	
t(4;11) translocation and/or MLL-AF4+	5 (7)
After blinatumomab treatment	
Complete MRD response ^a	
Yes	61 (82)
No	11 (15)
Not determined	2 (3)
Donor relationship	
Related	19 (26) ^b
Cord	4 (5)
Unrelated	49 (66)
Unknown	2 (3)
Matching of unrelated HSCT	
Matched, sibling	17 (23)
Matched, unrelated	20 (27)
Mismatched	25 (34)
Missing	12 (16)
HSCT conditioning regimen	
Myeloablative	55 (74)
Reduced/non-myeloablative	14 (19)
Missing	5 (7)

Data are n (%), except as noted. BCP-ALL: B-cell precursor acute lymphoblastic leukemia; CCR: continuous complete remission; HSCT: hematopoietic stem cell transplantation; MRD: minimal residual disease.

^aComplete MRD response was defined as no target amplification with a minimum sensitivity of 10^{-4} at the end of cycle 1.

^bIncluded 1 haploidentical donor.

analysis, the estimate for 100-day mortality after HSCT was 7%. The 100-day mortality reported after blinatumomab and HSCT in continuous CR in this analysis was well below published data for 100-day mortality after HSCT in adults with ALL [20]. However, a 100-day mortality analysis is not sufficient to fully evaluate the risks of HSCT. Transplant-related mortality occurs up to 2 years or more after HSCT [14]. In this analysis, the overall mortality of patients who did not have reported relapse after HSCT was considerable, but it was in line with outcomes in trials for inotuzumab [21] or autologous T cells engineered to express CD19-specific chimeric antigen receptor cells [22].

Major challenges for future trials include identifying patients who may benefit from blinatumomab without HSCT, such as older patients and those without a related or matched donor, and identifying how outcomes can be further optimized (e.g. by administering maintenance therapy after achieving an MRD complete response). Current standard recommendations advise giving blinatumomab before HSCT to high-risk patients with MRD [23]. The outcome of HSCT may be

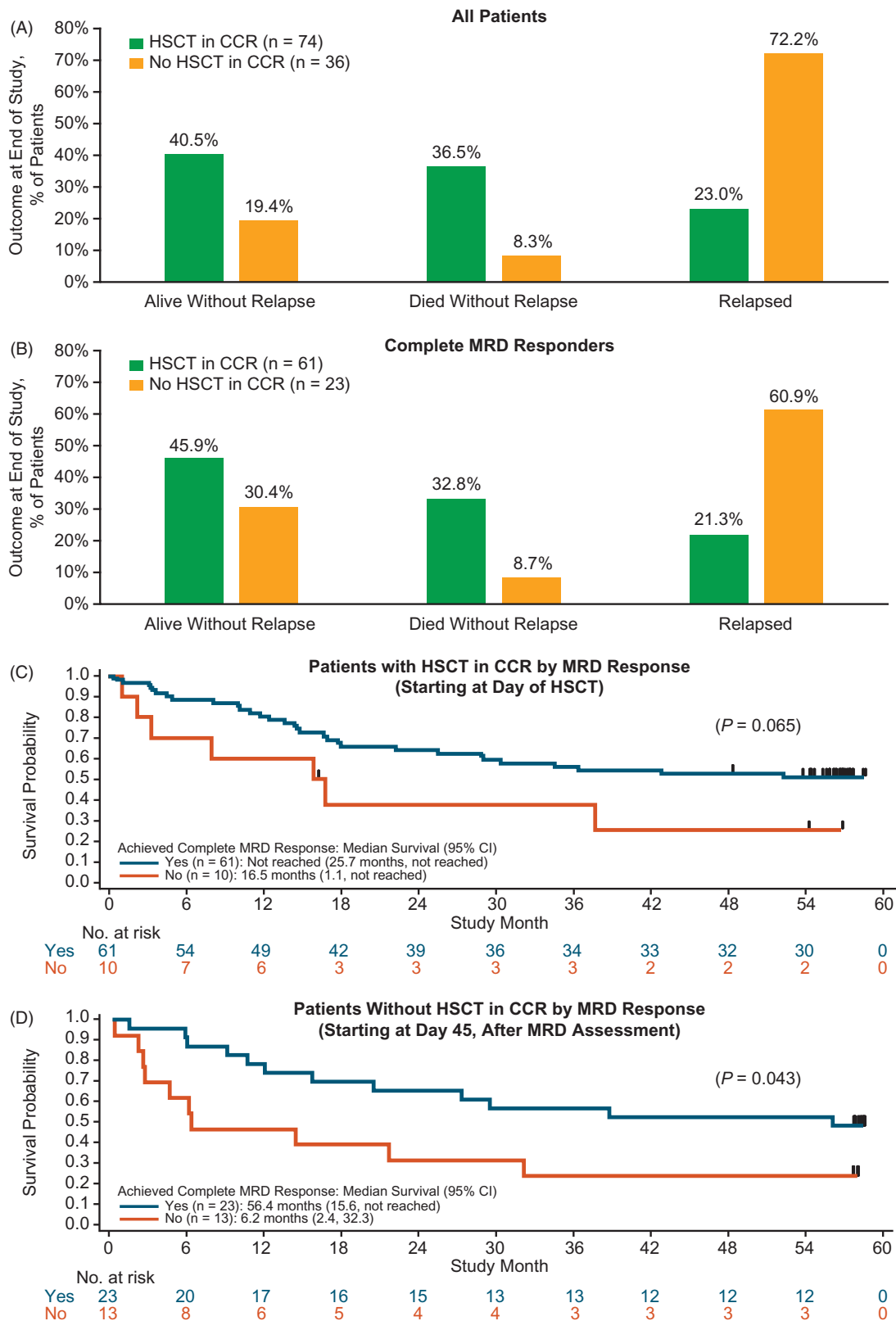


Figure 4. Outcomes with or without HSCT in CCR after blinatumomab. (A) Proportion of patients who were alive without relapse, died without relapse or relapsed, by the final visit at 5 years with or without HSCT in CCR after blinatumomab. (B) Proportion of patients with a complete MRD response during blinatumomab treatment who were alive without relapse, died without relapse or relapsed, by the final visit at 5 years with or without HSCT in CCR after blinatumomab. (C) Kaplan-Meier analysis of overall survival by complete MRD response, starting at the day of HSCT, among patients who received HSCT in CCR. (D) Kaplan-Meier analysis of overall survival by complete MRD response, starting at day 45, among patients who did not receive HSCT in CCR. CCR, continuous complete remission; CI, confidence interval; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease.

improved by better donor selection and selection of adequate conditioning regimens depending on age.

A strength of this analysis was the long-term follow-up of adults with BCP-ALL. Limitations included the single-arm design and the fact that the trial was not specifically designed and powered to examine the efficacy and safety of HSCT after blinatumomab treatment. Administration of HSCT, which was at the investigator's discretion, likely was used in patients who responded better to blinatumomab treatment and thus, represented a selected sub-set of blinatumomab recipients. Overall, 33% of evaluable patients did not receive HSCT while in continuous CR after blinatumomab treatment. Most of these patients relapsed and died during follow-up, but the trial was not designed to determine causality between HSCT use and the observed outcomes. Furthermore, no detailed data on the type of conditioning regimen were captured. The trial reflected real-world clinical practice with regard to HSCT, but for future trials, it would be of utmost importance to recommend standards for HSCT and to collect detailed documentation for HSCT. Nevertheless, the addition of HSCT after blinatumomab in appropriate patients may be beneficial, but long-term survival was also achieved in patients without additional HSCT.

In conclusion, these long-term 5-year follow-up data from the final analysis of the BLAST trial confirm the promising results of blinatumomab in adults with BCP-ALL and MRD, suggesting blinatumomab as a potential curative treatment in patients who achieved complete MRD response.

Author contributions

G.Z. and N.M. contributed to the concept and design of the study; N.G., H.D., M.Bo., C.G., C.F., M.Br., A.R., H-A.H., V.H., M.S.T., and R.C.B. collected patient data; all authors contributed to the analysis and interpretation of data; all authors contributed to the writing of the paper.

Disclosure statement

N.G. serves on an advisory board and speakers' bureau for and reports research support associated with the present work and travel support from Amgen; and serves on an advisory board and speakers' bureau for and reports travel support from Pfizer. G.Z. is an employee and stockholder of and reports patent royalties from Amgen. H.D. is an advisor for, serves on a speakers' bureau for and reports research support, consultancy, honoraria and travel/accommodation support from Amgen; is an advisor for and reports research support and honoraria from Roche/Genentech; is an advisor for, serves on a speakers' bureau for and reports honoraria and travel/accommodation support from Pfizer; is an advisor for, serves on a speakers' bureau for and reports research

support, honoraria and travel/accommodation support from Ariad (Incyte); is an advisor for and reports research support and honoraria from Jazz Pharma and Kite Pharma; is an advisor for and reports honoraria from Novartis, Agios, Sunesis, Ambit (Daiichi Sankyo), Karyopharm, Menarini, Astellas, Janssen, Servier, Seattle Genetics and Cellectis; and is a consultant and advisor for, serves on a speakers' bureau for and reports honoraria from Celgene. A.S. reports lecture fees from Amgen. M.Bo. reports consulting fees from Amgen, Pfizer, Bristol-Myers Squibb and Ariad Pharmaceuticals (Incyte); and research funding from Novartis. C.G. reports consulting fees from Amgen. C.F. serves on an advisory board for and reports research support associated with the present work from Amgen. M.Br. reports consulting fees from Amgen, Incyte and Roche; and research funding from Affimed and Regeneron. K.T. and N.M. are employees and stockholders of Amgen. H-A.H. reports research funding and travel support from Amgen, serves on advisory boards for Amgen, Pfizer, Jazz Pharmaceuticals, and Novartis, reports research funding from Regeneron. M.S.T. serves on an advisory board for and reports travel support from Amgen; reports travel support from Roche; serves on an advisory board for and reports travel support from Affimed and Regeneron; and serves on an advisory board for Gilead and Jazz Pharma. R.C.B. is an advisor for Amgen, Novartis, AstraZeneca, Genmab, GEMoAB, Cellex and Pfizer; and reports patent royalties from Amgen. A.R. and V.H. have no conflict of interest to disclose.

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