

Impact of high-sensitivity next-generation sequencing measurable residual disease and subsequent stem cell transplant in patients receiving blinatumomab for MRD-positive B-cell acute lymphoblastic leukemia

Blinatumomab is approved as measurable residual disease (MRD)-directed therapy in B-cell acute lymphoblastic leukemia (ALL) for MRD at a level of 10^{-3} or higher.¹ However, newer high-throughput next-generation sequencing (NGS) of immunoglobulin (IG) and T-cell receptor (TR) gene rearrangements can now track MRD with a sensitivity of 10^{-6} or 0.0001%.^{2,3} Several studies across different clinical contexts have demonstrated that low levels of MRD detected below the sensitivity of conventional multiparameter flow cytometry (MFC) or polymerase chain reaction (PCR) increase the risk of relapse and are associated with worse long-term survival.⁴⁻⁷ While blinatumomab is routinely used in clinical practice for levels of MRD below 10^{-3} , its efficacy for lower levels of MRD detected by more sensitive NGS-based assays and the role of consolidative allogeneic hematopoietic stem cell transplantation (HSCT) are not well-established.⁸ We conducted a retrospective analysis of patients with MRD-positive B-cell ALL in complete remission who received blinatumomab for the first time and who underwent NGS MRD assessment with ClonoSEQ (Adaptive Biotechnologies Co., Seattle, WA). Patients received up to four cycles of blinatumomab at standard doses, and patients with Philadelphia chromosome (Ph)-positive ALL received a concurrent tyrosine kinase inhibitor (TKI). For this study, only IG-calibrated samples (e.g., IgH, IgK, and/or IgL) were used for MRD assessment, as previously described.⁹ NGS MRD assessment were performed both prospectively as part of routine clinical care and retrospectively from available banked samples. Patients who had no detectable residual sequences by the clonoSEQ assay after blinatumomab were considered as “NGS MRD responders”. This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center and was conducted in accordance with the Declaration of Helsinki.

Between July 2015 and October 2023, 100 patients were treated with blinatumomab for MRD-positive B-cell ALL, 38 of whom had post-blinatumomab NGS assessment and are the primary subject of this analysis. Baseline characteristics are summarized in Table 1. Twenty-six patients (68%) had Ph-negative B-cell ALL and 12 patients (32%) had Ph-positive B-cell ALL. Among the 26 patients with Ph-negative B-cell ALL, 14 (54%) had at least one high-risk baseline cytogenetic feature, defined as poor-risk cytogenetics (e.g., low hypodiploidy/near triploidy, complex, or *KMT2A*

rearrangement), *TP53* mutation, and/or Ph-like B-cell ALL. The disposition of the 38 evaluable patients who received blinatumomab for MRD is shown in *Online Supplementary Figure S1*. The median follow-up for the study population is 22.2 months. Overall, 25 patients (66%) achieved NGS MRD negativity following blinatumomab (*Online Supplementary Table S1*). Among 27 patients who were assessed for NGS MRD after the first cycle of blinatumomab, 15 (56%) achieved NGS MRD negativity. Among the 12 patients who remained NGS MRD-positive after the first cycle of blinatumomab, three (25%) achieved NGS MRD negativity after additional cycles of blinatumomab. The overall NGS MRD response rate was higher in patients with Ph-positive B-cell ALL than in those with Ph-negative B-cell ALL (92% (11/12 patients) versus 54% (14/26 patients); $P=0.03$). The NGS MRD negativity rate was 69% (22/32 patients) for patients in first complete remission (CR1) compared and 50% (3/6 patients) for those in second complete remission (CR2). There were no significant differences in NGS MRD response rates in patients with or without prior inotuzumab ozogamicin (INO) exposure, or in Ph-negative patients with standard-risk or high-risk disease.

Achievement of NGS MRD negativity after blinatumomab was associated with excellent long-term outcomes (*Figure 1*). The median relapse-free survival (RFS) of NGS MRD responders and those who remained NGS MRD-positive at any level following blinatumomab (hereafter referred to as “non-responders”) were both not reached, and the 2-year RFS rates were 73% and 52%, respectively ($P=0.15$). The median overall survival (OS) of NGS MRD responders and non-responders was not reached and 25 months, respectively, and the 2-year OS rates were 91% and 48%, respectively ($P=0.02$). In patients with Ph-negative B-cell ALL, achievement of NGS MRD negativity after blinatumomab was prognostic in standard-risk but not in high-risk disease (*Online Supplementary Figure S2A-D*). Among the 14 high-risk patients, the median RFS of NGS MRD responders and non-responders were both not reached, and the 2-year RFS rates were 51% and 86%, respectively ($P=0.29$). The median OS of both high-risk NGS MRD responders and non-responders were not reached, and the 2-year OS rates were both 86% ($P=0.91$). Among the 12 patients with standard-risk disease, the median RFS of NGS MRD responders and non-responders were not reached and 11.9 months,

respectively, and the 2-year RFS rates were 100% and 20%, respectively ($P=0.02$). The median OS of standard-risk NGS

Table 1. Baseline characteristics at time of blinatumomab initiation.

Patient characteristic, N=38	N (%) or median [range]
Age, years ≥60 years	34 [18-72] 4 (11)
ECOG performance status 0 1 2	12 (32) 24 (63) 2 (5)
WBC at diagnosis $\times 10^9/L$	5.8 [1.9-53.8]
History of CNS/EM disease	2 (5)
Disease subtype Ph-negative Ph-positive	26 (68) 12 (32)
Karyotype Ph-positive Diploid Complex Low hypodiploidy/near triploidy <i>KMT2A</i> r High hyperdiploidy Other Insufficient metaphases	12 (32) 5 (13) 1 (2) 1 (2) 4 (11) 1 (2) 12 (32) 2 (5)
Ph-like ALL	6/26 (23)
<i>TP53</i> mutation	3 (8)
High-risk Ph-negative B-ALL*	14/26 (54)
Frontline therapy (CR1 only) Hyper-CVAD-based Mini-CVD-based Pediatric-inspired high intensity	22/32 (69) 7/32 (21) 2/32 (9)
Prior inotuzumab ozogamicin exposure	21 (55)
Disease status CR1 CR2 CR3 CR4	32 (84) 4 (11) 1 (2) 1 (2)
TKI (Ph-positive B-cell ALL only) Ponatinib	12/12 (100)
MRD status at blinatumomab start [†] NGS ⁺ /MFC ⁻ <0.0001% ≥0.0001% to <0.001% ≥0.001% MFC ⁺ <0.01% ≥0.01% to <0.1% ≥0.1% to <1% ≥1%	15 (39) 8 (21) 4 (11) 3 (8) 23 (61) 6 (16) 6 (16) 7 (18) 4 (11)

*High-risk defined as poor-risk cytogenetics (e.g., low hypodiploidy/near triploidy, complex, or *KMT2A* rearrangement), *TP53* mutation, and/or Philadelphia chromosome (Ph)-like B-cell acute lymphoblastic leukemia (ALL). [†]Next-generation sequencing (NGS) measurable residual disease (MRD) assessment performed using ClonoSEQ MRD Assay (Adaptive Biotechnologies Co., Seattle, WA). Multiparameter flow cytometry (MFC) MRD assessment performed using 6-color MFC. ECOG: Eastern Cooperative Oncology Group; WBC: white blood cell; CNS: central nervous system; EM: extramedullary; CR: complete remission; Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; Mini-CVD: low intensity therapy with cyclophosphamide, vincristine, and dexamethasone; TKI: tyrosine kinase inhibitor.

MRD responders and non-responders were not reached and 12.3 months, respectively, and the 2-year OS rates were 100% and 20%, respectively ($P=0.04$).

Relapse rates were higher in NGS MRD responders with prior INO exposure compared to NGS MRD responders who did not receive INO previously (*Online Supplementary Figure S2E, F*). The median RFS of NGS MRD responders with and without prior INO exposure was 17.2 months and not reached, respectively, and the 2-year RFS rates were 43% and 100%, respectively ($P=0.006$), and the 2-year OS rates were 43% and 79%, respectively ($P=0.10$). Outcomes in Ph-negative B-ALL and Ph-positive B-ALL subgroups are shown in *Online Supplementary Figure S2G-J*. The median RFS of NGS MRD responders and non-responders in Ph-negative B-ALL were both not reached, and the 2-year RFS rates were 67% and 57%, respectively ($P=0.39$). The median OS of NGS MRD responders and non-responders in Ph-negative B-ALL were both not reached, and the 2-year OS rates were 91% and 56%, respectively ($P=0.11$). There was only one NGS MRD non-responder in the Ph-positive B-ALL subgroup.

Two NGS MRD responders were bridged to transplant. Among seven patients who did not achieve NGS MRD negativity with blinatumomab and who subsequently underwent HSCT in MRD-positive CR, the median time from start of blinatumomab therapy to HSCT was 2.8 months (range, 1.8-4.1 months). We performed a landmark analysis to analyze the impact of HSCT on patients who did not achieve NGS MRD negativity with blinatumomab. The median RFS of HSCT and no HSCT in non-responding patients was not reached and 13.5 months, respectively, and the 2-year RFS rates were 71% and 27%, respectively ($P=0.20$; Figure 2A). The median OS of HSCT and no HSCT in non-responding patients was not reached and 25 months, respectively, and the 2-year OS rates were 71% and 27%, respectively ($P=0.24$; Figure 2B). The median OS of NGS MRD responders who did not undergo HSCT and non-responders who underwent HSCT were both not reached, and the 2-year OS rates were 95% and 71%, respectively ($P=0.14$).

In this study, we showed that adults with B-cell ALL who received blinatumomab for any level of MRD and achieved NGS MRD negativity had excellent outcomes, despite most of these patients not undergoing allogeneic HSCT following blinatumomab, with a 2-year RFS rate of 73% and a 2-year OS rate of 91%. In contrast, patients who did not achieve MRD negativity after blinatumomab had poor outcomes, with a 2-year RFS rate of 52% and a 2-year OS rate of 48%. Post-blinatumomab HSCT in MRD-positive remission

appeared to improve outcomes for these patients with suboptimal response to blinatumomab. Overall, these data demonstrate that high-sensitivity MRD as assessed by NGS improve prognostication in B-cell ALL and can identify patients who are predicted to have robust, long-term responses to blinatumomab. Lack of NGS MRD response to blinatumomab may also identify patients who may benefit from additional therapies, including consideration of HSCT. The optimal consolidative approach for patients who achieve MRD negativity after blinatumomab is controversial. In the BLAST trial, the benefit of HSCT consolidation after achieving MRD negativity was unclear.¹⁰ While patients who under-

went HSCT consolidation had lower rates of relapse, the potential survival benefit of HSCT was diminished by the introduction of transplant-related mortality; furthermore, 30% of patients who did not undergo HSCT remained in remission at 5-year follow-up, suggesting that durable remissions without consolidative HSCT are possible in some patients.¹¹ Emerging data suggests that early achievement of NGS MRD negativity after frontline therapy is associated with excellent outcomes, even in high-risk patients. Here, we show that NGS MRD negativity following blinatumomab was associated with superior survival outcomes across different B-cell ALL subgroups. The most durable responses

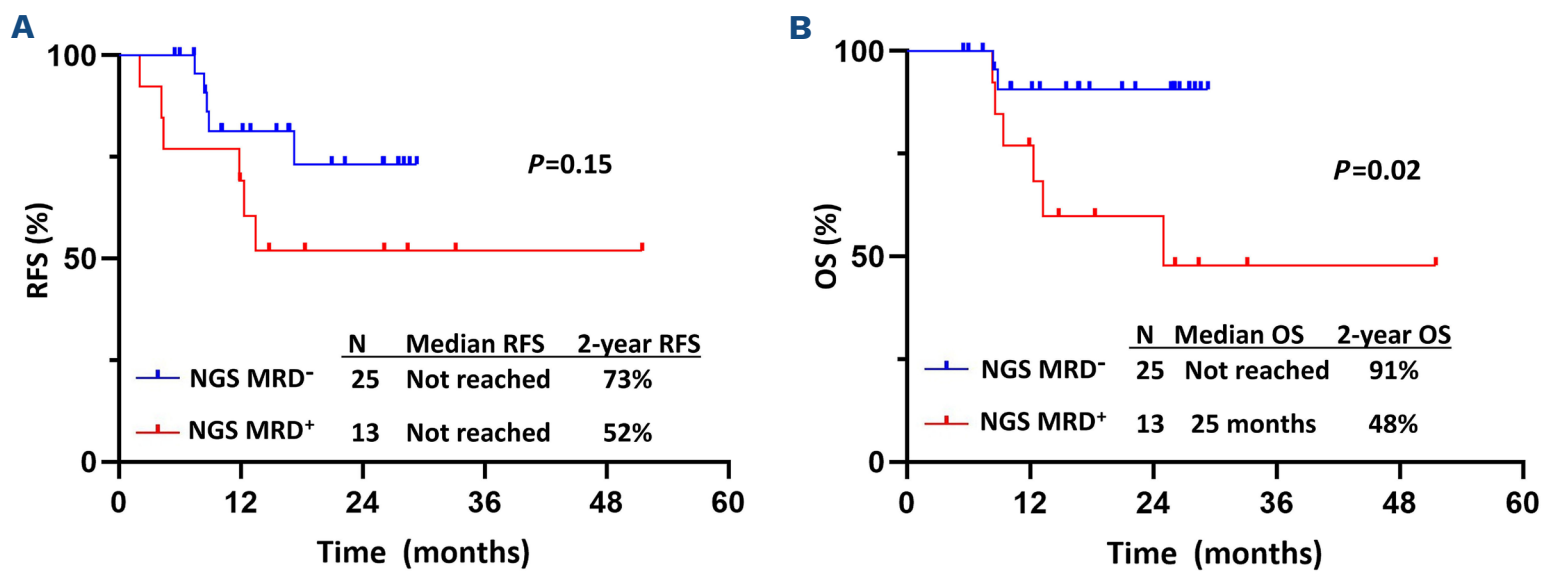


Figure 1. Impact of next-generation sequencing measurable residual disease negativity after blinatumomab. (A) Relapse-free survival (RFS) and (B) overall survival (OS). NGS: next-generation sequencing; MRD⁺: measurable residual disease-positive; MRD⁻: MRD-negative.

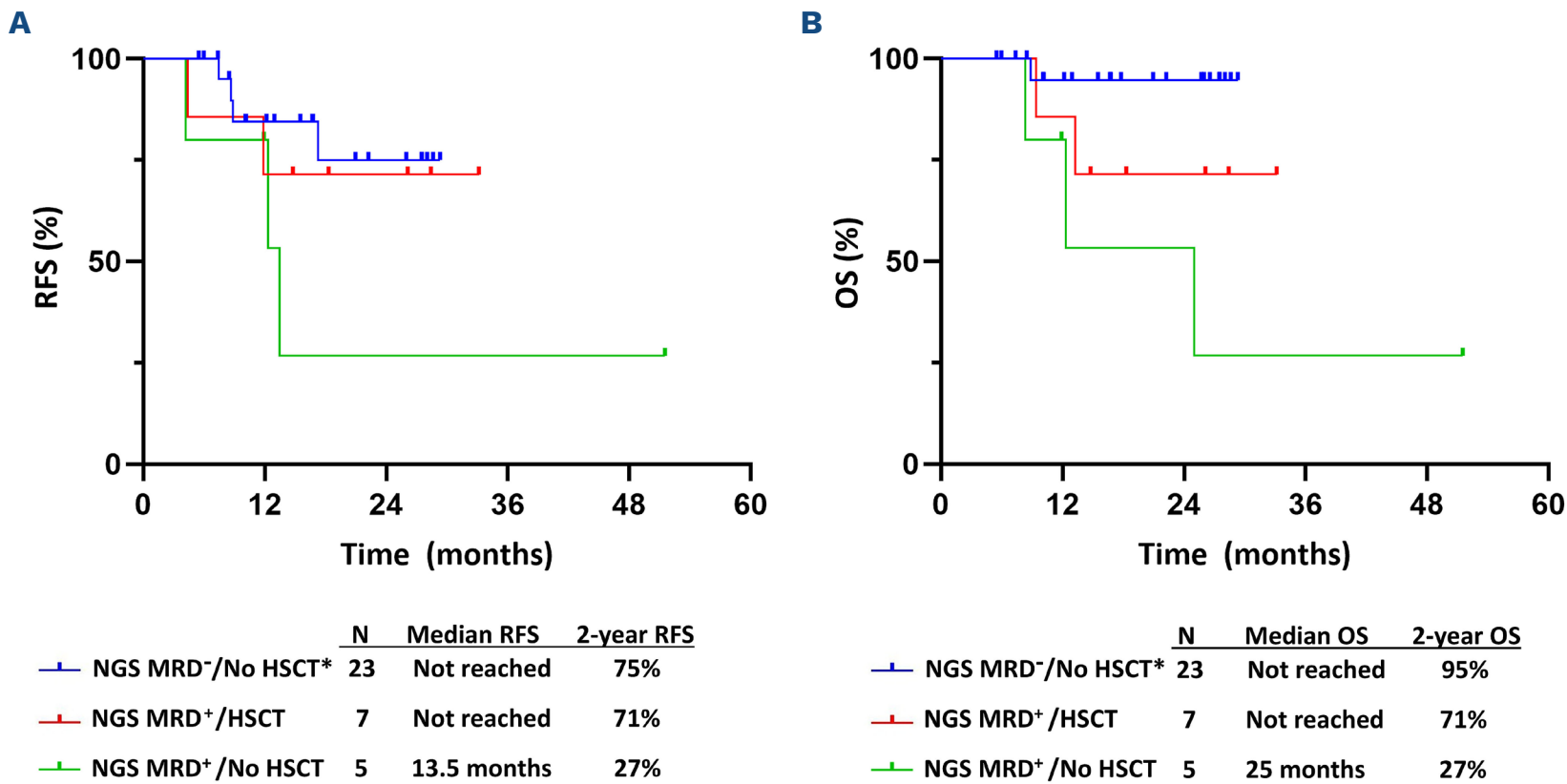


Figure 2. Impact of next-generation sequencing measurable residual disease response in patients receiving blinatumomab, stratified by consolidative allogeneic hematopoietic stem cell transplantation. (A) Relapse-free survival (RFS) and (B) overall survival (OS). *Two next-generation sequencing (NGS) measurable residual disease (MRD) responders were bridged to allogeneic hematopoietic stem cell transplantation (HSCT).

were observed in responding patients with standard-risk Ph-negative B-cell ALL (2-year RFS: 100%), suggesting that blinatumomab as MRD-directed therapy could be potentially curative for many patients, if deep MRD negativity is achieved. In contrast, we observed that patients with high-risk Ph-negative B-cell ALL who achieved NGS MRD negativity after blinatumomab had a 2-year RFS of only 51%, suggesting that blinatumomab may not be curative for many of these patients, even after a deep NGS MRD-negative response. Thus, our findings suggest that baseline cytomolecular risk should be combined with NGS MRD response after blinatumomab to aid in risk stratification and to inform selection of consolidative therapy.

Patients who did not achieve NGS MRD negativity after blinatumomab had poor outcomes, although allogeneic HSCT seemed to improve survival in these patients. Our data suggest that patients who do not achieve NGS MRD negativity with blinatumomab should undergo alternative, MRD-directed therapies. While we observed improved outcomes with HSCT, it is possible that outcomes would be further improved with other MRD-directed therapies, either as definitive therapy or followed by subsequent HSCT.^{12,13} For patients planned for allogeneic HSCT, efforts should be made to first eradicate MRD (when feasible), as detectable MRD prior to HSCT has been associated with poor outcomes in several studies, even if only low levels of MRD (e.g., 10^{-4} to 10^{-6}) are present.⁴

There are several limitations to our study. One limitation is the heterogeneity of our study population with regards to prior therapy exposure (e.g., 21 [55%] patients received INO prior to blinatumomab, 6 [16%] patients were treated with blinatumomab at CR2+, and 7/32 [21%] patients in CR1 received a low-intensity induction therapy) and disease subtype (12 [32%] patients with Ph-positive B-ALL concurrently treated with TKI). These differences in disease biology temper our ability draw definitive conclusions on the impact of blinatumomab alone on MRD. Furthermore, due to the retrospective nature of our study, there was no standardization in deciding which patients should undergo HSCT consolidation. Prospective studies are needed to determine how NGS MRD response should inform decisions about HSCT in remission.

In conclusion, our study shows that patients who receive blinatumomab for MRD-positive B-cell ALL and achieve deep levels of MRD-negative remission as assessed by NGS have superior survival outcomes and can have excellent, long-term remissions without allogeneic HSCT. In contrast, patients who do not achieve NGS MRD negativity with blinatumomab have poor outcomes and may benefit from allogeneic HSCT or alternative MRD-directed approaches. These findings highlight the importance of high-sensitivity NGS MRD assessment in evaluating the effectiveness of B-cell ALL therapy and in informing consolidative strategies in these patients.

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<https://doi.org/10.3324/haematol.2025.289318>

Received: September 30, 2025.

Accepted: March 16, 2026.

Early view: March 26, 2026.

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Disclosures

NJS has received consulting fees from Amgen, Pfizer Inc., GSK, Adaptive Biotechnologies, Autolus, and Sanofi; researching funding from Takeda Oncology, Astellas Pharma Inc., Xencor, GSK, NextCure, Ascentage, Novartis, Hemogenyx, and Vironexis; and honoraria from Adaptive Biotechnologies, Novartis, Amgen, Takeda Oncology, Pzifer Inc., Astellas Pharma Inc., and Sanofi. The other authors have no conflicts of interest to disclose.

Contributions

DN, EJ, and NJS designed the study and wrote the manuscript. DN and NJS analyzed the data. HK, WM, NJ, CN, PK, EJS, IK, FH, OK, MM, RG, and FR provided suggestions and revised the manuscript. EJ and NJS supervised the analysis. All authors read and approved the manuscript.

Acknowledgments

Adaptive Biotechnologies Co. performed the NGS MRD assay on samples at no cost to the authors.

Funding

The study was supported by an MD Anderson Cancer Center Support Grant (CA016672) and SPORC.

Data-sharing statement

Data supporting this study are available on request from the corresponding author.

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