

CRITICAL REVIEW

Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts

Nicholas J. Short¹  | Elias Jabbour¹  | Maher Albitar² | Marcos de Lima³ | Lia Gore⁴ | Jeffrey Jorgensen¹ | Aaron C. Logan⁵  | Jae Park⁶ | Farhad Ravandi¹ | Bijal Shah⁷ | Jerald Radich MD⁸ | Hagop Kantarjian¹ 

¹The University of Texas MD Anderson Cancer Center, Houston, Texas

²NeoGenomics Laboratories, Inc., Aliso Viejo, California

³University Hospitals, Cleveland, Ohio

⁴Children's Hospital Colorado and University of Colorado Cancer Center, Aurora, Colorado

⁵University of California San Francisco, San Francisco, California

⁶Memorial Sloan Kettering Cancer Center, New York, New York

⁷Moffitt Cancer Center, Tampa, Florida

⁸Fred Hutchinson Cancer Research Center, Seattle, Western Australia

Correspondence

Elias Jabbour, MD, Department of Leukemia, Unit 428, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
Email: ejabbour@mdanderson.org

Funding information

PLATO (Physicians Learning and Teaching in Oncology) Foundation

Abstract

Measurable residual disease (MRD) that persists after initial therapy is a powerful predictor of relapse and survival in acute lymphoblastic leukemia (ALL). However, the optimal use of this information to influence therapeutic decisions is controversial. Herein, we comprehensively review the role of MRD assessment in adults with ALL, including methods to quantify residual leukemia cells during remission, prognostic impact of MRD across ALL subtypes, and available therapeutic approaches to eradicate MRD. This review presents consensus statements and provides an evidence-based framework for practicing hematologists and oncologists to use MRD information to make rational treatment decisions in adult patients with ALL.

1 | INTRODUCTION

The vast majority of adults with acute lymphoblastic leukemia (ALL) achieve remission with standard chemotherapy regimens, but many of these patients ultimately relapse and die from leukemia.^{1,2} In these patients, relapse occurs despite achievement of morphologic remission (ie, bone marrow blasts <5%), suggesting that low levels of measurable residual disease (MRD), also called "minimal residual disease," persist in the remission bone marrow (Figure 1).³ Compared with morphologic assessment alone, sensitive methods of MRD quantification can better estimate the reduction in posttreatment disease burden and provide information about the leukemia biology and treatment response of

individual patients. Posttreatment MRD status is a powerful prognostic factor in all subtypes of ALL and, in many studies, supersedes historically relevant prognostic factors, including age, white blood cell count, and cytogenetics.⁴⁻⁷ Given the significant impact of MRD on survival outcomes in adults with ALL, many authorities suggest that MRD status can be used to inform postremission strategies, such as allogeneic hematopoietic stem cell transplantation (HSCT) in first remission. The development of novel approaches (eg, blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor [CAR] T cells) that are highly effective in eradicating residual disease has further increased the complexity of decision-making regarding MRD.

Herein we review the published data on MRD in ALL, with the goal of developing evidence-based consensus recommendations for the detection and management of MRD in adult patients with ALL.

Nicholas J. Short, Elias Jabbour, Jerald Radich and Hagop Kantarjian contributed equally to this study.

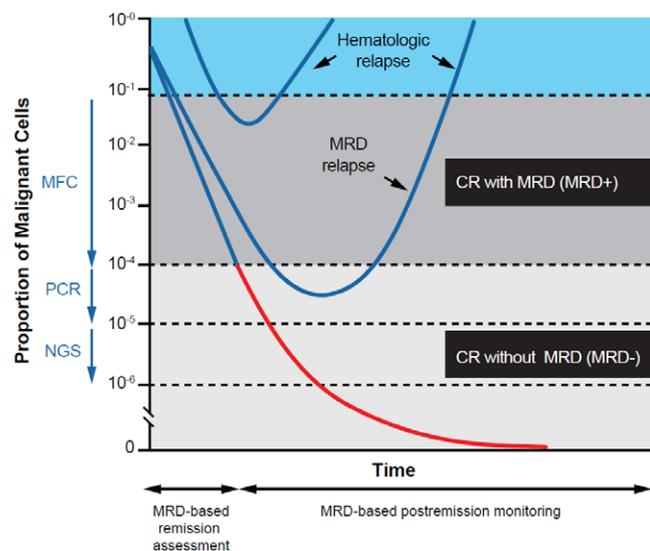


FIGURE 1 Patterns of response and relapse in ALL according to quantitative clearance of leukemic burden. Arrows represent sensitivity of assay. CR, complete remission; MFC, multiparameter flow cytometry; NGS, next-generation sequencing; PCR, polymerase chain reaction. Republished with permission of the American Society of Hematology, from “Has MRD monitoring superseded other prognostic factors in adult ALL?” Brüggemann M, Raff T, Kneba M, 120 (23), 2012; permission conveyed through copyright clearance center, Inc.³ [Color figure can be viewed at wileyonlinelibrary.com]

Specifically, we review various MRD detection methodologies and discuss how detection and quantification of MRD in various ALL subtypes correlate with outcomes. We also discuss evidence supporting various therapeutic options for patients with MRD-positive remission, including both HSCT and non-HSCT approaches, and provides consensus recommendations to help guide clinician decision-making in this setting.

2 | METHODS OF MRD ASSESSMENT

Various methods to quantify posttreatment MRD in patients with ALL are available in clinical practice and in the research setting, including multiparameter flow cytometry (MFC), quantitative polymerase chain reaction (PCR), and next-generation sequencing (NGS). The advantages and disadvantages of these various methods of MRD assessment are summarized in Table 1. Regardless of the methodology used, for optimal sensitivity MRD assessment should generally be performed on a bone marrow specimen, as levels of detectable MRD may be 1-3 logs lower in the peripheral blood than in the bone marrow.⁸⁻¹⁰ This difference between peripheral blood and bone marrow MRD assessment appears to be most pronounced in patients with B-cell ALL.¹⁰

2.1 | Flow cytometry

MFC is performed by identifying and tracking aberrant leukemia-associated immunophenotypes (LAIPs) on leukemic blasts. This can be done either by searching for the diagnostic aberrant LAIP in the remission sample (eg, aberrant expression of myeloid antigens or increased or decreased density of antigens normally expressed on benign B-cell precursors), or by measuring any difference in immunophenotypes

from the highly stereotypical normal immunophenotype distribution in the remission sample.¹¹ In most experienced centers in the United States, the latter “difference from normal” (DfN) approach is now preferred, in part because it does not require knowledge of the original immunophenotype. Challenges to interpretation include increased normal benign B-cell precursors during bone marrow recovery, which can potentially mask a small residual ALL population (false negative) or be misinterpreted as residual ALL (false positive). The DfN strategy is advantageous for detecting residual ALL populations even after a phenotypic shift, which may arise as a direct result of therapy, or due to a shift in clonal architecture.¹² Regardless of the method used, MRD assessment with MFC requires substantial expertise on the part of the interpreting pathologist, who appears to be the primary source of inconsistent interlaboratory interpretations. Although MFC MRD measurement has been standardized in Europe,¹³ there is currently no formal standardization of MFC MRD measurement across institutions and laboratories in the United States. Fresh, viable cells are also required for analyses. Despite these disadvantages, MFC-based MRD assessment is significantly faster, less expensive, and less labor-intensive than PCR-based methods. Standard flow-based methodologies are capable of detecting MRD with a sensitivity of approximately 1 leukemic cell per 10 000 nucleated cells. Techniques using ≥ 8 -color flow cytometry may achieve better sensitivity (theoretically as low as 10^{-6}), although such high levels of sensitivity require input of $2-5 \times 10^7$ nucleated cells, which is rarely obtainable from remission marrows.^{9,13}

2.2 | PCR

Quantitative PCR may be used to identify (1) clonal immunoglobulin heavy chain (*IGH*) gene rearrangements, (2) T-cell receptor (TCR) gene rearrangements, or (3) recurrent leukemia-associated translocations. While recombination of the V, D, and J segments of *IGH* and the genes encoding the TCR receptor complex are random events in normal B and T cells early in the maturation process, leukemia transformation subsequent to VDJ recombination results in identical *IGH* and TCR rearrangements being present in malignant lymphoblast clones in an individual patient. Notably, the PCR assay is directed at the junctional regions of these rearrangement events, which are the most diverse in sequence. Compared with North America, where MFC is more commonly used to detect MRD, PCR-based MRD assessment is used frequently in European countries, where a substantial effort by the EuroMRD consortium has been undertaken to standardize this assay.¹⁴ Furthermore, quantitative PCR is approximately 1 log more sensitive than can typically be achieved with MFC.¹⁵⁻¹⁷ However, quantitative PCR assays require construction of patient-tailored allele-specific oligonucleotide (ASO) primers, which is time-consuming and laborious. Additionally, because minor malignant subclones present at diagnosis may not be appreciated when developing patient-specific primers, these may be subsequently overlooked in remission samples, leading to false-negative results. Unlike flow cytometry, PCR-based MRD assessment of *IGH* or TCR rearrangements cannot be performed in the absence of a reference sample with high leukemic load in which leukemia-associated rearrangements can be clearly identified.

PCR can also be used to detect MRD in patients with recurrent leukemia-associated translocations, such as *BCR-ABL1*. Because PCR

TABLE 1 Methods of measurable residual disease assessment in ALL

Method	Specimen	Sensitivity	Advantages	Disadvantages
Flow cytometry for "difference from normal"	Fresh viable cells	$\sim 10^{-4}$	<ul style="list-style-type: none"> Fast Relatively inexpensive Potential to detect phenotypic shifts Does not require access to pretreatment specimens 	<ul style="list-style-type: none"> Confounders: Increased benign B-cell precursors during marrow recovery; potential phenotypic shifts Requires significant technical expertise Limited standardization (though attempts in progress)
RQ-PCR for <i>IGH</i> /TCR gene rearrangements	DNA	$\sim 10^{-4}$ to 10^{-5}	<ul style="list-style-type: none"> Sensitive Well standardized with consensus guidelines 	<ul style="list-style-type: none"> Time consuming and labor intensive Requires significant technical expertise May not detect small subclones at diagnosis, thus may miss clonal evolution Requires access to pretreatment specimens Expensive
RQ-PCR for recurrent gene fusions	RNA	$\sim 10^{-4}$ to 10^{-5}	<ul style="list-style-type: none"> Sensitive Uses standard primers utilized for diagnostic purposes 	<ul style="list-style-type: none"> Applicable to <50% of ALL cases Limited standardization
NGS	DNA	$\sim 10^{-6}$	<ul style="list-style-type: none"> Very sensitive Fast (uses consensus primers) Potential to track small subclones and clonal evolution 	<ul style="list-style-type: none"> Not standardized Requires complex bioinformatics Minimal clinical validation Requires access to pretreatment specimens Expensive

RQ-PCR, real-time quantitative polymerase chain reaction; TCR, T-cell receptor.

for these gene translocations is performed using the same universal primer probes used for diagnostic purposes, this method is generally simpler than using either MFC or patient-specific PCR. A sensitivity similar to patient-specific PCR assays can be reached with this approach (ie, up to 10^{-5}), although commercially available assays may not always provide this level of sensitivity. The primary drawback is that only a minority of adults with ALL carry a recurrent gene fusion that can be used as an MRD marker of their disease. These PCR assays are not fully standardized, which complicates the interpretation of results. Even though there has been careful standardization of molecular response using *BCR-ABL1* in chronic myeloid leukemia (CML),¹⁸ these molecular response milestones cannot necessarily be extrapolated to the majority of cases of Philadelphia chromosome (Ph)-positive ALL in which the p190 transcript is present. Furthermore, although most studies have evaluated the prognostic impact of *BCR-ABL1*-based MRD in patients with Ph-positive ALL, PCR for patient-specific *IGH* and TCR rearrangements may be more specific than *BCR-ABL1* monitoring, as *BCR-ABL1* can rarely be detected in non-ALL hematopoietic cells.¹⁹ This latter scenario may represent a "CML-like" Ph-positive ALL in which the *BCR-ABL1* residual disease status does not necessarily affect prognosis.²⁰ Despite these potential disadvantages, PCR for *BCR-ABL1* is the most common method used for MRD assessment of Ph-positive ALL in US academic centers and appears to be superior to MFC in predicting outcomes in this ALL subtype.²¹

2.3 | NGS

The development of NGS as a tool to identify MRD may overcome some of the limitations of the current MFC and PCR methodologies described above. In ALL, the targets of NGS-based MRD assays have thus far been the same leukemic clone-specific *IGH* and TCR gene rearrangements as with PCR assays.²²⁻²⁶ NGS utilizes rapid, parallel sequencing using consensus primers. Therefore, NGS does not require the construction of patient-specific reagents. This feature also makes

standardization and performance characterization possible. The sensitivity achieved with NGS is up to 1–2 logs deeper than with other currently available methods of MRD detection in the United States, and there is evidence that NGS can identify clinically significant MRD in patients who are MRD negative by other MRD methodologies (ie, MFC or PCR).²²⁻²⁶ It is important to note, however, that MFC and PCR can at least theoretically achieve similar levels of sensitivity as NGS if an adequate number of cells or DNA are analyzed, although this is not done in standard practice. In addition to a high degree of sensitivity, NGS is also highly specific for residual disease and may outperform other methods of MRD, particularly PCR.²⁷ NGS also offers the advantage of being able to track minor subclones, which may be missed with other methodologies; the importance of these subclones in driving relapse is becoming increasingly appreciated in ALL.^{28,29} However, despite the theoretically excellent sensitivity of NGS-based MRD assays (ie, up to 1 leukemia cell per 10^6 nucleated cells), large amounts of cells/DNA from the remission bone marrow are required to achieve this level of sensitivity, which may limit their utility in some scenarios. For example, NGS may not be optimal for quantification of MRD in post-treatment aplastic samples, as this may lead to overamplification of rare nonmalignant rearrangements and overestimation MRD. Like with ASO PCR, pretreatment samples are also required. Notably, on September 28, 2018, the US Food and Drug Administration approved the clonoSEQ NGS assay for the detection of MRD in ALL and multiple myeloma; this represents the first approval of an NGS-based test for MRD in any hematologic malignancy and is likely to lead to wider clinical adoption of this assay in the coming years.

2.4 | Consensus recommendations on MRD assessment methodologies

MRD assessment should be performed on bone marrow specimens for optimal sensitivity (particularly for B-cell ALL). PCR for *BCR-ABL1*

is preferable to MFC for patients with Ph-positive ALL. Depending on access to different assays, either MFC, ASO PCR, or NGS are reasonable MRD quantification techniques for patients with Ph-negative B-cell ALL or T-cell ALL. MFC should be performed in a high-volume clinical laboratory with a pathologist experienced in MFC-based MRD interpretation. ASO PCR should only be performed in well-standardized laboratories. Regardless of the method used, a sensitivity of at least 10^{-4} should be reached for adequate assessment of MRD.

3 | PROGNOSTIC AND PREDICTIVE IMPACT OF MRD IN ALL

3.1 | Pediatric ALL

The impact of MRD in determining outcomes in ALL was first appreciated in pediatric studies. Although a full discussion of the prognostic and therapeutic role of MRD assessment in childhood ALL is outside the scope of the present review, it is important to acknowledge the vital role that MRD assessment has played in informing prognosis and therapy allocation in this population. Achievement of MRD negativity after induction chemotherapy has been shown to be highly associated with long-term outcomes in numerous studies, including a meta-analysis of 20 pediatric studies incorporating data from over 10 000 patients.³⁰ Given the strong impact of MRD on survival in pediatric ALL, MRD status is now systematically used by all cooperative groups worldwide to risk-stratify patients and guide treatment decisions, including treatment intensification or deintensification.³¹⁻³⁸ For children with ALL who receive HSCT in first remission, levels of MRD before transplant are predictive for posttransplant relapse.³⁹⁻⁴¹ Similarly, higher levels of MRD after HSCT have been shown to predict impending relapse, particularly when detected after day +60 post-transplantation.⁴² Despite the very clear prognostic role of MRD in pediatric ALL, recent studies have suggested that other genetic factors (eg, *IKZF1* deletions co-occurring with other copy number alterations, also known as "IKZF1 plus") may influence MRD kinetics, the optimal cutoff for MRD assessment, and the predictive impact of MRD response.^{43,44} These findings all serve as a framework for future studies of MRD in adult ALL, including how MRD information can be used to rationally inform postremission therapies such as HSCT.

3.2 | T-cell ALL and Ph-negative B-cell ALL in adults

In adults with T-cell ALL or Ph-negative B-cell ALL, the achievement of MRD negativity is predictive for long-term outcomes regardless of whether MFC- or PCR-based assays are used.^{4-7,45-47} When comparing MRD studies, several important considerations influence the predictive impact of MRD, including the treatment regimen used, the sensitivity of the MRD assay and timing of assessment, and the rate of HSCT in the cohort, among others. Despite differences across studies, posttreatment MRD status has consistently emerged as one of the most powerful predictors of outcomes, and is frequently identified as the only independently prognostic factor for relapse and survival.⁴⁻⁶ For example, in a meta-analysis of 16 studies comprising 2076 adult patients with ALL (including T-cell ALL and both

Ph-negative and Ph-positive B-cell ALL), achievement of MRD negativity was associated with significant improvement in event-free survival (EFS) and overall survival (OS), with hazard ratios of 0.28 (95% Bayesian credible interval, 0.24-0.33) and 0.28 (95% Bayesian credible interval, 0.20-0.39), respectively.³⁰ The 10-year disease-free survival rate was 64% for patients who achieved MRD negativity compared with 21% for those who were MRD positive. The studies included in this meta-analysis evaluated MRD at the end of induction or early consolidation, using either MFC or PCR. Notably, the predictive impact of MRD clearance was consistent across therapies, methods and timing of MRD assessment, level of MRD cutoff, and ALL subtypes.

Recent reports have suggested that MRD information may be combined with cytogenetics or genomic profiling in order to further improve risk-stratification in adults with ALL.^{7,48,49} In particular, adult patients with Ph-like ALL, *MLL* gene rearrangement, and early T-cell precursor ALL appear to have relatively poor outcomes regardless of MRD status (when quantified at conventional levels of 10^{-4}).^{7,50-52} These disease subtypes are also more likely to have persistent MRD despite intensive therapy. Other cytogenetic abnormalities including low hypodiploidy and complex cytogenetics (ie, ≥ 5 chromosomal abnormalities) have also been reported to be associated with poor outcomes, independent of MRD, in some but not all studies.^{7,53}

3.3 | Ph-positive ALL in adults

In individual studies of chemotherapy plus a BCR-ABL1 tyrosine kinase inhibitor (TKI), achievement of a deeper molecular response (using reverse transcription [RT]-PCR of *BCR-ABL1* transcripts) has been associated with superior outcomes.^{19,54-56} In pooled analyses from MD Anderson Cancer Center of patients with Ph-positive ALL who received intensive chemotherapy plus a TKI but did not undergo HSCT in first remission, patients who achieved deeper molecular responses had better long-term survival than those with less-deep responses.^{21,57} In one analysis, patients who achieved a complete molecular response (CMR; ie, the absence of a quantifiable *BCR-ABL1* transcript by RT-PCR with a threshold of detection in the 10^{-4} to 10^{-5} range) after approximately 3 months of treatment had a 4-year OS rate of 66% despite not undergoing HSCT in first remission. The median OS for patients who achieved CMR by 3 months was 127 versus 38 months for patients who did not achieve CMR ($P = .009$). Achievement of CMR was the only variable independently predictive for OS by multivariate analysis.⁵⁷

MRD has also been suggested to predict outcomes in patients with Ph-positive ALL treated with lower-intensity regimens. In a GIMEMA study of younger patients with newly diagnosed Ph-positive ALL treated with dasatinib plus corticosteroids, patients who did not achieve CMR by day 85 were assigned to receive chemotherapy (clofarabine-cyclophosphamide) and/or allogeneic HSCT, depending on patient fitness and donor availability. Patients who achieved CMR received only TKI maintenance.⁵⁸ In an interim analysis of this prospective study, the outcomes of patients who achieved CMR were superior to those who did not (30-month disease-free survival rate 75% vs 44%, respectively; $P = .06$), despite the CMR patients receiving less intensive therapy.

3.4 | Relapsed or refractory ALL in adults

In adults, information about the prognostic and predictive impact of MRD in the salvage setting comes predominantly from studies of novel monoclonal antibodies such as inotuzumab ozogamicin and blinatumomab, or CAR T cells. Patients with relapsed or refractory ALL treated with blinatumomab who achieved MRD negativity using an allele-specific PCR assay (with sensitivity of at least 10^{-4}) had longer survival than patients who remained MRD positive, with a 67% reduction in the risk of death in patients who exhibited MRD response.^{59,60} In patients treated with inotuzumab ozogamicin in the salvage setting, achievement of MRD negativity by MFC (assessed at the end of treatment) was associated with longer remission durations and better survival (median OS 14.1 months if MRD negative vs 7.2 months if MRD positive).⁶¹⁻⁶³ In single-institution retrospective analyses, MRD status after salvage therapy has been reported to be an important predictive factor in adults with relapsed or refractory ALL.^{64,65} The impact of MRD negativity in the salvage setting may differ according to the number of prior lines of therapy received. In one retrospective analysis of adults with B-cell ALL in first or second salvage who received inotuzumab ozogamicin- or blinatumomab-containing regimens, MRD negativity at the time of morphologic remission was associated with superior survival only when achieved in first salvage. In contrast, patients in second salvage had poor outcomes regardless of MRD response when quantified at the level of 10^{-4} .⁶⁵

3.5 | Consensus recommendations on the timing of MRD assessments

- In adults with ALL undergoing frontline treatment, MRD from the bone marrow should be assessed at a minimum: after the end of induction, in early consolidation (approximately after 3 months of therapy), and then approximately every 3 months for at least 3 years (5 years for patients with Ph-positive ALL who do not undergo HSCT in first remission). Patients who undergo HSCT should have MRD assessment performed immediately prior to HSCT, and serial MRD measurements after HSCT (approximately every 3 months).
- In patients with relapsed or refractory ALL receiving salvage therapy, MRD should be assessed at least at the time of morphologic remission and at the end of treatment, particularly for patients in first salvage in whom this information has greater predictive importance.

4 | THERAPEUTIC APPROACHES FOR PATIENTS WITH PERSISTENT OR RECURRENT MRD

The detection of MRD in patients with ALL serves not only to predict outcomes; it can also inform risk-adapted strategies. For patients with high-risk disease, the goal is to increase the cure rate by intensifying therapies, such as HSCT in first CR, intensification of chemotherapy, or the introduction of novel agents. Conversely, it is also important to identify patients at relatively low risk for relapse, as the goal is to spare these patients from the potential morbidity of these high-intensity treatment approaches. For instance, the treatment-related mortality of HSCT for adults with ALL may be as high as 30%, with rates of acute

and chronic graft-versus-host disease approaching 50%.⁶⁶ Utilization of MRD assessment to help avoid allogeneic HSCT in appropriate patients represents a critically important treatment decision.

4.1 | Impact of MRD on decision to perform HSCT

4.1.1 | T-cell ALL and Ph-negative B-cell ALL

Several prospective studies have suggested that HSCT improves survival in adults with Ph-negative ALL who have persistently positive MRD after initial chemotherapy.^{5,6,48,67} In one study of 522 adults with Ph-negative ALL, HSCT benefited patients with poor MRD response (hazard ratio for OS 0.41; $P = .005$), but not those with adequate MRD response (defined as MRD level $<10^{-3}$ by PCR at the end of induction).⁴⁰ Similarly, the PETHEMA ALL-AR-03 trial evaluated adolescent and adult patients with Ph-negative ALL with high-risk baseline prognostic factors (eg, age 30-60 years, white blood cells $>30 \times 10^6/L$, or *MLL* gene rearrangement).⁶ Patients with poor day 14 bone marrow morphologic response (ie, $\geq 10\%$ blasts) and/or sub-optimal MRD response after induction and at the end of early consolidation (ie, MRD $\geq 5 \times 10^{-4}$ by MFC) were assigned to undergo myeloablative HSCT ($n = 71$), whereas patients with favorable early morphologic and MRD response were assigned to receive chemotherapy alone ($n = 108$). Patients with favorable response had 5-year relapse-free survival (RFS) and OS rates of 55% and 59%, respectively, despite the presence of historically adverse pretreatment prognostic characteristics and not undergoing HSCT in first remission.

Overall, HSCT has generally been shown to improve outcomes among patients with persistently positive MRD. HSCT seems to have less relative benefit in patients who achieve an optimal MRD response. However, when comparing patients who underwent HSCT, those who had achieved MRD negativity prior to HSCT have superior outcomes compared with those who continued to have detectable MRD. The differential outcomes by pre-HSCT MRD status in adults with ALL who undergo HSCT has been shown both when MRD is measured at the end of induction⁴⁸ and immediately prior to HSCT.^{8,25,41,68} Serial MRD assessment post-HSCT can also identify patients with impending relapse.^{8,25,69-71}

4.1.2 | Ph-positive ALL

In contrast to Ph-negative ALL, there are minimal prospective data in Ph-positive ALL regarding the relationship between MRD status and the role of HSCT in first remission. In a GRAALL study of imatinib-based regimens as frontline treatment for adults with Ph-positive ALL, HSCT was associated with a significant benefit in RFS for the whole cohort.⁷² However, when patients were stratified according to molecular response, those who achieved a major molecular response after the second cycle of therapy did not seem to benefit from HSCT. A retrospective analysis of patients treated with intensive chemotherapy plus various TKIs who did not undergo HSCT in first remission showed that patients who achieved CMR by 3 months had a 4-year OS rate of 66%. These results were suggestive that a majority of patients with Ph-positive ALL who achieve CMR can be cured with chemotherapy and TKI alone, without need for HSCT in first remission. Similar to the data in Ph-negative ALL, pre-HSCT MRD status appears to influence post-HSCT outcomes in Ph-positive ALL.^{55,73} Post-HSCT MRD may also predict for increased likelihood of relapse.⁵⁵

4.2 | Non-HSCT options for MRD positivity

Historically, further cycles of cytotoxic chemotherapy or HSCT were the only treatment modalities available to salvage patients with MRD-positive disease. The development of novel monoclonal antibodies and cellular therapies has increased the options for these patients. In phase III studies of the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin and the CD3-CD19 bispecific T-cell engager blinatumomab in adults with relapsed or refractory ALL, the MRD negativity rates in responders were 78% and 76%, respectively.^{62,74} Blinatumomab was also evaluated as an MRD-directed treatment in patients with B-cell ALL and persistent or recurrent MRD after intensive chemotherapy. In a study of 116 patients with MRD-positive ALL (65% of whom were in first remission), MRD negativity was achieved in 78% of patients after 1 cycle of blinatumomab, which translated to superior median RFS (23.6 vs 5.7 months; $P = .002$) and OS (38.9 vs 12.5 months; $P = .002$) compared with MRD nonresponders.⁷⁵ MRD responders in first remission had superior EFS compared with those in second or later remission who responded to blinatumomab. In a post-hoc analysis, there was no difference in RFS between patients who did or did not undergo post-blinatumomab HSCT in first remission ($P = .24$), whereas there was a significant benefit to HSCT for patients in second or later remission who underwent post-blinatumomab HSCT ($P = .02$). These phase II data contributed to the approval of blinatumomab by the US Food and

Drug Administration in March 2018 for the treatment of patients with B-cell ALL in first or second remission with MRD $\geq 0.1\%$. There are no randomized data comparing immediate HSCT versus blinatumomab followed by HSCT for patients with persistent or recurrent MRD, and therefore treatment decisions for this scenario must be extrapolated from and guided by phase II data.

CAR T cells have also been evaluated in the treatment of MRD-positive disease. In a study of 19-28z CAR T cells in patients with relapsed B-cell ALL, 21 patients in morphologic remission were treated (15 with MRD-positive disease and 6 who were MRD negative).⁷⁶ The median EFS and OS of these 21 patients with low-burden disease (ie, bone marrow blasts $<5\%$) were 10.6 and 20.1 months, respectively. These patients with low-burden disease had significantly lower rates of severe cytokine release syndrome and neurotoxic effects compared with patients not in morphologic remission at the time of CAR T-cell infusion.

4.3 | Consensus recommendations on the use of MRD to guide clinical decision-making

A recommended MRD-guided treatment algorithm for fit adult patients is shown in Figure 2. For patients with Ph-negative B-cell ALL or T-cell ALL who achieve MRD negativity within 3 months from the start of treatment (early consolidation), HSCT is recommended only in those with high-risk cytogenetic or genetic features (eg, Ph-like ALL, MLL

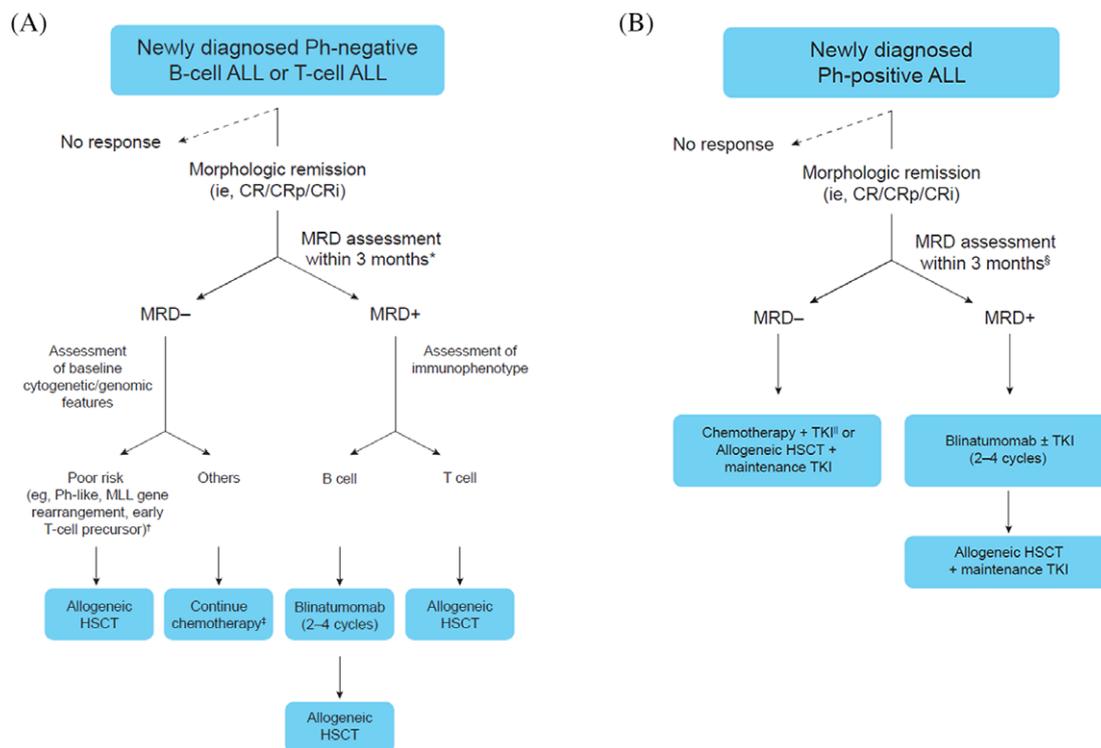


FIGURE 2 Consensus algorithm for MRD-based management of adults with ALL. (A) Newly diagnosed Ph-negative B-cell ALL or T-cell ALL. (B) Newly diagnosed Ph-positive ALL. *MRD should be assessed on a bone marrow specimen using an assay with a sensitivity of at least 10^{-4} . MRD negativity should be achieved within 3 months from the start of therapy. [†]Allogeneic HSCT may also be considered in patients with low hypodiploidy or complex karyotype. [‡]In patients who do not undergo HSCT, MRD should be assessed approximately every 3 months for at least 3 years. MRD should be assessed immediately prior to HSCT in all patients undergoing transplant. [§]MRD should be assessed with PCR for BCR-ABL on a bone marrow specimen. MRD negativity should be achieved within 3 months from the start of therapy. ^{||}In patients who do not undergo HSCT, MRD should be assessed approximately every 3 months for at least 5 years. MRD should also be assessed immediately prior to HSCT in all patients undergoing transplant. CRi, CR with incomplete blood count recovery; CRp, CR with incomplete platelet recovery; MLL, mixed lineage leukemia [Color figure can be viewed at wileyonlinelibrary.com]

gene rearrangement, or early T-cell precursor ALL). Given the poor outcomes of patients who undergo HSCT with detectable MRD, patients who remain MRD positive after initial therapy should be considered for MRD-directed therapies prior to HSCT. Blinatumomab for 2-4 cycles is recommended for patients with B-cell ALL and any level of detectable MRD prior to HSCT. Patients who achieve MRD negativity should undergo HSCT, whereas those who remain MRD positive should be considered for clinical trial (if available) or proceed to HSCT.

Patients with Ph-positive ALL who achieve CMR within 3 months of therapy may continue to be treated with chemotherapy plus a BCR-ABL1 TKI or undergo HSCT followed by maintenance TKI. Patients who remain MRD positive after 3 months of therapy should undergo HSCT followed by maintenance TKI. Blinatumomab for 2-4 cycles, with or without concomitant TKI, should be given prior to HSCT, in an attempt to convert to CMR prior to HSCT.

5 | FUTURE DIRECTIONS AND AREAS OF RESEARCH

While the prognostic impact of MRD assessment is clear across ALL subtypes, many important questions remain about the optimal method of MRD assessment and how this information should be incorporated into risk-adapted therapies. In particular, the deep sensitivity achievable with NGS holds significant promise in the improvement of risk-assessment and treatment determination of ALL, although large prospective studies of this technology are needed. Studies are also needed to evaluate the utility of peripheral blood MRD monitoring using these more sensitive NGS-based techniques, including the potential application of circulating cell-free DNA. The complex interaction between molecular and genomic changes in ALL and the prognostic impact of MRD should continue to be explored. As our knowledge of the genomic landscape of ALL evolves, it is likely that optimal assessment of relapse risk, and consequently postremission therapies, will incorporate both pretreatment genomic alterations and posttreatment MRD status. Finally, prospective MRD-guided studies are needed in order to optimize ALL therapy. The development of novel strategies (eg, monoclonal antibodies alone or in combinations with other antibodies or with chemotherapy; CAR T cells; Bcl-2 inhibitors) is needed to eradicate MRD that persists after initial therapy. Prospective studies should utilize the highest-sensitivity assays available (eg, NGS) and should assess whether such eradication of MRD can obviate the need for HSCT in this setting.

ACKNOWLEDGMENTS

The study was funded by the PLATO Foundation.

Editorial support was provided by Mary L. Smith, PhD, CMPP, from TRM Oncology, Atlanta, GA, and funded by the Plato Foundation.

DISCLAIMERS

Authorship

Contribution: All authors gathered and/or reviewed specific literature; E.J. and N.S. wrote the first draft; all authors reviewed and revised an

intermediate version of the manuscript, and all authors reviewed and approved the final draft.

CONFLICT OF INTEREST DISCLOSURES

N. Short: Consultant for Takeda.

E. Jabbour: Research grants from Amgen, Pfizer, Adaptive Biotechnologies, AbbVie, Takeda, BMS, Novartis.

M. Albitar: Employed by a diagnostic company that offers testing for MRD.

M. de Lima: Nothing to disclose.

L. Gore: Consulting/Medical advisory board service for Amgen, Celgene, Novartis, Roche/Genentech. Travel expenses paid by Amgen, BMS, Novartis, Roche/Genentech (for advisory board service noted above), US Food and Drug Administration. Stock in Amgen, Celgene, Clovis, Sanofi Paris. Research funding from NCI, Alex's Lemonade Stand Foundation, Children's Hospital Colorado Foundation, Hyundai Hope on Wheels Foundation, St. Baldrick's Foundation.

J. Jorgensen: Nothing to disclose.

A.C. Logan: Research funding from Astellas, Novartis, Pharmacyclics, Kite, Jazz. Consulting fees from Amgen, Incyte, Jazz, Pfizer, Shire.

J. Park: Consulting fees from Amgen, Shire, Novartis, Adaptive Biotechnologies, Kite Pharma.

F. Ravandi: Nothing to disclose.

B. Shah: Advisory board for Adaptive Biotechnologies. Honoraria, Pfizer. Speaker board, Amgen. Research grant from Incyte. Foundation support from Chotiner Research Foundation, Lymphoma Research Foundation, and NIH. CME advisory board from NCCN.

J. Radich: Scientific advisory board from Adaptive Biotechnologies. Laboratory research contracts with Novartis.

H. Kantarjian: Research grants from Amgen, Ariad, Astex, BMS, Novartis, Pfizer. Honoraria from AbbVie, Amgen, Ariad, BMS, Immunogen, Orsenix, Pfizer.

ORCID

Nicholas J. Short  <https://orcid.org/0000-0002-2983-2738>

Elias Jabbour  <https://orcid.org/0000-0003-4465-6119>

Aaron C. Logan  <https://orcid.org/0000-0002-1179-5879>

Hagop Kantarjian  <https://orcid.org/0000-0002-1908-3307>

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How to cite this article: Short NJ, Jabbour E, Albitar M, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts. *Am J Hematol*. 2018;1-9. <https://doi.org/10.1002/ajh.25338>