

# Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

March 2020

## Clinical Actionability of Measurable Residual Disease (MRD) Assessment in the Management of Patients With Hematologic Malignancies: A Case-Based Monograph

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**Abstract:** New treatments for hematologic malignancies have led to outcomes that are outpacing the ability of traditional measures of response to accurately capture a patient's depth of response and risk of relapse. Assessment of measurable residual disease (MRD) offers a high-sensitivity evaluation for remaining disease present in a patient. MRD is not a surrogate marker for the detection of cancer cells, but rather a direct measure of them. MRD has quickly become an important measurement of response in patients with multiple myeloma and acute lymphocytic leukemia. Retrospective and prospective studies indicate that MRD-negative patients have better outcomes, particularly progression-free and overall survival, compared with patients who are MRD-positive. Two methods have emerged as the primary strategies for assessing MRD: next-generation sequencing (NGS) and next-generation flow (NGF). Both methods measure detectable disease in the bone marrow. The clonoSEQ<sup>®</sup> Assay, which uses NGS technology, is cleared by the US Food and Drug Administration for the detection and monitoring of MRD in bone marrow samples from patients with multiple myeloma or B-cell acute lymphoblastic leukemia. This monograph discusses the supporting research and clinical use of MRD assessment among patients with multiple myeloma and acute lymphoblastic leukemia.

# Assessment of Measurable Residual Disease (MRD) in Multiple Myeloma: A Review of the Data

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## Historical Context of Assessing Treatment Response

The treatment paradigm for multiple myeloma has undergone a radical transformation throughout the past decade. Historically, any decrease in serum M protein was welcomed and considered a response, which could range from “minimal” to “stringent.” In 2016, the International Myeloma Working Group (IMWG) published consensus criteria for the definition of response in multiple myeloma.<sup>1</sup> The standard IMWG response criteria included in this consensus are listed in Table 1.

Newer therapies have led to outcomes that are quickly outpacing the ability of traditional measures of response to accurately capture a patient’s depth of response and, hence, the risk of relapse. Most patients who receive these newer treatment strategies achieve a response, many of which are deep and durable. In most patients, however, the disease will relapse. Relapse reflects the presence of underlying persistent disease (in the form of residual drug-resistant cancer cells) that is not quantifiable using the standard measures of response. Therefore, alternative methods to define disease response are needed.

## The Role of MRD

A better understanding of the biology of multiple myeloma has led to the development of newer, more sensitive and specific tools for disease prognostication and assessment of treatment response. The concept of measurable residual

disease (MRD) offers a high-sensitivity evaluation for any remaining or residual disease present in a patient’s body. Importantly, MRD is not a surrogate marker for the detection of cancer cells, but rather a direct measure of them. MRD also captures the presence of residual disease in bone marrow that appears normal according to both stains and conventional flow cytometry. MRD has quickly become an important measurement in the assessment of response in patients with multiple myeloma, as evidenced by its incorporation into the IMWG 2016 response criteria (Table 2).<sup>1</sup>

## Assessment of MRD

Two methods have emerged for assessing MRD: next-generation sequencing (NGS) and next-generation flow (NGF). Both methods are designed to measure detectable disease in the bone marrow. Each of these methods has benefits and drawbacks.

The clonoSEQ® Assay (Adaptive Biotechnologies), which uses NGS technology, was cleared by the US Food and Drug Administration (FDA) in September 2018 for the detection and monitoring of MRD in bone marrow samples from patients with multiple myeloma or B-cell acute lymphoblastic leukemia (ALL).<sup>2</sup> NGS identifies clonal-specific DNA sequences present in a patient’s bone marrow sample at baseline and follows those rearrangements to track disease after treatment. In this technique, the sequences of a patient’s immunoglobu-

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lin (Ig) genes are analyzed to identify rearranged *IgH* (VDJ), *IgH* (DJ), *IgK*, and *IgL* receptor gene sequences, as well as translocated *BCL1/IgH* (J) and *BCL2/IgH* (J) sequences. Each patient-specific gene rearrangement must first be established using a baseline sample obtained at the time of diagnosis. Following treatment, another sample is obtained and analyzed to determine the presence of the previously identified rearrangements. This NGS methodology is currently applicable to more than 92% of patients with multiple myeloma. It can assess samples containing up to 20 µg of DNA (approximately  $3 \times 10^6$  nucleated cells). This technology is compatible with either fresh or archived specimens, and can be used with fresh bone marrow aspirate, bone marrow aspirate slides, cell suspension or pellets, formalin-fixed paraffin-embedded (FFPE) slides or scrolls, and even purified genomic DNA from a patient's bone marrow sample. A decalcified bone marrow specimen should not be used for biopsy because decalcification will denature the DNA. The limit of detection of the NGS assay is  $6.8 \times 10^{-7}$ . Because this validated test is performed by a central laboratory, there is no requirement for multiple validations of the assay across laboratories. A drawback to the NGS methodology is the requirement for a baseline sample from the patient. However, because NGS

is compatible with archived specimens, this baseline sample can be analyzed at any point in the treatment continuum, as long as a sample from the time of diagnosis was taken and archived.<sup>3</sup> In addition, several days are required before the results are available.

In NGF, abnormal (clonal) plasma cells are identified and differentiated in a patient's bone marrow sample through the presence of an immunophenotypic pattern that is distinct from normal plasma cells. NGF uses fluorescently labeled antibodies to detect cell surface markers, quantifying positively labeled fluorescent cells as they pass (or flow) in front of a camera. Under the development of the EuroFlow™ Consortium, the NGF technique has evolved to include a number of surface markers to distinguish clonal plasma cells from normal plasma cells.<sup>4</sup> These markers include CD138, CD38, CD45, CD56, CD19, and cytoplasmic  $\kappa$  and  $\lambda$  immunoglobulin light chains. Other markers that may be of value include CD20, CD27, CD28, CD81, CD117, and CD200. Unlike NGS, the NGF technique is not cleared by the FDA for the detection of MRD.

NGF requires fresh material containing live cells, and therefore the test cannot be performed using archived specimens. This consideration is important because plasma cells die rapidly after they have been removed from the body, and therefore these specimens must be

**Table 1.** Standard IMWG Response Criteria

Response	Definition
<b>Stringent complete response (CR)</b>	A CR, with the additional requirement of a normal free light chain ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry ( $\kappa/\lambda$ ratio $\leq 4:1$ or $\geq 1:2$ for $\kappa$ and $\lambda$ patients, respectively, after counting $\geq 100$ plasma cells)
<b>Complete response (CR)</b>	Negative immunofixation on the serum and urine, with disappearance of any soft tissue plasmacytomas and fewer than 5% plasma cells in bone marrow aspirates
<b>Very good partial response (VGPR)</b>	Undetectable serum and urine M protein by immunofixation, but not on electrophoresis; or a $\geq 90\%$ reduction in serum M protein plus a urine M protein level $< 100$ mg per 24 hours
<b>Partial response (PR)</b>	<p>A <math>\geq 50\%</math> reduction of serum M protein plus reduction in 24-hour urinary M protein by <math>\geq 90\%</math> or to <math>&lt; 200</math> mg per 24 hours</p> <ul style="list-style-type: none"> <li>• If the serum and urine M protein are unmeasurable, a <math>\geq 50\%</math> decrease in the difference between involved and uninvolved free light chain levels is required in place of the M protein criteria</li> <li>• If serum and urine M protein are unmeasurable, and the serum free light chain assay is also unmeasurable, a <math>\geq 50\%</math> reduction in plasma cells is required in place of M protein (assuming the baseline bone marrow plasma cell percentage was <math>\geq 30\%</math>)</li> <li>• In addition to these criteria, if present at baseline, a <math>\geq 50\%</math> reduction in the size of soft tissue plasmacytomas is also required</li> </ul>
<b>Minimal response (MR)</b>	<p>A reduction of serum M protein from <math>\geq 25\%</math> to <math>\leq 49\%</math>, and a reduction in 24-hour urine M protein by 50% to 89%</p> <ul style="list-style-type: none"> <li>• In addition, if present at baseline, a <math>\geq 50\%</math> reduction in the size of soft tissue plasmacytomas is also required</li> </ul>

IMWG, International Myeloma Working Group.

Adapted from Kumar S et al. *Lancet Oncol.* 2016;17(8):e328-e346.<sup>1</sup>

**Table 2.** IMWG Criteria for MRD<sup>a</sup>

Term	Definition
<b>Sustained MRD-negative</b>	MRD negativity in the marrow (NGF, NGS, or both) and by imaging as defined below, with a confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
<b>Flow MRD-negative</b>	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method), with a minimum sensitivity of 1 in 10 <sup>5</sup> nucleated cells or higher
<b>Sequencing MRD-negative</b>	Absence of clonal plasma cells by NGS on bone marrow aspirate, in which the presence of a clone is defined as <2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the clonoSEQ platform (or validated equivalent method) with a minimum sensitivity of 1 in 10 <sup>5</sup> nucleated cells or higher
<b>Imaging plus MRD-negative</b>	MRD negativity as defined by NGF or NGS, plus disappearance of every area of increased tracer uptake found at baseline or during a preceding PET/CT; or decrease to less mediastinal blood pool standardized uptake value, or decrease to less than that of the surrounding normal tissue

<sup>a</sup>All require a complete response in addition to the criteria defined here.

CT, computed tomography; IMWG, International Myeloma Working Group; MRD, measurable residual disease; NGF, next-generation flow; NGS, next-generation sequencing; PET, positron emission tomography.

Data from Kumar S et al. *Lancet Oncol*. 2016;17(8):e328-e346.<sup>1</sup>

processed quickly. Therefore, if a particular center is not able to perform this test, the specimen must be rapidly shipped to a suitable one. Additionally, NGF requires a larger amount of sample material for processing vs NGS ( $2 \times 10^7$  nucleated cells, in order to achieve a sensitivity of  $10^{-6}$ ). The limit of detection for NGF varies across laboratories, but it can reach  $2 \times 10^{-6}$ . An advantage to NGF is that a baseline sample is not needed to interpret the result. In addition, the turnaround time is rapid, ranging from hours to days (depending on where the sample is processed). Currently, NGF is applicable to more than 95% of patients with multiple myeloma. Although there is no FDA-cleared NGF methodology, it is becoming more widely available and can be performed at many hospitals and other institutions with flow cytometry capabilities. However, there is a lack of standardization in the NGF method across laboratories.<sup>3</sup>

The NGS and NGF methodologies are both highly sensitive. However, it is key to realize that MRD negativity does not necessarily equate to a cure. Clinical studies have shown that patients with less than 1 cancer cell among 1 million cells can still relapse. These patients have a level of MRD that can be undetectable with these technologies.

### MRD as a Prognostic Marker

Multiple retrospective and prospective studies indicate that MRD-negative patients have better outcomes, particularly progression-free survival and overall survival, compared with patients who are MRD-positive. Clinical

trials in multiple myeloma have begun to incorporate assessment of MRD, allowing for meta-analyses to explore the association between MRD and patient outcomes.

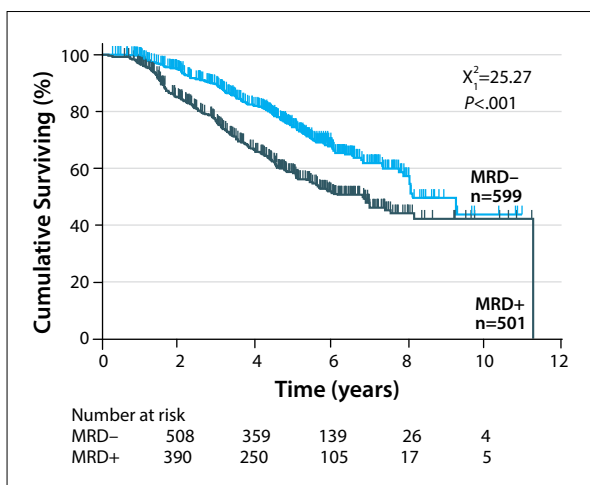
Landgren and colleagues performed a meta-analysis of published studies in which the association between MRD and survival status was examined in patients with newly diagnosed multiple myeloma.<sup>5</sup> The analysis evaluated 4 studies to identify the association with progression-free survival, and 2 for the association with overall survival. Patients who were MRD-positive had a significantly worse progression-free survival compared with those who were MRD-negative (hazard ratio [HR], 2.85; 95% CI, 2.17-3.74;  $P < .001$ ). Similarly, overall survival was significantly shorter among patients who were MRD-positive vs MRD-negative (HR, 2.08; 95% CI, 1.44-3.01;  $P < .001$ ).

A meta-analysis by Munshi and colleagues examined the utility of MRD in patients with newly diagnosed multiple myeloma.<sup>6</sup> The impact of MRD on progression-free survival was evaluated in 14 studies that included 1273 patients; 660 were MRD-negative and 613 were MRD-positive. The impact of MRD on overall survival was assessed in 1100 patients across 12 studies, of whom 599 were MRD-negative and 501 were MRD-positive. This study demonstrated that MRD had a significant impact on survival outcomes. The median progression-free survival was 54 months among patients who were MRD-negative vs 26 months among those who were MRD-positive. MRD-negative status was associated with significantly prolonged progression-free survival (HR,

0.41; 95% CI, 0.36-0.48;  $P < .0001$ ). Median overall survival was also significantly improved in patients who were MRD-negative compared with those who were MRD-positive, at 98 months vs 82 months (HR, 0.57; 95% CI, 0.46-0.71;  $P < .0001$ ; Figure 1).<sup>6</sup>

A second significant finding from this meta-analysis was that MRD appeared to be a better predictor of progression-free survival and overall survival than the conventional definition of a complete response.<sup>6</sup> Among patients achieving a conventional complete response, the median progression-free survival was 34 months among those who were MRD-positive vs 56 months among those who were MRD-negative (HR, 0.44; 95% CI, 0.34-0.56;  $P < .00001$ ). Similarly, the median overall survival was 82 months among MRD-positive patients vs 112 months among MRD-negative patients with a conventional complete response (HR, 0.47; 95% CI, 0.33-0.67;  $P = .00006$ ). In contrast, this analysis found that the impact of MRD on outcomes was less clear in those studies that were not restricted to patients who achieved a conventional complete response.

This meta-analysis also examined the prognostic value of MRD compared with other prognostic factors, using data from 11 of the studies that reported results from univariate and/or multivariate analyses.<sup>6</sup> In all 11 studies, MRD was a significant predictor of outcomes. The meta-analysis found that the best overall survival times were observed in patients with both favorable cytogenetics and MRD negativity. Overall survival was shorter in patients who had high-risk cytogenetics or who were MRD-positive. Patients with both high-risk cytogenetics and MRD positivity had significantly worse overall survival ( $P < .001$ ).



**Figure 1.** Overall survival according to MRD status in a meta-analysis of trials that enrolled patients with multiple myeloma. MRD, measurable residual disease. Adapted from Munshi NC et al. *JAMA Oncol.* 2017;3(1):28-35.<sup>6</sup>

## Importance of MRD in Clinical Decision-Making

Increasingly, clinicians are incorporating measurements of MRD into decision-making, particularly among patients with multiple myeloma who are entering very deep remissions in response to the newer standard-of-care therapies. Deeper responses are associated with a better prognosis in patients with multiple myeloma. Therefore, the goal of treatment should be to achieve MRD negativity. Questions remain regarding the best way to achieve this goal. It is important to incorporate MRD status as an endpoint in clinical studies. MRD could provide an early measure of which treatment arm is superior. MRD status is not specific to any type of therapy, and therefore this endpoint could be assessed in a variety of clinical trials, including those assessing a novel agent, bone marrow transplant, or maintenance therapy. Trial design should designate MRD assessment at multiple time points, as evidence suggests that patients with sustained MRD have the absolute best outcomes.

While we wait for studies to definitively establish the role of MRD, its best use in clinical practice is evolving. For example, there is a question of whether and when a patient should undergo the discomfort of a bone marrow procedure to assess MRD status in order to change, stop, or escalate a particular therapy. An area that remains unresolved is the utility of MRD status in deciding if and when to stop maintenance therapy after the initial intensive line of treatment. Maintenance regimens are clearly beneficial, but they can lead to toxicities. For example, cytopenias, fatigue, muscle cramping, and diarrhea are associated with lenalidomide, the most common agent used for maintenance. Although many of these side effects can be effectively managed, the duration of exposure to a drug such as lenalidomide can also lead to long-term sequelae (eg, secondary malignancies). MRD status might help inform the optimal length of time a patient should receive maintenance therapy.

Another area where MRD may aid clinical decision-making relates to solitary plasmacytomas (both bone-based and extramedullary). Recently, the IMWG redefined solitary plasmacytomas to include categories of a solitary plasmacytoma with a negative bone marrow, a solitary plasmacytoma with less than 10% clonal bone marrow plasma cells, and a solitary plasmacytoma with more than 10% clonal bone marrow plasma cells (myeloma).<sup>7</sup> MRD testing using the plasmacytoma as the source of DNA can allow further separation of the group of patients with a solitary plasmacytoma and a negative bone marrow.<sup>8</sup> Those who were MRD-positive had more aggressive disease that behaved like that of patients with a solitary plasmacytoma with less than 10% clonal bone marrow plasma cells. These patients also had a higher risk of progression to myeloma. In contrast, a large proportion of the patients who were



MRD-negative were cured with the appropriate amount of local radiation.<sup>8</sup>

Another controversial role for MRD is in patients with high-risk disease. Data suggest that these patients particularly benefit from achieving the lowest level of MRD possible. Periodic assessment of MRD throughout the treatment course may provide information that can help guide decisions regarding when to switch maintenance therapy in order to achieve an MRD level of zero.

In our experience, the primary reason why MRD assessment has not become a routine part of assessment and patient management is the requirement of a bone marrow sample. At our center, patients are typically willing to undergo this procedure to receive information on their MRD once they understand its significance. There is also the perceived drawback of the high cost of periodic bone marrow procedures and MRD testing. However, this cost may well be less than the continued expense of continued long-term expensive maintenance drugs and the cost of managing side effects.

### Relevance of MRD in Different Disease States

The prognostic value of MRD is not limited to multiple myeloma. MRD has been explored as a response measure in several other hematologic malignancies.<sup>9</sup> For example, reports have emerged linking MRD with outcomes in patients with acute myelogenous leukemia,<sup>10,11</sup> chronic lymphocytic leukemia,<sup>12,13</sup> and ALL.<sup>14-17</sup> The clonoSEQ Assay is also FDA-cleared for use in patients with ALL.<sup>2</sup>

### Patient Cases

#### Case 1

A male patient with multiple myeloma first presented 10 years ago. Fluorescence in situ hybridization (FISH) analysis detected no high-risk features at the initial presentation. At that time, he was treated with autologous stem cell transplant followed by continued lenalidomide maintenance for 2 years. During maintenance, he developed symptomatic pancytopenia that did not resolve with a decrease in the dose of lenalidomide. Significant fatigue led the patient to ask whether it was possible to stop treatment. We had been following his MRD status since his initial treatment. He had achieved MRD negativity (no detection in 10<sup>6</sup> cells) by 3 months after his transplant, and he maintained this status at 1 year and 2 years after the transplant. After discussing the situation with him, we decided it was possible to discontinue the lenalidomide because he had sustained MRD negativity for 2 years. Subsequently, we have performed a bone marrow aspiration every July, and analyzed the sample for MRD by NGS. He has remained MRD-negative every year since, which has convinced us that we

made the right decision 8 years ago when we stopped the lenalidomide maintenance. This patient benefited from a very long duration of remission following his transplant. Monitoring of MRD status spared him the side effects of long-term lenalidomide therapy.

#### Case 2

A young man with low-risk multiple myeloma underwent autologous stem cell transplant. He received lenalidomide maintenance for a year. Three months after transplant, he was MRD-negative (no detection in 10<sup>6</sup> cells). Repeat assessment at 1 year showed that he remained MRD-negative. At that point, he discontinued lenalidomide because he wanted to start a family. Six years later, he remains MRD-negative by NGS.

#### Case 3

A low-risk patient with multiple myeloma underwent autologous stem cell transplant, and received lenalidomide maintenance for 8.5 years afterward. He was hesitant to stop lenalidomide maintenance therapy based on concerns that the disease would recur. He developed multiple skin cancers, and every 2 or 3 months required Mohs micrographic surgeries. His dermatologist asked for us to discontinue lenalidomide, which might have been responsible for the skin cancers. Assessment of MRD showed that the patient was negative (no detection in 10<sup>6</sup> cells) on 2 occasions 6 months apart. After discussing these results with him, we stopped lenalidomide maintenance. We were comfortable doing so based on his low-risk status, length of lenalidomide maintenance, and persistent MRD-negative status.

For all 3 of these cases, it could be argued that stopping lenalidomide maintenance was justified based on the lack of measurable paraproteins in the blood. However, the evidence of MRD negativity gave both the physicians and the patients the confidence to discontinue therapy.

### Disclosure

*Dr Wolf is a consultant for Celgene, Amgen, Janssen, and Adaptive Biotechnologies.*

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# Assessment of MRD in Patients With Hematologic Malignancies: Clinical Insights

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## MRD as a Significant Prognostic Factor in Multiple Myeloma: Data From the IFM

In 2018, Perrot and colleagues published an important analysis of MRD using data from the phase 3 Intergroupe Francophone du Myélome (IFM) trial (IFM 2009).<sup>1</sup> The IFM 2009 study enrolled 700 patients from France, Belgium, and Switzerland between 2010 and 2012.<sup>2</sup> All patients had newly diagnosed multiple myeloma, were ages 65 years or younger, and were considered eligible for autologous stem cell transplant. Patients were randomly assigned to 1 of 2 treatment arms: a conventional dose strategy consisting of 8 cycles of lenalidomide, bortezomib, and dexamethasone; or a more intensive dose approach consisting of 3 cycles of lenalidomide, bortezomib, and dexamethasone followed by high-dose melphalan (200 mg/m<sup>2</sup>) and autologous stem cell transplant, then subsequent consolidation with an additional 2 cycles of lenalidomide, bortezomib, and dexamethasone. All patients received lenalidomide maintenance therapy for 12 months.

At the time of the design of the IFM 2009 trial in 2008, the NGS method was not available for assessing MRD. Assessment of MRD was performed with multi-

parametric flow cytometry in all patients who achieved a very good partial response or better following consolidation. However, this flow cytometry technique had a low sensitivity of 10<sup>-4</sup> (detection of 1 malignant cell in 10,000 bone marrow cells). Bone marrow samples were collected from these patients at both the start and end of maintenance therapy for measurement of MRD. Patients who did not achieve at least a very good partial response or who did not enter the maintenance phase of the trial were considered MRD-positive. MRD status was assessed in 224 of 366 patients at the beginning of maintenance therapy, and in 183 of 239 patients after maintenance therapy. Overall, 138 patients underwent MRD assessment at both time points.

In the subsequent analysis by Perrot and colleagues, the archived specimens were re-evaluated for MRD status with NGS.<sup>1</sup> MRD negativity was defined as <10<sup>-6</sup> (defined as the absence of malignant cells in 1,000,000 bone marrow cells). Initially, 233 patients had previously been identified as MRD-negative by multiparametric flow cytometry. Of these, 120 (52%) were confirmed as MRD-negative by NGS.

Several important findings were reported in this reanalysis. Use of the deepest MRD level as a threshold to determine MRD status was associated with better outcomes.<sup>1</sup> Progression-free survival was longer among patients with an MRD of  $<10^{-6}$  vs an MRD of  $10^{-5}$  or  $10^{-4}$ . Overall, 25% of patients achieved MRD negativity at least once during maintenance therapy: 54 of 264 patients (20%) treated with lenalidomide, bortezomib, and dexamethasone alone, and 73 of 245 patients (30%) treated with lenalidomide, bortezomib, and dexamethasone plus transplant (adjusted odds ratio for undetectable MRD, 1.65; 95% CI, 1.10-2.49;  $P=.02$ ). The rate of MRD negativity was not significantly impacted by baseline patient characteristics, such as age ( $P=.14$ ), sex ( $P=.19$ ), International Staging System disease stage ( $P=.61$ ), or cytogenetic risk profile ( $P=.40$ ). Among patients who began maintenance therapy, MRD negativity was seen in 31.3% of those with a very good partial response and 49.5% of those with a complete response ( $P=.006$ ). Similarly, at the completion of maintenance therapy, the rates of MRD negativity were 20.5% in patients who achieved a very good partial response and 59.7% in those with a complete response ( $P<.001$ ).<sup>1</sup>

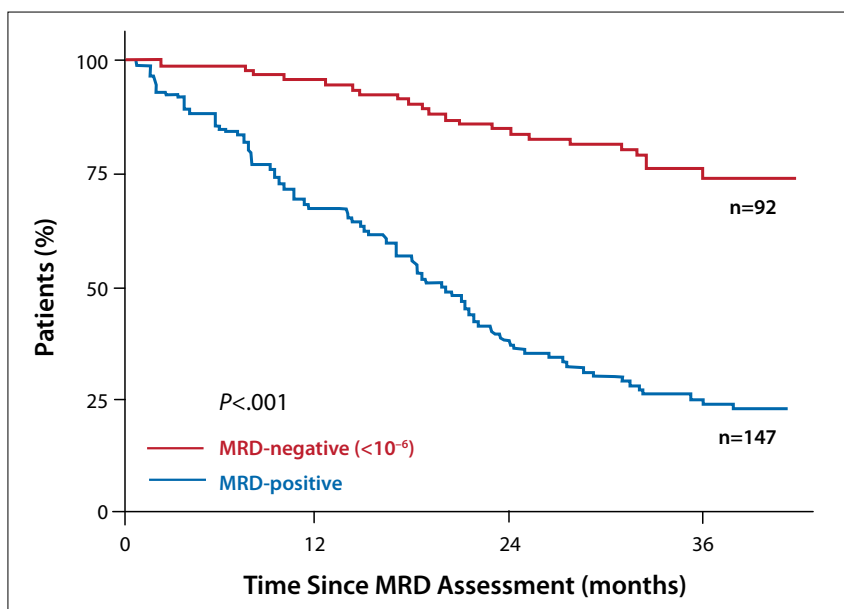
MRD as determined by NGS was a highly significant prognostic factor for survival outcomes.<sup>1</sup> This association remained regardless of whether MRD was assessed before initiation of maintenance therapy or after completion of 12 months of maintenance therapy. Progression-free survival was significantly longer in patients who were MRD-negative vs MRD-positive by NGS at both the start of maintenance therapy (HR, 0.22; 95% CI, 0.15-0.34;  $P<.001$ ) and after 12 months of maintenance (HR, 0.18; 95% CI, 0.12-0.29;  $P<.001$ ; Figure 2). The median progression-

free survival from the start of maintenance therapy was not reached among MRD-negative patients vs 29 months among MRD-positive patients ( $P<.001$ ). Similarly, the median progression-free survival from the completion of maintenance therapy was not reached among MRD-negative patients vs 20 months among MRD-positive patients ( $P<.001$ ). A similar significant difference was found in an analysis of the modified intention-to-treat population (HR, 0.19; 95% CI, 0.13-0.26;  $P<.001$ ). The observed benefit in progression-free survival associated with MRD negativity remained consistent across patient subgroups.

Overall survival was significantly prolonged among patients who were MRD-negative vs MRD-positive (Figures 3 and 4). Median overall survival was not reached in either group. Survival analyses demonstrated similar rates of both progression-free survival and overall survival in patients who maintained MRD negativity both before maintenance and after 12 months of maintenance therapy. Survival among these patients was in turn significantly superior to those who were either MRD-positive at both measurements or who became positive at the later measurement.

Another important point in this analysis was that once a patient achieved MRD negativity, outcome was similarly superior regardless of treatment. Additionally, comparison of NGS-based MRD-positive vs MRD-negative status was a more robust prognostic indicator for progression-free survival than either standard-definition complete response or multiparametric flow cytometry.<sup>1</sup>

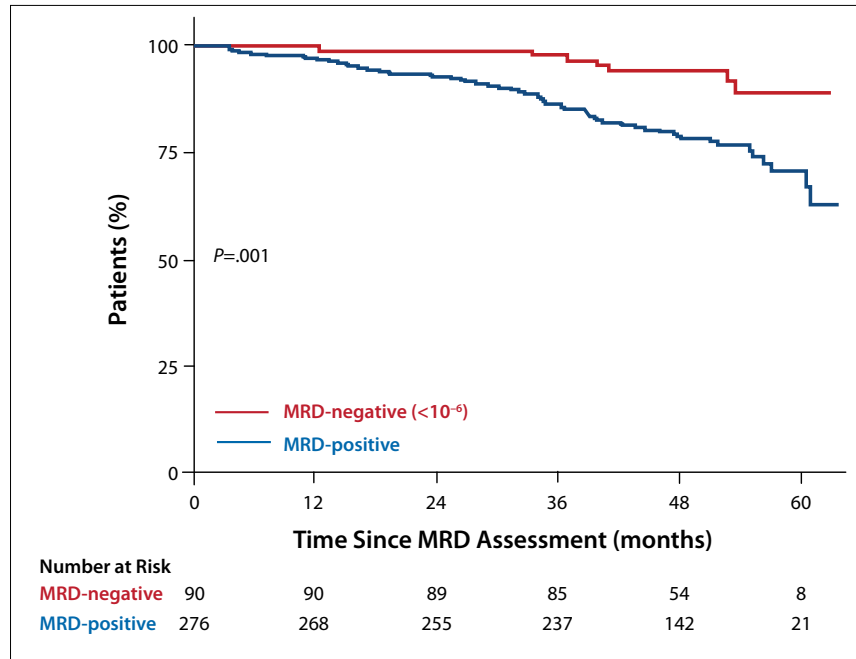
The observation that MRD negativity was more important than the treatment used to achieve it was also observed in the ALCYONE trial (A Study of Combination of Daratumumab and Velcade [Bortezomib]



**Figure 2.** Progression-free survival according to MRD status after maintenance therapy in an analysis of patient samples from the IFM/DFCI 2009 trial using next-generation sequencing. IFM/DFCI 2009, Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute; MRD, measurable residual disease. Adapted from Perrot A et al. *Blood*. 2018;132(23):2456-2464.<sup>1</sup>



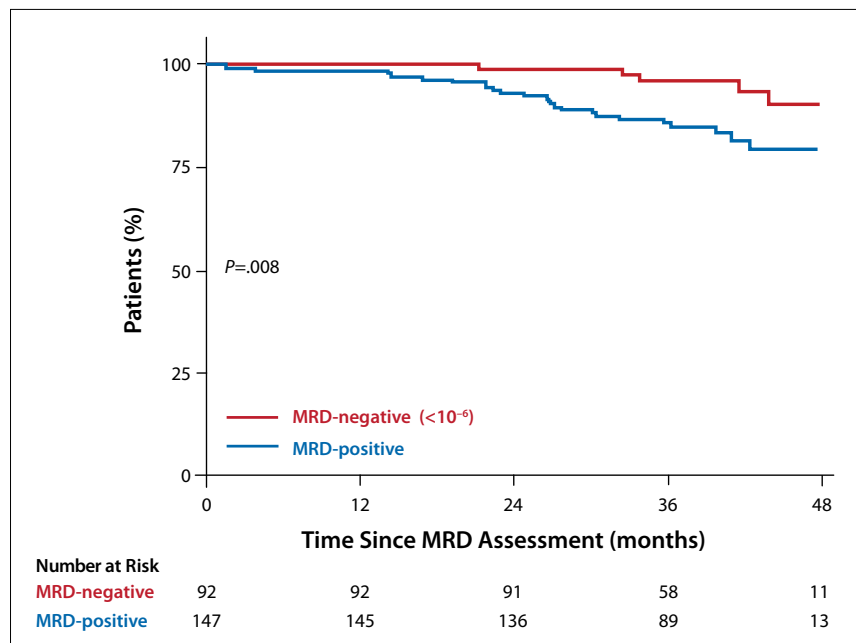
**Figure 3.** Overall survival according to MRD status at the start of 12 months of maintenance therapy in an analysis of patient samples from the IFM/DFCI 2009 trial using next-generation sequencing. IFM/DFCI 2009, Intergroupe Francophone du Myélome/ Dana-Farber Cancer Institute; MRD, measurable residual disease. Adapted from Perrot A et al. *Blood*. 2018;132(23):2456-2464.<sup>1</sup>



Melphalan-Prednisone [DVMP] Compared to Velcade Melphalan-Prednisone [VMP] in Participants With Previously Untreated Multiple Myeloma).<sup>3</sup> This trial assessed the addition of daratumumab to standard bortezomib, melphalan, and prednisone in patients with previously untreated multiple myeloma. In the overall population, the median progression-free survival was not reached with daratumumab plus bortezomib, melphalan, and

prednisone vs 18.1 months with bortezomib, melphalan, and prednisone alone (HR, 0.50; 95% CI, 0.38-0.65;  $P<.001$ ). However, when the data were analyzed according to MRD status by NGS, patients who were MRD-negative (threshold of  $10^{-5}$ ) achieved similar durations of progression-free survival regardless of their treatment arm. MRD-negative patients had a better outcome compared with patients who were MRD-positive.

**Figure 4.** Overall survival according to MRD status after 12 months of maintenance therapy in an analysis of patient samples from the IFM/DFCI 2009 trial using next-generation sequencing. IFM/DFCI 2009, Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute; MRD, measurable residual disease. Adapted from Perrot A et al. *Blood*. 2018;132(23):2456-2464.<sup>1</sup>



### Which Patients With Multiple Myeloma Should Undergo MRD Testing?

The question of which patients with multiple myeloma should undergo MRD testing remains to be defined. A multitude of different patient groups can be considered. For example, MRD assessment may have an important impact among patients receiving maintenance treatment, given the cost and risk of side effects associated with prolonged therapy. Another subgroup might be patients with a deep and sustained complete response following intensive induction therapy. Patients in the post-transplant setting are excellent candidates for MRD testing. At our center, post-transplant patients return at day 100 and undergo MRD testing through NGS analysis.

The role of MRD testing in clinical decision-making is an important point of discussion between physicians and patients. It is important to educate patients regarding the concept of MRD negativity, particularly as it relates to risk for relapse and prognostic implications for progression-free and overall survival. In my practice, as soon as I receive the MRD report, I immediately communicate the results to the patient. Patients tend to be greatly relieved to learn they are MRD-negative. I now perform bone marrow procedures more frequently. Previously, the approach had been to obtain bone marrow samples at sporadic visits, and perhaps to help guide a change in therapy. However, the monitoring ability of MRD has made bone marrow procedures a more common component of patient management.

### The Evolving Role of MRD Testing

The next frontier for MRD testing in multiple myeloma is currently being explored. There is the question of whether

assessment of MRD in multiple myeloma will reach a level of robustness to gauge continued response—or even early evidence of progression—in patients categorized with a complete response according to all other parameters. MRD has been used in this way among patients with ALL, where the degree of detected disease correlates with the risk for clinical progression.

My center has implemented a standardized method for collection and assessment of MRD. Such a protocol must be established at every center. One factor to include in this standardization is how to obtain the bone marrow sample (typically an aspirate). It is well documented that the second and third aspirate pulls become hemodiluted. Therefore, one point of standardization would be to mandate that the first aspirate pull be used to assess MRD.

### Disclosure

*Dr Fonseca is a consultant with Amgen, BMS, Celgene, Takeda, Janssen, AbbVie, Pharmacyclics, Merck, Sanofi, Kite, and Juno. He has served on the scientific advisory board of Adaptive Biotechnologies. Mayo Clinic holds the patent in his name for the prognostication of multiple myeloma based on genetic categorization of the disease.*

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## Assessment of Measurable Residual Disease (MRD) in Adult Patients With Acute Lymphocytic Leukemia: Best Use and a Case Report

Lori Muffly, MD

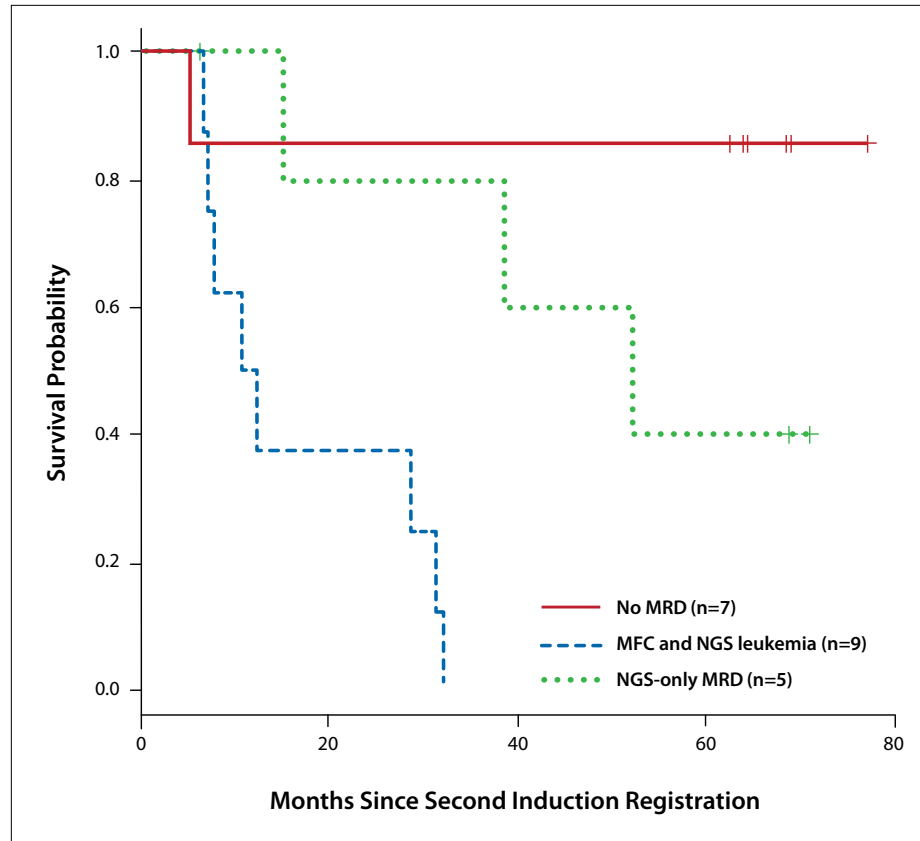
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### Assessing MRD in ALL

The traditional definition for response in ALL by morphologic assessment is less than 5% leukemic blasts in the bone marrow. With the advent of NGF and NGS testing, a new definition for MRD has emerged: the detection of no

blasts in at least  $10^{-4}$  (10,000) bone marrow cells. (Assays with even higher sensitivity are available.) Although MRD is highly prognostic in adult ALL, leukemia relapse may still occur in patients with an MRD response following induction and consolidation therapy. The optimal

**Figure 5.** Overall survival according to MRD status as assessed by next-generation sequencing in a study of patients with adult B-cell acute lymphoblastic leukemia. MFC, multiparameter flow cytometry; MRD, measurable residual disease; NGS, next-generation sequencing. Adapted from Sala Torra O et al. *Biol Blood Marrow Transplant.* 2017;23(4):691-696.<sup>2</sup>



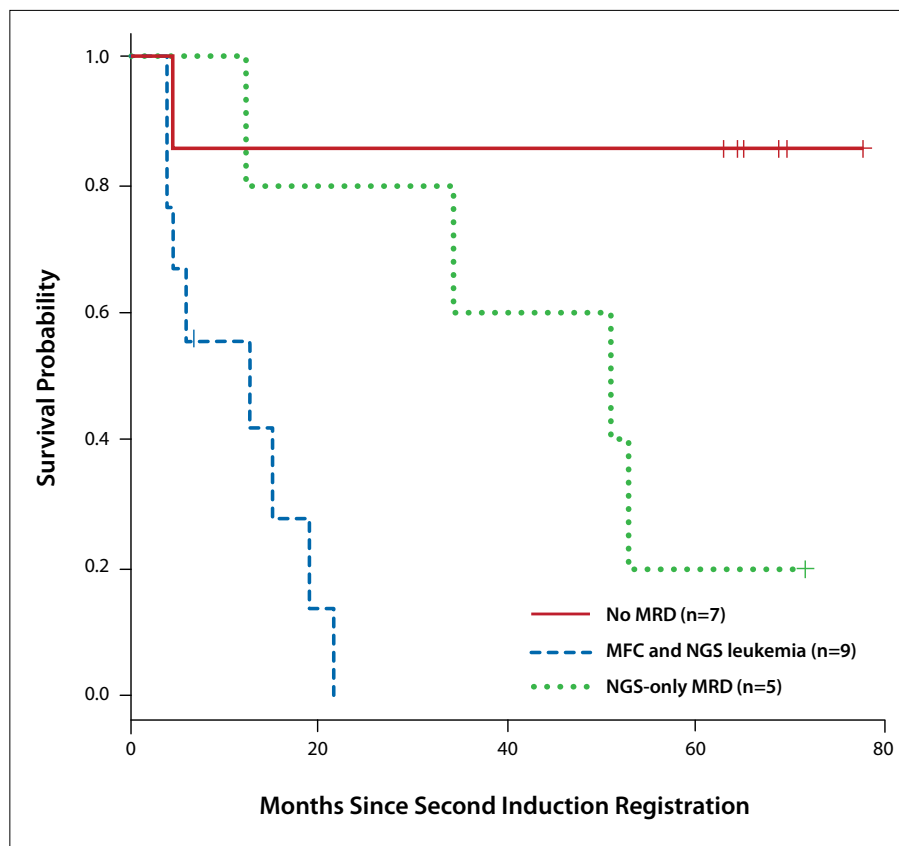
timing and duration of MRD monitoring during and after frontline therapy is typically protocol-dependent. Patients with persistent MRD following induction and/or consolidation therapy have inferior outcomes. Clearance of MRD is an important goal of therapy for adult ALL and an endpoint in interventional clinical trials.

As in multiple myeloma, the main methods to assess for MRD in ALL are via NGF or NGS. Additionally, quantitative polymerase chain reaction (PCR) is frequently used for MRD monitoring in adults with Philadelphia chromosome (Ph)-positive ALL in the United States. Across Europe, allele-specific oligonucleotide PCR is routinely used for patients with Ph-negative ALL. In the United States, flow cytometry has been the most commonly utilized method for MRD assessment in adult ALL. The main benefit of flow cytometry is that the results are typically reported quickly, within 24 to 48 hours, allowing clinicians to make real-time therapeutic decisions based on MRD assessment. There are validated and sensitive MRD flow cytometry laboratories throughout the country, enabling flow-based MRD testing for patients treated at centers that do not have internal MRD flow assays. Although NGF is faster and typically less expensive than NGS, NGF is limited by a sensitivity of ALL MRD detection of approximately  $10^{-3}$  to  $10^{-4}$  from the bone marrow.

Alternatively, NGS technologies, as described in detail in the above sections pertaining to multiple myeloma, are able to detect ALL MRD at an approximate sensitivity of  $10^{-6}$  in the bone marrow. As previously stated, the currently available NGS technologies require an initial diagnostic sample containing leukemia blasts in order to establish baseline clonal sequences. In ALL, as in multiple myeloma, fresh bone marrow or peripheral blood containing at least 5% ALL blasts is preferred, but archived diagnostic bone marrow samples may be used. The majority (approximately 90%) of adult ALL samples will harbor a diagnostic, trackable MRD sequence at baseline.

Although NGS-based MRD has a more sensitive limit of detection, it is currently unclear whether this added sensitivity provides significant prognostic value in adult ALL. A study from the Children's Oncology Group (COG) evaluated NGF and NGS in 619 paired pretreatment and end-induction marrow samples obtained from pediatric ALL patients treated in 2 COG clinical trials.<sup>1</sup> Overall, children with standard-risk ALL who were MRD-negative by both assays had excellent 5-year event-free survival (98.1%) and overall survival (100%). However, patients who were MRD-negative by NGF and MRD-positive by NGS (n=55) tended to have inferior outcomes more aligned with those of patients who were positive according to NGF. In a smaller group of 32 adult ALL patients enrolled in a

**Figure 6.** Relapse-free survival according to MRD status as assessed by next-generation sequencing in a study of patients with adult B-cell acute lymphoblastic leukemia. MFC, multiparameter flow cytometry; MRD, measurable residual disease; NGS, next-generation sequencing. Adapted from Sala Torra O et al. *Biol Blood Marrow Transplant.* 2017;23(4):691-696.<sup>2</sup>



cooperative group study, 17% of patients had MRD according to NGS but not NGE. These patients had an intermediate outcome compared with patients who were MRD-negative by both methods (who had the best outcome) and those who were MRD-positive by both methods (who had the worst outcome; Figures 5 and 6).<sup>2</sup>

An additional advantage of NGS for MRD detection is the ability to evaluate MRD using the peripheral blood. Typically, the bone marrow has been the specimen of choice for measuring MRD status in patients with ALL. However, there are data and clinical evidence to suggest that peripheral blood can be a source for MRD analysis by NGS.<sup>2-4</sup> Although NGS detection of MRD in the peripheral blood appears to be less sensitive than detection in the bone marrow (due to disease biology), blood testing allows for more frequent monitoring and is less invasive, and may therefore improve the patient experience. Additional research is required to determine the optimal frequency and duration of MRD testing using the peripheral blood in different clinical scenarios.

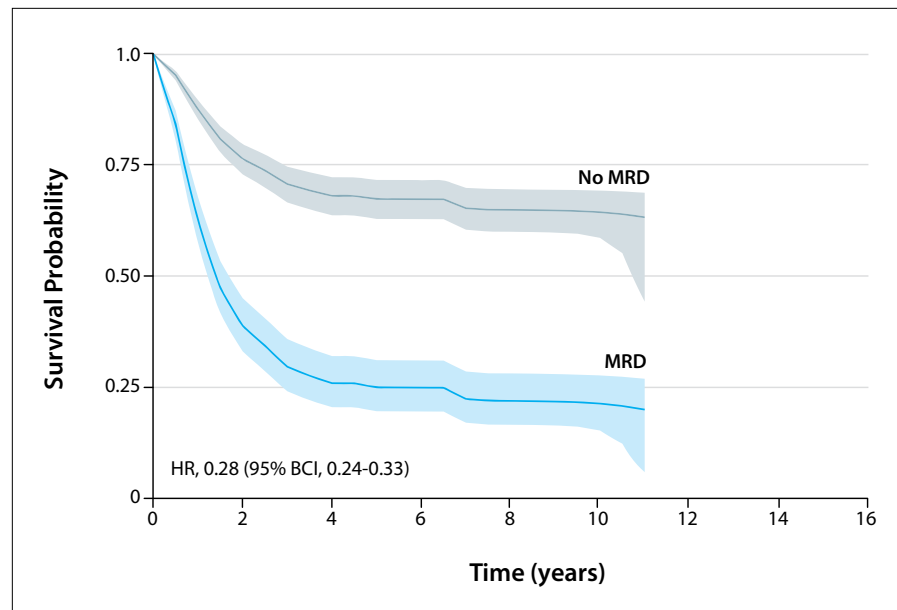
### Current Use of MRD in Patients With ALL

MRD is a centerpiece for ALL management, and now plays a critical role not only in pediatric ALL, but also adult ALL. Monitoring of MRD in adult patients with ALL should be included when assessing therapeutic response,

in treatment decision-making, during prognostication, and prior to and following hematopoietic cell transplant. Optimal monitoring time points may be dictated by the specific ALL protocol. However, the standard time points to assess MRD in adult ALL include after induction and consolidation therapy, prior to maintenance therapy, and peritransplant. Persistence of MRD should result in MRD-directed strategies, including the use of blinatumomab (see below). Although the real-world incorporation of MRD into the management of adult ALL is currently unknown, anecdotally it appears that hematologists and medical oncologists caring for adult ALL patients are increasingly recognizing that assessment of MRD status is an integral component of treating these patients.

Berry and colleagues performed a meta-analysis to examine the prognostic role of MRD in ALL.<sup>17</sup> A total of 39 studies, encompassing 13,637 pediatric and adult patients, were included. MRD negativity was associated with improved event-free survival in both pediatric (HR, 0.23; 95% CI, 0.18-0.28) and adult (HR, 0.28; 95% CI, 0.24-0.33; Figure 7) patients. Among patients who were MRD-negative, the 10-year event-free survival was 77% in the pediatric cohort and 64% in the adult cohort. Among patients who were MRD-positive, these rates were 32% and 21%, respectively. A similar association was found between MRD-negative status and overall survival.

**Figure 7.** Event-free survival according to MRD status among adults with acute lymphoblastic leukemia in a meta-analysis. BCI, Bayesian credible interval; HR, hazard ratio; MRD, measurable residual disease. Adapted from Berry DA et al. *JAMA Oncol.* 2017;3(7):e170580.<sup>5</sup>



Improved overall survival outcomes were demonstrated in both pediatric (HR, 0.28; 95% CI, 0.19-0.41) and adult (HR, 0.28; 95% CI, 0.20-0.39) patients.

The authors of this meta-analysis also performed a subgroup analysis to further examine the association between MRD-negative status and event-free survival.<sup>17</sup> The association remained consistent and strong across all subgroups examined. For example, hazard ratios for event-free survival favored MRD-negative status regardless of whether assessment was by flow cytometry (HR, 0.27; 95% CI, 0.20-0.36 in pediatric patients and HR, 0.32; 95% CI, 0.20-0.51 in adult patients) or polymerase chain reaction (HR, 0.20; 95% CI, 0.11-0.35 in pediatric patients and HR, 0.24; 95% CI, 0.18-0.32 in adult patients). Similarly, the association between MRD status and event-free survival remained regardless of the cutoff value used to determine MRD status. The association was stronger with a cutoff value of less than 0.0001 (HR, 0.18; 95% CI, 0.11-0.29 in pediatric patients and HR, 0.21; 95% CI, 0.14-0.32 in adult patients) vs 0.0001 (HR, 0.30; 95% CI, 0.20-0.46 in pediatric patients and HR, 0.29; 95% CI, 0.21-0.39 in adult patients). MRD status was associated with event-free survival regardless of whether MRD was detected at the completion of the induction phase (HR, 0.20; 95% CI, 0.15-0.28 in pediatric patients and HR, 0.33; 95% CI, 0.24-0.44 in adult patients) or the consolidation phase (HR, 0.20; 95% CI, 0.15-0.28 in pediatric patients and HR, 0.33; 95% CI, 0.24-0.44 in adult patients). Among patients who are Ph-negative, the hazard ratio for event-free survival was 0.17 (95% CI, 0.07-0.42) in children and 0.28 (95% CI, 0.22-0.37) in adults. The hazard ratio for event-free survival was 0.21 (95% CI, 0.14-0.30) among

children with the B-cell phenotype and 0.28 (95% CI, 0.17-0.46) among adults with the B-cell phenotype. In randomized controlled trials, the hazard ratio was 0.19 (0.12-0.29) in the pediatric population and 0.31 (95% CI, 0.21-0.45) in the adult population. Among the database population, the hazard ratio for event-free survival was 0.29 (95% CI, 0.18-0.45) and 0.25 (95% CI, 0.18-0.33), respectively.

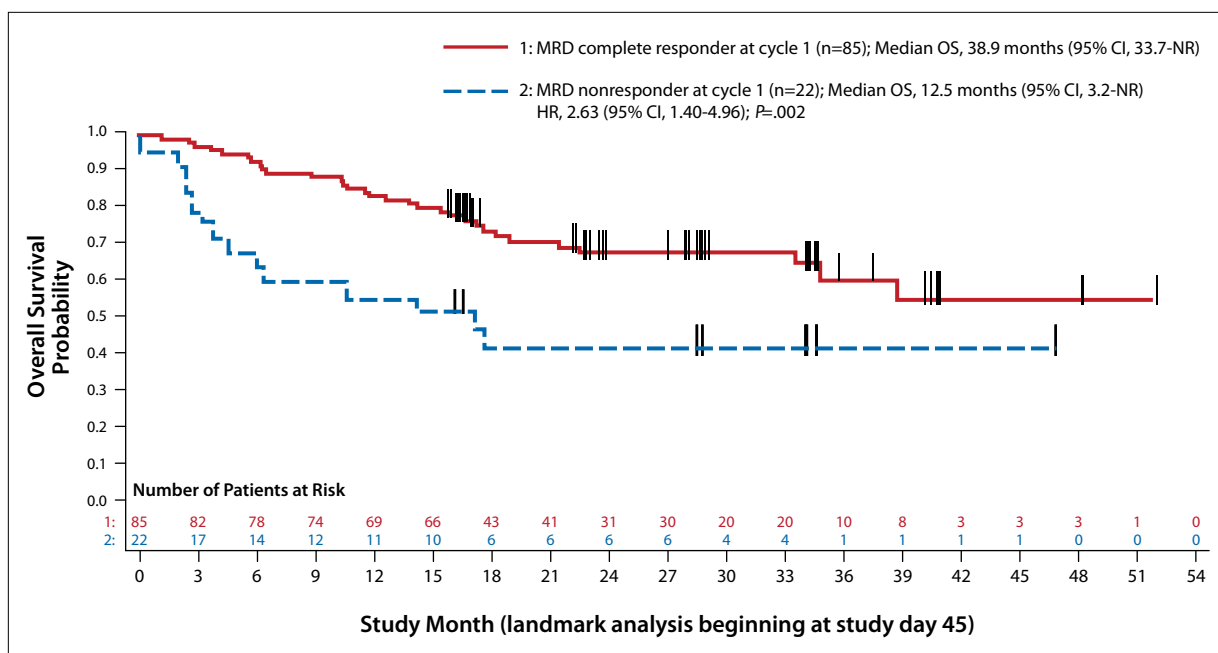
### The Evolving Role of MRD in ALL

The conditional approval of blinatumomab for an MRD indication represents a shift in drug approvals in the United States, with the recognition of MRD as a surrogate endpoint. In 2018, blinatumomab received conditional approval from the FDA for the treatment of B-cell precursor ALL in first or second complete remission with MRD levels of 0.1% or higher in adults and children.<sup>6</sup> This approval was based on a phase 2 trial that demonstrated MRD responses in 88% of 116 adult ALL patients with persistent MRD of  $10^{-3}$  or higher following chemotherapy.<sup>7</sup> Overall survival according to MRD status is shown in Figure 8. Confirmatory trials are underway, as are studies by US cooperative groups evaluating incorporation of blinatumomab and inotuzumab into frontline therapy for adult patients with ALL.<sup>8,9</sup> It is hoped that early MRD eradication with targeted novel agents will translate into improved survival in adult ALL.

### Patient Case

A 25-year-old woman presented with leukocytosis ( $120,000/\text{mm}^3$ ) and was diagnosed with B-cell ALL with a *CRLF2* translocation, consistent with Ph-like ALL. She had central nervous system (CNS) 1 disease. The patient





**Figure 8.** Overall survival according to MRD response during cycle 1 in a study of blinatumomab in adults with B-cell precursor acute lymphoblastic leukemia. Patients were not censored for allogeneic HSCT and post-blinatumomab chemotherapy. HR, hazard ratio; HSCT, hematopoietic stem cell transplant; MRD, measurable residual disease; NR, not reached; OS, overall survival. Adapted from Gökbuget N et al. *Blood*. 2018;131(14):1522-1531.<sup>7</sup>

received induction therapy following a pediatric regimen. After induction, NGF assessment of the bone marrow demonstrated a disease level of 0.8%. The patient received consolidation therapy following the same pediatric protocol. After consolidation, persistent MRD (0.5%) was noted by NGF. The patient then received 2 cycles of blinatumomab. She was MRD-negative according to both NGF and NGS following cycle 2. She proceeded to allogeneic hemopoietic cell transplant. Bone marrow MRD was negative at 3 months post-transplant. The patient underwent MRD monitoring of the peripheral blood by NGS every 2 to 3 months for the first year following transplant, and MRD remained negative.

This case provides a typical example of how I use blinatumomab to clear residual MRD. Although this patient proceeded to transplant, there are ongoing studies evaluating whether transplant is necessary in all adult ALL patients with early detection of MRD. There are also limited data to inform the duration of MRD monitoring after transplant. My practice has been to monitor MRD using NGS—typically from the peripheral blood—for the first 2 years following transplant.

#### Disclosure

*Dr Muffly has received research funding from Servier, Adaptive Biotechnologies, and Astellas. She has performed consult-*

*ing and is a member of advisory boards for Pfizer, Kite, and Amgen.*

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# Slide Library

## Measurable Residual Disease (MRD)

- The concept of MRD offers a high-sensitivity evaluation for any remaining or residual disease present in a patient's body
- MRD is not a surrogate marker for the detection of cancer cells, but rather a direct measure of them
- MRD has quickly become an important measurement in the assessment of response in patients with multiple myeloma, as evidenced by its incorporation into the IMWG 2016 response criteria

IMWG, International Myeloma Working Group

## MRD in Hematologic Malignancies

- MRD has been explored as a response measure in several hematologic malignancies:
  - Multiple myeloma<sup>1,2</sup>
  - Acute myelogenous leukemia<sup>3,4</sup>
  - Chronic lymphocytic leukemia<sup>5,6</sup>
  - Acute lymphoblastic leukemia<sup>7-9</sup>

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## Assessment of MRD: Next-Generation Flow (NGF)

- In NGF, abnormal (clonal) plasma cells are identified and differentiated in a patient's bone marrow sample through the presence of an immunophenotypic pattern that is distinct from normal plasma cells
- NGF uses fluorescently labeled antibodies to detect cell surface markers, quantifying positively labeled fluorescent cells as they pass (or flow) in front of a camera
- Under the development of the EuroFlow™ Consortium, the NGF technique has evolved to include a number of surface markers to distinguish clonal plasma cells from normal plasma cells

## Assessment of MRD: Next-Generation Sequencing (NGS)

- NGS identifies clonal-specific DNA sequences present in a patient's bone marrow sample at baseline and follows those rearrangements to track disease after treatment
- The clonoSEQ® Assay, which uses NGS technology, was cleared by the FDA in September 2018 for the detection and monitoring of MRD in bone marrow samples from patients with multiple myeloma or B-cell acute lymphoblastic leukemia
- This validated test is performed by a central laboratory

FDA, US Food and Drug Administration

## MRD as a Prognostic Marker in Multiple Myeloma

- Multiple retrospective and prospective studies indicate that MRD-negative patients have better outcomes, particularly progression-free survival and overall survival, compared with patients who are MRD-positive<sup>1,2</sup>
- Clinical trials in multiple myeloma have begun to incorporate assessment of MRD, allowing for meta-analyses to explore the association between MRD and patient outcomes<sup>1,2</sup>
- MRD may be a better predictor of progression-free survival and overall survival than the conventional definition of a complete response<sup>2</sup>

1. Landgran O et al. *Bone Marrow Transplant*. 2016;51(12):1545-1548. 2. Munch NC et al. *JAMA Oncol*. 2017;3(1):24-31.

## The Role of MRD in Acute Lymphoblastic Leukemia (ALL)

- MRD now plays a critical role in pediatric and adult patients with ALL
- Monitoring of MRD in adult patients with ALL should be included when assessing therapeutic response, in treatment decision-making, during prognostication, and prior to and following hematopoietic stem cell transplant
- In 2018, blinatumomab received conditional approval from the FDA for the treatment of adults or children with B-cell precursor ALL in first or second complete remission with MRD levels of 0.1% or higher

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