clonoSEQ®

MULTIPLE MYELOMA

With current therapies, complete response (CR) is reached in 30-50% of multiple myeloma (MM) patients.[1] However, most of these patients will experience relapse due to the persistence of residual tumor cells, or measurable residual disease (MRD).[2]

Clinical utility of MRD evaluation in MM has been established

Clinical practice guidelines recommend MRD testing as a Category 2A recommendation for multiple myeloma patients after each treatment stage (e.g., induction, high-dose therapy/ASCT, consolidation, maintenance) at times of suspected complete response. Next-generation sequencing (NGS) is specifically included in these guidelines among the recommended tools for MRD assessment.[3]

PROGNOSTIC VALUE

The clonoSEQ® Assay can predict progression-free survival in myeloma patients

MRD-negativity* (as measured by clonoSEQ at 10^{-5} sensitivity) was associated with longer PFS than MRD-positivity, regardless of the treatment received

In the ALCYONE (NCT02195479) study of 706 patients with newly-diagnosed, transplant-ineligible multiple myeloma, patients received bortezomib, melphalan, and prednisone (VMP) with or without daratumumab (D-VMP). Patients were assessed by clonoSEQ (at a sensitivity level of 10^{-5}) at study screening, and time of CR/sCR, as well as at 12, 18, 24, and 30 months in patients who had achieved a CR/sCR following initiation of induction. After 18 months of follow-up, the proportion of MRD-negative patients in the experimental treatment arm was more than three times higher than in the control group (22.3% versus 6.2%, P<0.001; Figure 1). Additionally, regardless of treatment arm, MRD-negative patients had longer PFS than MRD-positive patients (Figure 2).[4] The MRD-negativity rate data from this study has been incorporated in an FDA-approved product label for the treatment of newly-diagnosed, transplant-ineligible multiple myeloma patients.[5]

THE CLONOSEQ ASSAY OFFERS REFINED MRD ASSESSMENT

- *Clinical guidelines include NGS MRD testing after each treatment stage.[3]*
- *clonoSEQ is a highly sensitive method of MRD assessment. Deeper sensitivity is correlated with better outcomes pre- and post-maintenance.[7]*
- *MRD-negativity by the clonoSEQ Assay predicted longer time to progression and overall survival.[8, 9]*
- *Regardless of therapy received, patients who are MRD-negative by clonoSEQ have longer progression free survival than patients who are MRD-positive by clonoSEQ.[4]*

*** Per multiple myeloma clinical practice guidelines, in the setting of CR, MRD-negativity is defined as the absence of detectable cancer cells using a validated method with a minimum sensitivity of 10^{-5} nucleated cells or higher.[6] MRD status should be evaluated in the context of clinicopathological features and is not a determination of the absence of disease.**

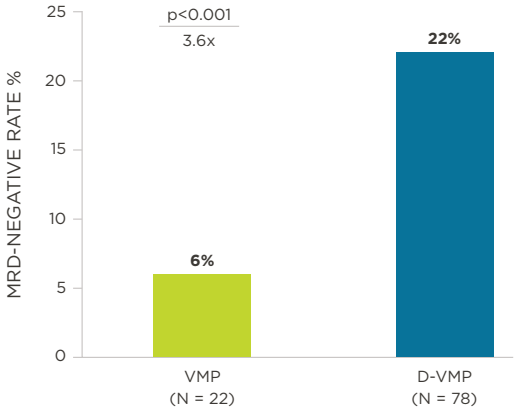


Figure 1: *Comparison of clonoSEQ MRD-negativity rate in the control arm (VMP) versus the experimental arm (D-VMP)*

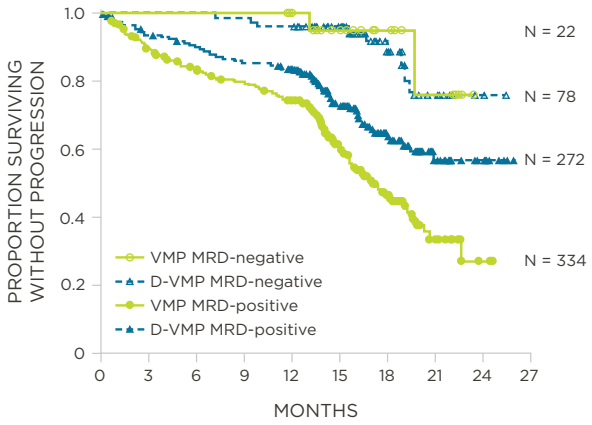


Figure 2: *Correlation of clonoSEQ MRD status and PFS*

clonoSEQ MRD-negative patients have longer progression-free survival

The POLLUX study assessed 569 relapsed and refractory multiple myeloma patients to determine if the addition of daratumumab to lenalidomide and dexamethasone (Rd) resulted in prolonged progression-free survival. MRD was assessed at three levels of sensitivity (10^{-4} to 10^{-6}) by clonoSEQ at the time of suspected complete response (CR). At all evaluated thresholds, MRD-negativity by clonoSEQ was associated with longer PFS relative to MRD-positivity (Figure 3, 10^{-6} sensitivity shown). Additionally, the rate of MRD-negativity at all evaluated thresholds (10^{-4}, 10^{-5}, 10^{-6}) was significantly higher in the experimental treatment arm than in the control arm (by 3-5x). Specifically, at a sensitivity level of 10^{-5}, the rate of MRD-negativity was 22.4% in the experimental group (DRd) versus 4.6% in the control group (Rd; P<0.001).[10]

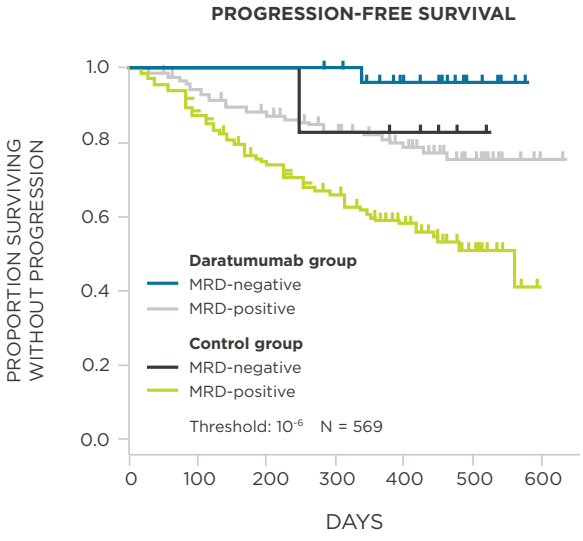


Figure 3: *Correlation of clonoSEQ MRD status and PFS*

PROGNOSTIC VALUE

The clonoSEQ Assay has prognostic value in multiple myeloma

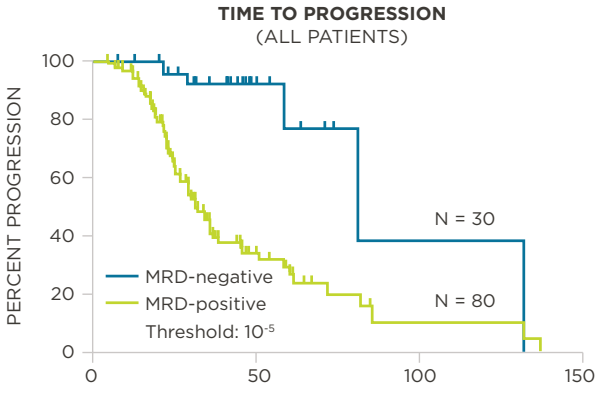
Significant difference in 12-month PFS in MRD-negative patients by NGS

A study of 45 patients with smoldering or newly-diagnosed multiple myeloma treated with carfilzomib, lenalidomide, and dexamethazole showed that there was a significant difference in 12-month progression free survival in patients who were MRD-negative versus MRD-positive by NGS (P=0.02).[8]

MRD by NGS predicts time to tumor progression and overall survival

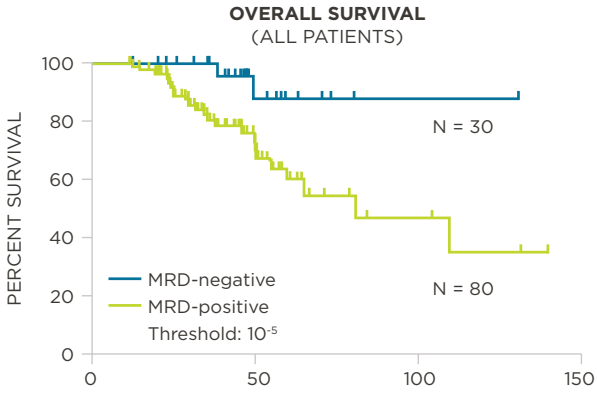
A study of 133 patients on GEM clinical trials (GEM00, GEM05, and GEM2010) found that MRD assessment by NGS was prognostic for time to progression (TTP; Figure 4) and overall survival (OS; Figure 5).[9]

- NGS identified two subgroups of CR patients that had significantly different TTP.[9]
- clonoSEQ MRD identified trackable sequences in 121/133 patients (91%).[9]
- There were 82 concordant MRD results between NGS and flow cytometry. There were 17 discordant MRD cases: 12 were NGS MRD-positive and flow MRD-negative; 5 were NGS MRD-negative and flow MRD-positive.



Median 80 mo. (MRD-negative) vs. 31 mo. (MRD-positive)
p <0.0001

Figure 4: *MRD-negativity by NGS was associated with significantly longer TTP*



Median not reached (MRD-negative) vs. 81 mo. (MRD-positive)
p = 0.02

Figure 5: *MRD-negativity by NGS was associated with significantly longer OS*

SENSITIVITY MATTERS

MRD-negativity at deeper sensitivity correlates with improved outcomes pre- and post-maintenance

Better outcomes for patients who achieve lower levels of disease burden (deeper response) pre-maintenance

When assessing MRD by clonoSEQ, pre-maintenance, patients (N=246) were stratified by level of MRD detected (≥10^{-4}, 10^{-4} – 10^{-5}, 10^{-5} – 10^{-6}, <10^{-6}). Patients with the deepest level of MRD-negativity (<10^{-6}), had superior PFS compared to clonoSEQ MRD-positive patients with disease >10^{-6} (P<0.0001, Figure 6).[7]

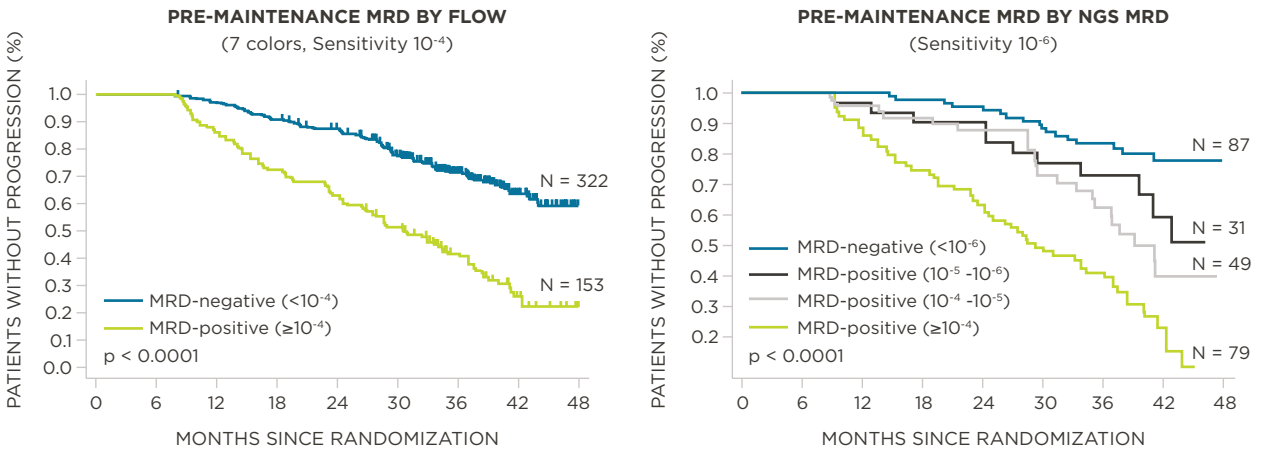


Figure 6: *Correlation of pre-maintenance MRD, assessed by flow cytometry and clonoSEQ, to PFS*

Better outcomes for patients who achieve lower levels of disease burden (deeper response) post-maintenance

When assessing by NGS MRD, patients (N=178) were stratified by level of MRD (≥10^{-4}, 10^{-4} – 10^{-5}, 10^{-5} – 10^{-6}, <10^{-6}). Patients with the deepest level of MRD-negativity (<10^{-6}) had superior PFS compared to clonoSEQ MRD-positive patients with disease >10^{-6} (P<0.0001, Figure 7).[7]

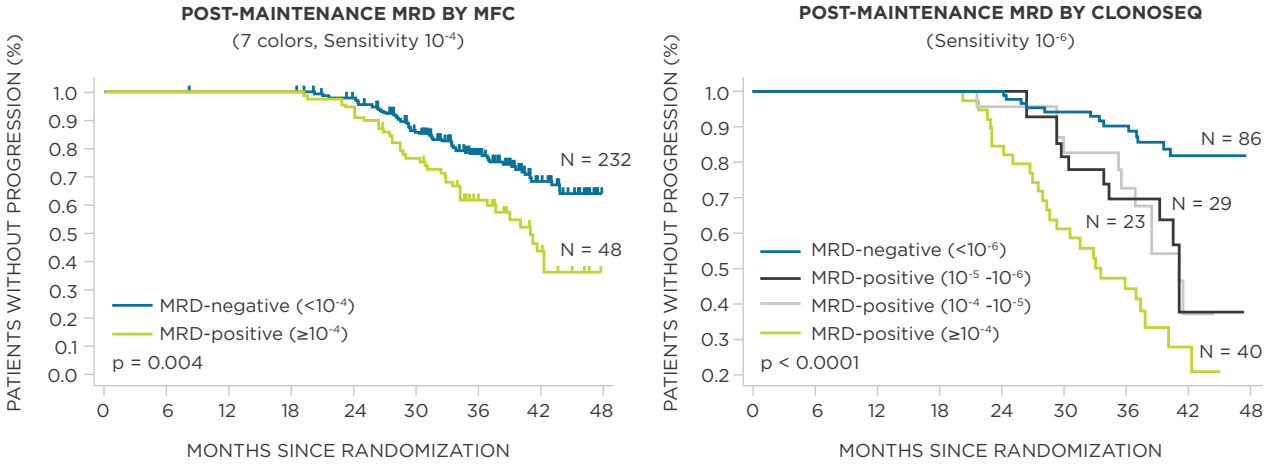


Figure 7: *Correlation of post-maintenance MRD, assessed by flow cytometry and clonoSEQ, to PFS*

ADDITIONAL PATIENTS CAPTURED WITH CLONOSEQ MRD DETECTION

clonoSEQ MRD testing identified additional MRD-positive patients who were MRD-negative by flow cytometry

Additional 84 MRD-positive patients captured pre-maintenance

In a study evaluating MRD in 475 patients, 322 patients had no detectable disease by flow cytometry, of which 163 patients were assessed by clonoSEQ. Of the clonoSEQ-assessed patients, 84 were identified as MRD-positive. These 84 patients had worse PFS compared to patients who had no detectable MRD by flow and were NGS MRD-negative (P=0.0002, Figure 8).[7]

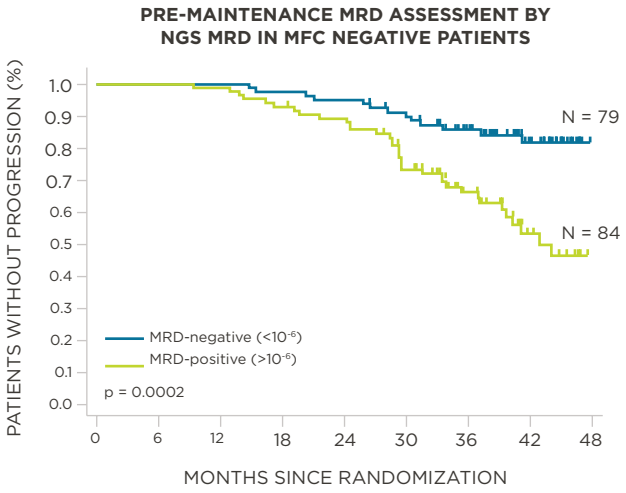


Figure 8: *Pre-maintenance assessment of MRD by NGS in patients who were MRD-negative by flow cytometry*

Additional 42 MRD-positive patients captured post-maintenance

Post-maintenance, 232 patients had no detectable MRD by flow cytometry, of which111 were then assessed by clonoSEQ. Of these 111 patients, 42 were identified as MRD-positive by clonoSEQ. These patients had worse PFS compared to patients who were MRD-negative by flow and clonoSEQ (P=0.0006, Figure 9).[7]

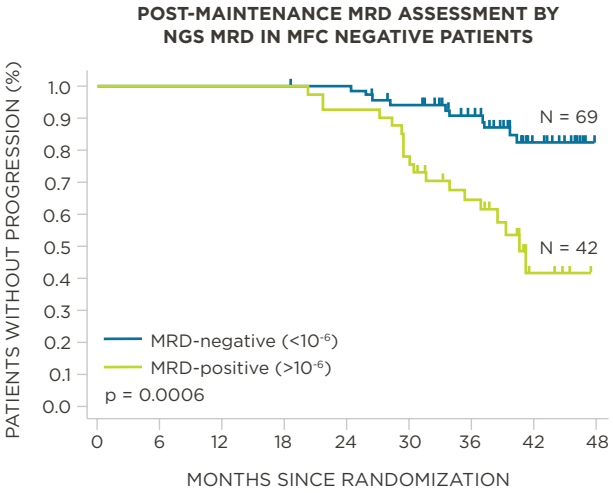


Figure 9: *Post-maintenance assessment of MRD by NGS in patients who were MRD-negative by flow cytometry*

Conclusions

- Clinical guidelines include NGS MRD testing after each treatment stage.[3]
- clonoSEQ is a very sensitive method of MRD assessment. Deeper sensitivity is correlated with better outcomes pre- and post-maintenance.[7]
- MRD-negativity by clonoSEQ MRD predicted longer time to progression and longer overall survival.[8, 9]
- Regardless of therapy received, patients who are MRD-negative by clonoSEQ have longer progression free survival than patients who are MRD-positive by clonoSEQ.[4]

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3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed [February 19, 2020]. To view the most recent and complete version of the guideline, go online to NCCN.org.**

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The test is indicated for use by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making and in conjunction with other clinicopathological features.

MRD values obtained with different assay methods may not be interchangeable due to differences in assay methods and reagent specificity. The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings. The clonoSEQ Assay is for use with specimens collected in EDTA tubes. Results may vary according to sample time within the course of disease or by sampling site location. The assay may overestimate MRD frequencies near the limit of detection (LoD). The MRD frequency LoD varies based on the amount of gDNA that is tested and using lower gDNA input may prevent MRD detection at low frequencies. Sample processing and cell enrichment strategies may affect the measured MRD frequency. The volume and cellularity of sampled input material may affect the ability to detect low levels of disease. False positive or false negative results may occur for reasons including, but not limited to: contamination; technical and/or biological factors such as the type of rearrangement or the size of the junction region. The assay has been validated with the Illumina NextSeq500 and 550.

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