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.  

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). 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.  

* 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. MRD status should be evaluated in the context of clinicopathological features and is not a determination of the absence of disease.

The clonoSEQ Assay is sold as a CLIA-certified laboratory service and is not cleared by the FDA. clonoSEQ should not be used as the sole determinant of patient care.
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 1: Comparison of clonoSEQ MRD-negativity rate in the control arm (VMP) versus the experimental arm (D-VMP)](image1)

![Figure 2: Correlation of clonoSEQ MRD status and PFS](image2)

![Figure 3: Correlation of clonoSEQ MRD status and PFS](image3)
**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 dexamethasone 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.

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

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

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

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

![Pre-maintenance assessment of MRD by NGS in patients who were MRD-negative by flow cytometry](image)

**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 which 111 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

![Post-maintenance assessment of MRD by NGS in patients who were MRD-negative by flow cytometry](image)

**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.\(^4\)

REFERENCES

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* Study author’s research was funded, in part, via product grants from Adaptive.

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