Background: Measurable residual disease (MRD) as assessed by next generation sequencing (NGS) using bone marrow (BM) aspirate carries prognostic significance in multiple myeloma (MM). Though its analytical sensitivity reaches $10^{-6}$, MRD assessed from BM may be vulnerable to false negatives due to patchy or extramedullary disease, or due to inadequate aspirate sample. Mass spectrometry (MS) is a promising peripheral blood (PB) assay that may approximate current methods of MRD detection.

Aims: In this phase 2 study evaluating the safety and efficacy of extended daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) without autologous stem cell transplant (ASCT) in newly diagnosed MM, we are evaluating the concordance of MRD by NGS in BM and by MS in PB.

Methods: Forty-one patients have been enrolled from two MM Research Consortium sites into this phase 2 study (planned enrollment 45 patients). All patients receive 24 cycles of Dara-KRd in 28-day cycles without ASCT. With optional stem cell collection for ASCT-eligible candidates after cycle 4. MRD by NGS was assessed from BM aspirates by the clonoSEQ® assay (Adaptive Biotechnologies) with a limit of detection $<10^{-6}$. MRD by MS was evaluated using both an automated MALDI-TOF (EXENT) and liquid-chromatography-MS (LC-MS) by the Binding Site Group (assays under development). Paired PB MS and BM NGS samples were available for 13 patients at early (post-cycle 4) and 18 patients at later (cycles 8-24) timepoints. There were 44 paired NGS/EXENT samples (14 post-cycle 4) and 42 paired NGS/LC-MS samples (13 post-cycle 4). Cohen’s kappa test was used to assess concordance between MS and NGS samples.

Results: For the early post-cycle 4 timepoint, there was low agreement between NGS (sensitivity threshold $10^{-6}$) and MS; there was 46% agreement (Cohen’s kappa -0.18) between NGS and EXENT and 54% agreement (Cohen’s kappa -0.15) between NGS and LC-MS. Of the discordant cases for NGS and EXENT, 4/7 (57%) were NGS-/EXENT+. Two of these 4 patients converted to EXENT- at C8. For discordant NGS/LC-MS cases, 5/6 (83%) were NGS-/LC-MS+. None converted to LC-MS-.

For the later timepoints (cycles 8-24), there was higher concordance between NGS and MS. There was 63% agreement (Cohen’s kappa 0.27) between NGS and EXENT and 59% agreement between NGS and LC-MS (Cohen’s kappa 0.13). Of the discordant cases for NGS and EXENT, 4/11 (36%) were NGS-/EXENT* and 1 of these cases was followed by conversion to EXENT+. For discordant NGS/LC-MS cases, 9/12 (75%) were NGS-/LC-MS+. None converted to LC-MS-.

With median follow-up of 10 months, there have been no progressions or deaths among these patients. The prognostic significance of persistent NGS* or LC-MS* patients cannot be determined at this time and requires longer follow-up.
Summary/Conclusion: MRD assessment by MS (EXENT and LC-MS) in PB and NGS in BM serve complementary roles. Early in treatment, MS positivity may represent false positives due to immunoglobulin recycling. EXENT from PB appears to more closely approximate the sensitivity of MRD by NGS at a sensitivity threshold of $10^{-5}$, while LC-MS from PB appears to reach and possibly exceed the sensitivity of MRD by NGS in BM at a sensitivity threshold of $10^{-6}$. The prognostic significance of persistent LC-MS positivity is unclear and requires longer follow-up.

| Table 1: Comparison of MRD Assessment Methods |
|-----------------------------------------------|
|                  | MS(+) | NGS(+) | Both Positive | Both Negative |
|-------------------|--------|--------|---------------|---------------|
| **End of Cycle 4**|        |        |               |               |
| EXENT vs NGS      | 30.8   | 23.1   | 38.5          | 7.7           |
| LC-MS vs NGS      | 38.5   | 7.7    | 53.8          |               |
| **Cycles 8-24**   |        |        |               |               |
| EXENT vs NGS      | 13.3   | 13     | 30.0          | 33.3          |
| LC-MS vs NGS      | 13.8   | 10.3   | 44.8          | 13.8          |

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