

825P-Ultra-Sensitive cfDNA analysis for Minimally Invasive Measurable Residual Disease Detection and Profiling in Multiple Myeloma

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INTRODUCTION

MRD assessment in bone marrow (BM-MRD) is one of the most relevant prognostic factors in multiple myeloma (MM). Nevertheless, MRD is an established test in MM clinical trials but not in routine practice and the use of less invasive methods empowered to monitor MRD in peripheral blood (PB), could facilitate its implementation

AIM

Investigate new highly sensitive multimodal methods to assess PB-MRD in MM patients.

METHOD

- ✓ This study recruited a total of 243 patients who were on monitoring at the time of MRD assessment in PETHEMA/GEM clinical trials and in all of them BM-MRD was processed using NGF.
- ✓ In 83 patients, PB-MRD was examined in cell-free DNA (cfDNA) using CloneSight, a highly sensitive ($>10^{-4}$) NGS method based on patient specific multiplexed amplicon mini-panels covering somatic mutations identified at diagnosis.
- ✓ Two cases using PhasED-Seq as an implementation with multiple somatic mutations in individual DNA fragments have also been included to further improve the sensitivity of cfDNA detection.
- ✓ In all cases, PB-MRD was then evaluated using BloodFlow, another high-sensitive method (10^{-7}) that combines immunomagnetic enrichment with next-generation flow (NGF) cytometry.

RESULTS

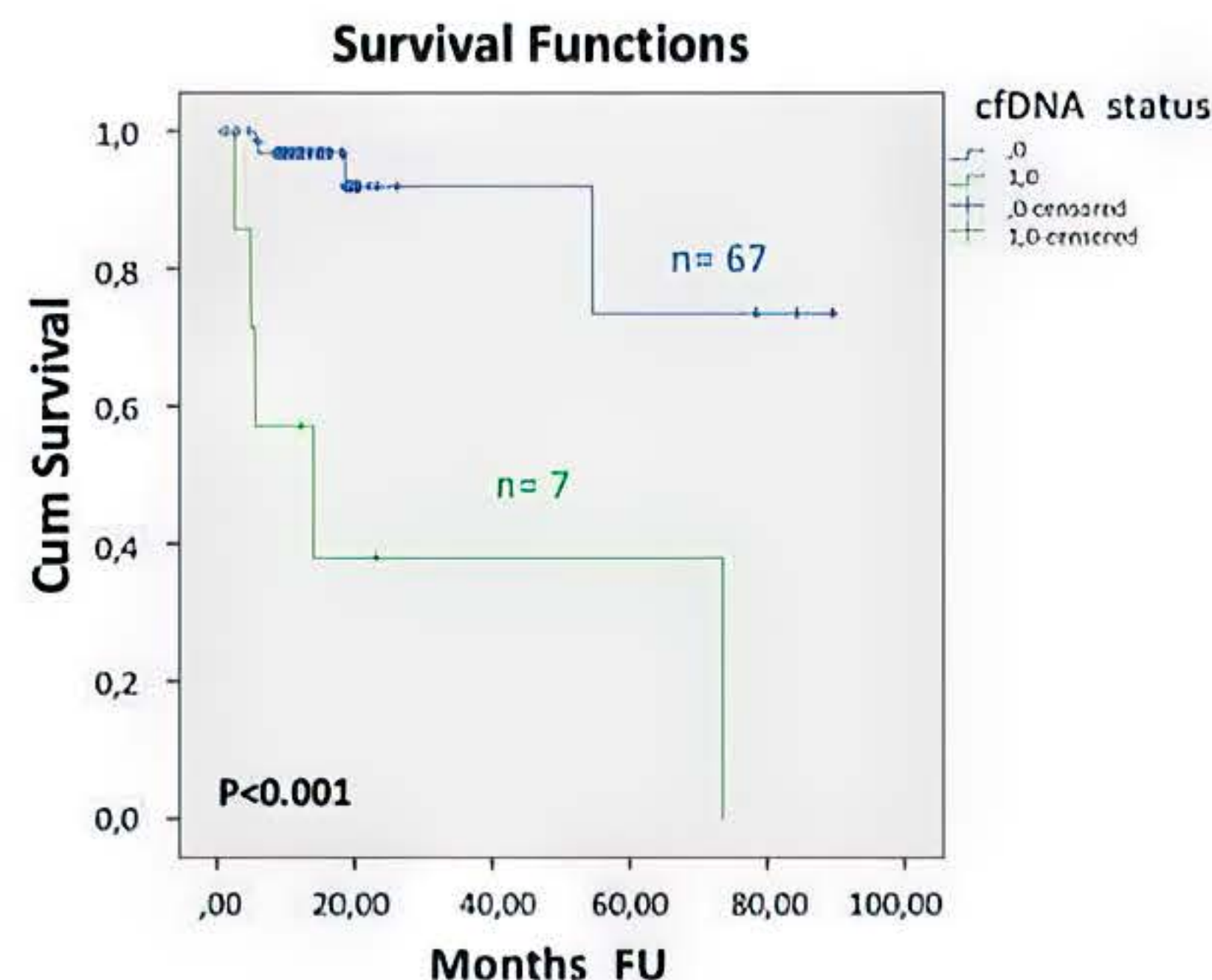


Figure 1. Kaplan-Meier curves are depicted to illustrate progression-free survival (PFS) outcomes in the overall cohort under study monitoring by PB-MRD test. The landmark median PFS of patients with negative vs positive PB-MRD using CloneSight was NR vs 14 months, respectively (HR:11.7, $P<.001$).

Follow-ups per patient

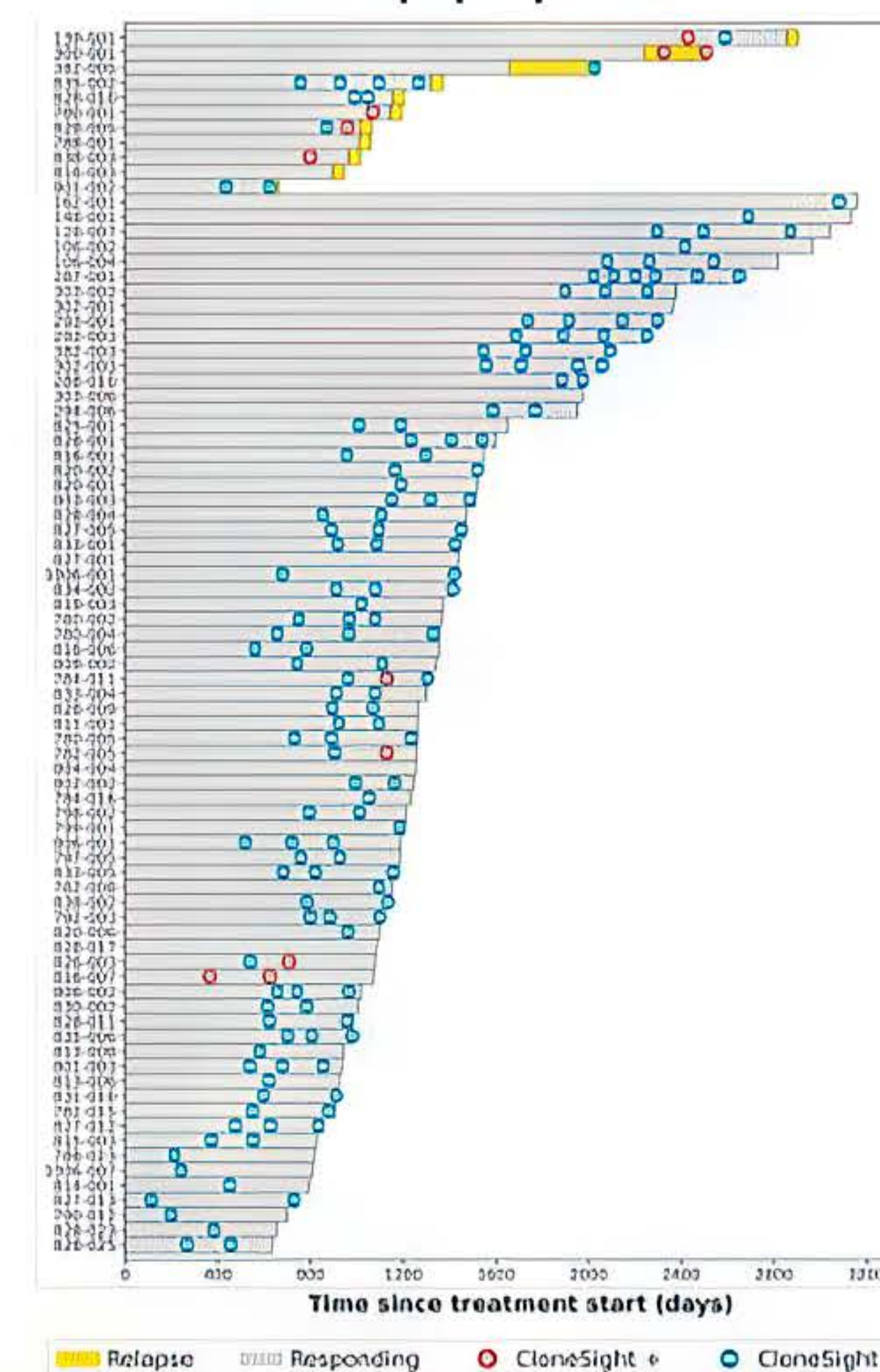


Figure 2. Swimmer-plot analysis of the different follow-up time-points screened for all patients with sample available. CloneSight was performed in a total of 83 patients, of whom 9 could not be studied due to the absence of suitable somatic mutations for PB-MRD tracking (88% applicability). A total of 194 longitudinal samples were studied, of which 12 (6%) were PB-MRD positive, from 9 of the 74 (12%) patients. In 166 of the 194 samples, BM-MRD was simultaneously analyzed using NGF. The concordance between PB-MRD using CloneSight and BM-MRD using NGF was 67% (62% double negative and 5% double positive MRD results). The frequency of CloneSight-/NGF+ and CloneSight+/NGF- discordant assessments was 31% and 2%, respectively.

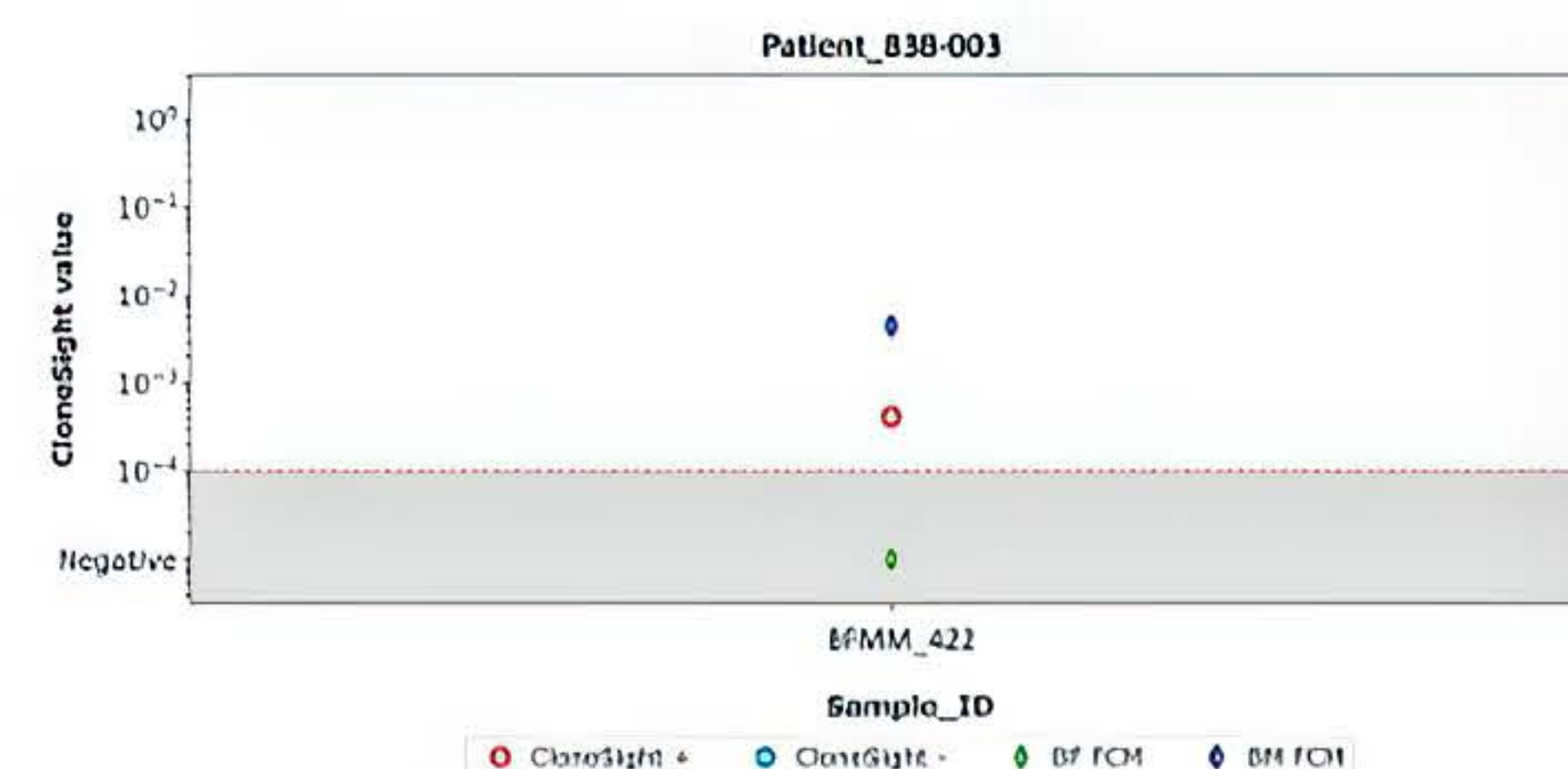


Figure 3. Example plot of the determination of the MRD value for the only patient CloneSight+ who relapsed. Of note, only 3 of the 74 (4%) MRD negative patients relapsed thus far. Upon analyzing PB-MRD with both methods described above, another 4/74 patients were CloneSight-/BloodFlow+, of whom 1 progressed. Of note, the only case (1/74) being CloneSight+/BloodFlow- relapsed (Patient_838-003). The negative predictive value (NPV) of double negative MRD detection in PB using BloodFlow was about 80%. CloneSight also offered a high PPV of 100%. For every time point, the MRD value is defined by the biomarker with higher mean.

CONCLUSIONS

- ❖ Our findings suggest that CloneSight and BloodFlow, are empowered to assess PBMRD with high sensitivity based on the respective detection of cfDNA and circulating tumor cells (CTCs).
- ❖ Moreover, the presence of mutations and CTCs, was systematically associated with a shorter PFS.
- ❖ A common feature among these methods was to achieve a high PPV, indicating that identification of such events in the group of BM-MRD-positive patients could stratify those at immediate risk of relapse.

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