PERIPHERAL BLOOD CLONOTYPIC MASS SPECTROMETRY-BASED MRD STRATIFICATION IDENTIFIES PATIENTS AT INCREASED RISK OF PROGRESSION AFTER QUADRUPLET THERAPY IN NDMM

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INTRODUCTION

In newly diagnosed multiple myeloma (NDMM), many patients achieve complete or stringent complete response (CR/sCR) following quadruplet induction. Measurable residual disease (MRD) testing helps to further stratify outcomes but traditionally requires painful bone marrow (BM) sampling, highlighting the need for sensitive, minimally invasive biomarkers of MRD. M-inSight mass spectrometry allows non-invasive, longitudinal detection of clonotypic monoclonal proteins in peripheral blood (PB). Unlike binary tests, M-inSight provides continuous quantitative readouts, but clinically validated thresholds remain undefined. Data from two prospective trials is used to propose how to stratify patients with M-insight.

AIM

- **Primary :** Evaluate a ROC-derived PB M-Insight cutoff for PFS.
- **Secondary:** Assess independence/complementarity with BM NGS MRD 10^{-5}; compare double-negative (PB–/BM–) vs other MRD states; quantify assay concordance (κ).

METHOD

We analyzed CR/sCR patients from two prospective NDMM trials (EloKRD and DaraKRD; no transplant). Eligibility for this post-hoc analysis required samples with M-protein concentrations sufficient for clonotypic peptide tracking. PB was collected at C0, C4, C8, C12, C18, C24, C36, C48, and C60, and the nadir across visits defined best PB-MRD. BM-MRD was assessed by NGS at 10^{-5} sensitivity (10^{-6} when available) at the same visits. Concordance used time-matched PB/BM pairs, with an exploratory comparison of PB nadir versus best BM. Using 48-month progression, ROC analysis identified a Youden-optimal PB threshold to classify MRD (negative vs positive), and survival was analyzed with Kaplan–Meier and Cox models; "double-negative" denotes PB–/BM–.

RESULTS

Among 64 CR/sCR patients, **33 were included in the M-inSight analysis**, with **155 samples analyzed**. Baseline characteristics, PFS, and OS did not differ between included and excluded patients.

ROC analysis identified a cutoff with strong prognostic value (1,25 mg/dL); AUC = 0.77; sensitivity 75%; specificity 76%). Patients above this threshold had **significantly shorter PFS (log-rank p = 0.002; HR = 8.76; 95% CI: 1.7–45.1, p=0.009).**

Addition of BM MRD further refined risk stratification. Patients not achieving **double-negativity (M-inSight PB positive or BM MRD-positive) had worse outcomes (HR = 8.12; 95% CI: 0.94–70.2; p = 0.057; C-index = 0.713).** Although not statistically significant, **the survival curves were clearly separated (log-rank p = 0.02)**, potentially indicating meaningful clinical differentiation in this small cohort.

In a multivariable Cox model including PB M-Insight and BM MRD 10^{-5} (complete cases n = 27; 6 events), both were independent predictors of PFS (Table 2; model LR p = 0.009; C-index = 0.80).

Agreement between best response **PB M-inSight and BM NGS MRD at 10^{-5} was low (Cohen's kappa = 0.043; p = 0.82)**, suggesting potential complementarity, though further investigation is warranted. In time-matched, same-visit PB/BM pairs, agreement was similarly limited (κ = 0.14; p = 0.24; n = 61).

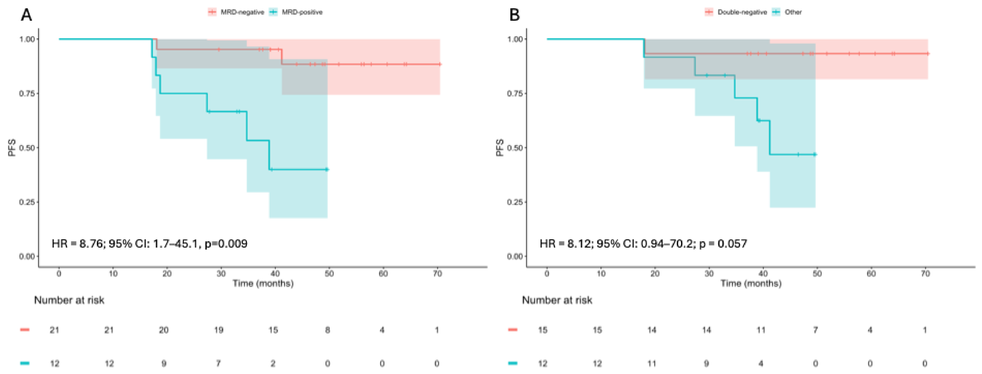

Figure 1. *Progression-free survival by MRD status with univariate Cox proportional hazard models. (A) Peripheral-blood MRD (mass-spectrometry): negative vs positive. (B) Composite MRD: double-negative (PB–/BM–) vs all other combinations. Shaded bands = 95% CI; ticks = censoring; numbers at risk shown below. Cox HRs (95% CI) and p-values are annotated on each panel.*

	Included(33)	Excluded (31)	P-value
Age (mean)	60.56 (±8.45)	58.43(±10.05)	0.36
Best Overall response CR/sCR	6/27	2/29	0.26
Isotype FLC/IgA/IgG	4/5/24	8/9/14	0.08
ISS I/II/III	16/13/4	12/13/6	0.63
High risk	20/33	11/31	0.08
Gender male	23/33	18/31	0.48
Race White/Black/Asian/other	17/9/0/7	19/5/1/6	0.56

Table 1. *Baseline characteristics of the analytic cohort ("Included", n = 33) versus those not analyzed ("Excluded", n = 31).*
CR = complete response; sCR = stringent complete response; FLC = free light chain; ISS = International Staging System. No statistically significant differences were detected between groups (all P > 0.05).

Variable	HR	95%CI		P-value
		lower	upper	
PB MRD-positive	9.1	1.5	56.5	0.02
BM 10^{-5} MRD-positive	6.5	1.2	36.86	0.03

Table 2. *Multivariable Cox model of PFS including both assays. PB MRD (M-Insight, ROC-derived cut-off) and BM NGS MRD 10^{-5} were modeled together to estimate their independent effects. PB, peripheral blood; BM, bone marrow; MRD, measurable residual disease.*

CONCLUSIONS

- PB M-Insight ROC cutoff stratifies PFS (log-rank p=0.002; HR≈8.8).
- Independent predictors: PB M-Insight and BM NGS 10^{-5} (HR≈9.1 and 6.5).
- Double-negative = lowest risk; combining assays improves stratification (HR≈8.1; LR/score p=0.02).
- Complementary signals: Low concordance (κ≈0.04) suggests additive information.
- Clinical take-home: PB mass spectrometry is non-invasive and suited for serial monitoring; findings are exploratory (small n) and need validation.

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