# CLONOTYPIC PEPTIDE MASS SPECTROMETRY TO MONITOR M-PROTEIN REDUCTION IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA FROM IKEMA STUDY

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## INTRODUCTION

Relapsed/refractory multiple myeloma (RRMM) remains difficult to monitor with bone marrow aspiration (BMA)–based minimal residual disease (MRD) techniques such as next generation sequencing (NGS) or flow cytometry (NGF), due to their invasive nature, spatial heterogeneity of disease and calibration failure. M-inSight (Sebia) is an ultrasensitive mass spectrometry assay that sequences patient specific clonotypic peptides from baseline monoclonal (M)-protein and enables longitudinal quantification of these peptides in serum. This blood-based approach offers the potential for a more consistent and patient friendly method to monitor disease burden, particularly in RRMM where BMA MRD evaluation can be limited.

## AIM

Assess the feasibility analysis of M-inSight to monitor serum M protein kinetics in IsaKd–treated patients.

## METHOD

The IKEMA phase 3 trial (CT.gov identifier; NCT03275285) evaluated isatuximab plus carfilzomib and dexamethasone (IsaKd) versus Kd alone in RRMM after 1–3 prior lines of therapy.

Serum samples (n = 392) from 89 RRMM patients from the IsaKd arm of the IKEMA study collected between 2017 and 2023 were analyzed with M-inSight.

Clonotypic peptides were identified by LC–MS/MS sequencing of baseline M-protein, and longitudinal serum samples were quantified using high resolution mass spectrometry. M-protein concentrations were tracked at predefined clinical timepoints (prior to cycle initiation), including 12 months (±2 months), to assess assay applicability, longitudinal detectability, and quantitative dynamic range in this RRMM cohort.

## RESULTS

Clonotypic peptides were successfully identified in 98% of the baseline samples, allowing longitudinal quantification of serum M-protein across the entire RRMM.

Patients with available BMA NGS data, 99% of those who were **MRD-positive at $10^{-6}$** had an **M-protein concentration above 0.0002 g/dL** (MS pos).

| | IgG | IgA | FLC | Overall |
|---|---|---|---|---|
| Patients | 62 | 20 | 7 | 89 |
| Clonotypic peptides identification | 62 (100%) | 20 (100%) | 5 (71.4%) | 87 (97.8%) |
| *kappa*-LC | 54 | 13 | 4 | 71 |
| Average M-protein concentration at baseline (g/dL) | 1.86 | 1.49 | 0.55 | 1.67 |
| Lowest M-protein concentration (g/dL) and (% decrease) | 0.00009 (>99.99%) | 0.00001 (>99.99%) | 0.00008 (>99.99%) | 0.00001 (>99.99%) |

*Table: Number of patents per isotype, success rate and average M-protein concentration at baseline measured by SPEP.*

**M-protein reduction at 12 months (±2 months) treatments:**

Serum was available for 36 patients, who showed a **mean reduction of M-protein of 92%** (SD 10%), **with 50% achieving >99% decline,** consistent with **deep molecular response** and M-protein levels between **0.00017 and 0,028 g/dL**.

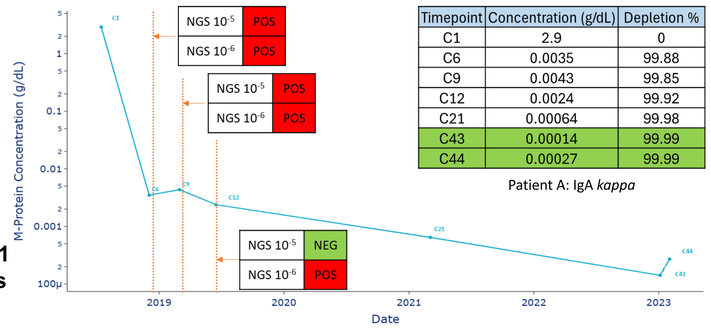
**Sustained protein depletion** (above 90%, concentrations ranging between **0.0001 g/dL and 0,1 g/dL**) was measured on **22 out of these 36 patients even after 3 years after treatment**, which is consistent with profound molecular suppression, reflecting disease control.

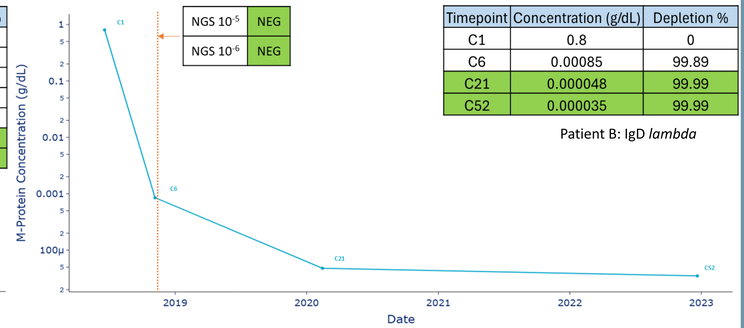
| Timepoint | Concentration (g/dL) | Depletion % |
|---|---|---|
| C1 | 2.9 | 0 |
| C6 | 0.0035 | 99.88 |
| C9 | 0.0043 | 99.85 |
| C12 | 0.0024 | 99.92 |
| C21 | 0.00064 | 99.98 |
| C43 | 0.00014 | 99.99 |
| C44 | 0.00027 | 99.99 |

Patient A: IgA *kappa*

| Timepoint | Concentration (g/dL) | Depletion % |
|---|---|---|
| C1 | 0.8 | 0 |
| C6 | 0.00085 | 99.89 |
| C21 | 0.000048 | 99.99 |
| C52 | 0.000035 | 99.99 |

Patient B: IgD *lambda*




*Figures: Example of kinetics curves of two patients with MS MRD neg in green. Left: patient with M-protein concentration at 7 time points over 44 months and NGS assessment at 3 timepoints. Right: patient with M-protein concentration at 4 time points over 52 months and NGS assessment measured at one timepoint.*

## CONCLUSIONS

- This analysis highlights the feasibility of **deploying M-inSight for long-term minimally invasive MRD monitoring in a large RRMM trial**, where BMA-based assessment is often limited by invasiveness and patchy disease distribution.
- **M-inSight** enabled **sensitive M-protein quantification** and detailed longitudinal monitoring of treatment kinetics, **delivering data on remission and residual disease up to 3 years post-treatment**. It addressed a key gap in long-term follow-up: in IKEMA, BMA MRD was often not performed after initial assessment of MRD negativity (around 1 year), limiting insights into sustained MRD negativity.
- **M-inSight provides a robust, non-invasive tool for MRD monitoring in RRMM**, allowing long-term follow-up without bone marrow sampling.

## REFERENCES

Di Stefano et al, Blood, 142, 1, 2023, 3360

## CONTACT INFORMATION

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