Duration of Minimal Residual Disease Negativity Predicts Durable Disease Control in Multiple Myeloma: A Meta-Analysis of 8,900 Patients

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1 Context

Minimal residual disease (MRD) negativity is an established prognostic marker in multiple myeloma, yet the optimal duration and consistency of MRD clearance required for durable remission remain undefined. This meta-analysis is the first to integrate data across MRD assessment methods, treatment lines, and maintenance strategies to quantify the prognostic impact of sustained MRD negativity and its validity as a surrogate endpoint for PFS — a question of growing importance as regulators consider MRD-based endpoints for accelerated trial designs.

2 Objective

To determine whether the duration of MRD negativity independently predicts progression-free survival across modern multiple myeloma regimens, and to validate sustained MRD negativity as a surrogate endpoint for long-term disease control, including the duration and sensitivity threshold linked to maximal risk reduction.

3 Design

A systematic review and meta-analysis following PRISMA guidelines was conducted. PubMed, Embase, Web of Science, and Cochrane Library were searched from 2015 through March 2026. Random-effects models generated pooled hazard ratios (HRs) and 95% confidence intervals (CIs) to account for anticipated clinical and methodological heterogeneity, with subgroup analyses by MRD detection method (next-generation flow [NGF] vs next-generation sequencing [NGS]), therapy line, and maintenance use.

4 Setting

Data were drawn from multicentre phase II/III trials and observational cohorts spanning North America, Europe, and Asia, allowing assessment of consistency across differing treatment and regulatory environments.

5 Participants

Twenty-three studies including 8,947 patients with newly diagnosed or relapsed multiple myeloma were analysed, spanning first-line and relapsed/refractory settings. Sustained MRD negativity was defined as two consecutive negative assessments ≥12 months apart at a sensitivity ≥10^{-5}.

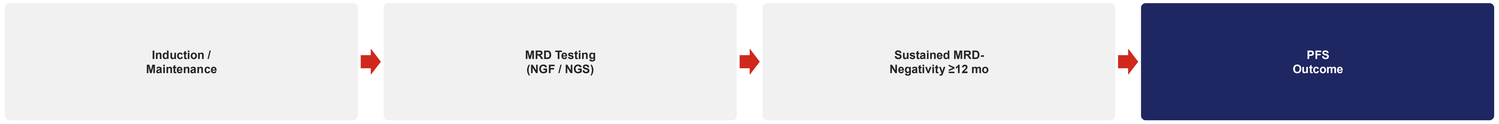
6 Interventions

Triplet and quadruplet regimens incorporating proteasome inhibitors, IMiDs, and CD38-targeted antibodies, with or without autologous transplantation and maintenance therapy — reflecting evolving standard-of-care across transplant-eligible and -ineligible patients.

7 Main Outcome Measures

Association between sustained MRD negativity and progression-free survival, with analyses accounting for detection method, therapy line, and maintenance status to ensure the relationship was not confounded by these factors.

Results



HR 0.38

62% lower progression risk vs transient/MRD-positive disease (95% CI 0.29–0.50; p<0.001)

8,947

patients across 23 pooled studies (I^2=24%)

≥24 mo

sustained MRD negativity duration with the greatest PFS benefit

- Sustained MRD negativity was associated with a 62% reduction in progression risk compared with transient or MRD-positive disease.
- Benefit was consistent across MRD modalities (NGF vs NGS), therapy lines, and maintenance status.
- Low between-study heterogeneity (I^2=24%) supported the robustness of the pooled estimate.
- Sensitivity analyses confirmed the findings were robust, with no significant publication bias detected.
- Patients maintaining MRD negativity ≥24 months achieved the greatest PFS benefit.
- The MRD–PFS relationship held consistently across North America, Europe, and Asia, supporting broad generalizability.

Conclusions

Sustained MRD negativity is a robust surrogate endpoint for progression-free survival in multiple myeloma, with the strength of benefit consistent across detection methods, treatment lines, and maintenance strategies — reinforcing its reliability across diverse clinical settings.

These findings support integrating sustained MRD-negativity into clinical trial design and response-adapted therapeutic strategies to individualize treatment duration and intensity — potentially enabling shorter trials and earlier efficacy readouts without compromising the reliability of survival predictions.

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