Minimal Residual Disease Negativity in Newly Diagnosed Multiple Myeloma: From Surrogate Endpoint Validation to the Unanswered Question of Maintenance-Free Remission

A. Sharma[1], S. Sidhu[2], S. Haldule[2], S. Kumar[3]

1. Yale New Haven Hospital, Department of Internal Medicine, New Haven, CT, USA, 06150
2. University of Connecticut, Department of Internal Medicine, Farmington, CT, USA
3. Neag Comprehensive Cancer Center, University of Connecticut Health, Farmington, CT, USA

INTRODUCTION

- Minimal residual disease (MRD) negativity is the most powerful intermediate endpoint in newly diagnosed multiple myeloma (NDMM)
- FDA 2025 draft guidance recognizes it as a potential primary endpoint.
- Translation to maintenance interruption decisions remains prospectively unvalidated.

OBJECTIVES

To quantify the MRD-survival association in NDMM and define the unanswered gap around MRD-guided maintenance interruption.

DESIGN

- Evidence synthesis of PubMed-indexed meta-analyses (2020 to 2026) with dual-reviewer screening
- three meta-analyses (4,907 to 15,304 patients; 7 to 15 trials) provide primary estimates.

SETTING

Phase 2 and 3 induction trials in NDMM (7 to 15 per meta-analysis).

PATIENTS OR OTHER PARTICIPANTS

- Adults with NDMM
- MRD assessed by next-generation sequencing or flow cytometry.

INTERVENTIONS

- TE-NDMM trials: daratumumab-based (GRIFFIN, PERSEUS, MASTER) and isatuximab-based (ISKIA, ADVANCE).
- TIE-NDMM trials: daratumumab-based (CEPHEUS) and isatuximab-based (BENEFIT).
- All compared CD38 antibody-based quadruplets versus non-CD38 antibody triplets.
- MRD negativity assessed at 10^{-5} and 10^{-6} at 12 months.

MAIN OUTCOMES MEASURES

- Individual- and trial-level MRD-survival associations
- sustained MRD negativity rates at 12 or more months.

RESULTS

- Twelve-month MRD negativity was strongly associated with PFS in NDMM (OR 4.02; 95% CI 2.57 to 5.46)
- with trial-level R-squared of 0.84 confirming MRD as a robust surrogate
- Pooled analysis of CD38 antibody-based quadruplets versus non-CD38 antibody triplets show increased MRD negativity rates at 10^{-5} (RR 1.39; 95% CI 1.23 to 1.58) and 10^{-6} (RR 1.62; 95% CI 1.36 to 1.94), with PFS HR 0.55 (95% CI 0.46 to 0.66) and OS HR 0.65 (95% CI 0.53 to 0.79)
- In TE-NDMM, quadruplets achieved MRD negativity at 10^{-5} in 66 to 75% versus 39 to 48% with triplet
- Sustained MRD negativity in 32 to 48% versus 7 to 16%.
- In TIE-NDMM, quadruplets yielded fourfold higher sustained MRD negativity (RR 3.999; 95% CI 1.094 to 8.403).

CONCLUSIONS

- Sustained 12-month MRD negativity is the strongest validated surrogate in NDMM per FDA draft guidance.
- Trials testing MRD-guided maintenance interruption (MASTER-2, DRAMMATIC) are urgently needed to spare patients from indefinite maintenance toxicity.

KEYWORDS
Multiple myeloma, newly diagnosed, minimal residual disease, progression-free survival, surrogate endpoint, maintenance therapy, daratumumab, isatuximab, meta-analysis

CONTACT INFORMATION

Sukhmani Sidhu, MBBS

PGY3 Internal Medicine, University of Connecticut

Email ID- ssidhu@uchc.edu

REFERENCES

1. Ntanasis-Stathopoulos I, Filippatos C, Ntanasis-Stathopoulos A, et al. Evaluating Minimal Residual Disease Negativity as a Surrogate Endpoint for Treatment Efficacy in Multiple Myeloma: A Meta-Analysis of Randomized Controlled Trials. *Am J Hematol*. 2025;100(3):427-438. doi:10.1002/ajh.27582
2. Ficek J, Kalaitzaki E, Yuan SS, et al. Association of Minimal Residual Disease Negativity Rates With Progression Free Survival in Frontline Therapy Trials for Newly Diagnosed Multiple Myeloma: A Meta-analysis. *Clin Lymphoma Myeloma Leuk*. 2023;23(5):e213-e221. doi:10.1016/j.clml.2023.02.005
3. Landgren O, Prior TJ, Masterson T, et al. EVIDENCE meta-analysis: evaluating minimal residual disease as an intermediate clinical end point for multiple myeloma. *Blood*. 2024;144(4):359-367. doi:10.1182/blood.2024024371
4. Zweegman S, Facon T, Hungria V, et al. Daratumumab in transplant-ineligible or -deferred newly diagnosed multiple myeloma: minimal residual disease in CEPHEUS. Blood Adv. 2026;10(16):5594-5606. doi:10.1182/bloodadvances.2026019937
5. Usmani SZ, Facon T, Hungria V, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nat Med*. 2025;31(4):1195-1202. doi:10.1038/s41591-024-03485-7
6. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;390(4):301-313. doi:10.1056/NEJMoa2312054
7. Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Oncol*. 2022;40(25):2901-2912. doi:10.1200/JCO.21.01935
8. Voorhees PM, Sborov DW, Laubach J, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): final analysis of an open-label, randomised, phase 2 trial. *Lancet Haematol*. 2023;10(10):e825-e837. doi:10.1016/S2352-3026(23)00217-X
9. Gay F, Roeloffzen W, Dimopoulos MA, et al. Isatuximab, carfilzomib, lenalidomide and dexamethasone in newly diagnosed multiple myeloma: a randomized phase 3 trial. *Nat Med*. 2026;32(5):1773-1782. doi:10.1038/s41591-026-04282-0
10. Perrot A, Touzeau C, Lambert J, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone induction in newly diagnosed myeloma: analysis of the MIDAS trial. *Blood*. 2025;146(1):52-61. doi:10.1182/blood.2024026230
11. Leleu, X., Hulin, C., Lambert, J. *et al.* Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial. *Nat Med* **30**, 2235–2241 (2024). https://doi.org/10.1038/s41591-024-03050-2
12. Ranganathan S, Prasad V. Minimal residual disease negative: A novel endpoint for accelerated approval; What providers should know. *J Cancer Policy*. 2025;45:100588. doi:10.1016/j.jcpo.2025.100588

COI: SK: Advisor to J&J and Sanofi; research funding J&J, BMS. No other financial disclosures.