Triplet vs Quadruplet Induction Regimens in Transplant-Eligible and Ineligible Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-Analysis of Randomized Trials

E. TAYAR[1], A. BITAR[1], C. AKEL[1], R. HADDAD[1], R. BOUDELEH[1], R. ISHAC[2]

[1]*University of Houston/HCA Healthcare Clear Lake, Webster, TX, USA*

[2]*MD Anderson Cancer Center, Houston, TX, USA*

INTRODUCTION

Triplet regimens have historically represented a major frontline standard in newly diagnosed multiple myeloma. The addition of anti-CD38 monoclonal antibodies to established triplet backbones has produced deeper responses and improved disease control in recent randomized trials. However, the magnitude and consistency of benefit across transplant-eligible and transplant-ineligible populations remain clinically important..

AIM

To evaluate the **efficacy and safety of frontline quadruplet regimens compared with triplet regimens** in adults with newly diagnosed multiple myeloma, including transplant-eligible and transplant-ineligible populations.

METHOD

- PRISMA-conformant systematic search of PubMed/MEDLINE, ClinicalTrials.gov, was performed through January 2026.
- Eligible studies were phase 2–3 randomized controlled trials enrolling newly diagnosed multiple myeloma and comparing a triplet regimen with an anti-CD38–containing quadruplet regimen.
- Outcomes included PFS, OS, CR, MRD negativity, and grade ≥3 AEs
- Hazard ratios and risk ratios were pooled using fixed-effect and random-effects models. Heterogeneity was assessed using I^2.

CONCLUSIONS

- Anti-CD38–based quadruplet regimens improve depth of response and progression-free survival compared with triplet therapy in newly diagnosed multiple myeloma in both transplant-eligible and transplant-ineligible patients.
- Although toxicity is modestly increased, the magnitude of MRD and PFS benefit supports quadruplet therapy as a preferred frontline strategy for appropriate patients.
- Longer follow-up is needed to confirm overall survival benefit and refine patient selection.

RESULTS

- Five randomized trials including 3,198 patients met inclusion criteria. Included studies represented both transplant-eligible and transplant-ineligible populations and included **GRIFFIN, PERSEUS, ALCYONE, CEPHEUS, and IMROZ**.
- Quadruplet therapy significantly **improved progression-free survival** compared with triplet therapy, with a pooled fixed-effect hazard ratio of approximately 0.68 (95% CI, 0.60–0.77). Benefit was consistent across transplant-eligible and transplant-ineligible subgroups.
- Quadruplet therapy also produced **deeper responses**. MRD negativity was markedly improved, with a pooled risk ratio of approximately 1.8 (95% CI, 1.5–2.2). Complete response or stringent complete response rates were also increased, with a pooled risk ratio of approximately 1.4.
- Overall survival data remain immature across several studies. The pooled estimate favored quadruplet therapy but did not demonstrate a statistically definitive survival advantage at current follow-up.
- Safety analysis showed higher rates of grade ≥3 hematologic toxicities and infections with quadruplet therapy, but no clear excess treatment-related mortality.

ACKNOWLEDGEMENTS

This research was supported by HCA Healthcare. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA healthcare or any of its affiliated entities

CONTACT INFORMATION

Elias Tayar, MD

University of Houston / HCA Healthcare Clear Lake

Webster, TX, USA

elias.tayar@hcahealthcare.com

REFERENCES

1. Voorhees PM, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: GRIFFIN. Lancet Haematol. 2020.
2. Sonneveld P, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma: PERSEUS. N Engl J Med. 2024.
3. Mateos MV, et al. Daratumumab plus bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma: ALCYONE. N Engl J Med. 2018.
4. San-Miguel J, et al. Daratumumab plus VRd for transplant-ineligible or transplant-deferred NDMM: CEPHEUS. Nat Med. 2025.
5. Facon T, et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for transplant-ineligible NDMM: IMROZ. N Engl J Med. 2024.
6. Page MJ, et al. PRISMA 2020 statement. BMJ. 2021.