Isolating the Anti-CD38 Component Effect in Newly Diagnosed Multiple Myeloma: A Component-Based Network Meta-Analysis of Phase 3 Randomized Trials

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INTRODUCTION

Contemporary treatment of newly diagnosed multiple myeloma (NDMM) has shifted toward quadruplet regimens incorporating anti-CD38 monoclonal antibodies (daratumumab, isatuximab) with proteasome inhibitor and immunomodulatory drug backbones. However, the independent contribution of the anti-CD38 component—disentangled from backbone agents—remains unquantified. Component-based network meta-analysis (CNMA) enables isolation of individual treatment components within multi-drug regimens to estimate class-specific effects.

METHODS

We conducted a systematic CNMA of six phase 3 randomized controlled trials in NDMM (CASSIOPEIA, ALCYONE, MAIA, GRIFFIN, PERSEUS, IMROZ; N=3,963 patients). Each regimen was decomposed into binary components (anti-CD38, bortezomib, lenalidomide, thalidomide, autologous stem cell transplantation). An additive weighted least-squares component model with Der Simonian-Laird heterogeneity estimation was applied to two primary outcomes: progression-free survival (PFS) hazard ratios and grade ≥3 infection risk ratios. Component effects were estimated independently, adjusting for all backbone elements.

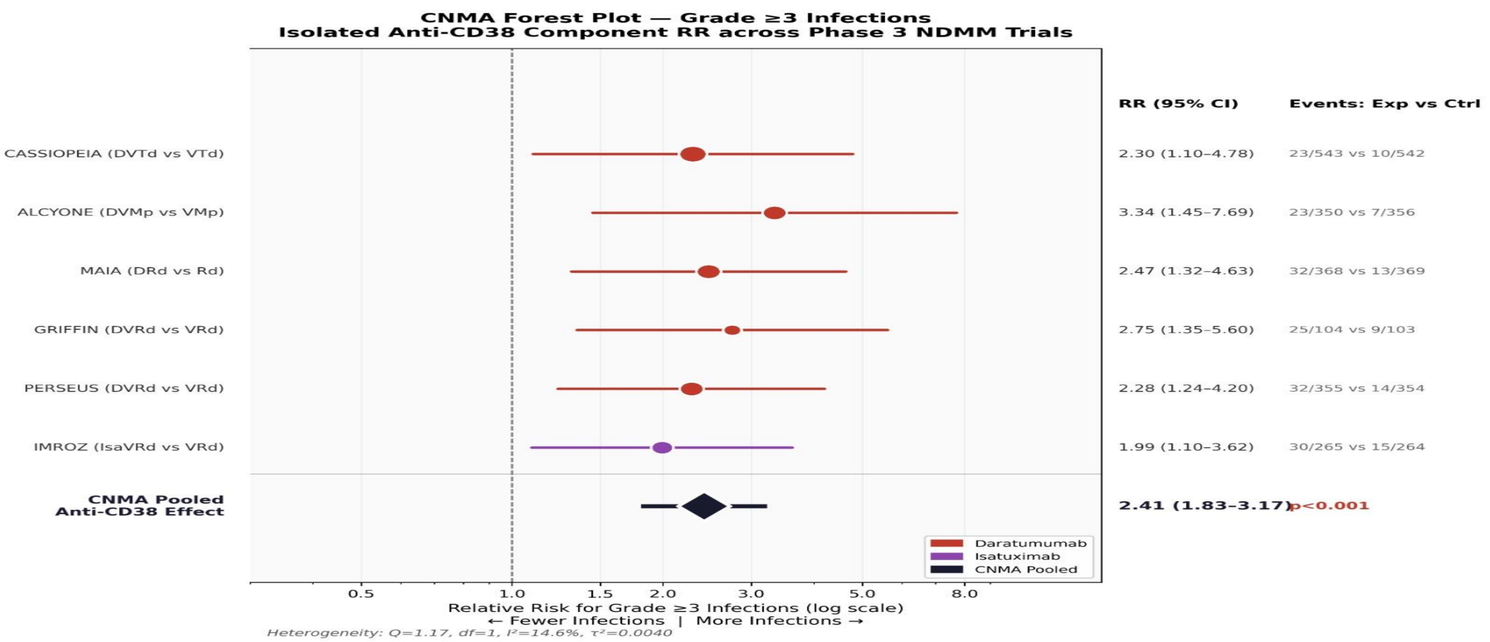
RESULTS:

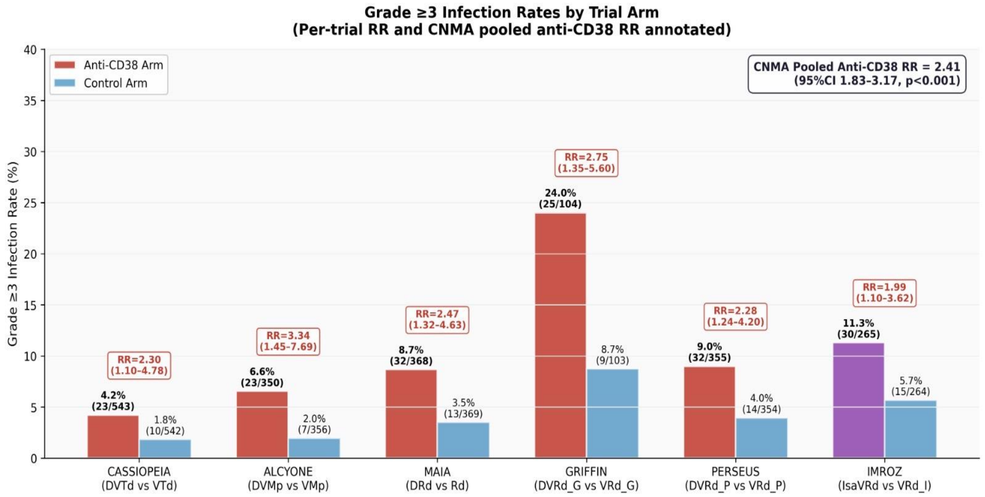
The anti-CD38 component demonstrated a PFS hazard ratio of 0.479 (95% CI 0.418–0.549, p<0.001), corresponding to a 52.1% relative risk reduction, with moderate heterogeneity (I^2=66.7%, τ^2=0.0121). Grade ≥3 infection risk increased 141.3% with anti-CD38 exposure (RR 2.413, 95% CI 1.835–3.174, p<0.001; I^2=14.6%, τ^2=0.0040). All backbone components (bortezomib, lenalidomide, thalidomide, autologous transplantation) yielded null effects (HR/RR=1.00, p>0.05) after accounting for anti-CD38, indicating no independent contribution to either outcome. The anti-CD38 effect was consistent across transplant-eligible and transplant-ineligible populations and across proteasome inhibitor versus immunomodulatory drug backbones.

CONCLUSIONS:

Anti-CD38 monoclonal antibodies are the sole active component driving PFS benefit in contemporary NDMM quadruplet regimens, with a backbone-agnostic class effect. The substantial infection risk elevation supports routine intravenous immunoglobulin prophylaxis in anti-CD38-treated patients. These findings establish anti-CD38 therapy as the critical efficacy determinant in NDMM, independent of partner agents, and inform risk-benefit counseling and supportive care strategies in clinical practice.

RESULTS





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