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INPLASY

Efficacy of CD38 mAb-based quadruplet regimens compared with conventional triplet regimens in newly diagnosed multiple myeloma with reduced performance status: A systematic review and meta-analysis of randomized controlled trials

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Corresponding author:
Bin Hu

hubindoctor@sina.com

Author Affiliation:
Department of Hematology, Changde Hospital, Xiangya School of Medicine, Central South University (First People's Hospital of Changde City).

Hu, B; Fang, D; Jiang, L; Cao, JX; Li, TQ; Wang, J.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INPLASY registration number: INPLASY202670055

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 July 2026 and was last updated on 16 July 2026.

INTRODUCTION

Review question / Objective Whether CD38 mAb-based quadruplet regimens are superior to conventional triplet regimens in NDMM patients with reduced performance status remains an unresolved clinical question.

Rationale For patients with newly diagnosed multiple myeloma (NDMM), a triplet regimen consisting of a proteasome inhibitor, an immunomodulatory agent, and dexamethasone has long been the standard induction therapy. CD38 monoclonal antibodies (mAbs), such as daratumumab and isatuximab, exert multifaceted anti-myeloma effects, including Fc-dependent immune effector activity, direct pro-apoptotic effects, and immunomodulation via elimination of CD38-expressing immunosuppressive cell. The addition of a CD38 mAb to a backbone triplet regimen has led to the establishment of quadruplet therapies, which are now widely adopted as induction therapy for NDMM. However, the benefit of CD38 mAb-based quadruplet regimens is not uniform across all patient subgroups. While substantial efficacy has been shown in fit patients with good performance status, the risk-benefit profile in NDMM patients with reduced performance status remains poorly defined. Reduced performance status, typically defined as an Eastern Cooperative Oncology Group (ECOG) performance status score ≥1, is common in clinical practice and is often associated with older age, a higher burden of comorbidities (e.g., renal impairment, cardiovascular disease, diabetes), and decreased physiological reserve. These patients are particularly vulnerable to treatment-related adverse events, including infections, cytopenias, and organ toxicities, and may have lower tolerability to intensive chemotherapy or targeted agents. Consequently, although quadruplet regimens offer the potential for deeper responses, they may also impose a higher risk of toxicity, leading to dose reductions, treatment delays, or early discontinuation – factors that could attenuate the anticipated survival gain.

Condition being studied Multiple myeloma is a haematological malignancy characterised by the clonal proliferation of malignant plasma cells within the bone marrow. This aberrant expansion disrupts normal haematopoiesis, leading to cytopenias, and stimulates excessive osteoclast activity, resulting in osteolytic bone lesions, pathological fractures, and hypercalcaemia. The paraprotein—a monoclonal immunoglobulin produced by the neoplastic cells—may cause renal impairment, hyperviscosity syndrome, and recurrent infections due to immune paresis. Clinically, the disease is often preceded by asymptomatic precursor states, namely monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma. Diagnosis relies on bone marrow biopsy, serum and urine protein electrophoresis, and imaging studies. Although multiple myeloma remains largely incurable, therapeutic advances—including proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and chimeric antigen receptor T-cell therapy—have substantially improved patient outcomes and survival.

METHODS

Search strategy Search strategy and terms in PubMed database

Research question as searched in PubMed on 15-07-2026
CD38 monoclonal antibodies
((((((((((((((((((daratumumab[Title/Abstract]) OR (Darzalex[Title/Abstract])) OR (humax CD38[Title/Abstract])) OR (humax CD 38[Title/Abstract])) OR (humax-CD38[Title/Abstract])) OR (humax-CD 38[Title/Abstract])) OR (antiCD38[Title/Abstract])) OR (anti CD38[Title/Abstract])) OR (anti-CD38[Title/Abstract])) OR (isatuximab[Title/Abstract])) OR (SAR650984[Title/Abstract])) OR (SAR650984[Title/Abstract])) OR (Sarclisa[Title/Abstract])) OR (isatuximab-irfc[Title/Abstract])) OR (felzartamab[Title/Abstract])) OR (mor202[Title/Abstract])) OR (MOR 202[Title/Abstract])) OR (MOR-202[Title/Abstract])) OR (mor03087[Title/Abstract])
Multiple myeloma
("Multiple Myeloma"[Mesh]) OR ((((((((((((((((((Multiple Myelomas[Title/Abstract]) OR Myelomas, Multiple[Title/Abstract]) OR Myeloma, Multiple[Title/Abstract]) OR Myeloma, Plasma-Cell[Title/Abstract]) OR Myeloma, Plasma Cell[Title/Abstract]) OR Myelomas, Plasma-Cell[Title/Abstract]) OR Plasma-Cell Myeloma[Title/Abstract]) OR Plasma-Cell Myelomas[Title/Abstract]) OR Myelomatosis[Title/Abstract]) OR Myelomatoses[Title/Abstract]) OR Plasma Cell Myeloma[Title/Abstract]) OR Cell Myeloma, Plasma[Title/Abstract]) OR Cell Myelomas, Plasma[Title/Abstract]) OR Myelomas, Plasma Cell[Title/Abstract]) OR Plasma Cell Myelomas[Title/Abstract]) OR Kahler Disease[Title/Abstract]) OR Disease, Kahler[Title/Abstract]) OR Myeloma-Multiple[Title/Abstract]) OR Myeloma Multiple[Title/Abstract])
Study
("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (Meta-Analysis[ptyp] OR Review[ptyp] OR systematic[sb])
Limitations
((rat OR Rats OR Mouse OR Mice OR pig OR pigs OR cow OR cows OR sheep OR chicken* OR dog OR dogs) NOT human [mesh])

Combine: (“Daratumumab” AND “Multiple myeloma” AND “Study”) NOT Limitations.

Participant or population Patient population: NDMM individuals having an ECOG performance status score >1.

Intervention CD38 mAb-based quadruple therapy.

Comparator Triple therapy.

Study designs to be included Randomized controlled trials (RCTs).

Eligibility criteria Endpoints: minimal residual disease (MRD) negativity rate (using a 10^{-5} threshold) and PFS.

Information sources A systematic literature search was conducted independently by two researchers across several electronic databases, namely PubMed, EMBASE, and the Cochrane Library. Only peer-reviewed RCTs with complete full-text manuscripts met the inclusion criteria. Studies not published in English, along with those that were unpublished or still ongoing, were not considered. To achieve thorough retrieval, the bibliographies of all qualifying articles were screened manually to detect further relevant studies.

Main outcome(s) The primary aim was to evaluate differences between the two treatment groups with respect to the MRD negativity rate and PFS.

Quality assessment / Risk of bias analysis The methodological rigor of every study included was independently evaluated by two reviewers. Quality

assessment for each RCT was performed using the Cochrane Collaboration's Risk of Bias tool.

Strategy of data synthesis Analyses were carried out employing RevMan (version 5.4). Heterogeneity across studies was assessed using the I^2 statistic, with values ranging from 25% to 50% regarded as low, 50% to 75% as moderate, and exceeding 75% as high. Given the anticipated clinical and methodological heterogeneity among the trials included, a random-effects model was designated a priori as our principal analytical approach. This model delivers a more cautious and broadly applicable estimate by incorporating both within-study and between-study variation. A fixed-effect model was deemed suitable only under circumstances where the I^2 statistic suggested negligible heterogeneity ($I^2 \leq 25\%$) and the studies were qualitatively considered highly consistent regarding their design and participant characteristics.

Subgroup analysis We conducted subgroup analyses for PFS according to three factors: ECOG performance status score (≥1 or ≥2), CD38 mAb type (daratumumab vs. isatuximab), and transplant candidacy (eligible or ineligible).

Sensitivity analysis Sensitivity analyses were conducted to evaluate how the exclusion of individual studies influenced the aggregated results.

Country(ies) involved All authors are affiliated with institutions in China.

Keywords CD38 monoclonal antibodies, quadruplet regimens, multiple myeloma, reduced performance status, meta-analysis.

Contributions of each author

Author 1 - Bin Hu.
Email: hubindoctor@sina.com
Author 2 - Dan Fang.
Author 3 - Ling Jiang.
Author 4 - Jinxia Cao.
Email: valentina8805@163.com
Author 5 - Tianqi Li.
Author 6 - Jun Wang.
Email: angela80824w@sina.com