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Efficacy and Safety of Isatuximab Combination Therapy in Multiple Myeloma: A Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 October 2025 and was last updated on 8 October 2025.

INTRODUCTION

Review question / Objective Review Question/Objective: To systematically evaluate and compare the efficacy and safety of isatuximab-based combination therapy versus standard therapy in adults with newly diagnosed or relapsed/refractory multiple myeloma by synthesizing evidence from randomized controlled trials.

Rationale Despite significant therapeutic advances, multiple myeloma (MM) remains an incurable malignancy for most patients, with a recurring pattern of relapse. This underscores the persistent need for novel, effective treatment strategies. The introduction of anti-CD38 monoclonal antibodies, beginning with daratumumab, marked a transformative step in MM therapy, validating CD38 as a critical therapeutic target.

Isatuximab is a distinct anti-CD38 antibody that binds a unique epitope and is reported to induce tumor cell death through multiple, non-overlapping mechanisms, including direct apoptosis and immunomodulatory effects. Its use has expanded from the relapsed/refractory setting (RRMM) to frontline treatment for newly diagnosed MM (NDMM), supported by positive results from recent Phase III trials such as ICARIA-MM, IKEMA, IMROZ, and GMMG-HD7.

However, the evidence for isatuximab is spread across individual clinical trials with varying designs, patient populations, and combination regimens. This leads to several challenges: the magnitude of its benefit on key outcomes like progression-free survival (PFS) and overall survival (OS) may differ across studies; its impact on the depth of response, particularly minimal residual disease (MRD) negativity—a key surrogate for long-term outcomes—is not fully consolidated; and its safety profile relative to standard therapies requires a comprehensive overview. Furthermore, crucial

questions remain regarding its efficacy in specific patient subgroups, such as those with high-risk cytogenetics.
While previous meta-analyses have explored the class of anti-CD38 antibodies, the body of evidence for isatuximab has grown substantially and warrants an updated, dedicated synthesis. A quantitative pooling of data from all relevant randomized controlled trials (RCTs) is necessary to provide more precise and powerful estimates of its efficacy and safety. This meta-analysis was therefore conducted to definitively address these gaps, offering clinicians and policymakers a robust, high-level evidence base to inform the integration of isatuximab into the MM treatment paradigm.

Condition being studied Multiple myeloma is a hematologic malignancy, meaning a cancer that originates in the blood-forming cells. It is characterized by the uncontrolled proliferation of plasma cells, a type of white blood cell normally responsible for producing antibodies. In multiple myeloma, these cancerous plasma cells accumulate in the bone marrow, crowding out healthy blood cells and leading to a classic set of symptoms and complications.
Despite being a relatively uncommon cancer, it is the second most prevalent blood cancer globally. The disease is considered largely incurable for the majority of patients, with a typical pattern of response to initial therapy followed by relapse. Treatment has evolved significantly with the introduction of proteasome inhibitors, immunomodulatory drugs, and, more recently, monoclonal antibodies. However, the relapsing-remitting nature of the disease creates a continuous need for new, effective therapeutic options to improve survival and the quality of life for patients.

METHODS

Search strategy The systematic literature search was conducted using the following major electronic databases from their inception until September 2025:
PubMed
EMBASE
Cochrane Central Register of Controlled Trials (CENTRAL)
Web of Science

Search Terms and Strategy
The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and free-text keywords to comprehensively capture all relevant studies. The strategy was built around three core concepts:
Intervention: "isatuximab" and its related terms.
Disease: "multiple myeloma" and its synonyms.
Study Design: "randomized controlled trial."

Participant or population Adult patients with newly diagnosed or relapsed/refractory multiple myeloma.

Intervention Isatuximab-based combination therapy.

Comparator Standard therapy regimens without isatuximab.

Study designs to be included Randomized Controlled Trials (RCTs).

Eligibility criteria Inclusion Criteria
Studies were included if they met the following criteria, which align with the PICOS elements:
Study Design: Randomized Controlled Trials (RCTs).
Population: Adult patients (≥ 18 years) with newly diagnosed multiple myeloma (NDMM) or relapsed/refractory multiple myeloma (RRMM).
Intervention & Comparison: Compared an isatuximab-containing regimen with a standard therapy that did not include isatuximab.
Outcomes: Reported on at least one of the pre-specified efficacy outcomes (PFS, OS, ORR, VGPR or better, MRD negativity) or safety outcomes (grade ≥3 adverse events).

Exclusion Criteria
The authors applied the following additional exclusion criteria:
Study Design:
Non-randomized studies (e.g., cohort studies, case-control studies).
Case reports, reviews, editorials, and conference abstracts (unless they were the only available source for an otherwise eligible RCT, as was the case for the Iskia trial).
Data Integrity and Availability:
Studies with overlapping or duplicate patient populations. If multiple publications reported on the same trial, the most complete and recent publication was selected to avoid double-counting.
Ongoing trials without available results.
Studies published in languages other than English.
Reporting:
Studies that did not report sufficient data on the outcomes of interest for extraction and analysis.
These criteria were implemented to ensure the meta-analysis synthesized high-quality, unique,

and analyzable evidence from the most relevant clinical trials.

Information sources Electronic Databases: A systematic search was performed in the following major international databases from their inception to September 2025:
PubMed
EMBASE
Cochrane Central Register of Controlled Trials (CENTRAL)
Web of Science

Supplementary Search Methods: To ensure a thorough identification of studies, the following additional strategies were employed:
Reference List Checking: The reference lists of retrieved full-text articles and relevant review articles were manually screened to identify any potentially eligible studies not captured by the electronic database search.
Clinical Trial Registers: While not explicitly stated as a primary source, the methodology of checking for "ongoing trials without available results" implies that clinical trial registries (such as ClinicalTrials.gov) were likely consulted to identify the status of relevant studies.
Grey Literature: The search included conference abstracts, as one of the included studies (Iskia) was incorporated based on its conference abstract when it was the only available source.
The search was restricted to studies published in the English language. There was no mention of contacting study authors for additional data or information.

Main outcome(s) Efficacy Outcomes:
Progression-free survival (PFS): Time from randomization to disease progression or death from any cause. Effect measure: Hazard Ratio (HR) with 95% Confidence Interval (CI).
Overall survival (OS): Time from randomization to death from any cause. Effect measure: HR with 95% CI.
Overall response rate (ORR): Proportion of patients achieving a partial response or better. Effect measure: Risk Ratio (RR) with 95% CI.
VGPR or better rate: Proportion of patients achieving a very good partial response or better. Effect measure: RR with 95% CI.
MRD negativity rate: Proportion of patients achieving minimal residual disease-negative status. Effect measure: RR with 95% CI.
Timing for PFS/OS was based on the longest available follow-up in each trial. Response and MRD outcomes were assessed at protocol-defined timepoints.

Safety Outcomes:
Incidence of any grade ≥3 adverse events. Effect measure: RR with 95% CI.
Incidence of fatal adverse events. Effect measure: RR with 95% CI.
Incidence of specific grade ≥3 adverse events (e.g., neutropenia, thrombocytopenia, anemia, pneumonia, diarrhea, fatigue). Effect measure: RR with 95% CI.
Safety outcomes were assessed throughout the treatment period in each trial.

Additional outcome(s) No additional outcomes beyond the main efficacy and safety endpoints were specified or analyzed in this systematic review. The analysis was exclusively focused on the pre-specified outcomes of:
Efficacy: PFS, OS, ORR, VGPR or better, and MRD negativity.
Safety: Grade ≥3 adverse events (any, fatal, and specific hematologic and non-hematologic events).
The subgroup analyses conducted (by disease status: NDMM vs. RRMM, and by cytogenetic risk) were not defined as separate outcomes but were pre-specified investigations to explore the consistency of the primary PFS outcome across different patient populations. Therefore, no other outcomes, such as quality of life, time to next treatment, or cost-effectiveness, were included.

Data management The process was conducted independently by two investigators to minimize error and bias. The mechanism for managing records and data involved several key steps:
Record Management: The identification and screening of records from databases were performed by two independent investigators. They initially screened titles and abstracts, followed by a full-text assessment of potentially eligible studies.
Data Extraction: Data from the included studies were extracted independently by two reviewers using a pre-designed electronic form. This standardized form captured:
Study characteristics (author, year, design, sample size).
Participant characteristics (age, disease status, cytogenetic risk).
Intervention details (regimen, dosage).
Outcomes data (HRs with 95% CIs for time-to-event outcomes; event counts and totals for dichotomous outcomes).
Conflict Resolution: Any discrepancies identified during the screening or data extraction phases were resolved through discussion between the two reviewers. If a consensus could not be reached, a third reviewer was consulted to arbitrate and make a final decision.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included randomized controlled trials (RCTs) were assessed using the Cochrane Collaboration's Risk of Bias tool.
The assessment was performed independently by two reviewers. The tool was used to evaluate key domains, including:
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other potential sources of bias

For each domain, judgments of "low risk," "high risk," or "unclear risk" of bias were made.
Any disagreements between the two reviewers were resolved through discussion. If a consensus could not be reached, a third reviewer was consulted to arbitrate and make a final decision.
The authors noted that the primary concern across most studies was performance bias due to their open-label design. However, they considered this risk mitigated for the primary efficacy endpoints in four of the five trials, as blinded Independent Review Committees or central laboratory assessments were used, thereby reducing detection bias.

Strategy of data synthesis The data analysis was performed using RevMan 5.4 and Stata 14 software. The synthesis strategy was as follows:
Effect Measures:
For time-to-event outcomes (PFS and OS), the pooled Hazard Ratio (HR) with a 95% confidence interval (CI) was calculated.
For dichotomous outcomes (ORR, VGPR, MRD negativity, and adverse events), the pooled Risk Ratio (RR) with a 95% CI was calculated.
Model Selection:
The choice between a fixed-effect model and a random-effects model (DerSimonian and Laird method) was determined by the degree of statistical heterogeneity.
A fixed-effect model was used for analyses with low heterogeneity (I^2 statistic 0.1 for the Chi^2 test).
A random-effects model was adopted for analyses with substantial heterogeneity ($I^2 \geq 50\%$ and $p \leq 0.1$).
Assessment of Heterogeneity:
Statistical heterogeneity was quantified using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.
Subgroup Analysis:
Pre-specified subgroup analyses were conducted to explore potential sources of heterogeneity and differences in treatment effect based on:
Disease status (Newly Diagnosed MM vs. Relapsed/Refractory MM)
Cytogenetic risk (standard-risk vs. high-risk)
Handling of Limited Data:
The authors noted that the limited number of studies (often only 2-3 per comparison) precluded the use of pre-specified sensitivity analyses or formal tests for publication bias (e.g., funnel plots, Egger's test), as these methods are unreliable with so few studies. Instead, the robustness of findings was assessed through the pre-specified subgroup analyses and careful inspection of forest plots.

Subgroup analysis By Disease Status: The primary efficacy outcome, Progression-free Survival (PFS), was analyzed separately for two distinct patient populations:
Patients with Newly Diagnosed Multiple Myeloma (NDMM)
Patients with Relapsed/Refractory Multiple Myeloma (RRMM)
This analysis was intended to determine if the benefit of isatuximab was consistent across different treatment settings.
By Cytogenetic Risk: A more detailed subgroup analysis of PFS was conducted, stratified by both disease status and cytogenetic risk profile:
Within NDMM patients: Comparison of the treatment effect between those with standard-risk and high-risk cytogenetics.
Within RRMM patients: Comparison of the treatment effect between those with standard-risk and high-risk cytogenetics.
The purpose of this analysis was to evaluate whether the efficacy of isatuximab was modulated by a patient's underlying genetic risk, a key prognostic factor in multiple myeloma.

Sensitivity analysis While sensitivity analyses were pre-specified to assess the robustness of the synthesized results, the limited number of included studies (5 RCTs in total, often with only 2-3 studies available for each outcome comparison) precluded their use.
The rationale is that with such a small number of studies, sensitivity analysis methods like the sequential removal of each study to assess its influence on the overall result would yield unstable and unreliable estimates. This decision is in line with methodological guidance from sources like the Cochrane Handbook, which cautions against such practices when the number of studies is very low.
Therefore, instead of statistical sensitivity analyses, the robustness of the findings was evaluated

through the pre-specified subgroup analyses (by disease status and cytogenetic risk) and careful inspection of the forest plots.

Language restriction The search was restricted to studies published in the English language.

Country(ies) involved China.

Other relevant information Handling of Non-English Studies: While the initial database search was not language-restricted, the final eligibility criteria explicitly excluded studies published in languages other than English.
Assessment of Reporting Biases: The authors state that the risk of bias due to missing results (e.g., publication bias) was not formally assessed for any synthesis. This decision was due to the limited number of included studies (fewer than 10), as statistical tests for funnel plot asymmetry are known to be unreliable in this context.
Certainty of Evidence: The review did not include a formal assessment of the overall certainty or confidence in the body of evidence for each outcome (e.g., using the GRADE approach).
Conflict Resolution: The process for resolving disagreements between reviewers during study selection, data extraction, and quality assessment involved discussion and, if necessary, consultation with a third reviewer to reach a consensus.
Planned Analyses: The authors note that some pre-planned analyses (sensitivity analysis, formal assessment of publication bias) were not performed due to an insufficient number of studies, as per methodological guidelines.

Keywords Isatuximab; multiple myeloma; randomized controlled trials; efficacy; safety; meta-analysis.

Dissemination plans Publication in a Peer-Reviewed Scientific Journal: The manuscript is prepared for submission to an academic journal to ensure rigorous peer review and to reach the target audience of clinicians and researchers in hematology and oncology.

Contributions of each author

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