Discrepancies between guideline recommendations and regulatory approvals in multiple myeloma - importance of evidence stratification of a living systematic literature review (SLR)

HSD36

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OBJECTIVES

- To understand the gap between guideline recommendations and regulatory approvals in the rapidly evolving landscape of combination therapies in multiple myeloma, through a living SLR

BACKGROUND

- Treatment guidelines in oncology summarize the clinical benefit from clinical trials or real-world evidence aiming to highlight all available treatment options based on the most robust data
- However, for some of the guideline recommended therapies, the regulatory endorsement is not pursued or not yet available, leading to reimbursement challenges and uncertainty around safety and quality data for off-label use[1]
- In the US, insurers often reimburse oncology drugs listed in recognized guidelines, even if the use is off-label. This reduces the pressure on manufacturers to seek formal label approvals or updates[2]
- Although this allows access to a wider variety of therapies, payer-specific interpretations of the compendia may create coverage disparities. Moreover, this practice relies heavily on the accuracy of guideline interpretation and timely availability of evidence for therapies that have not undergone a more rigorous regulatory review[3,4]
- In contrast, in Europe, most nations use evidence-based health technology assessments to support treatment access and reimbursement, which significantly limits the use of off-label treatments. In this context, guidelines are auxiliary tools, used to define the unmet need, assist with prioritization of drugs for reimbursement, and define the standard of care against which a new drug must be compared[5]

METHODS

- A daily-updated REal-time AI-assisted Living SLR REAL-SLR, compliant with PRISMA guidelines was conducted in multiple myeloma
- Clinical trials published in English were identified from PubMed and major conferences proceedings and assessed using Population, Intervention/Comparators, Outcomes, and Study design (PI/COS) framework (**Table 1**)
- The review assisted by artificial intelligence (AI) was conducted in two steps. First review was conducted using a proprietary AI model and was followed by a second review and conflict resolution conducted by human researchers
- Clinical trials supporting regulatory approvals and guideline recommendations without publication timeframe restrictions, those from PubMed published since 2020, and conference abstracts from American Society of Hematology, International Myeloma Society, and European Hematology Association (2024-2025) were included in the review
- Studies were stratified by treatment/disease pathways, interventions, outcomes and subgroups categories. Guideline recommendation and regulatory approval tags based on the population characteristics and investigated interventions were added to the corresponding studies

Table 1. PICOS statement

Element	Inclusion
Patient population	• Patients diagnosed with symptomatic multiple myeloma or smoldering myeloma
Intervention and Comparators	• Any pharmacological intervention (including biologics, cell treatments, vaccines, etc.) and stem-cell transplant used for the treatment of myeloma
Outcomes measures	• Overall survival and mortality • Progression-free survival • Other progression measures (such as duration of response, time to progression, time to next treatment) • Response rates (such as complete response, very good partial response, objective response rate, minimal residual disease) • Quality of life (measures such as EORTC QLQ-C30, EORTC MY-20, and EQ-5D utility) • Safety (treatment-related adverse events [AEs], grade ≥3 and serious AEs, AEs of special interest and discontinuations)
Study design	• Prospective interventional studies including randomized and non-randomized trials, any phase • Pooled analyses of trials • External control trials
Restrictions	• English language

Figure 2. Studies containing therapies with regulatory approval and guideline recommendation

	USA Guidelines	FDA	EHA Guidelines	EMA
Overall	267	160	140	163
NDMM	129	58	65	55
RRMM	142	107	82	112

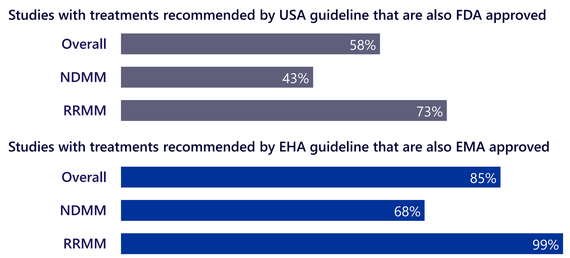


Figure 3. Agreement between USA guidelines and EHA guideline

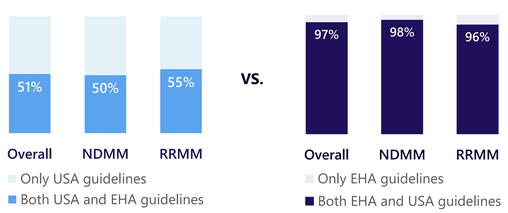
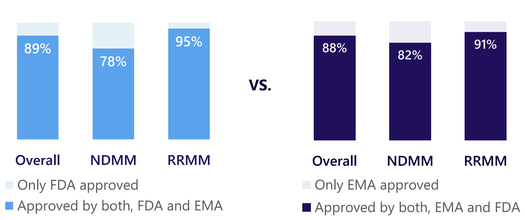
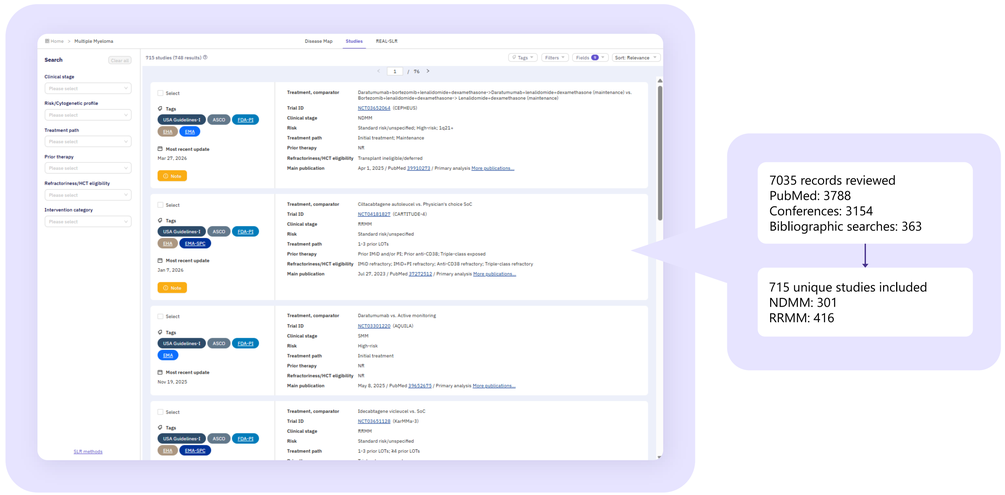


Figure 4. Agreement between FDA and EMA drug approvals





RESULTS

- The daily-updated REAL-SLR contained 715 studies of 7035 total screened in multiple myeloma as of March 18, 2026 (**Figure 1**)
- Studies were stratified and tagged with guideline recommendations or regulatory approvals (**Figure 1**) based on:
  - Clinical stage: newly diagnosed multiple myeloma (NDMM, 301 studies, 42%), relapsed/refractory multiple myeloma (RRMM, 416 studies, 58%), and smoldering myeloma (20 studies, 2.8%)
  - Risk/cytogenetic profile: standard risk, high risk, presence of del(17p)/TP53 mutation, t(11;14), 1q21+, extramedullary disease, or plasma cell leukemia
  - Treatment path: initial treatment, consolidation, conditioning, maintenance (for NDMM), 1-3 prior lines of therapy (LOTs), and ≥4 prior LOTs (for RRMM)
  - Prior therapy: prior immunomodulatory drug (IMiD) and/or proteasome inhibitor (PI), prior anti-CD38 monoclonal antibody, triple-class exposed, prior BCMA-targeted therapy, prior CAR-T
  - Transplant eligibility (for NDMM): transplant eligible, transplant ineligible/deferred
  - Refractoriness (for RRMM): IMiD refractory, PI refractory, IMiD+PI refractory, anti-CD38 antibody refractory, triple-class refractory, non-refractory
- Among all studies including treatments recommended by USA guidelines, 58% were also approved by the Food and Drug Administration (FDA) (**Figure 2**)
- When considering studies with NDMM populations, only 43% of those with USA guideline recommendation were also FDA approved, in contrast with 73% among studies with RRMM populations (**Figure 2**)
- Among studies including treatments recommended by the European Hematology Association (EHA), 85% were also approved by the European Medicines Agency (EMA) (**Figure 2**)
- A similar trend was observed when analyzing studies in NDMM and RRMM: 68% and 99% of studies including treatments recommended by EHA guidelines were also approved by EMA, respectively (**Figure 2**)
- Only approximately half of the studies with treatments recommended by USA guidelines also had a recommendation from EHA guideline (**Figure 3**)
- Almost all studies with treatments recommended by EHA guideline were also recommended by USA guidelines (**Figure 3**)
- There was a better agreement FDA and EMA regulatory approvals: 89% of studies with FDA-approved treatments were FDA and EMA approved (**Figure 4**)

ABBREVIATIONS

EHA, European Hematology Association; EMA, European Medicines Agency; FDA, Food and Drug Administration; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma

CONCLUSIONS

- REAL-SLR revealed a large gap between regulatory approval status and guideline recommendations in MM in the US, but not in Europe
- The results may reflect the guideline-driven reimbursement policies in the US, but also the multi-drug combination strategies commonly used in MM
- Guideline recommendations are sometimes supported by "surrogate" trial evidence (ie, population with different prior exposure/refractoriness) or by real-world clinical practice
- Interestingly, the discrepancy is more evident for NDMM compared to RRMM. Possible reasons:
  - large variety of guideline recommended multi-drug combinations, including chemotherapy, for which official label updates were not pursued
  - among 7 therapies recommended for maintenance, only one is currently FDA approved
- There is a continual need to review evidence in real-time and efficiently disseminate the findings to enable reliable updates to the guidelines and assist clinicians in making informed treatment decisions

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