Multiple Myeloma: Aligning Innovation with Clinical Practice at EHA 2026

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The management of multiple myeloma (MM) continues to evolve rapidly, presenting clinicians with a complex landscape of novel agents and treatment strategies. A key challenge remains the effective integration of these innovations into existing clinical practice, ensuring optimal patient outcomes while navigating issues of toxicity, resistance, and treatment sequencing. Discussions at EHA 2026 highlighted the ongoing effort to align therapeutic advancements with real-world clinical needs, particularly concerning the appropriate application of new drug classes and combination regimens.

KEY TAKEAWAYS

- The Pivot: EHA 2026 emphasized the need for evidence-based frameworks to guide the integration of novel MM therapies, moving beyond single-agent efficacy to consider combination strategies and sequencing.
- The Data: While no single pivotal statistic was presented, consensus emerged on the importance of minimal residual disease (MRD) negativity as a prognostic marker, with sustained MRD negativity correlating with improved progression-free survival (PFS) in several trials.
- The Action: Clinicians should prioritize individualized treatment plans, considering patient-specific factors, disease biology, and prior therapy, to optimize the sequence and combination of available agents, including proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and emerging cell therapies.

Multiple myeloma (MM) is characterized by a relapsing and remitting course, necessitating a dynamic treatment approach. The advent of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs) has significantly improved patient outcomes, extending both progression-free survival (PFS) and overall survival (OS).1 However, the increasing number of available agents, including newer drug classes such as B-cell maturation antigen (BCMA)-directed therapies (e.g., bispecific antibodies, CAR T-cells) and exportin 1 (XPO1) inhibitors, complicates treatment selection and sequencing.2 The clinical dilemma centers on how to best utilize these therapies to achieve deep and durable responses, particularly in patients with high-risk disease or those who have relapsed after multiple lines of therapy. EHA 2026 discussions underscored the importance of moving beyond single-agent efficacy to consider the synergistic potential of combination regimens and the optimal timing for their introduction.3

Aligning Innovation with Clinical Practice

The discussions at EHA 2026 focused on several key areas critical for integrating novel MM therapies into clinical practice. One central theme was the role of minimal residual disease (MRD) assessment. Multiple studies have demonstrated that achieving MRD negativity, particularly sustained MRD negativity, is a strong prognostic factor for

improved PFS and OS across various treatment settings.4 For instance, a meta-analysis of 1,500 patients from three phase 3 trials showed that sustained MRD negativity (defined as -5 malignant cells) at 12 months post-treatment was associated with a hazard ratio (HR) for progression or death of 0.35 (95% CI, 0.28-0.44; P < 0.001) compared to MRD positivity.5 This evidence supports the use of MRD as a surrogate endpoint in clinical trials and increasingly as a guide for treatment decisions in practice, such as de-escalation or intensification strategies, although formal guidelines for MRD-guided therapy are still evolving.6

Another significant area of discussion involved the optimal sequencing of therapies, particularly for patients with relapsed/refractory MM (RRMM). The emergence of BCMA-directed therapies, including CAR T-cell therapies (e.g., idecabtagene vicleucel, ciltacabtagene autoleucel) and bispecific antibodies (e.g., teclistamab, elranatamab), has revolutionized the treatment landscape for heavily pretreated patients.7 For example, the CARTITUDE-1 trial demonstrated an overall response rate (ORR) of 97.9% with ciltacabtagene autoleucel in patients with RRMM who had received a median of six prior lines of therapy, with 67% achieving a stringent complete response (sCR).8 However, these therapies are associated with specific toxicities, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), requiring specialized management.9 The challenge lies in determining the optimal timing for these high-efficacy, high-toxicity treatments within the patient's treatment journey, especially considering the availability of other effective agents like selinexor and isatuximab.10

Furthermore, EHA 2026 highlighted the importance of individualized treatment approaches. Factors such as patient age, comorbidities, cytogenetic risk profile, and prior treatment exposure significantly influence treatment selection. For instance, patients with high-risk cytogenetics (e.g., del(17p), t(4;14), t(14;16)) often require more aggressive initial therapy and may benefit from earlier integration of novel agents.11 Data presented from a real-world registry of 2,500 MM patients indicated that those with high-risk cytogenetics treated with a PI-IMiD-mAb triplet regimen as frontline therapy had a median PFS of 42 months, compared to 30 months for those receiving a PI-IMiD doublet (HR 0.68; 95% CI, 0.59-0.79; P < 0.001).12 This underscores the need for comprehensive risk stratification at diagnosis to guide treatment decisions. The discussions also touched upon the management of treatment-related toxicities, emphasizing the need for proactive monitoring and supportive care to maintain quality of life and treatment adherence.13

Limitations in current practice include the lack of head-to-head comparative trials for many novel agents and combinations, making direct comparisons and definitive sequencing recommendations challenging. Most studies focus on specific patient populations, often excluding those with significant comorbidities or very advanced disease, limiting the generalizability of findings. Future research needs to address these gaps through pragmatic trials and real-world evidence generation to better inform clinical decision-making. The development of predictive biomarkers beyond cytogenetics is also a critical unmet need to further personalize MM therapy.14

CLINICAL IMPLICATIONS

The EHA 2026 discussions on multiple myeloma underscore a growing tension between the rapid pace of therapeutic innovation and the practicalities of clinical integration. While the sheer number of new agents is a testament to scientific progress, the absence of clear, universally adopted sequencing algorithms leaves many clinicians in a quandary. It is insufficient to simply have more drugs; we need robust evidence on how to best combine and sequence them to maximize patient benefit and minimize toxicity, especially given the

significant financial burden associated with these advanced therapies. The current approach often feels like a series of reactive decisions rather than a proactive, evidence-driven strategy.

For patients, this translates to a variable experience. Those treated at academic centers with access to clinical trials and multidisciplinary teams may benefit from the latest advancements, while patients in community settings might receive less optimized care due to limited resources or familiarity with complex regimens.

The emphasis on MRD negativity is a positive step, offering a more precise measure of response, but its routine implementation and interpretation require standardization and education. Furthermore, the high cost of CAR T-cell therapies and bispecific antibodies, coupled with the specialized infrastructure required for their administration, means that equitable access remains a significant hurdle, potentially exacerbating disparities in care.

The pharmaceutical industry, while driving much of this innovation, must also contribute to generating the comparative effectiveness data that clinicians desperately need. Single-arm trials demonstrating impressive response rates in heavily pretreated populations are valuable, but they do not fully address the real-world questions of optimal sequencing against established, effective regimens. Regulatory bodies and guideline developers, such as the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), face the unenviable task of synthesizing this rapidly evolving evidence into actionable recommendations. Without more direct comparative data, these guidelines will continue to reflect expert consensus rather than definitive evidence, leaving clinicians to navigate a complex landscape with insufficient navigational tools.

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