CELMoDs Show Promise in Relapsed/Refractory Multiple Myeloma

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Managing relapsed/refractory multiple myeloma (RRMM) presents an ongoing clinical challenge, with patients often exhausting established treatment options and requiring novel therapeutic approaches. Emerging research on Cereblon E3 ligase modulators (CELMoDs) at ASCO 2026 indicates a potential new class of agents that may improve outcomes in this difficult-to-treat population.1

KEY TAKEAWAYS

- The Pivot: CELMoDs represent a distinct class of immunomodulatory drugs with a novel mechanism of action, offering new therapeutic avenues for RRMM.
- The Data: Early phase trials indicate CELMoDs can induce objective response rates (ORR) of 30-60% in heavily pretreated RRMM patients.
- The Action: Clinicians should monitor ongoing CELMoD trials, as these agents may soon expand the treatment landscape for patients with RRMM.

Multiple myeloma remains an incurable haematological malignancy, with a significant proportion of patients experiencing relapse and becoming refractory to standard therapies, including proteasome inhibitors, immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies.1 The evolving treatment landscape necessitates continuous investigation into agents with novel mechanisms of action to overcome resistance and improve survival.2 Patients with RRMM often present with high-risk cytogenetics, extramedullary disease, and prior exposure to multiple lines of therapy, underscoring the need for effective, tolerable new options.3 The incidence of multiple myeloma is approximately 7.1 per 100,000 persons per year, with a median age at diagnosis of 69 years. Despite significant advancements in treatment over the past two decades, including the introduction of novel agents, a substantial number of patients eventually exhaust available therapeutic options, leading to a critical unmet need for new strategies. Relapsed/refractory multiple myeloma (RRMM) is defined by disease progression on or within 60 days of the last therapy, or failure to achieve at least a minimal response to prior therapy. This patient population typically has a poor prognosis, with decreasing response rates and shorter durations of response with each subsequent line of therapy. The development of resistance mechanisms to established drug classes, such as upregulation of drug efflux pumps, mutations in drug targets, or activation of alternative survival pathways, further complicates treatment decisions in RRMM.

Understanding Emerging CELMoD Research

Cereblon E3 ligase modulators (CELMoDs) represent a new generation of immunomodulatory agents distinct from thalidomide, lenalidomide, and pomalidomide.4 These compounds, such as iberdomide and mezigdomide, exhibit

enhanced cereblon binding affinity, leading to more potent degradation of Aiolos and Ikaros, key transcription factors involved in myeloma cell survival and proliferation.5 This increased degradation results in superior anti-myeloma activity and enhanced T-cell co-stimulation compared to earlier IMiDs.6 The precise mechanism involves the recruitment of Aiolos and Ikaros to the cereblon E3 ubiquitin ligase complex, leading to their ubiquitination and subsequent proteasomal degradation. This targeted protein degradation approach offers a distinct advantage by effectively reducing the levels of these critical transcription factors, thereby inhibiting myeloma cell growth and enhancing immune responses.

Early phase clinical trials of CELMoDs in RRMM have demonstrated promising efficacy. For instance, studies of mezigdomide (CC-92480) in heavily pretreated patients, including those refractory to IMiDs, proteasome inhibitors, and anti-CD38 antibodies, have reported objective response rates (ORR) ranging from 30% to 60%, depending on the dose and patient population.7 In one Phase 1/2 study, patients receiving mezigdomide monotherapy achieved an ORR of 40% (N=100), with a median duration of response of 7.6 months.8 The safety profile generally includes myelosuppression, particularly neutropenia (Grade 3/4 in 50-70% of patients), and gastrointestinal toxicities, which are typically manageable with dose modifications and supportive care.9 These trials typically enrolled patients who had received a median of 5-6 prior lines of therapy, with a significant proportion having triple-class refractory disease, meaning they were refractory to at least one IMiD, one proteasome inhibitor, and one anti-CD38 antibody. The studies employed a dose-escalation design followed by an expansion cohort, allowing for the identification of a recommended Phase 2 dose.

Iberdomide (CC-220) has similarly shown activity in RRMM. In a Phase 1/2 trial, iberdomide monotherapy achieved an ORR of 26.4% (N=182) in a heavily pretreated population, with a median progression-free survival of 3.7 months.10 When combined with dexamethasone, the ORR increased to 31.5%.11 Common adverse events included neutropenia (Grade 3/4 in 47% of patients) and infections.12 These data suggest that CELMoDs can induce responses in patients with limited therapeutic alternatives, including those with triple-class refractory disease.13 The patient populations in these iberdomide studies were also heavily pretreated, with many having prior exposure to lenalidomide and pomalidomide, highlighting the potential for CELMoDs to overcome IMiD resistance. The trials typically involved oral administration of iberdomide on a 28-day cycle, with varying dosing schedules explored to optimize efficacy and manage toxicity.

The ongoing research at ASCO 2026 is expected to provide further insights into optimal dosing, combination strategies, and the long-term efficacy and safety of these agents. Studies are exploring CELMoDs in combination with other anti-myeloma drugs, such as dexamethasone, proteasome inhibitors, and anti-CD38 antibodies, to enhance response rates and overcome resistance mechanisms.14 The potential for CELMoDs to restore sensitivity to IMiDs in refractory patients is also a key area of investigation.15

Limitations of current data include the early phase nature of many trials, primarily focusing on heavily pretreated populations, which may not fully represent the broader RRMM patient spectrum. The follow-up duration in some studies remains relatively short, limiting conclusions on long-term survival benefits. The small sample sizes in initial cohorts also limit the generalizability of safety and efficacy findings. Furthermore, the heterogeneity of patient populations in terms of prior therapies and disease characteristics makes direct comparisons between studies challenging. Future research will need to address the optimal sequencing of CELMoDs within the treatment paradigm, identify predictive biomarkers for response, and further characterise their safety profiles in larger patient cohorts and in combination regimens.16 The

development of strategies to mitigate myelosuppression, a common adverse event, will also be crucial for broader clinical implementation.

CLINICAL IMPLICATIONS

The emergence of CELMoDs like mezigdomide and iberdomide offers a tangible expansion of the therapeutic armamentarium for relapsed/refractory multiple myeloma, a patient population with increasingly limited options. Clinicians currently face the challenge of managing patients who have progressed on multiple lines of therapy, including IMiDs, proteasome inhibitors, and anti-CD38 antibodies. The observed objective response rates of 30-60% in these heavily pretreated individuals are not merely incremental; they represent a meaningful opportunity to extend disease control and improve quality of life where few alternatives exist. While myelosuppression, particularly neutropenia, is a consistent adverse event, it appears manageable, suggesting that these agents could be integrated into practice with appropriate monitoring and supportive care.

From an industry perspective, the development of CELMoDs highlights a successful strategy in drug design: refining existing drug classes to enhance potency and overcome resistance. This approach, rather than solely pursuing entirely novel targets, demonstrates the value of iterative improvement. Companies like Bristol Myers Squibb, with their investment in this class, are positioning themselves to address a critical unmet need. The ongoing exploration of CELMoDs in combination regimens is particularly astute, as it acknowledges the complex, multi-drug nature of myeloma treatment and seeks to maximise efficacy by leveraging synergistic mechanisms. The market for RRMM therapies is competitive, but agents that can demonstrate efficacy in triple-class refractory disease will undoubtedly carve out a significant niche.

For patients, the prospect of new, effective oral therapies is significant. The convenience of an oral agent, even with potential side effects, can improve adherence and reduce the burden of frequent hospital visits associated with intravenous treatments. While the data are still maturing, the consistent activity of CELMoDs in patients who have exhausted other options provides a renewed sense of hope. The challenge will be ensuring equitable access to these therapies once approved and integrating them into existing treatment algorithms in a way that optimises patient outcomes without undue toxicity or financial strain on healthcare systems. The ASCO 2026 presentations will be critical in shaping the clinical perception and future adoption of these promising compounds.

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