

CELMoDs in Multiple Myeloma: Optimizing RRMM Treatment With Potent Immunomodulatory Drugs

Q: Why are new treatments such as CELMoDs needed in multiple myeloma (MM)?

A: MM remains a **highly heterogeneous** and **genomically complex** disease, with clonal evolution and **diverse resistance mechanisms** contributing to relapse and treatment refractoriness. **Many patients receive multiple lines of therapy early in their course**, including triplet or quadruplet regimens and, increasingly, T cell–redirecting therapies such as CAR T cells and bispecifics, limiting options in later lines.¹⁻⁶

Outcomes remain particularly poor in high-risk subgroups, including those with **adverse cytogenetics**, elderly or frail patients **who may not tolerate intensive regimens**, and those with **triple-/penta-refractory or post-BCMA disease**. In these settings, existing therapies often fail to overcome resistant disease biology.

CELMoDs are a novel oral option with enhanced cereblon binding and immunomodulatory activity, making them **effective even in heavily pretreated, IMiD-refractory, and biologically high-risk populations**. Their oral route of administration may also support patient-centered care by improving convenience and reducing clinic burden, though adherence remains an important consideration.^{7,8}

Q: What are CELMoDs?

A: **CELMoDs (cereblon E3 ligase modulators)** are a novel class of oral immunomodulatory agents designed to bind cereblon, a substrate receptor of the CRL4^{CRBN} E3 ubiquitin ligase complex. Like traditional IMiDs (e.g., lenalidomide, pomalidomide), **CELMoDs promote the degradation of key transcription factors Ikaros and Aiolos, leading to direct antitumor effects and T- and NK-cell activation**. However, CELMoDs have **increased cereblon binding specificity and affinity** and **more potent substrate degradation**, resulting in enhanced anti-myeloma activity, including in IMiD-refractory disease.^{7,8}

Key agents in this class include: **Iberdomide (CC-220)** and **Mezigdomide (CC-92480)**

CELMoDs offer a mechanistically distinct yet complementary approach to current therapies, addressing a critical need in MM. CELMoDs exert **broad immunostimulatory effects** that surpass those of traditional IMiDs. By enhancing cereblon binding and promoting more efficient degradation of Ikaros and Aiolos, CELMoDs **increase IL-2 production, augment T-cell proliferation, and activate NK cells**. Preclinical data suggest CELMoDs **reverse features of T-cell exhaustion and improve T-cell fitness**, including enhanced cytotoxic function and memory phenotype formation.⁹⁻¹⁷

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Q: In which settings are CELMoDs currently being studied or considered?

A: CELMoDs are under active investigation across the MM treatment continuum, with the most advanced data in **relapsed/refractory (R/R) setting**, particularly in **triple- or penta-class refractory disease**, including patients previously treated with BCMA-directed therapies or those with high-risk features such as extramedullary disease.¹⁸⁻³³

- **Ongoing Phase 3 studies in R/R MM:**

- **SUCCESSOR-1:** Mezigdomide + bortezomib + dex vs pomalidomide + bortezomib + dex in patients with 1–3 prior lines, including prior lenalidomide.
- **SUCCESSOR-2:** Mezigdomide + carfilzomib + dex vs carfilzomib + dex in patients with ≥1 prior lines, including prior lenalidomide and anti-CD38 therapy.
- **EXCALIBER-RRMM:** Iberdomide + daratumumab + dex vs daratumumab + bortezomib + dex in patients who received 1-2 prior lines of anti-myeloma therapy.

- **Early-phase studies:**

- **Mezigdomide + dexamethasone (dex) (CC-92480-MM-001):** Phase 1/2 trial in heavily pretreated, triple-class refractory patients.
- **Mezigdomide + bortezomib-dex, carfilzomib-dex, daratumumab-dex, or elotuzumab-dex (CC-92480-MM-002):** Phase 1/2 study in R/R MM, including those refractory to IMiDs, PIs, and anti-CD38 antibodies.
- **Mezigdomide + EZH2, BET, or MEK inhibitors (CA057-003):** Phase 1/2 trial of biologically rational combinations to overcome resistance.
- **Mezigdomide + elranatamab (MELT-MM):** Phase 1/2 study in combination with BCMA-targeted bispecific antibody therapy.
- **Iberdomide + dex ± daratumumab, bortezomib, or carfilzomib (CC-220-MM-001):** Phase 1/2 study of iberdomide-containing doublets or triplets in R/R MM after ≥2-3 prior lines of therapy.
- **Iberdomide + ixazomib-dex (IFM I2D):** Phase 2 study of all-oral triplet regimen in second-line R/R MM.
- **Iberdomide + cyclophosphamide-dex (ICON):** Phase 2 study in heavily pretreated, dual/triple-class refractory.
- **Iberdomide + carfilzomib + daratumumab + dex (ReKInDLE):** Phase 2 study assessing combination followed by iberdomide monotherapy after 1-3 prior lines, including lenalidomide, anti-CD38, and carfilzomib.
- **Iberdomide + elranatamab (MagnetisMM-30):** Phase 1b study in combination with a BCMA-targeted bispecific antibody.

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Q: What are common adverse events associated with CELMoDs?

A: CELMoDs are generally well tolerated but associated with class-related and agent-specific toxicities.¹⁸⁻³²

- **Hematologic:** Neutropenia, anemia, thrombocytopenia
- **Non-hematologic:** Fatigue, gastrointestinal symptoms (nausea, diarrhea), rash, neuropathy

Infection risk, including serious infections, has been observed, particularly in heavily pretreated patients. **Prophylactic antimicrobials, IVIG for hypogammaglobulinemia, and growth factor support** should be considered based on patient risk. **Dose interruptions, reductions, and supportive care measures** are effective for managing toxicities, and close monitoring during early treatment cycles is recommended.

Q: What is the role of minimal residual disease (MRD) in assessing response to therapy?

A: Minimal residual disease (MRD) assessment has become a critical tool in evaluating treatment response in MM.³³⁻⁴⁰ **MRD-negative complete response (CR)**, particularly at highly sensitive thresholds (e.g., 10^{-5} to 10^{-6} by next-generation sequencing or flow cytometry), **is strongly correlated with improved PFS and OS**. Sustained MRD negativity further refines risk stratification, indicating durable disease control and a lower likelihood of relapse.

As a result, **MRD negativity is increasingly accepted as a surrogate endpoint in clinical trials** and has received regulatory recognition, such as the FDA ODAC's April 2024 endorsement of MRD-negative CR as a surrogate for PFS, to support accelerated drug development. Sustained MRD negativity is also emerging as a goal of therapy, offering a **marker of durable remission** and a potential benchmark for achieving a functional cure.

CELMoDs have shown promising MRD negativity rates, including those with high-risk features. Multiple ongoing clinical trials of CELMoDs incorporate MRD-negative CR as an endpoint to assess depth and durability of response, including the CC-92480-MM-001 and CA057-003 trials in R/R MM. These studies highlight the growing role of MRD in guiding clinical development, enabling earlier assessment of treatment benefit, and informing personalized MM care strategies.

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