Advancing Clinical Expertise in CELMoDs: Transforming Multiple Myeloma Treatment

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 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.[12-20]

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

A: CELMoDs are under active investigation across the treatment continuum in MM.[11,21-36,46-54] The most advanced development is in the **relapsed/refractory 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, where early-phase studies have shown encouraging activity. These agents are also being studied in **earlier lines of therapy**, including **transplant-ineligible NDMM**, and as **post-transplant maintenance**, with the potential to replace lenalidomide in frontline or maintenance settings.

Key combinations under investigation include:

Relapsed/Refractory MM: Doublets and Triplets

- ***Mezigdomide + dexamethasone (dex) (CC-92480-MM-001):*** Phase 1/2 trial in heavily pretreated, triple-class refractory patients.
- ***Mezigdomide combinations* with bortezomib-dex, carfilzomib-dex, daratumumab-dex, and elotuzumab-dex *(CC-92480-MM-002):*** Phase 1/2 study in patients with 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 evaluating biologically rational combinations to overcome resistance.
- ***Mezigdomide + elranatamab + dex (MELT-MM):*** Phase 1/2 study assessing potential synergy 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 patients with relapsed/refractory MM after ≥2-3 prior lines of therapy.
- ***Iberdomide + ixazomib-dex (IFM I2D):*** Phase 2 study of an all-oral triplet regimen in second-line relapsed/refractory MM, including those early in relapse.

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- ***Iberdomide + cyclophosphamide-dex (ICON):*** Phase 2 study in heavily pretreated, dual- or triple-class refractory relapsed/refractory MM patients.
- ***Ongoing Phase 3 studies in relapsed/refractory MM:***
    - **SUCCESSOR-1:** Mezigdomide + bortezomib + dex vs pomalidomide + bortezomib + dex in patients with 1–3 prior lines, including lenalidomide and a proteasome inhibitor.
    - **SUCCESSOR-2:** Mezigdomide + carfilzomib + dex vs carfilzomib + dex in patients with 1–3 prior lines, including 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.

Newly Diagnosed MM (NDMM): Transplant-Ineligible or Post-ASCT Maintenance

- ***Iberdomide + dex or + bortezomib-dex or + daratumumab-dex (CC-220-MM-001 expansion cohorts):*** Investigating CELMoD triplets in transplant-ineligible NDMM.
- ***Iberdomide + dex (GEM-IBERDARAX):*** Phase 2 study evaluating doublet in transplant-ineligible NDMM.
- ***Iberdomide maintenance post-ASCT (CC-220-MM-020):*** Phase 2 trial of post-transplant maintenance in transplant-eligible NDMM.
- ***Iberdomide + daratumumab-dex vs. iberdomide + daratumumab-dex + carfilzomib (COMMANDER):*** Phase 1/2 study in NDMM post-transplant.
- ***Iberdomide + subcutaneous daratumumab (IBEX; NCT06107738):*** Phase 1/2 study in NDMM patients post-ASCT who remain MRD-positive.
- ***Iberdomide quadruplet(isatuximab-iberdomide-bortezomib-dexamethasone) and MRD-guided iberdomide-based maintenance in NDMM (DETERMINATION-2)***

Ongoing Phase 3 Trials in Frontline/Maintenance Settings:

- ***GMMG-HD9/DSMM XVIII (NCT06216158):*** Iberdomide monotherapy vs iberdomide + isatuximab as post-ASCT maintenance in transplant-eligible NDMM.
- ***GEM21menos65 (NCT05558319):*** Comparing bortezomib + lenalidomide + dex (VRD) extended + ASCT, isatuximab + VRD + ASCT, and isatuximab + VRD + iberdomide + ASCT in transplant-eligible NDMM.
- ***MIDAS/IFM 2020-02 (NCT04934475):*** Evaluating an MRD-adapted consolidation and maintenance strategy following Isa-KRd induction, with lenalidomide maintenance post-ASCT for standard-risk or isatuximab plus iberdomide maintenance for those with high risk.
- ***EXCALIBER-Maintenance (NCT06107738):*** Comparing iberdomide vs lenalidomide maintenance following ASCT in transplant-eligible NDMM.

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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.[11,22-25,32,33,37]

- **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.[38-45] **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 a primary endpoint to assess depth and durability of response, including the EXCALIBER-Maintenance (NCT05827016), GMMG-HD9/DSMM XVIII (NCT06216158), GEM21menos65 (NCT05558319), and MIDAS / IFM 2020-02 (NCT04934475) studies of iberdomide; the CC-92480-MM-001 and CA057-003 trials of mezigdomide also evaluate MRD-negativity as a key secondary or exploratory endpoint.

These trials 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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References

1. *Rajkumar. Am J Hematol. 2022;97(8):1086-1107.*
2. *Kaiser. J Clin Oncol. Stalker. Curr Oncol. 2022;29(7):4464-4477.*
3. *Eek. Patient Prefer Adherence. 2016;10:1609-1621.*
4. *Morgan GJ, et al. Nat Rev Cancer. 2012;12(5):335-48.*
5. *Manier S, et al. Nat Rev Clin Oncol. 2017;14(2):100-13.*
6. *Samur MK, et al. Blood. 2023;141(14):1724-36.*
7. *Matyskiela, et al. J Med Chem. 2018;61:535.*
8. *Hansen, et al. J Med Chem. 2020;63:6648.*
9. *Lonial. ASCO 2019. Abstr 8006.*
10. *Lonial. Lancet Haematol. 2022;9:e822.*
11. *Richardson. N Engl J Med. 2023;389(11):1009-22.*
12. *Van Oekelen, et al. ASH 2021. Abstr 730.*
13. *Van Oekelen, et al. Cell Rep Med. 2024;5:101584.*
14. *Chen, et al. ASH 2023. Abstr 4686.*
15. *Amatangelo. Blood. 2018;132:1935.*
16. *Bjorklund. ASH 2021. Abstr 2669.*
17. *Aleman A, et al. Blood. 2024;144(supplement 1):3259.*
18. *Meermeier EW, et al. Blood 2024;144(supplement 1):356.*
19. *Kurtova A, et al. HemaSphere 2025;9(S1):PS1674.*
20. *Aleman A, et al. HemaSphere 2025;9(S1):PF685.*
21. *Richardson. J Clin Oncol. 2020;38(15_suppl): abstract 8500.*
22. *Oriol. Clin Lymphoma Myeloma Leuk. 2023;23(Suppl 2):S31.*
23. *Sandhu. Blood. 2024;144(supplement 1):1025.*
24. *Richardson. Blood. 2023;142(supplement 1):1013.*
25. *Hartley-Brown. Cancers (Basel). 2024;16(6):1166*
26. *Costa, et al. Blood. 2024;144 (Supplement 1): 677.*
27. *Costa, et al. HemaSphere. 2025;9(S1).*
28. *Byun, et al. HemaSphere. 2025;9(S1):PB2298.*
29. *Lonial. Blood. 2021;138(suppl 1):abstract 162.*
30. *Lonial. Blood. 2022;140(suppl 1):abstract 1918.*
31. *Touzeau. HemaSphere. 2024;8(S1):1621-2.*
32. *Korst. HemaSphere. 2024;8(S1):1589-90.*
33. *Touzeau, et al Br J Haematol. 2025 May;206(5):1366-1372.*
34. *Richardson. Clin Lymphoma Myeloma Leuk. 2023;23(Suppl_1):S495-S496.*
35. *Richardson. J Clin Oncol. 2023;41(16_suppl):abstract TPS8070.*
36. *Lonial. J Clin Oncol. 2023;41(16_suppl):abstract TPS8069.*
37. *Lonial. HemaSphere. 2021;5(S2):49-50, Abstract S187.*
38. *Munshi NC, et al. Blood Adv. 2020;4(23):5988-99.*
39. *Avet-Loiseau et al. Clin Lymphoma Myeloma Leuk. 2020;20(1):e30-7.*
40. *Anderson KC, et al. Clin Cancer Res. 2021;27(19):5195-212.*
41. *Ntanasis-Stathopoulos I, et al. Am J Hematol. 2025;100(3):427-38.*
42. *Landgren O, et al. Blood. 2024;144(4):359-67.*
43. *ODAC meeting, April 12, 2024, i2TEAMM presentation: https://www.fda.gov/media/177738/download.*
44. *Shi Q, et al. J Clin Oncol. 2025;43(11):1289-301.*
45. *Coffey DG, et al. Nat Commun. 2023;14(1):5335.*
46. *Amatangelo. Blood. 2024;144(Supplement 1):1973.*
47. *White et al. HemaSphere, 2025;9(S1):PF737*
48. *Puig N, et al. HemaSphere 2025;9(S1):PS1784.*
49. *Liu. Expert Rev Hematol. 2024;17(8):445–65.*
50. *Perrot. Blood. 2025;2024026230.*
51. *Perrot. ASCO 2025. Abstract 7500.*
52. *Gay. Hemasphere. 2024;8(S1):1703-4.*
53. *Callander N, et al. Blood. 2024;144(Supplement 1):3365.*
54. *Kin A, et al. Blood. 2024;144(Supplement 1):7007.*