Gastrointestinal Toxicities and Hepatotoxicity Profiles of Emerging CELMoDs vs Next Generation Proteasome Inhibitors in Relapsed/Refractory Multiple Myeloma: A Systematic Review With Pooled Proportion Analysis

Faiza Khalid MD[1], Raj Nandan Chennuri MD[2], Haroon Alamy MD[3], Laiba Manzoor MBBS[4], Shaiza Maryam MBBS[5], Iman Khan MBBS[6], Sravani Bhavanam MD[7], Ashesh Das MBBS[8]

[1] Sheikh Zayed Medical College, Rahim Yar Khan, Pakistan
[2] New York Medical College/St. Clare's and St. Mary's Hospital, Denville, NJ, USA
[3] Desert Regional Medical Center, Palm Springs, CA, USA
[4] Dow University of Health Sciences, Karachi, Pakistan
[5] Shifa International Hospital, Islamabad, Pakistan
[6] Ziauddin Medical University, Karachi, Pakistan
[7] Brookdale University Hospital and Medical Center, Brooklyn, NY, USA
[8] KPC medical College and hospital Kolkata india

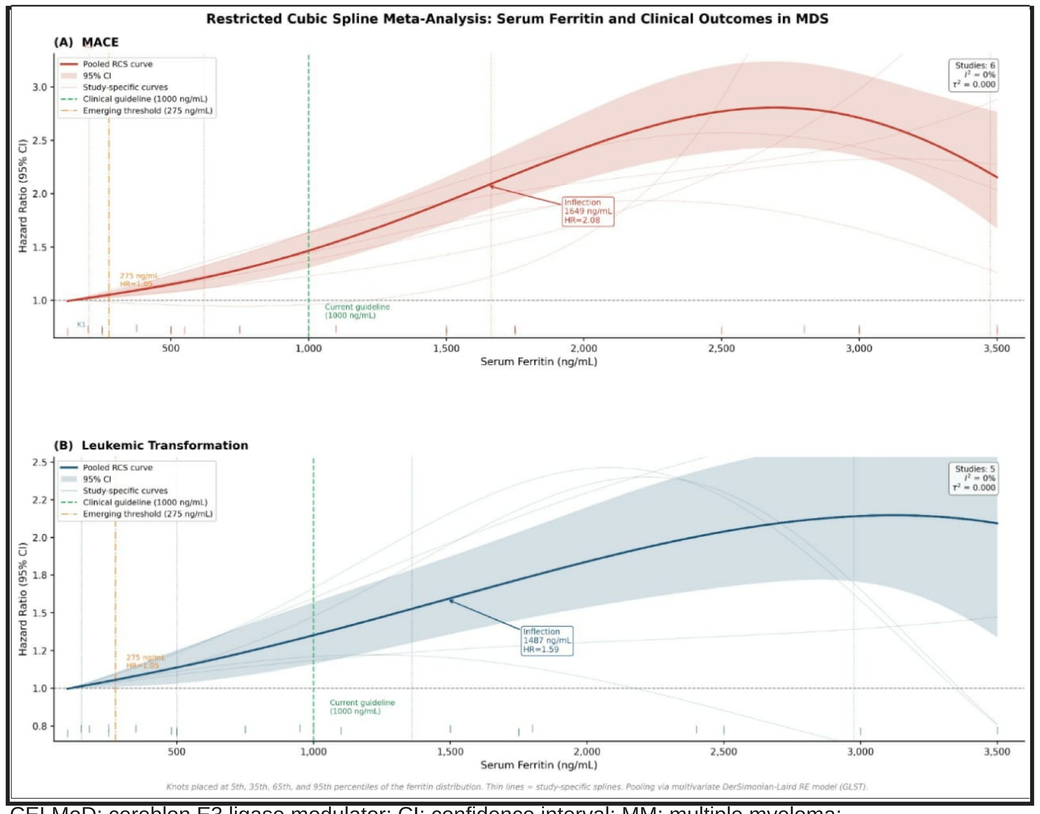
Introduction

Cereblon E3 ligase modulators (CELMoDs) represent a novel therapeutic class for relapsed/ refractory multiple myeloma (RRMM), but comparative gastrointestinal and hepatic safety data vs next-generation proteasome inhibitors (PIs) remain limited.

We conducted a systematic review with pooled proportion analysis to indirectly compare grade ≥3 gastrointestinal and hepatotoxicity profiles.

Methods

We systematically identified phase 1/2 CELMoD trials (mezigdomide, iberdomide) and phase 3 PI trials (ixazomib, carfilzomib, bortezomib) in RRMM populations. We systematically searched PubMed, Medline, Embase, and the Cochrane Library from inception to April 2026 to identify relevant studies. Published safety data were extracted from peer-reviewed sources. Single-proportion meta- analysis with logit-transformed DerSimonian- Laird random-effects models was performed separately for each drug class. Between-class comparison was conducted via meta-regression. This represents an indirect comparison in the absence of head-to-head randomized trials.



CELMoD: cereblon E3 ligase modulator; CI: confidence interval; MM: multiple myeloma;
PI: proteasome inhibitor; RR: relapsed/refractory; VMP: bortezomib, melphalan, and prednisone

Contact Information: Name: Faiza Khalid
Email: faiza.khalid.173@gmail.com
Contact number: +1 (347) 922-6530

Results

1) Three CELMoD studies (N=312 total) and 4 PI trials (TOURMALINE-MM1, ENDEAVOR, APEX, VMP; N=1414 total) met inclusion \ criteria.
2) One iberdomide study in smoldering myeloma was excluded due to population mismatch.
3) Grade ≥3 diarrhea: 3.8% (95% CI, 1.9 –7.3) for CELMoDs vs 5.3% (95% CI, 3.6 –7.8) for PIs. Meta-regression *P*=0.257,Risk difference: −1.6% High PI class heterogeneity(*I²*=66.7%, *P*=0.029)
4)Grade ≥3 hepatotoxicity: 1.3% (95% CI, 0.5–3.5) for CELMoDs vs 1.7% (95% CI, 1.1–2.5) for PIs. Meta-regression *P*=0.672, Risk difference: −0.3% No heterogeneity detected (*I²*=0.0%)
5)Data limitations: Grade 3+ diarrhea counts required estimation for CELMoD trials; PI data were directly extracted from safety tables.

Conclusion

This indirect comparison suggests that grade ≥3 gastrointestinal and hepatic toxicities may be infrequent with both CELMoDs and next-generation PIs in patients with heavily pretreated RRMM, with numerical trends that do not reach statistical significance favoring CELMoDs. Substantial heterogeneity within the PI class reflects known mechanistic differences across agents. Data quality limitations and the indirect nature of this comparison preclude definitive conclusions. Direct head-to-head randomized trials are needed to establish comparative safety profiles and inform treatment selection in RRMM.