MM-902: Concomitant Proton Pump Inhibitor Use and Outcomes During Proteasome Inhibitor–Based Therapy for Multiple Myeloma: A Real-World Propensity Score–Matched Cohort Study Using the TriNetX Network

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BACKGROUND

- PPIs are taken by roughly one-third of patients with multiple myeloma (MM), most often for dexamethasone gastroprotection and bisphosphonate-related dyspepsia.[1]
- Plausible mechanisms of harm on proteasome inhibitor (PI) therapy include CYP2C19 inhibition (bortezomib is metabolized by CYP3A4 and CYP2C19),[3] PPI-associated hypomagnesemia,[5] and acid suppression with gut dysbiosis and infection risk.[4]
- A pooled analysis of three MM trials linked PPI use to worse overall survival (adjusted HR 1.32, 95% CI 1.08–1.62).[1] A Danish registry reported similar excess mortality across hematologic malignancies.[2]
- This signal has not been tested in a large, real-world, multi-institutional PI-treated MM population.

OBJECTIVE

- Primary — Determine whether concomitant PPI use during PI-based therapy for MM is associated with increased 3-year all-cause mortality.
- Secondary — Determine whether PPI use is associated with infectious (sepsis, pneumonia) and electrolyte (hypomagnesemia, hypocalcemia) outcomes that could plausibly mediate a mortality difference.

METHODS

Design Retrospective propensity score–matched cohort study.
Data source TriNetX US Collaborative Network; de-identified electronic health record data, January 2015 – January 2023.
Population Patients with MM initiating bortezomib, carfilzomib, or ixazomib within 1 month of diagnosis. Excluded: plasma cell leukemia, MGUS.
Exposure Concomitant PPI use vs no PPI use.
Matching 1:1 propensity score matching on demographics; GERD, chronic kidney disease, hypertension, diabetes, heart failure, ischemic heart disease, smoking, liver disease; and concomitant immunomodulatory drugs and zoledronic acid. Balance assessed by standardized differences.
Outcomes (3 y) Primary: all-cause mortality. Secondary: sepsis, pneumonia, hypomagnesemia, hypocalcemia.
Analysis Risk difference and risk ratio with 95% confidence intervals.

DISCLOSURES & CONTACT

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Conflicts of interest: [confirm before printing]

Data: TriNetX US Collaborative Network (de-identified, aggregated patient counts).

PPI use during proteasome inhibitor therapy was associated with **higher 3-year mortality.**

PPI COHORT	NO-PPI COHORT
25.9%	**20.8%**
395 / 1525 deaths	317 / 1525 deaths

Risk difference +5.1% (95% CI 2.1–8.1), P = 0.0008 · **Risk ratio** 1.25 (95% CI 1.10–1.42)

Before matching 1651 PPI vs 2955 no PPI → after 1:1 propensity score matching, 1525 patients per cohort. Median follow-up 1095 days in both cohorts.

Every outcome moved in the same direction, and no 95% confidence interval crossed 1.0.

CONCLUSIONS

1. PPI use during PI-based MM therapy was associated with a 5.1% absolute and 25% relative increase in 3-year all-cause mortality.
2. Sepsis, pneumonia, hypomagnesemia, and hypocalcemia were all more frequent in PPI users, pointing toward infection and electrolyte pathways rather than a purely pharmacokinetic interaction.
3. This real-world cohort reproduces the direction and magnitude of the pooled trial signal (adjusted HR 1.32).[1]
4. Association, not causation. The findings are hypothesis-generating and cannot establish a causal effect.
5. They support periodic review of PPI indication in MM[6] and prospective evaluation of acid-suppression strategy in this population.

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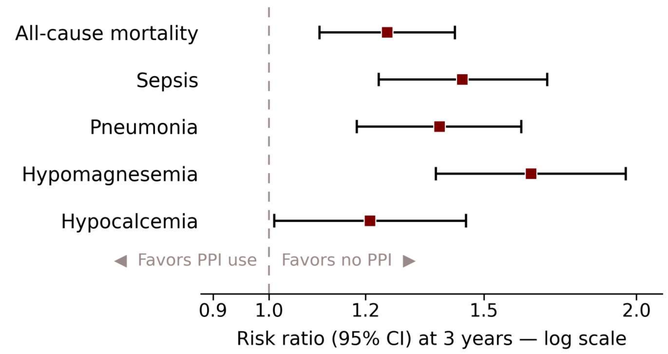
RESULTS — OUTCOMES

Table 1. Three-year outcomes after 1:1 propensity score matching (n = 1525 per cohort).

Outcome	Risk ratio (95% CI)
All-cause mortality	**1.25 (1.10–1.42)**
Sepsis	**1.44 (1.23–1.69)**
Pneumonia	**1.38 (1.18–1.61)**
Hypomagnesemia	**1.64 (1.37–1.96)**
Hypocalcemia	**1.21 (1.01–1.45)**

Figure 1. Risk ratios for the primary and secondary outcomes at 3 years after matching.



LIMITATIONS & STRENGTHS

Limitations

- PPI exposure was not randomized; confounding by indication (reflux, steroid burden, frailty) may persist after matching.
- TriNetX lacks ISS stage, cytogenetic risk, and performance status — prognostic factors absent from the propensity model.
- PPI agent, dose, and duration were not modeled, and electrolyte outcomes are open to ascertainment bias if PPI users have magnesium checked more often.
- A dedicated pharmacokinetic study found no omeprazole–bortezomib interaction,[3] arguing against CYP2C19 inhibition as the mechanism.

Strengths

- First multi-institutional real-world replication of the trial-level PPI signal in PI-treated MM.
- Large matched cohort (1525 per arm) with a uniform 3-year analytic window.
- Effect estimates are concordant across all five prespecified outcomes.