Concomitant Proton Pump Inhibitors Do Not Worsen Immune Checkpoint Inhibitor Outcomes Despite a Prognostically Unfavorable Baseline BMI Imbalance

A Real-World Confounder Analysis

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KEY CLINICAL MESSAGE

Concomitant PPI use was not associated with worse ICI outcomes, despite significantly lower baseline BMI among PPI users.

MECHANISTIC RATIONALE — WHY PPIs COULD PLAUSIBLY AFFECT ICI BIOLOGY

PPI use → Gastric acid suppression → Gut microbiome dysbiosis → Altered microbial metabolites & immune signaling

POTENTIAL EFFECT ON ICI EFFICACY

- Altered dendritic-cell activation
- Impaired CD8+ T-cell priming / effector function
- Potentially less favorable tumor immune microenvironment
- ↓ ICI response, PFS, OS (hypothesized)

Tested here via: disease progression & all-cause mortality

POTENTIAL EFFECT ON ICI TOXICITY

- Altered intestinal barrier + microbial translocation
- Dysregulated immune activation
- Potentially ↑ immune-related adverse events (irAEs)
- Particularly relevant to ICI-related colitis

Tested here via: all-grade irAEs

This microbiome-mediated rationale is biologically plausible: PPI use has been associated with reduced gut microbial diversity, including depletion of Ruminococcaceae and Bifidobacterium — short-chain-fatty-acid-producing taxa separately implicated in ICI response.4,5 Effects on other response-associated taxa (e.g., Akkermansia muciniphila) are less consistent across studies, and the clinical association between PPIs and ICI outcomes overall remains heterogeneous. This study tests both sides of that hypothesis directly (efficacy and toxicity) in a real-world cohort.

PRIOR LITERATURE vs. THIS REAL-WORLD COHORT

PRIOR LITERATURE

Multiple meta-analyses link PPI use with reduced ICI efficacy - pooled hazard ratios of approximately **1.29–1.40 for overall survival** and **1.20–1.34 for progression-free survival**.1–3 Evidence is largely from solid-tumor cohorts and may be vulnerable to unmeasured confounding.

BUT

THIS REAL-WORLD COHORT

129 patients on ICI therapy (PPI n=65, No PPI n=64), logistic regression across three prespecified outcomes, with systematic confounder assessment:

Progression	Mortality	irAEs
OR 1.20	OR 1.13	OR 1.53
p=0.62	p=0.82	p=0.27

WHY THIS MATTERS

Prior meta-analyses have linked PPI exposure to inferior ICI efficacy, but much of the evidence comes from solid-tumor populations and may be vulnerable to baseline confounding.

CLINICAL QUESTION

Does concomitant PPI use independently associate with worse outcomes during ICI therapy?

STUDY DESIGN

MULTI-CENTER RETROSPECTIVE COHORT

129 patients treated with ICI for solid tumors or lymphoma

PPI users	No PPI
n = 65	n = 64

PRIMARY ENDPOINTS

- Disease progression
- All-cause mortality
- All-grade immune-related adverse events (irAEs)

LOGISTIC REGRESSION

Confounders assessed: age, sex, BMI, ECOG performance status, smoking status, and neutrophil-to-lymphocyte ratio (NLR).

COHORT SNAPSHOT

64.8±11.9 Mean age (yrs)	57.4% Age ≥65	51.2% Female
39.5% Lung cancer	73.6% PD-1 inhibitor use	4.7% Lymphoma

BALANCE CHECK: **Age p=0.65 • ECOG p=0.35 • Smoking p=0.61 • NLR p=0.95**

All three prespecified outcomes were numerically higher in the PPI group, but none reached statistical significance.

THE KEY CONFOUNDER: BASELINE BMI

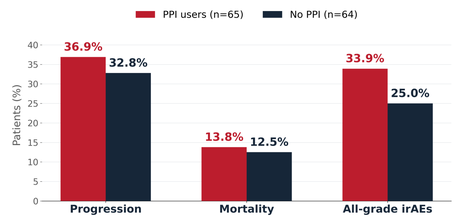
BMI WAS SIGNIFICANTLY LOWER IN PPI USERS

p = 0.03 • a lower BMI could plausibly bias outcomes toward worse prognosis

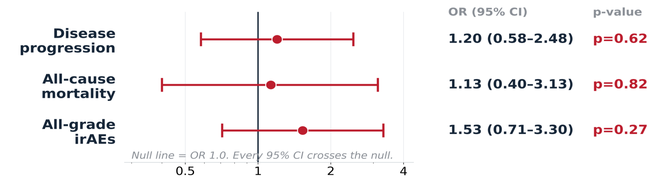
Δ BMI = −2.1 kg/m² in PPI group

Why it matters: lower BMI is itself associated with poorer cancer outcomes in ICI-treated patients (pooled HR 0.62–0.73 favoring higher BMI for OS).3 This creates a baseline disparity that would be expected to bias findings against the PPI group.

CLINICAL OUTCOMES



FOREST PLOT — LOGISTIC REGRESSION



INTERPRETATION

ALL THREE PRESPECIFIED OUTCOMES CROSSED THE NULL

irAE: potential signal — not statistically significant

The absence of a significant association persisted despite a baseline BMI imbalance that would be expected to bias toward worse outcomes in the PPI group. This supports a cautious interpretation of prior PPI–ICI associations: patient-level differences may contribute substantially to previously observed effects.

Age, ECOG, smoking, and NLR were well balanced.

WHAT THIS STUDY ADDS

Despite a significantly lower baseline BMI among PPI users, concomitant PPI exposure was not significantly associated with progression, mortality, or all-grade irAEs in this real-world ICI cohort.

The discordance from prior literature highlights the potential impact of baseline confounding and the need for stronger causal methods.

LIMITATIONS & NEXT STEPS

- Retrospective design
- Modest sample size; wide confidence intervals
- Logistic regression rather than time-to-event modeling
- Residual / unmeasured confounding remains possible

NEXT: Cox modeling + propensity-score–matched analyses across diverse oncologic populations, including hematologic malignancies.

BOTTOM LINE

Real-world PPI use was not associated with worse ICI outcomes in this cohort.

The lower BMI observed among PPI users highlights why baseline patient characteristics must be considered when interpreting PPI–ICI associations.

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