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Impact of proton pump inhibitors use and potency on Immunotherapy (ICI) outcomes and gut microbiome in advanced NSCLC and RCC

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Background

PPIs are frequently prescribed to prevent treatment-related gastric toxicity. However, evidence suggests they may impair ICI efficacy, possibly via gut microbiome disruption, with effects linked to PPI potency. We investigated how PPI use and potency affect ICI outcomes and gut microbiome changes.

Methods

In the NCT04567446 study, patients (pts) with advanced NSCLC (n=531) and RCC (n=183) treated with ICIs in France and Canada provided baseline stool samples for metagenomic sequencing. PPIs use at baseline was assessed, and potency was standardized using omeprazole equivalence. Microbiome analysis included alpha- and beta-diversity (Shannon and PCoA with PERMANOVA), TOPOSCORE and VIP Analysis. Multivariate Cox models (MVA) for overall survival (OS) included clinical and microbiota variables.

Results

In NSCLC, 141 (27%) pts received PPIs prior to ICIs. PPI use was associated with shorter OS (median 12.2 vs. 18.7 months (m), HR 1.53, 95% CI 1.18–1.90, p 0.048), particularly in those receiving ICI alone (median 10.8 vs. 18.1 m, HR (CI 95%) 1.675 (1.266-2.216), p 0.01). This effect was independent of PPI potency. The microbiome study showed significant beta-diversity differences between the two groups (PERMANOVA: p 0.00106), altered TOPOSCORE reflecting a shift in microbiome composition, enrichment in SIG1 species including oral taxa (such as oral streptococci) or oropharyngeal commensals (e.g. *Veillonella* spp.), as well as a tolerogenic profile (*Enterocloster clostridioformis*), among PPI users, more pronounced with high-potency PPIs, suggesting a possible dose-dependent effect. In NSCLC multivariate analysis, both ECOG and presence of SIG1 taxa (SIG1: HR 1.97, 95% CI 1.42–2.76, p<0.0001) remained independently associated with worse OS. Similar microbiome trends emerged in RCC patients.

Conclusions

PPIs use was linked to reduced OS in NSCLC patients receiving ICIs. This adverse outcome may be mediated by PPI-induced gut microbiome dysbiosis, potentially driven by reduced gastric acidity allowing swallowing of supraglottic commensals. These findings support cautious PPIs use and underscore the potential of microbiome-informed tools, like TOPOSCORE for pt stratification and clinical decision-making.

Legal entity responsible for the study

L. Zitvogel.

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Disclosure

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