Lung cancer is the second most common cancer diagnosed worldwide and the first most common cause of cancer-related deaths in both men and women. Although the introduction of immunotherapy with immune checkpoint inhibitors (ICIs) offered new hopes for patients with advanced non–small cell lung cancer (NSCLC), almost doubling 5-year overall survival (OS) with respect to chemotherapy, there is still an unmet need for optimizing outcomes, especially among nonresponders, who represent approximately one-third of patients.

In recent years, several retrospective studies have suggested that there may be a potential interference of concomitant medications, such as steroids, antibiotics, and proton pump inhibitors (PPIs), with immunotherapy outcomes. Particularly, a history of PPI administration at the beginning of treatment or during treatment has been associated with worse outcomes in patients receiving ICIs, especially anti-PD-L1 (programmed cell death 1 ligand 1) agents. PPI might change the composition of the gut microbiome due to the downstream translocation of oral commensals, thus altering its immunomodulating properties and impairing ICI activity. In fact, as recently demonstrated by Derosa et al, a precise equilibrium of symbiotic bacteria with the right relative abundance of Akkermansia muciniphila (ie, <4.799%), is more associated with ICI outcomes in patients with NSCLC than PD-L1 levels, although the type of bacteria might play a role as well. Some of these studies provided conflicting results or remained inconclusive due to their small sample size and retrospective nature, although a recent large meta-analysis by Lopes et al conducted of 20,042 patients with different tumors treated with ICIs concluded that progression-free survival (PFS) (hazard ratio [HR], 1.28; 95% CI, 1.15–1.42) and OS (HR, 1.37; 95% CI, 1.23–1.52) were negatively associated with PPI. Nevertheless, whether PPIs are associated with immunotherapy response is still to be prospectively determined.

Kawachi and colleagues retrospectively evaluated clinical factors associated with outcomes of first-line anticancer treatment in 2 groups of patients (balanced by propensity score matching) with advanced NSCLC and PD-L1 levels of 50% or more treated with ICI monotherapy or a combination of ICI and chemotherapy. In the ICI monotherapy group, factors associated with a poorer PFS at a multivariate level were lower PD-L1 (50%-89%) and the use of concomitant PPI, whereas in the ICI and chemotherapy group, only smoking history and Eastern Cooperative Oncology Group performance status were associated with PFS. After adjusting the cohorts to compare outcomes according to PPI exposure, patients with a history of PPI administration showed significantly longer median (IQR) PFS (19.3 months [9.0 months to not reached] vs 5.7 [2.4 to 15.2] months; \( P = .002 \)) and median (IQR) OS (not reached [9.0 months to not reached] vs 18.4 [10.5 to 50.0] months; \( P = .03 \)) in the ICI plus chemotherapy group than in the ICI monotherapy group. Conversely, patients without PPI exposure exhibited similar outcomes in both the ICI plus chemotherapy and ICI monotherapy groups (median [IQR] PFS, 18.8 months [6.6 months to not reached] vs 10.6 months [2.7 months to not reached]; \( P = .26 \); median [IQR] OS, not reached vs 29.9 months; \( P = .21 \)).

These findings support the hypothesis that PPI usage might be negatively associated with immunotherapy as a single agent rather than being a prognostic factor itself and are in line with results of the post hoc pooled analysis of OAK and POPLAR trials that evaluated atezolizumab vs docetaxel in patients with advanced NSCLC in the second-line setting. Indeed, in this randomized context, Chalabi and colleagues showed that in the atezolizumab group, median OS and PFS were...
significantly shorter in patients who received PPI (median OS, 9.6 months vs 14.5 months; HR, 1.45; 95% CI, 1.20-1.75; P < .001; median PFS, 1.9 months vs 2.8 months; HR, 1.30; 95% CI, 1.10-1.53; P = .001), whereas there was no significant association of PPI use with PFS or OS in the docetaxel group. Similarly, Hopkins et al4 conducted a pooled analysis of the IMvigor210 and IMvigor211 trials, corroborating the negative association of PPI with survival in patients with metastatic urothelial carcinoma who received an ICI; the use of PPI was significantly associated with worse OS and PFS in the atezolizumab group (OS HR, 1.52; 95% CI, 1.27-1.83; P < .001; and PFS HR, 1.38; 95% CI, 1.18-1.62; P < .001), whereas no such correlation was observed in the chemotherapy group (OS HR, 1.16; 95% CI, 0.93-1.47; P = .19; PFS HR, 1.11; 95% CI, 0.89-1.37; P = .35).

The new hypothesis emerging from the article by Kawachi and colleagues6 is that when ICIs are combined with chemotherapy, the possible detrimental outcomes of PPI appear attenuated, hinting at a futuristic approach of treatment selection based not only on clinical pathological factors, but also on concomitant medications. These studies share common limitations, including their retrospective nature, the different definitions of the timing of concomitant use, the different races and ethnicities among the cohorts (and consequently different microbiomes),7 and the association of PPI use with other potential variables (eg, advanced age, poorer Eastern Cooperative Oncology Group performance status, the use of steroids, and additional comorbidities). Thus, the role of PPI (as well as that of other concomitant medications) should be confirmed in prospective trials taking into account these confounding factors. Meanwhile, Tomita and colleagues8 hypothesized that the dysbiosis induced by PPI could be restored by a live biotherapeutic bacterial strain, *Clostridium butyricum* MIYAIRI 588 (CBM588), and retrospectively analyzed a cohort of 118 patients with advanced NSCLC treated with first-line ICI. Those who received PPIs and CBM588 (25 patients) had improved PFS (HR, 0.52; 95% CI, 0.29-0.94; P = .03) and OS (HR, 0.42; 95% CI, 0.19-0.92; P = .03) compared with those who received PPI without CBM588 (75 patients). Nonetheless, while waiting for conclusive results, we should consider the real necessity of PPI prescription in every patient on a daily basis when starting anticancer therapies with potential interference (such as ICI) and evaluate their interruption when feasible.

**ARTICLE INFORMATION**

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