Antibiotic Exposure and Immune Checkpoint Inhibitors in Patients With NSCLC: The Backbone Matters

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In this issue of the *Journal of Thoracic Oncology*, Hopkins et al. 1 performed a pooled post-hoc analysis of the IMPower130, IMPower131, IMPower150, OAK, and POPLAR phase 3 trials aiming to evaluate the impact of antibiotics (ATBs) and proton pump inhibitors (PPIs) taken within 30 days of treatment initiation on overall survival (OS) and progression-free survival (PFS) from atezolizumab-containing regimens. Study results confirmed prior findings about the negative impact of PPIs on immune checkpoint inhibitor (ICI) efficacy. 2 Nevertheless, the detrimental role of prior ATB (pATB) was not confirmed.

The published study reassuringly concludes that the efficacy of atezolizumab-containing regimens in comparison to control groups is preserved irrespective of ATB exposure. This conclusion, however, does not consider that influence of ATB strongly depends on therapeutic modality and timing of ATB. Pooling efficacy estimates from chemotherapy-free ICI regimens and chemoimmunotherapy (with or without bevacizumab) combinations represent, in our view, an intrinsic flaw of the analysis.

We previously described the differential impact of pATB in a large cohort of patients with NSCLC and programmed cell death-ligand 1 expression more than or equal to 50% treated with first-line pembrolizumab monotherapy and clearly revealed that the detrimental effect of ATB was restricted to pembrolizumab recipients compared with a perfectly matched chemotherapy cohort. 3

NSCLC has especially benefited from chemoimmunotherapy combinations, as likely effect of the synergistic efficacy of the two treatment modalities. Therefore, we recently explored the impact of ATB in an international cohort of patients treated with first-line chemoimmunotherapy, highlighting that neither pATB nor concomitant ATB (cATB) exposure was associated to PFS and OS. 4

These findings suggest that the detrimental impact of pATB might be balanced by the addition of cytotoxic chemotherapy in a sort of diminished reliance on the gut microbiome composition in comparison to chemotherapy-free ICI regimens. Although taxane-based chemotherapy has been linked to the shift of microbiota composition, balancing the scale toward unfavorable bacteria associated with ATB, such as *Clostridia* spp., 5 the cytotoxic immunogenic cell death may broaden the tumor neoantigen load, eventually enhancing the adaptive immune response to programmed cell death protein 1 (PD-1) blockade, 6 independently from the worse clinical conditions that can be related to the underlying indication for ATB prescription. 7
When considering the primary evidence scrutinized by Hopkins et al., we should be mindful that the experimental arm of three of five studies consisted of chemotherapy-containing regimens. A previously published pooled analysis of the POP-LAR and OAK trials already confirmed the detrimental role of pATB on atezolizumab-treated patients in comparison to docetaxel. In addition, the rate of pATB exposure, but not PPI exposure, dropped from more than 25% to 7% in the study of Hopkins et al. in comparison to these previously published data, with a consequential unbalance across exposure groups. This downward trend might be a consequence of the increasing body of evidence suggesting a detrimental role for pATB with ICI-based regimens, which led to a progressive reduction of clinicians’ attitude toward ATB prescription during the trial screening window, to such an extent that nowadays a washout period from systemic ATB is a requirement increasingly listed among eligibility criteria for clinical trials with investigational immunotherapies.

Although highlighting that ATB can be safely administered in patients about to start a chemo-immunotherapy is a point of great interest, ATB-related dysbiosis should be carefully balanced with chemotherapy-free ICI regimens, as an accumulating body of evidence now provides a causal link between ATB exposure, destruction of the gut microbiome, and diminished efficacy of ICI therapy, even though the mechanistic process still has to be fully elucidated. This concept is supported by meta-analyses revealing ATB, administered in more than 25% patients with cancer, has deleterious effects regardless of timing but more so when ATB was administered before ICI.

Hopkins et al. reported an increased prescription of cATB after treatment initiation as a likely result of bone marrow suppression and chemotherapy-induced neutropenia during the induction phase of chemoimmunotherapy regimens. Despite the positive immortal time bias that could be associated to any concomitant factor, Hopkins et al. revealed an association between ATB use within 30 days postatezolizumab initiation and shortened survival, which conflicts with our time-adjusted analysis of cATB during chemoimmunotherapy.

Interestingly, the authors reported a PFS gain for experimental arms in comparison to control arms, with a significant interaction p value for ATB-exposed patients. Some ATBs can help induce a positive “eubiotic” effect on the gut microbiota by targeting the gram-positive bacteria, including butyrate-producing bacteria. Preclinical evidence suggests that metronidazole-induced shifting microbiome composition can elicit a favorable antitumor immune response, whereas ongoing clinical trials are investigating the alleged synergistic role of oral vancomycin to PD-1 blockade in patients with liver tumors, through the induction of CXCL16 expression. From this perspective, a detailed breakdown of ATB classes, types, and route of administration throughout the experimental and control arms would be especially beneficial for elucidating the possible effect of specific ATB therapies.

Moving to PPIs, evidence regarding their detrimental effect on immunotherapy outcomes is more recent but consistent. Chronic treatment with PPIs is associated with decreased bacterial richness and profound changes in the gut microbiota. PPIs concordantly exhibit a significant enrichment of “oral” microbes driven by both altered stomach acidity and direct compound effect consisting in Enterococcus, Staphylococcus, Streptococcus, and Rothia genera in the feces. Considering the association of high alpha diversity and high relative abundances of Ruminococcaceae and Faecalibacterium with enhanced antitumor immune activity, these PPI-associated shifts of microbiota may have a critical impact on responses to immunotherapy.

In the present analysis, PPI administration was not associated with a detrimental effect across the chemotherapy cohorts, but a reduced magnitude of benefit for atezolizumab-containing regimens compared with the control arms in PPI recipients was reported. Similar results were already reported by the same group across the three arms of the IMpower150, with a PPI-dependent detrimental effect restricted to atezolizumab-containing regimens. Nevertheless, we suggest again caution in pooling efficacy estimates from two different treatment strategies (chemo-immunotherapy and chemotherapy-free ICI regimens) for the above-mentioned reasons about ATBs.

Taken together, we feel that the conclusions drawn by Hopkins et al. should be carefully weighed against the therapeutic modality of choice and balanced between beneficial and harmful microbial species in play during treatments. Although ATB exposure and associated intestinal dysbiosis remain a highly concerning adverse prognostic factor in patients treated with ICI mono-therapy, additional studies are needed to properly understand whether pATB may be safe in chemo-immunotherapy combinations recipients. Nevertheless, the findings reported by Hopkins et al. further highlight the importance of some learning points for the management of patients with NSCLC about to start an ICI-based treatment.

First, a detail reporting of concomitant medications across study arms should be promoted even in prospective randomized trials, as it is usually done with demographics and clinic-pathologic characteristics. This
would be beneficial in elucidating their possible role as immune modulators and confounders. Second, there is an increasing need for microbiota profiling beforeICI-based treatment to assess the presence and abundance of commensals as novel biomarker for efficacy and toxicity. Third, there is a need for interventional investigations to determine tailored interventions to promote microbiota recovery and improve patients’ outcome.

It is our hope that such measures will help to gain a better understanding of the complex interplay between patient’s microbiota, non-oncologic medications, and immunotherapy efficacy, to develop clinical recommendations for the optimization of concomitant medications in immuno-oncology in the future.

**CRediT Authorship Contribution Statement**

Alessio Cortellini, Lisa Derosa, Francesco Facchini,et al: Study concept and design, Analysis and interpretation of data, Drafting of the manuscript, Manuscript review and approval.

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**References**


