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Antibiotic use and reduced effectiveness of second-line immunotherapy for lung cancer: all the time or just at the start of treatment?

It was with interest that we read the paper by Chalabi et al.[1] in *Annals of Oncology* describing an unplanned analysis of two randomized clinical trials suggesting reduced overall survival when antibiotics and proton-pump inhibitors are used at the time of initiation of second-line immunotherapy for metastatic non-small-cell lung cancer. The rationale for their investigation was that these drugs modulate the microbiome which plays a key role in regulating the host innate and acquired immune response. That the association was less pronounced in the docetaxel group adds to the probability of causality.

In the analysis, the use of antibiotics was defined as any use within a window of 30 days before and 30 days after the start of first study treatment. Considering that many patients with lung cancer are prescribed antibiotics during the course of their disease, this exposure definition does not answer the question do antibiotics have any impact when used while on immunotherapy (and not at start) and how long any impact may last.

To explore this further we have conducted an additional analysis with the same source data as those used by Chalabi et al.[1] In our analysis, we have explored the level of antibiotic use while on study treatment plus repeated the survival analysis with the so-called landmark method, wherein the study cohort was restricted to patients surviving up to at least 90 days and 180 days, respectively.[2]

Our additional analyses showed that the intensity of antibiotic use was much higher around the start of clinical trial study treatment compared with later on (Figure 1) and that at the two landmark points there was no association of antibiotics with overall survival after immunotherapy [hazard ratios: 1.05 (95% CI 0.79—1.39) and 0.83 (95% CI 0.56—1.23), respectively].

We consider our additional analyses relevant to further understand if the association of antibiotics with reduced immunotherapy effectiveness is likely to be causal. The high intensity of antibiotic use around the start of study treatment could be explained by symptoms of rapidly progressive disease at that time. Patients often receive antibiotics as an empirical way to relieve their symptoms or to treat pneumonia that occurs because of obstruction of the proximal airway.[3] Considering that patients with rapidly progressive disease have worse prognosis without early disease control, this might explain the temporal association of antibiotics with survival in the first months following start of immunotherapy. Some survival time is needed for an immune response to emerge, whereas early disease control is more probable with chemotherapy (i.e. docetaxel). Differential drop-out of the patients with worse prognosis in the first months can be the explanation why an association of antibiotics with survival cannot be detected later on.

In our opinion, a next step to bring this important research question further would be to eliminate differences in early disease control from chemotherapy by replication of the analysis of Chalabi et al.[1] with data from clinical trials comparing chemotherapy with the combination of chemotherapy and immunotherapy in a first-line setting.

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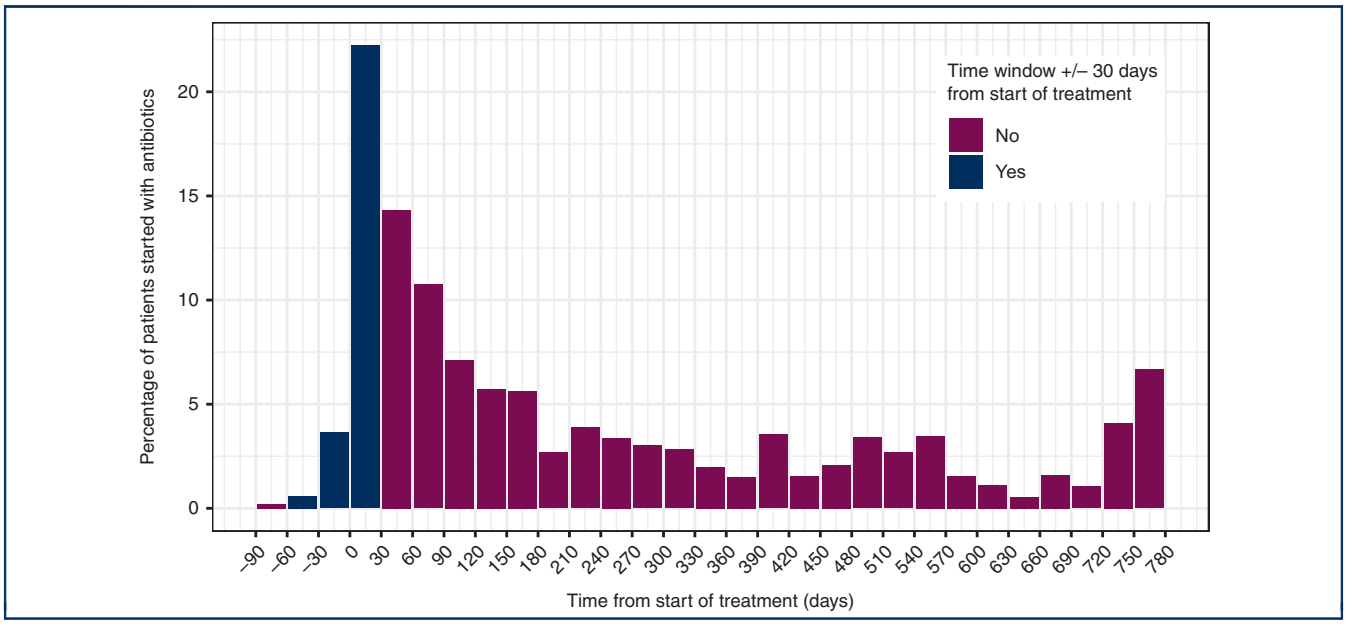

Figure 1. Percentage of patients (alive) who start antibiotics from 90 days before study treatment up to 780 days after start.
Bins are 30-day periods with the day marked on the *x*-axis included in the left bin.

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Androgen deprivation therapy in unlikely to be effective for treatment of COVID-19

Recent literature has reported that patients with prostate cancer treated with androgen deprivation therapy (ADT) have a lower incidence of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), an observation which has been widely reported by media outlets, together with speculation that ADT may be a potential treatment for coronavirus disease 2019 (COVID-19). The study by Montopoli et al.[1] was conducted at a population level in Italy, a region experiencing a high level of COVID-19 cases. They observed in a cohort of men with prostate cancer that those prescribed ADT were less likely to report COVID-19 (4/5273 cases versus 114/37 161, odds ratio 4.05, 95% confidence interval 1.55—10.59, $P = 0.00043$). Benefits were also observed for classification of mild and severe disease and were used as a basis of the conclusion that 'ADT, based on luteinizing hormone-releasing hormone (LHRH) agonist/antagonists or AR inhibitors, may be considered to reduce SARS-CoV-2 infections or complications in high-risk male populations.'