Letter comments on: The effects of antibiotics on the efficacy of immune-checkpoint inhibitors in non-small cell lung cancer patients differ according to PD-L1 expression

Dear Editor,

We read with great interest the paper entitled “The effects of antibiotics on the efficacy of immune checkpoint inhibitors in patients with non-small-cell lung cancer differ based on PD-L1 expression”, by Ochi and collaborators [1].

In this retrospective study, the authors assessed the impact of antibiotic (ATB) therapy on the outcomes of 531 patients with advanced non-small-cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICI) (anti-PD-1 or anti-PD-L1 antibody). In particular they investigated these effects layering by PD-L1 expression, which was available for 265 patients (48.2%). Interestingly, ATB treatment was significantly associated with a shorter median overall survival (OS), but not progression free survival (PFS), in 98 patients who received ATB (18.5%). While this effect was not observed at the multivariate analysis in patients with PD-L1 < 50%, the data uncovered a significantly shorter median PFS and OS in ATB-treated patients with PD-L1 ≥ 50%, thus raising the assumption that the ATB detrimental effect on ICI outcomes depends on the PD-L1 status.

This paper, whose results are line with previous studies [2], surely adds a relevant tile towards a better understanding of the pharmacological interactions of ATB with ICI treatment. However, we would discuss some key points, in order to lay the groundworks for future studies and applications on the current topic.

Firstly, as already mentioned by the authors, there is an imbalance between the group of patients who received an ATB treatment (n=98) and those who did not (n=433). Moreover, the proportion of patients with a poor performance status (PS), being this an independent negative prognostic factor confirmed at the multivariate analysis, was significantly higher in the ATB group (p=0.034). Splitting the data based on the line of treatment in PD-L1 ≥ 50% patients, the authors did not find significant correlation between ATB use and ICI outcomes in first-line. On the contrary, when ICI was administered in second-line, ATB-treated patients had a shorter PFS and OS than the counterpart, although this subgroup of patients represents a very small number (n=4 vs 43, respectively). Hence, we could not exclude that the overall effect of ATB in NSCLC patients has been strongly driven by the four ATB-treated patients with PD-L1 ≥ 50% who received ICI in second-line, whose better characterization would be helpful.

In order to confirm the findings by Ochi et al, we assume that a critical point would be the investigation of ATB on a control group of NSCLC patients who did not receive ICI. In this regard, a similar study led by Cortellini et al compared the effect of ATB use between two groups of NSCLC patients treated with either

first-line ICI or chemotherapy, finding a negative impact of ATB only in patients who received ICI [3]. Since in this study other drugs such as proton pump inhibitors or corticosteroids significantly impaired treatment outcomes [3], it would be interesting to explore the relationship between other concomitant medications and ICI efficacy in the Ochi cohort.

Focusing on the ATB use, the authors did not provide information regarding the duration and the reason for the ATB treatment; we believe that it is important to explore the ATB intent because this might be a prognostic factor itself. Infections could indeed affect more often patients with a poor clinical status, which might influence, independently, the outcomes of ICI therapy. Not least, a rapidly progressing lung disease may manifest itself with dyspnea, cough or fever, symptoms which could be mistaken as an infection, leading to a prompt use of ATB treatment.

When it comes to the timing of the ATB treatment, which were mainly β-lactams, the authors collected data on ATB use within two months before or a month after the start of ICI. In agreement with Belluomini and collaborators, the stronger detrimental effect on OS and PFS has been reported when ATBs are administered in the 42 days before ICI starting, with a progressive decrease of the effect with later exposures, and no differences when considering ATB therapy within 60 days before or anytime during ICI treatment [4]. Therefore, an analysis of the data according to the timing of ATB use may lead to further considerations.

Lastly, a biological rationale for the link between PD-L1 expression and ATB-induced impairment of ICI efficacy is still lacking. Growing evidence suggests that dysbiosis and modifications of the microbiome in NSCLC patients are involved in the creation of an inflammatory status, which can lead to cancer development and evolution [5]. In this regard, ATB use is associated with both dysbiosis and reduced response to immunotherapy, which in turn reflect alterations in the composition of tumor immune microenvironment (TIME) [6]. Analysis of the TIME before and after ATB use might uncover differential alterations of T-cell infiltration and immune cells subpopulations on the basis of PD-L1 tissue levels.

In conclusion we are grateful to Ochi and collaborators for their study on the impact of ATB use in patients with NSCLC treated with ICI, which lay the groundworks for future research aimed to understand the link between ATB use, microbiome and ICI therapy outcomes.

References

[1] Ochi N, Ichihara E, Takigawa N, Harada D, Inoue K, Shibayama T, et al. The effects of antibiotics on the efficacy of immune checkpoint inhibitors in patients with non–small-cell lung cancer differ based on PD-L1 expression. Eur J Cancer 2021;149:73–81. https://doi.org/10.1016/j.ejca.2021.02.040.

[2] Lurienne L, Cervesi J, Duhalde L, de Gunzburg J, Andremont A, Zalcman G, et al. NSCLC Immunotherapy Efficacy and Antibiotic Use: A Systematic Review and Meta-Analysis. J Thorac Oncol 2020;15:1147–59. https://doi.org/10.1016/j.jtho.2020.03.002.

[3] Cortellini A, Di Maio M, Nigro O, Leonetti A, Cortinovis DL, Aerts JGJV, et al. Differential influence of antibiotic therapy and other medications on oncological outcomes of patients with non-small cell lung cancer treated with first-line pembrolizumab versus cytotoxic chemotherapy. J Immunother Cancer 2021;9. https://doi.org/10.1136/jitc-2021-002421.

[4] Belluomini L, Caldart A, Avancini A, Dodi A, Trestini I, Kadrija D, et al. Infections and immunotherapy in lung cancer: A bad relationship? Int J Mol Sci 2021;22:1–19. https://doi.org/10.3390/ijms22010042.

[5] Halley A, Leonetti A, Gregori A, Tiseo M, Deng DMEI, Giovannetti E, et al. The role of the microbiome in cancer and therapy efficacy: Focus on lung cancer. Anticancer Res 2020;40:4807–18. https://doi.org/10.21873/anticanres.14484.

[6] Khan U, Ho K, Hwang EK, Peña C, Brouwer J, Hoffman K, et al. Impact of Use of Antibiotics on Response to Immune Checkpoint Inhibitors and Tumor Microenvironment. Am J Clin Oncol 2021;44:247–53. https://doi.org/10.1097/COC.0000000000000813.