Letter to the Editor

# Smoking signature as a biomarker for immunotherapy

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A recent study by Yang *et al.* reported that the smoking signature displayed a better performance than programmed death-ligand 1 (PD-L1) expression in predicting the pathological response in patients with non-small cell lung cancer (NSCLC). Based on the authors' conjecture, this possibly resulted from increased tumor mutational burden (TMB) and/or microsatellite instability (MSI) relating to smoking exposure (1). Because TMB and MSI data were unavailable in this study, we could only refer to previous studies to fully understand this speculation, during which we found that some points in the study are open to debate.

First and foremost, correlation between smoking signature and pathological response to immune checkpoint inhibitor (ICI) therapy are more likely to be mediated by TMB rather than MSI, since MSI that is often found in metastatic colorectal cancer is rarely seen in NSCLC (2,3). For patients with NSCLC, mediation analysis suggested that the effect of smoking information on clinical outcomes of ICI therapy was largely mediated by the increased TMB (4). TMB has been shown to be an independent predictor ICI response (4). Therefore, we suggest that this conjecture ought to be treated with caution.

Further, a dose-response relationship between smoking history and TMB has been illuminated in patients with NSCLC (5,6). Although TMB data is unavailable in the study in discussion, patients with the same smoking status as "heavy smoking" of this study showed a TMB of ≥10 mutations per megabase (mut/Mb) (5,6). Notably, in patients with advanced NSCLC, first-line treatment with nivolumab plus ipilimumab was associated with longer progression-free survival than chemotherapy for patients with a TMB of ≥10 mut/Mb, irrespective of PD-L1 status (7); NSCLC patients with a TMB of ≥12.3 mut/Mb may well have an overall survival benefit from ICI therapy (8). These studies possibly explain why heavy smoking status could better predict the benefit of immunotherapy in NSCLC patients, which, unfortunately, was not elaborate on by the authors.

To sum up, the incomplete information of TMB and MSI fails to support the authors' conjecture. Since the evaluation of smoking status is not always accurate because of biases (such as recall bias and reporting bias), we suggest focusing attention on uncovering and verifying the correlation between TMB and ICI therapy in NSCLC.

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