Letter to the Editor

Implementation of smoking signature as an improved biomarker predicting the response to immunotherapy

Haitang Yang[1#^], Wenyan Ma[2#], Feng Yao[1]

[1]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [2]Clinical Research Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

[#]These authors contributed equally to this work.

Correspondence to: Feng Yao. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, West Huaihai 241, Shanghai 200030, China. Email: yaofeng@shsmu.edu.cn.

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We thank Li *et al.* for showing interest in our recent work demonstrating the use of heavy smoking history as a potential marker for predicting the clinical responses to immune checkpoint inhibitors (ICIs) in non-small cell lung cancer patients (1).

Li *et al.* specifically raised important and complementary points on the potential interpretations of smoking signature as a biomarker candidate predictive of ICIs response. Drawing on literature-based evidence, they proposed that the better response to ICIs associated with heavy exposure to tobacco is more likely to be due to the increased tumor mutational burden (TMB), as opposed to microsatellite instability (MSI). As they pointed out, lung cancer is rarely associated with high MSI, although the detailed smoking information in these studied cohorts has not been specified (2,3). Available research also supports the association between TMB and smoking exposure (4-6). In this regard, we appreciated and agreed with Li and colleagues that TMB weights more than MSI in terms of interpreting the above observations. Nonetheless, a well-designed study is needed to investigate the link of tobacco exposure with TMB, and in particular, whether the heavy smoking history holds equal weights to high TMB for predicting response to ICIs in the clinic. Addressing this question would greatly improve the cost-effectiveness of ICIs, and facilitate the clinical practice.

In conclusion, despite the limitations mentioned by Li *et al.*, our study revealed that lung cancer patients with heavy smoking history had improved responses to ICIs. Superior biomarkers for predicting the response to ICIs are urgently required to select patients for ICIs, smoking signature is a promising marker because of its high clinical utility and low cost.

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^ ORCID: 0000-0002-8732-5910.

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