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Nivolumab plus Ipilimumab in Non–Small-Cell Lung Cancer

TO THE EDITOR: Although more than 10% of the patients in the CheckMate 227 trial conducted by Hellmann et al. (Nov. 21 issue)[1] had never smoked, the effect of smoking status on survival was not fully discussed. Striking differences in the clinical and molecular characteristics of lung cancers between smokers and those who have never smoked have been identified, suggesting that the cancers are separate entities.[2]

In one trial,[3] patients who had never smoked had poorer responses to nivolumab (as compared with docetaxel) than current or former smokers (hazard ratio for overall survival, 1.02 vs. 0.70). In a meta-analysis involving 1981 patients, antibodies to programmed death ligand 1 (PD-L1) were less effective in those who had never smoked than in smokers (hazard ratio, 0.8; 95% confidence interval, 0.54 to 1.06; $P>0.05$).[4] Moreover, in another meta-analysis of 11 trials, as compared with chemotherapy, immune checkpoint inhibitor therapy was associated with significantly lower overall survival among patients who had never smoked than among smokers (pooled hazard ratio, 0.91 vs. 0.79; $P=0.04$).[5]

The efficacy of immune checkpoint inhibitors has been correlated with higher neoantigen burdens and more mutations in DNA-repair pathway genes, a correlation that could have been affected by tobacco exposure.[6] In this respect, concerns have been raised regarding the inclusion of patients who have never smoked in trials of immune checkpoint inhibitors. The clinical benefits of these agents in patients with lung cancer who have never smoked need to be further explored.

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TO THE EDITOR: Hellmann et al. reported longer overall survival with nivolumab plus ipilimumab than with chemotherapy in the first-line treatment of patients with advanced non–small-cell

lung cancer in whom at least 1% of tumor cells expressed PD-L1. Nevertheless, the curves for overall survival (the primary end point) crossed after the first 6 months, and the prespecified subgroup analysis for the risk of death suggested the possible lack of benefit from immunotherapy among patients with liver metastases (20% of the entire analysis population). Could the early deaths of these patients in the group receiving nivolumab plus ipilimumab have been at least partially accountable for the decline in the curve for overall survival with immunotherapy during the first 6 months, and for the subsequent long-term benefit observed in what was therefore a positively selected population?[1] An exploratory analysis of overall survival with the exclusion of patients with liver metastases might address this issue. Also helpful would be additional details on the number of patients with liver metastases in each treatment group who died in the first 6 months.

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THE AUTHORS REPLY: Kim and Shin note that the molecular characteristics of lung cancers in smokers and those who have never smoked differ, a factor that may contribute to the differential efficacy of immune checkpoint inhibitors. We agree with this observation, and our trial, consistent with the standard approach, excluded patients with known *EGFR* mutations and *ALK* translocations, the two most common, targetable molecular abnormalities in patients who have never smoked. However, smoking status alone does not determine the possibility of long-term benefit from immune checkpoint inhibitors. In a recent 5-year update of the CheckMate 017 and 057 trials, 6 of 68 patients in the nivolumab group who had never smoked were alive at 5 years.[1-3] At the time of the final analysis of CheckMate 227 (minimum follow-up, 29 months), 18 of 56 patients who had never smoked and had been randomly assigned to receive nivolumab plus ipilimumab were still alive. More precise tools are needed to identify the phenotypes of patients who are unlikely to have a response to immune checkpoint inhibitors.

Bersanelli et al. propose the presence of liver metastases as a possible explanation for an early detriment to survival seen in some patients. In an exploratory analysis of CheckMate 227, the shape of the Kaplan–Meier curves in patients without liver metastases mirrored that of the overall population, suggesting that liver metastases alone do not account for the initial difference in survival. An investigation of the clinical and biologic characteristics associated with an elevated risk of early detriment or enhanced probability of response from combination therapy with immune checkpoint inhibitors is ongoing.

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Since publication of their article, the authors report no further potential conflict of interest.

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