Correspondence

Lack of clearly defined role for anti-programmed death-(ligand) 1 therapy in epidermal growth factor receptor mutated non-small cell lung cancer

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Response to: Tay RY, Ackermann CJ, Califano R. Immunotherapy in tyrosine kinase inhibitor-naïve advanced epidermal growth factor receptor-mutant non-small cell lung cancer-driving down a precarious road in driver-mutated lung cancer. Transl Lung Cancer Res 2018;7:S377-80;

Casaluce F, Gridelli C. Immunotherapies in the management of epidermal growth factor receptor mutated non-small cell lung cancer: a role will be found? Transl Lung Cancer Res 2018;7:S370-2;

Ward J, Morgensztern D. Role of immune checkpoint blockers in patients with EGFR mutation. Transl Lung Cancer Res 2018;7:S385-7.

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We thank the authors who contributed thoughtful editorials to this journal in response to our phase II study evaluating pembrolizumab in epidermal growth factor receptor (EGFR)-mutant, programmed death-ligand 1 (PD-L1)+, tyrosine kinase inhibitor (TKI) naïve patients with advanced non-small cell lung cancer (NSCLC). Specifically, the comments by Tay *et al.*, Casaluce and Gridelli, and Ward and Morgensztern, were insightful and perceptive both with respect to the interpretation of our study and the more general topic of anti-PD-(L)1 therapy in EGFR-mutant NSCLC (1-3). There are a number of issues raised by these editorials that we would like to further emphasize in this correspondence.

First, we would like to emphasize that anti-PD-(L)1 monotherapy has been shown to have minimal activity in EGFR-mutant NSCLC and, as such, should only be considered after all other therapies that have been shown to be more effective in this patient population, such as EGFR TKIs, platinum-doublet chemotherapy, and probably docetaxel ± ramucirumab, have been exhausted. Although our study evaluated pembrolizumab in only 10 EGFR-mutant, TKI naïve patients, the lack of objective response observed was striking, especially since seven of these patients had PD-L1 expression ≥50% (4). In pretreated EGFR-mutant patients, ample evidence suggests that anti-PD-(L)1 therapy is inferior to docetaxel, at least with respect to progression free survival (PFS) (5).

Second, anti-PD-(L)1 therapy appears to be more toxic in NSCLC patients with EGFR mutations, likely based on interactions with other agents used to treat EGFR-mutant disease. When anti-PD-(L)1 therapy was administered in combination with an EGFR TKI, significant lung and liver toxicity was observed on two phase I studies (6,7). Although the small number of pembrolizumab treated EGFR-mutant, TKI naïve patients, on our trial precludes definitive conclusions regarding this sequencing of therapies, the occurrence of one lifelong pembrolizumab associated adverse event, adrenal insufficiency, and the potential contribution of pembrolizumab to a case of fatal pneumonitis that occurred during subsequent TKI therapy, raise significant concern (4). Finally, an increased incidence of interstitial pneumonitis was observed when an EGFR-TKI was administered either concomitantly or sequentially with nivolumab in a large retrospective analysis (8). These findings suggest that anti-PD-(L)1 therapy should be used with caution in EGFR-mutant patients.

Third, the underlying factors responsible for the reduced anti-PD-(L)1 benefit observed in EGFR-mutant patients are incompletely understood. Potential explanations for the observed lack of response to anti-PD-(L)1 in EGFR-mutant patients include the lower tumor mutational burden, lack of CD8+ tumor-infiltrating lymphocytes, and increase in

immunosuppressive factors, such as CD73, in the tumor microenvironment of EGFR-mutant disease (9-11). Underscoring the differences in biology between EGFR-mutant and EGFR-wild type disease, is the observation that tumoral PD-L1 expression does not appear to be as strongly predictive of response to anti-PD-(L)1 therapy in EGFR-mutant compared to EGFR-wild type disease (4,12). Ultimately, much work still needs to be done to identify the factors leading to the decreased anti-PD-(L)1 benefit observed in EGFR-mutant patients.

It is also important to mention that the most promising recent immunotherapy results reported in EGFR-mutant NSCLC patients come from the IMpower150 trial. In a subset analysis of EGFR-mutant patients treated after TKI failure, a trend towards improved overall survival (OS) and PFS was observed with the addition of atezolizumab to platinum-doublet chemotherapy plus bevacizumab (ABCP) (OS: HR, 0.61; 95% CI: 0.29–1.28), (PFS: HR, 0.61; 95% CI: 0.36–1.03) (13). Importantly, safety was also shown to be similar between the EGFR-mutant subgroup and the intention-to-treat population (13). Although the results from this subgroup analysis are encouraging, the Food and Drug Administration (FDA) approval for ABCP, as well as pembrolizumab plus platinum-doublet chemotherapy, is limited to EGFR/ALK wild-type patients (14,15). Also, we don't know how many patients subsequently went back to an EGFR TKI or what the outcome was among those patients.

In conclusion, anti-PD-(L)1 therapy has ushered in a new era of improved treatment options for patients with advanced NSCLC, but those whose tumors harbor EGFR-mutations appear to derive significantly less benefit from these therapies and experience disproportionately higher toxicity compared to patients with EGFR-wild type disease. Further, PD-L1 appears to be less predictive of response to anti-PD-(L)1 therapy in EGFR-mutant disease. Taken together, it is inappropriate in the opinion of the authors to administer anti-PD-(L)1 prior to exhaustion of potentially effective EGFR TKIs and, although the EGFR-mutant subset survival analysis from the IMpower150 trial is intriguing, no clear role for immunotherapy has been found, to date, in EGFR-mutant disease. Thus, there is a need for additional preclinical and translational work to identify rationale approaches to immunotherapy in EGFR-mutant disease to assure this patient population is not left behind from the immunotherapy wave that is sweeping medical oncology.

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Footnote

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