Editorial Commentary

Combining immunotherapy and epidermal growth factor receptor kinase inhibitors: worth the risk?

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Provenance: This is an invited article commissioned by the Section Editor Kaiping Zhang, PhD (AME College, AME Group, China).

Comment on: Yang JC, Gadgeel SM, Sequist LV, *et al.* Pembrolizumab in Combination With Erlotinib or Gefitinib as First-Line Therapy for Advanced NSCLC With Sensitizing EGFR Mutation. J Thorac Oncol 2019;14:553-9.

Submitted Mar 20, 2019. Accepted for publication Mar 26, 2019.

doi: 10.21037/atm.2019.03.6

View this article at: http://dx.doi.org/10.21037/atm.2019.03.6

Immunotherapy has improved survival in advanced non-small cell lung cancer (NSCLC) and offers the potential for meaningful, durable responses in a subset of patients. Ongoing efforts are focused on extending these benefits to more patients. In a recent study, Yang *et al.* explore combinations of pembrolizumab with either erlotinib or gefitinib with that goal in mind (1). Erlotinib and gefitinib, first generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were administered concurrently with the anti-PD-1 antibody pembrolizumab in patients with EGFR mutant NSCLC in two cohorts of the KEYNOTE-021 trial. The authors concluded that the combination of erlotinib plus pembrolizumab was tolerable, based on their 19-patient cohort. They felt the combination of gefitinib and pembrolizumab was not tolerable, as 5 out of 7 patients developed grade 3–4 hepatotoxicity. The response rate was high, but consistent with prior EGFR TKI monotherapy studies.

Immunotherapy has been generally disappointing in patients with EGFR mutant NSCLC. While PD-1 and PD-L1 inhibitors improved survival compared to second line chemotherapy in NSCLC, the EGFR mutant subset did not derive as much benefit (2,3). Pooled analyses have verified the lack of a survival benefit with checkpoint inhibitor monotherapy in previously treated, EGFR mutant NSCLC (4,5). In a retrospective study, the response rate to single agent checkpoint inhibitors was only 3.6% in patients with EGFR or ALK alterations, compared to 23.3% in wild-type tumors (6). This has been balanced by some faint signals of efficacy. The first-line combination of carboplatin, paclitaxel, bevacizumab and atezolizumab showed a progression-free survival and overall survival benefit compared to carboplatin, paclitaxel and bevacizumab in the exploratory subset of patients with EGFR mutations (after prior TKI therapy) (7). Importantly, the long-term follow up of the phase I study of nivolumab noted a 16% 5-year survival (8) in the overall study and several of these long-term survivors had EGFR mutant disease. Responses to immunotherapy are possible for EGFR mutant NSCLC, if unlikely; efforts to induce immune responses are certainly justified.

Combining EGFR TKIs with checkpoint inhibitors does have preclinical rationale. In preclinical models, EGFR signaling has an impact on the microenvironment, suppressing immune-mediated anti-tumor responses via cytokines such as IL-6, TGF-β1 and progranulin (9,10). EGFR activation induces PD-L1 expression (11). PD-L1 can then upregulate YAP1 and contribute to TKI resistance (12). However, no clear clinical benefit to these combinations has been demonstrated and there are some concerns about the safety of this therapeutic strategy.

The TATTON trial explored various combinations with osimertinib, a third generation EGFR TKI. One arm combined osimertinib with durvalumab. While pneumonitis is uncommon with osimertinib monotherapy (2.9%) and with durvalumab monotherapy (2%), concurrent treatment in this study led to a 38% incidence of pneumonitis (13). Other combinations have reinforced safety concerns. A

phase I study of gefitinib plus durvalumab in 10 patients with EGFR mutant NSCLC led to grade 3–4 adverse events in 4 patients including elevated liver enzyme and interstitial lung disease (14). A phase I trial of erlotinib plus atezolizumab in 28 TKI naïve EGFR-mutant patients reported grade 3-4 adverse events in 39% of patients (15).

There is also concern about the safety of sequential immunotherapy followed by TKI therapy. An important phase II study explored pembrolizumab monotherapy in patients with EGFR mutant NSCLC expressing PD-L1 who were treatment naïve (including no prior TKI therapy) (16). In 10 patients with a confirmed EGFR mutation, no responses were seen. More troublesome was the observation that subsequent EGFR TKI therapy had notable toxicity, including a case of fatal pneumonitis. In a retrospective analysis, patients treated with immunotherapy before receiving osimertinib had a 15% incidence of immune-mediated toxicity, despite discontinuation of immunotherapy prior to TKI initiation (17). If at least a year had passed after immunotherapy before starting osimertinib, no immune-mediated events were noted. This may reflect the long functional half-life of checkpoint inhibitors; sequential use may approximate concurrent use if immunotherapy is given first.

Efforts to induce an immune-mediated anti-tumor response in EGFR mutant NSCLC are worthwhile and this avenue of research should continue. As impressive as EGFR TKI responses can be, they are typically transient, and the benefit of immunotherapy should someday extend to all patients with NSCLC. However, combining immunotherapy and TKI therapy in EGFR mutant NSCLC may not be a safe therapeutic strategy. An understanding of the differences in the tumor microenvironment between EGFR mutant and EGFR wild-type NSCLC will be critical to proper drug development in this patient population. The small study by Yang *et al.* reports that gefitinib plus pembrolizumab is not tolerable and this is clear. However, the conclusion that erlotinib plus pembrolizumab is safe is somewhat premature. Larger studies are needed to verify these findings and the risk of adverse events with these combinations needs to be justified by a clear improvement in efficacy. This will not be measured in response rate; it will be measured in long term survival. Until this is clearly shown, combinations of EGFR TKIs and checkpoint inhibitors need to be avoided in routine clinical practice and a better understanding of the mechanisms of immune resistance in EGFR mutant NSCLC should be established before large clinical studies are launched.

Acknowledgments

None.

Footnote

Conflicts of Interest: SV Liu has served as a paid consultant/advisory board member for Apollomics, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Genentech/Roche, Heron, Ignyta, Janssen, Merck, Pfizer, Regeneron, Taiho and Takeda/Ariad; he reports research funding (inst) from AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Clovis, Corvus, Esanex, Genentech/Roche, Ignyta, Lilly, Lycera, Merck, Molecular Partners, OncoMed, Pfizer, Rain Therapeutics, and Threshold. H Latif has no conflicts of interest to declare.

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Cite this article as: Latif H, Liu SV. Combining immunotherapy and epidermal growth factor receptor kinase inhibitors: worth the risk? Ann Transl Med 2019;7(Suppl 3):S76. doi: 10.21037/atm.2019.03.6

