Editorial Commentary

Is the game over for PD-1 inhibitors in *EGFR* mutant non-small cell lung cancer?

Maria A. Velez[1], Timothy F. Burns[2,3]

[1]Department of Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [2]Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, PA, USA; [3]Department of Medicine, Division of Hematology-Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, USA

Correspondence to: Timothy F. Burns, MD, PhD. UPMC Hillman Cancer Center, Hillman Cancer Center Research Pavilion, Office: Suite 2.18e Lab: 2.7, 5117 Centre Avenue, Pittsburgh, PA 15213-1863, USA. Email: burnstf@upmc.edu.

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The immune checkpoint inhibitor pembrolizumab, has been shown to be efficacious and to have significant and durable antitumor activity in a subset of patients with advanced non-small cell lung cancer (NSCLC). Most notably in NSCLC with high expression of the programmed death ligand-1 (PD-L1). Similarly, there is abundant data to support the use of epithelial growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as first-line therapy in patients whose tumors harbor *EGFR* mutations (1). However, these patients will inevitably progress on these targeted agents and there has been strong interest in examining whether immune checkpoint inhibitors could be effective in these patients (2). To date, the data for use of immune checkpoint inhibitors either after EGFR TKIs or in combination with EGFR TKIs has been extremely disappointing (3). Data to support the use of these agents in the front-line setting in *EGFR* mutant PD-L1 positive NSCLC patients, was encouraging but sparse. While there is ample published data showing that there are associations between PD-L1 expression and EGFR signaling in NSCLC, whether this could affect response to immunotherapy is not well established and the use PD-1 and PD-L1 inhibitors in this clinical setting remains controversial (4). In a recent study, Lisberg *et al.* examined whether the anti-PD-1 agent, pembrolizumab could be effective in *EGFR* mutant patients prior to receiving an EGFR TKI (5).

Preclinical data to support or reject the use of PD-1 inhibitors such as pembrolizumab in patients with *EGFR* mutant NSCLC is conflicting. It is well established that patients who harbor *EGFR* mutations have lower nonsynonymous mutational burden than *EGFR* WT patients. This is important as the tumor mutational burden has been associated with higher response to PD-1/PD-L1 inhibitors (6). Similarly, data from pre-clinical studies show that *EGFR*-mutated NSCLC tumors lack T-cell infiltration and have a more immunosuppressive tumor microenvironment, which could potentially negatively impact the response to PD-1/PD-L1 inhibitors (7). Conversely, there is also data to suggest that activating *EGFR* mutations led to PD-L1 upregulation in NSCLC as well as animal models showing increase survival after PD-1 therapy in EGFR driven adenocarcinoma (8-10). However, similar efficacy has not been observed in the clinic. A retrospective study compared the objective response rate (ORR) after treatment with PD-1/PD-L1 inhibitors in *EGFR* WT patients and *EGFR* mutant patients (11). Of the 22 evaluable patients with *EGFR* mutations, most had already progressed on an EGFR-TKI before receiving treatment with a PD-1/PD-L1 inhibitor, and three received combination therapy with both agents after progression. Only 1 out of the 22 patients in the *EGFR* mutant group obtained an objective response to treatment compared to 7

out of the 30 patients with *EGFR* WT tumors, suggesting that *EGFR* mutant patients do not respond to anti-PD-1/PD-L1 inhibitors as well as *EGFR* WT patients do. Furthermore, a pooled analysis which included data from five clinical trials evaluating PD-1/PD-L1 inhibitors in NSCLC patients, showed that prolonged overall survival (OS) was only observed in *EGFR* WT patients but not the *EGFR* mutant patients (12).

In contrast to the preclinical and clinical data in *EGFR* mutant patients who received immunotherapy after an EGFR TKI, experience from the KEYNOTE-001 trial suggested that patients with *EGFR* mutant tumors may have improved survival outcomes after receiving first-line pembrolizumab (13). In the KEYNOTE-001 trial, a small number of EGFR TKI naïve *EGFR* mutant patients (n=4) received pembrolizumab and had an improved ORR, progression-free survival (PFS) and OS after treatment with pembrolizumab compared to *EGFR* mutant patients who had received previous treatment with an EGFR TKI and subsequently received pembrolizumab (ORR of 50% and median OS of 18 months compared to ORR of 4% and OS of 4 months, respectively) (13). To formally test whether pembrolizumab could be effective in the EGFR TKI naïve setting, Lisberg *et al.* conducted a phase II trial to evaluate the response of *EGFR* mutant, PD-L1 positive (≥1%), TKI naïve patients with advanced NSCLC, to the PD-1 inhibitor, pembrolizumab (5). The inclusion criteria comprised the following; patients with advanced NSCLC, with sensitizing or non-sensitizing *EGFR* mutations who had PD-L1 positive tumors, defined as ≥1% tumor membranous staining by immunohistochemistry (IHC) using the 22C3 pharmDx test. This study excluded patients who had previously received treatment with either an EGFR TKI or a PD-1/PD-L1 inhibitor. The primary endpoint was ORR to pembrolizumab using the Response Evaluation Criteria in Solid Tumors 1.1, the secondary endpoints included safety of the drug as well as PFS and OS.

Of the 25 patients that were screened for the study, 14 patients (56%) screened failed and only 11 patients were enrolled. Most of these patients were treatment naïve (82%), had PD-L1 expression levels ≥50% (73%), were never smokers (54%) and were female (63%). The duration of follow-up was 7.7 months (233 days). Efficacy results showed that the only patient who had an objective response (ORR of 9%) to pembrolizumab at the time of data cut-off, did not truly harbor an *EGFR* mutation, and this was the result of a laboratory error. Taking this into consideration the ORR was 0% for the 10 patients who met inclusion criteria. In terms of adverse events (AE), 5 patients (46%) experienced treatment related AE, one of which had grade 3 transaminitis. Based on these results the study was discontinued due to futility.

After the study was discontinued, 9 patients underwent subsequent therapy. Two patients received chemoradiation and the remaining 7 patients received erlotinib for a median duration of treatment of about 3.5 months. Two patients died on erlotinib and 6 out of 7 patients who received TKIs experienced side effects. Notably, one patient experienced grade 5 pneumonitis thought to be secondary to the EGFR TKI although a causal link to prior pembrolizumab could not be excluded.

The aims of this study were to evaluate the feasibility and safety of pembrolizumab in patients with PD-L1 positive, *EGFR* mutant NSCLC before an EGFR TKI. This study hypothesized that the use of pembrolizumab in this patient population, before EGFR TKIs would lead to better clinical outcomes, defined as an ORR greater than 26%. Three key components would warrant the use of pembrolizumab in this setting: (I) the clinical benefit of pembrolizumab would have to be greater before administration of an EGFR TKI; (II) the benefits with an EGFR TKI would be unaffected by prior therapy; and (III) the safety profile would be equivalent as if the agents were given in reversed. The present study failed to demonstrate a clinical benefit from pembrolizumab in *EGFR* mutant patients and potentially raised questions about subsequent side effects with EGFR TKIs given as the next therapy.

As authors allude to in the manuscript, this study has several limitations, an important one is the small sample size of the study and the fact that it enrolled less than half of the patients that it initially sought out to do. This decreases the power of the study, and thus its ability to truly evaluate the feasibility of a therapeutic intervention in a population. Another important limitation of the study is the short follow-up time of only about 7 months to data cut-off, whereas studies showing the clinical benefits of pembrolizumab in the *de novo* setting had a follow-up of about twice as long (14). Furthermore, most of the patients included in the study were female (63%) and never smokers (54%), two populations that seem to derive less benefit from the PD-1/PD-L1 inhibitors (13,15). Conversely, most of the patients were also treatment naïve (82%) and PD-L1 ≥50% (73%) which are associated with improved response to pembrolizumab (16).

Certainly, while the study has the limitations mentioned

above, it is important to note its strengths. This is the first prospective trial to evaluate the use of PD-1 inhibitors in the first-line setting for *EGFR* mutant patients. Before the publication of this study all the data to evaluate this treatment strategy in the *EGFR* mutant population had been speculative, coming from retrospective studies and subset analysis from clinical trials designed to answer different questions. Furthermore, while sample size of the study was small it is representative of the patient population affected by *EGFR* mutant NSCLC (1). Additionally, the results from the study support previously published data indicating the lack of benefit from PD-1/PD-L1 inhibitors in *EGFR* mutant NSCLC as authors conclude that pembrolizumab is not an appropriate therapeutic choice in patients with treatment naïve *EGFR* mutant, PD-L1 positive NSCLC.

Although single agent immunotherapy is unlikely to be effective in *EGFR* mutant patients, other trials have assessed the combination of anti-PD-1/anti-PD-L1 agents in combination with chemotherapy or EGFR TKIs in the *EGFR* mutant population, with mixed results. The IMpower 150 trial evaluated the combination of carboplatin, paclitaxel and bevacizumab plus or minus the PD-L1 inhibitor, atezolizumab, in patients with both *EGFR* WT and *EGFR* mutant NSCLC (17). Results showed that PFS was significantly longer in *EGFR* mutant patients who received atezolizumab in addition to chemotherapy and bevacizumab as compared to those who only received chemotherapy and bevacizumab (9.7 *vs.* 6.1 months, HR 0.59; 95% CI, 0.37 to 0.94). It is important to denote that there were 108 patients in this subgroup of the study, but this also included patients with *ALK* translocations. Additionally, most of the patients with *EGFR* mutations included in this study had already received and failed first line treatment with EGFR TKIs. Thus, these results cannot be extrapolated to the treatment naïve setting in *EGFR* mutant patients. Similarly, the PACIFIC trial compared durvalumab, a PD-L1 inhibitor, as consolidation therapy after chemotherapy in patients with stage III NSCLC. In a subgroup analysis, patients with *EGFR* mutations also benefited from durvalumab after chemotherapy. However, this failed to reach statistical significance and like the aforementioned study these patients received fist-line treatment with another agent before receiving durvalumab (18). The TATTON trial was a phase Ib study that evaluated the combination of osimertinib in combination with durvalumab in both the EGFR TKI pretreated patients as well as in EGFR TKI treatment-naïve patients. Unfortunately, the rates of treatment-related AE were high and 38% of patients developed interstitial lung disease, leading to study discontinuation (19). Similarly other published studies that have evaluated the combination or EFGR TKIs with PD-1 or PD-L1 inhibitors have been limited by the toxicity rates, leading in many instances to treatment discontinuation (20).

To our knowledge, this phase II trial conducted by Lisberg *et al.* is the only prospective published study thus far that has evaluated PD-1 inhibitors as monotherapy in the front-line setting for patients with *EGFR* mutant NSCLC. While PD-L1 identification by IHC seems to be a good prognostic and predictive indicator to response in NSCLC, this does not seem to be the case for *EGFR* mutant patients. As thus, with the published data that is currently available, there is not a current role for the use of PD-1/PDL-1 inhibitor in the front line setting for *EGFR* mutant patients. After progression of an EGFR TKI, *EGFR* mutant patients have traditionally been treated with a platinum doublet and recent data suggest that these patients may benefit from combined chemoimmunotherapy. In addition, with development of new immunotherapeutic agents as well as possibly other predictive biomarkers, this is likely not the end for the use of immunotherapy in *EGFR* mutant patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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