

Square peg, round hole? Programmed death-1 inhibitors in epidermal growth factor receptor-mutant non-small cell lung cancer

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Immune checkpoint inhibitors have emerged as powerful new agents in the management of advanced, non-small cell lung cancer (NSCLC). In particular, monoclonal antibodies targeting the programmed death-1 (PD-1) receptor and its ligand, PD-L1, have transformed treatment approaches for patients with advanced lung cancer. In a series of pivotal studies, the PD-1 inhibitors nivolumab and pembrolizumab and the PD-L1 inhibitor atezolizumab produced significant improvements in overall survival compared to standard single-agent chemotherapy in previously treated patients (1-4). These data helped establish PD-1 pathway inhibitors as standard therapies for patients with advanced NSCLC after disease progression on platinum-doublet chemotherapy. More recently, PD-1 inhibitors have also been explored in the treatment-naïve setting, and one agent, pembrolizumab, has gained regulatory approval for the first-line treatment of select patients (i.e., PD-L1 high expressers) and in combination with platinum-doublet chemotherapy in unselected, non-squamous NSCLC (5,6). Despite this progress, however, a significant proportion of NSCLC patients do not respond to checkpoint inhibition, and there is an urgent need to identify potential biomarkers of response.

Initial preclinical studies raised hopes that two important molecular subsets of NSCLC, patients with epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements, may be associated

with sensitivity to PD-1 pathway inhibition. In these initial studies, oncogenic EGFR and ALK signaling was found to induce PD-L1 overexpression in cell line models (7-10). Furthermore, treatment with EGFR and ALK tyrosine kinase inhibitors (TKIs) resulted in enhanced interferon gamma production, decreased apoptosis of T cells, and reductions in PD-L1 expression in *in vitro* co-culture systems (8-10), suggestive of possible enhanced anti-tumor immunity. Importantly, similar results were also observed in *in vivo* models. Specifically, Akbay and colleagues investigated the activity of PD-1 inhibitors in EGFR-mutant transgenic mouse models, finding that PD-1 inhibitors led to tumor regression and improvements in overall survival compared to untreated mice (7). Taken together, these preliminary studies generated initial enthusiasm for the role of immune checkpoint inhibitors in EGFR-mutant and ALK-rearranged NSCLC patients.

In the manuscript accompanying this editorial, Lee and colleagues provide the most comprehensive assessment of the clinical activity of PD-1/PD-L1 inhibitors in EGFR-mutant NSCLC to date (11). In this study, the authors performed a meta-analysis of three randomized trials [Checkmate 057 (1), Keynote 010 (3), and POPLAR (12)] comparing PD-1 pathway inhibition with single-agent docetaxel in patients previously-treated with platinum-doublet chemotherapy. Consistent with the results of each individual trial included in the meta-analysis, treatment

with an immune checkpoint inhibitor was associated with a significant reduction in the risk of death in the overall intention-to-treat population [hazard ratio (HR): 0.70, 95% CI: 0.61–0.80; $P < 0.0001$]. Collectively, these studies also demonstrated that PD-1/PD-L1 inhibitors were associated with significant reductions in the risk of death in the EGFR wild-type subgroup [HR: 0.66, 95% CI: 0.58–0.76; $P < 0.0001$] (11). However, among 186 EGFR-mutant patients, there was no difference in overall survival between those receiving an immune checkpoint inhibitor and those treated with single-agent docetaxel (HR: 1.05, 95% CI: 0.70–1.55; $P = 0.81$). Of note, these findings are consistent with a recent single-institution retrospective analysis, which found that immune checkpoint inhibitors had minimal anti-tumor activity [objective response rate (ORR) of 3.6%] among EGFR-mutant or ALK-positive patients compared to EGFR/ALK wild-type patients (ORR: 23.3%) (13). Likewise, in the recently published phase III OAK trial, immune checkpoint inhibition again showed no overall survival benefit compared with docetaxel among EGFR-mutant NSCLC patients (HR: 1.24) (4).

Collectively, the above clinical data raise several important questions. First, why do EGFR-mutant NSCLC patients appear to derive less benefit from checkpoint inhibition compared to EGFR wild-type patients? Based upon their meta-analysis, Lee and colleagues suggest several possible hypotheses (11). The first centers on PD-L1 expression. In NSCLC, PD-L1 expression is an important, albeit imperfect, predictive biomarker of response to PD-1 pathway inhibition. To date, studies evaluating the frequency of PD-L1 expression in EGFR-mutant NSCLC have been conflicting (7,13–15). Indeed, the frequency of PD-L1 expression among EGFR-mutant patients has ranged from 11–72% (7,13–15), likely reflecting differences in study populations, technical factors, and significant variability in scoring algorithms and assays. Interestingly, even despite high PD-L1 expression, EGFR-mutant patients may be less responsive to PD-1 inhibition. For example, in a subgroup analysis of KEYNOTE 001, EGFR-mutant patients with high PD-L1 expression [defined as a tumor proportion score (TPS) of $\geq 50\%$] experienced objective responses at half the rate of EGFR wild-type patients (20% versus 40%, respectively) (16). Moreover, there was no difference in overall survival between PD-L1 high (TPS $\geq 50\%$) and PD-L1 low ($< 1\%$) EGFR-mutant NSCLC patients treated with pembrolizumab (17). Thus, it appears that PD-L1 expression alone is a less reliable predictor of response to PD-1 pathway inhibition in EGFR-mutant NSCLC.

One potential explanation for the above findings is that

there may be important differences in the mechanisms driving PD-L1 overexpression in EGFR-mutant versus EGFR wild-type patients. More specifically, two different mechanisms of PD-L1 overexpression have been described to date (18). Adaptive immune resistance refers to the upregulation of PD-L1 in response to interferon gamma secreted by infiltrating immune cells. By contrast, innate immune resistance refers to the intrinsic induction of PD-L1 expression due to constitutive oncogenic signaling (e.g., EGFR, ALK) in the absence of infiltrating immune cells. Teng and colleagues have suggested that the latter tumor microenvironment may be less responsive to PD-1 inhibition given the lack of T cells (19). Of note, our group recently performed a retrospective analysis of EGFR-mutant lung cancers and found that concurrent PD-L1 expression and presence of CD8+ tumor infiltrating lymphocytes (TILs) was rare (13). Thus, the lack of adaptive immune resistance in the tumor microenvironment among EGFR-mutant patients may also partly explain the limited clinical activity of PD-1/PD-L1 inhibitors in this subgroup.

Beyond PD-L1 expression, tumor mutation burden (i.e., the number of nonsynonymous mutations in a tumor) has also been explored as a predictive biomarker for immune checkpoint inhibitors (20). A high mutation burden may enhance tumor immunogenicity by increasing the number of potential neoantigens that can be recognized by the host immune system. Indeed, Rizvi and colleagues first reported that a higher mutation burden was associated with durable clinical benefit (complete response, partial response, or stable disease ≥ 6 months) among NSCLC patients receiving pembrolizumab (20). More recently, tumor mutation burden has also been explored in prospective studies. For example, in the phase III Checkmate 026 trial, first-line nivolumab did not improve progression-free survival (PFS) compared to platinum-doublet chemotherapy in the overall study population; however, among patients with a high tumor mutation burden, nivolumab was associated with a higher ORR and longer PFS compared to chemotherapy (21). Importantly, tumor mutation burden appears to be linked with smoking exposure. Indeed, in one study, never-smokers with NSCLC had an average mutation frequency approximately 10-fold less than that of smokers with NSCLC (22). Perhaps not surprisingly, EGFR mutations are also associated with low tumor mutation burden (23), likely reflecting the general lack of tobacco exposure among these patients. Thus, EGFR-mutant lung cancers may be less immunogenic and therefore less responsive to immune checkpoint blockade.

Table 1 Select clinical trials of EGFR inhibitors and immune checkpoint inhibitors

Combination	Phase	Sample size	Preliminary findings	NCT
Erlotinib + nivolumab	I	21	Grade 3/4 adverse events in 24%; ORR 19% (ORR 15% among patients with acquired erlotinib resistance) (26)	NCT01454102
Osimertinib + durvalumab	I	34	ILD in 38% of patients (15% with grade 3/4 ILD); ORRs 67% and 21% in T790M+ and T790M- tumors, respectively (27)	NCT02143466
Gefitinib + durvalumab	I	20	Treatment-related grade 3/4 adverse events lead to discontinuation in 4 (20%) patients; ORR 79% (28)	NCT02088112
Erlotinib + atezolizumab [†]	I	28	Grade 3/4 adverse events in 39% (SAEs 50%); ORR 75%, median DOR 9.7 months (29)	NCT02013219
Erlotinib + nivolumab or ipilimumab [†]	I	14	N/A	NCT01998126
Afatinib + pembrolizumab	I	38	N/A	NCT02364609

[†], separate arms evaluating ALK inhibitors plus immune checkpoint inhibitors for ALK-rearranged lung cancer. DOR, duration of response; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; N/A, not available; ORR, objective response rate; SAEs, serious adverse events; ALK, anaplastic lymphoma kinase.

While NSCLC patients with EGFR mutations generally have lower response rates to PD-1 pathway inhibition, there are clearly some patients who derive benefit. Moving forward, it will be crucial to characterize these patients on a clinical, pathologic, and molecular level. Do these patients have certain clinical features (e.g., smoking) or a high mutational burden? Are specific EGFR activating mutations or particular resistance profiles associated with greater benefit? Recently, work by Haratani and colleagues have begun to explore these questions (24). In a small cohort of EGFR-mutant NSCLC patients treated with nivolumab (N=25), the authors found that PD-1 responders had significantly higher CD8+ TIL density and nonsynonymous tumor mutation burdens. Moreover, T790M-negative patients experienced a longer median PFS on nivolumab compared to T790M-positive patients, but this difference was not statistically significant (HR: 0.48; P=0.099). In the future, similar translational efforts will be needed to further define features associated with response to PD-1 inhibitors among EGFR-mutant NSCLC patients.

Another critical question moving forward is whether we can therapeutically manipulate EGFR-mutant tumors to make them more immunogenic. One commonly proposed approach has been to use EGFR TKIs to prime EGFR-mutant tumors with the hypothesis that this will induce immunogenic cell death. Of note, in a recent follow-up report from the phase I AURA trial, a subset of EGFR-mutant NSCLC patients underwent pre- and on-treatment (day 15±7 days) biopsies after receiving the third-generation

EGFR inhibitor osimertinib (25). Interestingly, osimertinib generally led to reductions in PD-L1 expression and an increase in CD8+ TILs, suggesting that EGFR inhibitors may lead to acute changes consistent with a more favorable immune microenvironment. To date, multiple clinical trials evaluating the combination of EGFR TKIs and PD-1/PD-L1 inhibitors have been launched (*Table 1*); however, several of these trials have encountered unexpected toxicities. For example, in the phase I TATTON trial, the combination of osimertinib and the PD-L1 inhibitor durvalumab was associated with drug-induced pneumonitis in 38% of patients, with 15% experiencing grade 3 or 4 pulmonary toxicity (27). Based upon this high rate of pneumonitis, enrollment to this arm of the study has been suspended. It should be noted that PD-1/PD-L1 inhibitors generally have long half-lives (e.g., nivolumab half-life =25 days); thus, patients may still be at risk for drug-induced toxicity when initiating subsequent therapies. As an example, Takakuwa *et al.* recently described the case of a patient with EGFR-mutant NSCLC who was briefly treated with nivolumab followed by osimertinib (30). Despite a total of 37 days from nivolumab discontinuation to initiation of osimertinib, the patient developed symptomatic interstitial lung disease, highlighting one of the challenges of integrating PD-1/PD-L1 inhibitors into the care of EGFR-mutant patients.

Given the observed toxicities of EGFR TKIs plus immune checkpoint inhibitors outlined above, alternative combination approaches for EGFR-mutant NSCLC patients have been explored. For example, Hellmann and

colleagues recently reported results from a phase I study of the CTLA-4 inhibitor ipilimumab in combination with nivolumab (31). Interestingly, objective responses were observed in four of eight patients with *EGFR* mutations treated with the combination. Notably, among the four responders, three were former or current smokers, and three had high ($\geq 50\%$) PD-L1 expression levels. Thus, it's unclear whether these findings will be generalizable to a typical EGFR-mutant population. Nonetheless, a phase III trial evaluating nivolumab plus ipilimumab versus platinum-doublet chemotherapy plus nivolumab versus platinum-doublet chemotherapy alone in EGFR-mutant, T790M negative NSCLC patients progressing on first-line EGFR inhibitor therapy (NCT02864251) has been launched.

Finally, what are clinicians to do when managing patients with advanced, EGFR-mutant NSCLC in the interim? Is there still a role for PD-1/PD-L1 inhibitor monotherapy? My current practice is to start newly diagnosed, EGFR-mutant patients on an EGFR inhibitor as initial therapy—regardless of PD-L1 status. In subsequent lines of therapy, I tend to prioritize available targeted therapy options (e.g., based upon T790M status) and systemic chemotherapy instead of PD-1 pathway inhibition. In EGFR-mutant patients who have progressed despite available targeted therapies and standard cytotoxic chemotherapy (e.g., platinum-doublet, docetaxel), PD-1 pathway blockade remains in the armamentarium, though clinicians should consider pursuing clinical trials of PD-1 based combinations. Ultimately, with carefully designed clinical trials and strong translational science, we may be able to gain deeper insights into the immune landscape of EGFR-mutant lung cancers and expand the reach of immune checkpoint inhibitors to this patient population.

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Footnote

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