Editorial

Nivolumab for refractory metastatic squamous non-small-cell lung cancer: fulfilling an unmet need

Kristen A. Marrone, Patrick M. Forde

Lung Cancer Research Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA
Correspondence to: Patrick M. Forde, MD. Lung Cancer Research Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, CRB1 Room G92, Baltimore, MD, USA. Email: pforde1@jhmi.edu.

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Lung cancer is the leading cause of cancer death in the United States and worldwide (1,2). Approximately 85% of cases involve non-small-cell lung cancer (NSCLC), of which 30% will be squamous cell histology. Of those squamous cell lung cancers diagnosed yearly, it is estimated that more than 50% are metastatic at diagnosis. Until recently, the recommended treatment for good performance status patients with metastatic squamous lung cancer consisted of first-line platinum doublet chemotherapy followed, upon disease progression, by second-line single agent chemotherapy (1). Median overall survival from initial diagnosis of metastatic squamous lung cancer in patients who receive first-line platinum doublet chemotherapy ranges from 8-11 months (3,4). Therefore, effective new therapies are desperately needed. Building upon durable objective responses to the anti-programmed death-1 (anti-PD-1) antibody, nivolumab, reported in phase I studies, Rizvi *et al*. have recently published the results of a single-arm phase II trial of single-agent nivolumab in pretreated metastatic squamous lung cancer (5). In conjunction with headline results from a randomized phase III trial in second-line metastatic squamous lung cancer confirming improved OS for nivolumab compared with docetaxel, these data have led to the FDA approval of nivolumab for the treatment of metastatic squamous lung cancer after prior platinum-based chemotherapy (6).

Immunotherapy, an approach to modulate a patient's own immune system thus destroying cancer cells, has demonstrated preliminary efficacy and safety in several phase I studies in advanced NSCLC (7,8). The programmed death-1 (PD-1)/programmed death ligand-1 (PDL-1) pathway has been identified as a co-inhibitory pathway that may be activated by cancer cells to protect against host immune system elimination (8). The use of nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, to 'turn off' this inhibition, and upregulate immunosurveillance therefore destroying cancer cells, is an area of active study in advanced squamous cell lung cancer.

In "Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous NSCLC (CheckMate 063): a phase II, single arm trial" by Rizvi *et al*., the investigators enrolled 117 patients with stage IIIB or IV squamous cell NSCLC from 27 international sites between November 2012 and July 2013. These patients had all received at least two prior therapies, and 76% were less than three months from completion of their previous regimen suggesting that this was not a population with slowly progressive or indolent cancer. The dose of nivolumab (3 mg/kg every 2 weeks until disease progression or unacceptable side effects) was not modified throughout the trial, and treatment after progression was permitted if a patient had investigator-assessed clinical benefit and was otherwise tolerating therapy. The primary endpoint of the study was objective response rate (ORR) by RECIST 1.1 and was confirmed by an independent radiology review committee. The ORR in this study was 14.5% and responses occurred independently of age, sex, baseline performance status, region, ethnicity and number of previous treatments. Exploratory endpoints included evaluation of exposure-response relationships, characterize pharmacokinetics, immunogenicity, safety and tolerability of nivolumab; as well as calculations of progression-free survival and overall survival of all treated patients. The authors also evaluated

the association between the proportion of patients with an ORR and PD-L1 expression in all patients. Median time to response was 3.3 months and median duration of stable disease was 6 months; median duration of response was not reached at the time of report. Median progression-free survival was 1.9 months, and median overall survival was 8.2 months. Pretreatment archival tumor samples from 88% of participants were assessed for PD-L1 expression; 25 of these 76 patients (33%) were found to have PD-L1 positive tumors (≥5% expression). The authors report that responses occurred more frequently in PD-L1 positive tumors however it should be noted that the difference in ORR between PD-L1 positive versus negative was not statistically significant. Treatment-related adverse events were reported by 74% of patients, and were most commonly fatigue, decreased appetite and nausea. Grade 3-4 toxicities, most commonly fatigue, pneumonitis and diarrhea, occurred in 17% of patients. Treatment-related adverse events led to study discontinuation for 14 of 117 (12%) patients, most commonly pneumonitis (4%) and fatigue (2%). Two deaths were attributed by the investigator to nivolumab; one patient died of hypoxic pneumonia 28 days after the last dose of nivolumab, and another patient passed away from an ischemic stroke 41 days after the last dose of nivolumab. The authors concluded that nivolumab monotherapy provides clinically meaningful activity and an acceptable safety profile for patients with advanced refractory squamous NSCLC.

Discussion

Rizvi *et al*. demonstrated that nivolumab is a safe therapeutic option for advanced squamous NSCLC. Indeed, this study was cited by the FDA as establishing a promising safety profile that, in combination with interim analysis results of the Phase III CheckMate-017, has led to approval of nivolumab for use in advanced squamous NSCLC with progression on or after platinum-based chemotherapy (6). With the exception of ECOG performance status (all patients on this study were ECOG 0-1) the patient cohort in this study was a realistic reflection of advanced squamous lung cancer patients, all patients were heavily pretreated and shared characteristics indicative of an aggressive biology. The dosing of nivolumab, obtained from prior phase I studies, demonstrated an ORR not significantly different to that reported in other studies of nivolumab in advanced NSCLC (7). Using RECIST 1.1 criteria and an independent radiology review ensured that the data would be generalizable and in general there was good concordance between the assessments.

When discussing the results of single-arm, phase II studies in advanced cancer an important question is what constitutes "success". While the ORR in this study was more than acceptable for the patient population (one might expect an ORR of 5-10% with generic single agent chemotherapy in this patient group), what is most attractive is the likely durability of response. In a previous phase I study of nivolumab in 129 patients with heavily pretreated NSCLC the median duration of response was 17 months (9). This duration of response to a systemic therapy is unprecedented in the treatment of advanced NSCLC. While long-term follow up on the current study is not yet mature, one might expect a similar prolonged benefit for those patients who do respond. Predicting which patients will respond to immune checkpoint inhibition has proven challenging. The authors note that numerically at least more patients with PD-L1 positive tumors had an objective response however this difference was not statistically significant. At present PD-L1 expression on tumors cannot be recommended as a rigorous biomarker for the selection of NSCLC patients for treatment with nivolumab.

Overall, nivolumab appeared to be well-tolerated, with the rate of adverse events lower than in similar studies evaluating cytotoxic chemotherapy, in addition the two patient deaths on this study appear to have been multifactorial. Further studies are needed to identify those patients at risk for potential immunologic adverse events, so they can be evaluated and treated appropriately. As has been found in other studies, progression-free survival is not a particularly relevant endpoint in immunotherapy trials given the tendency for these agents to benefit a subgroup of patients who derive prolonged benefit i.e., the tail on the survival curve. As a primary endpoint, overall survival of patients treated with nivolumab is being actively assessed in other studies (including in the first-line setting), and the results of these studies are being actively analyzed at this time. This will assist us in more fully understanding where nivolumab belongs in the treatment paradigm of NSCLC. Overall, CheckMate 063 identifies a promising role for nivolumab in the role of fulfilling the unmet need of new treatment options in progressive metastatic squamous NSCLC.

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Footnote

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