

Into the Clinic With Nivolumab and Pembrolizumab

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Disclosures of potential conflicts of interest may be found at the end of this article.

INTRODUCTION

There once was a dearth of U.S. Food and Drug Administration (FDA)-approved therapies for metastatic non-small cell lung cancer (NSCLC). From the 1970s to the early 2000s, there were only six approved drugs: cisplatin, carboplatin, vinorelbine, paclitaxel, gemcitabine, and docetaxel. Researchers were disappointed when a highly anticipated landmark study showed no difference in survival among four different platinum doublets [1]. However, in the last several years, we have seen an incredible explosion of new drugs, ranging from small molecule tyrosine kinase inhibitors to immunotherapy agents. In 2015 alone, we witnessed FDA approvals for two exciting immunotherapy drugs: nivolumab for treatment of squamous and nonsquamous NSCLC and pembrolizumab for treatment of programmed death-ligand 1 (PD-L1) expressing NSCLC. Both FDA approvals are discussed in this issue of *The Oncologist*. Still, questions abound regarding best practice and target populations, and this commentary aims to address these issues.

Nivolumab

On March 4, 2015, the FDA granted approval to nivolumab for treatment of patients with metastatic squamous NSCLC after progression on platinum-based therapy. Seven months later, the FDA approved the drug for patients with nonsquamous NSCLC in the same setting.

The clinical trial CheckMate 017 [2] compared nivolumab and docetaxel in patients with advanced squamous cell NSCLC who had failed first-line chemotherapy. There was an overall survival (OS) benefit for nivolumab at 9.2 months versus docetaxel at 6.0 months, as well as an increased response rate of 20% versus 9%. In patients with advanced squamous cell NSCLC, nivolumab provided a survival benefit regardless of PD-L1 expression (objective response rates [ORRs]: 17% in patients with <1% tumor PD-L1 expression, 17% in $\geq 1\%$ PD-L1 expression, and 19% in $\geq 10\%$ PD-L1 expression). Interestingly, this is in contrast to the single-arm, phase 2 trial in squamous NSCLC, CheckMate 063 [3], in which the response rate was 14% in patients with tumor PD-L1 expression <5% and 24% in those with tumor PD-L1 expression of $\geq 5\%$.

Similarly, CheckMate 057 [4] compared these two agents in advanced nonsquamous cell NSCLC, with similar findings of improved OS (12.2 months vs. 9.4 months) and response rate (19% vs. 12%) for nivolumab. In patients with PD-L1-negative nonsquamous cell NSCLC, however, the objective response rate clearly correlated with PD-L1 expression (ORR: 9% in patients with

<1% tumor PD-L1 expression, 31% in $\geq 1\%$ PD-L1 expression, and 37% in $\geq 10\%$ PD-L1 expression), as did the survival (OS: 10.5 months in patients with <1% tumor PD-L1 expression, 17.7 months in $\geq 1\%$ PD-L1 expression, and 19.9 months in $\geq 10\%$ PD-L1 expression). Still, the PD-L1-negative group fared comparably in terms of survival against the comparator docetaxel, and this is the basis for the broad approval of nivolumab as a second-line treatment for unselected NSCLC.

Of note, CheckMate 017 and 057 compared nivolumab with docetaxel; one could argue that a new benchmark may be docetaxel and ramucirumab. In the REVEL trial [5], docetaxel and ramucirumab demonstrated a median OS of 10.5 months versus 9.1 months with docetaxel, as well as improved response rates (23% vs. 14%). Furthermore, for patients with epidermal growth factor inhibitor (*EGFR*) mutations, and for never-smokers, the benefit for nivolumab has been less clear, although the data do not clearly favor docetaxel either. Nevertheless, given nivolumab's improved safety profile (30% of patients receiving nivolumab experienced a grade 3 or 4 event, compared with 54% of patients receiving docetaxel), and possibly increased durability of response, nivolumab remains a reasonable option for all patients needing second-line therapy. In addition, the immune-related side effects are usually treatable and reversible if caught early, without necessarily affecting survival outcomes [6, 7].

Pembrolizumab

On October 2, 2015, the FDA granted accelerated approval for pembrolizumab for treatment of patients with metastatic NSCLC whose disease has progressed after other treatments. In contrast to nivolumab, pembrolizumab was approved with a companion diagnostic, the PD-L1 immunohistochemistry (IHC) 22C3 pharmDx. This approval was based on a 495-patient phase I trial called KEYNOTE-001.

During the KEYNOTE-001 study [8], the optimal PD-L1 cutpoint was defined as a proportion score (PS) $\geq 50\%$ staining of tumor cells for PD-L1. These patients had a very impressive ORR of 45%, compared with 17% in the PS 1%–49% group, and 11% in the PS <1% group. Furthermore, the responses were durable, with patients with a PS score $\geq 50\%$ having a median progression-free survival (PFS) of 6.3 months (12.5 months in previously untreated patients). Overall survival has not yet been reached in this group. Of note, pembrolizumab showed efficacy in both the previously treated (ORR 44%) and treatment-naïve population (ORR 50%).

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Since the approval, the 1,034-patient phase II–III KEYNOTE-010 trial [9] was published, which compared pembrolizumab with docetaxel for previously treated patients with PD-L1-positive, advanced NSCLC. When compared with docetaxel in patients with PS $\geq 50\%$ (representing 28.5% of patients with a PD-L1 result), the hazard ratio for overall survival was 0.54 (95% confidence interval [CI]: 0.38–0.77; $p = .0002$) for pembrolizumab 2 mg/kg, and 0.50 (95% CI: 0.36–0.70; $p < .0001$) for pembrolizumab 10 mg/kg. The median OS was 14.9 months for pembrolizumab 2 mg/kg, 17.3 months for pembrolizumab 10 mg/kg, and 8.2 months for docetaxel. As seen with the nivolumab trials, pembrolizumab was associated with fewer high-grade treatment-related adverse events than docetaxel; pneumonitis and severe skin reactions were the only grade 3–5 adverse events of special interest seen in $\geq 1\%$ of patients.

Similar to the nivolumab studies, there was no clear survival benefit for pembrolizumab in the subset of patients with an *EGFR* mutation, even in those patients with PS $\geq 1\%$. This difference likely speaks to the relative genomic simplicity of a cancer driven by targetable mutations as opposed to a smoking-associated one.

CLINICAL SIGNIFICANCE OF PD-L1 TESTING AND BEYOND

There are now two commercial PD-L1 IHC assays available. The Dako PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Glostrup, Denmark, <http://www.dako.com>) is a companion diagnostic using monoclonal mouse anti-PD-L1, clone 22C3. A positive score of PD-L1 $\geq 50\%$ is required for treatment with pembrolizumab. In contrast, the Dako PD-L1 IHC 28-8 pharmDx (Agilent Technologies) is a standalone complementary diagnostic test using monoclonal rabbit anti-PD-L1, clone 28-8.

One of the issues for consideration around these assays is the use of archived versus new tissue procurement. The data from KEYNOTE-010 suggest that PD-L1 testing on both archival and new tissue is acceptable because the survival hazard ratios seemed comparable between archived and contemporary tumor samples. Another important point is that the PD-L1 assay is limited to samples obtained by surgical resection or core needle biopsy; this may represent a challenge in cases for which cytology is the only diagnostic tissue available.

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Clearly, PD-L1 is not the ideal biomarker. For example, we know that PD-L1 expression can be heterogeneous even within the same tumor specimen [10], and therefore there may be false negatives depending on the location of the biopsy. Furthermore, we know from CheckMate 017 that there may be benefit even in patients whose tumors do not express PD-L1, so we continue to look for methods to differentiate whom to treat with immunotherapy. One study [11] suggested that increased mutational burden load may predict a more robust effect with the PD-1 checkpoint inhibitors; however, the sample size of this analysis was small and whole-exome sequencing is not readily available and remains time, cost, and labor intensive.

All things considered, the PD-L1 score may help navigate treatment decisions and is a reasonable test to obtain upfront. For example, in melanoma, we saw that ipilimumab plus nivolumab resulted in a better PFS than either agent alone for patients with $< 5\%$ PD-L1 expression [12], suggesting that the combination may help improve response rates in those patients who otherwise may not respond. We hope to translate the same paradigm to lung cancer, where we have ongoing combination immunotherapy clinical trials showing comparable activity irrespective of PD-L1 status [13].

FUTURE DIRECTIONS

The stories of nivolumab and pembrolizumab continue to unfold, with ongoing trials in the frontline metastatic, adjuvant, and neo-adjuvant settings. Researchers are also actively exploring these drugs in combination settings, whether it be with other immunotherapy, chemotherapy, or targeted agents. Although many controversies surround PD-L1 testing, and clinicians may at times be overwhelmed with choices, this is certainly an excellent problem to confront. We are living in an incredible era for oncology and drug development, and seeing even a few patients with a durable response to immunotherapy pushes us to explore further.

DISCLOSURES

Naiyer A. Rizvi: Merck, Novartis, AstraZeneca, Roche (C/A), Merck, Novartis, AstraZeneca, Roche, Bristol-Myers Squibb (RF), Gritstone Oncology (OI). The other author indicated no financial relationships. (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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EDITOR'S NOTE: See the related FDA Approval Summaries by Dickran Kazandjian et al. (page 634) and Joohee Sul et al. (page 643).