Lung cancer is the leading cause of worldwide cancer-related deaths and is usually diagnosed at advanced stages when the prognosis is poor. In contrast to the substantial progress seen in the development of targeted therapies against tumors with oncogene addiction (eg, EGFR and ALK alterations, most often found in adenocarcinoma non–small-cell lung cancer [NSCLC]), there has been little progress in the development of highly effective treatments targeting genetic alterations predominantly found in metastatic squamous cell (SQ) NSCLC. Table 1 highlights drugs approved by the US Food and Drug Administration (FDA) for second-line SQ NSCLC.

New drugs focus on targeting the immune system. Pathways involved in inhibiting antitumor T-cell responses (activation of the inhibitory coreceptors cytotoxic T-lymphocyte–associated protein 4 and programmed cell death protein 1 [PD-1] on T cells) allow tumors to evade the immune system. Nivolumab (Opdivo; Bristol-Myers Squibb Company), a monoclonal antibody directed against PD-1, is one of the first of a class of drugs that block T-cell inhibitory signal pathways by preventing engagement of PD-1 to its ligands. Recent high-throughput genomic analyses have shown that NSCLC has a substantial amount of DNA damage, molecular heterogeneity, and mutational burden (reflecting tobacco carcinogen exposure). It is thought that the increase in mutational burden gives rise to neoantigens and tumor immunogenicity, which is important for tumor sensitivity to PD-1 axis blockade.

Clinical Trial Designs

Two studies of nivolumab assessing efficacy in metastatic SQ NSCLC have been reported. Study CA209063 (CM063) was a single-arm, multinational trial in patients with metastatic SQ NSCLC (n = 117), which had progressed after treatment with 2 systemic regimens including platinum-based doublet chemotherapy and is well described by Rizvi et al. Patients received nivolumab, 3 mg/kg, as an intravenous infusion every 2 weeks until progression or occurrence of toxic effects. The
primary outcome was Response Evaluation Criteria in Solid Tumors version 1.1 objective response rate (ORR), as determined by a blinded independent review committee.

In April 2014, the FDA determined that based on the “modest” ORR (15%) in CM063, further information from the ongoing randomized study should be provided to support a regulatory decision. The FDA requested the results of a planned interim analysis of the primary end point, overall survival (OS), from the randomized trial (study CA209017 [CM017]), well described by Brahmer and colleagues. On December 19, 2014, the FDA received the external data monitoring committee (DMC) report, which stated that the O’Brien-Fleming boundary had been crossed and that nivolumab demonstrated superior OS vs docetaxel. Based on these results, the FDA informed Bristol-Myers Squibb to submit the final component of the Biologics License Application (BLA) for nivolumab.

On January 10, 2015, the DMC statisticians presented the report to the full DMC, who recommended that, in light of the positive nivolumab results, CM017 patients randomized to the docetaxel arm be allowed to cross over to receive nivolumab.

The CM017 study was an open-label, multicenter, multinational, randomized (1:1) trial in patients whose disease had progressed during or after 1 prior platinum-based chemotheraphy regimen. Key eligibility criteria included histologically or cytologically documented SQ NSCLC with stage IIIB-IV disease (International Association for the Study of Lung Cancer, version 720) or with recurrent or progressive disease following multimodal therapy. Patients received nivolumab (n = 135), 3 mg/kg, intravenously every 2 weeks, or docetaxel (n = 137), 75 mg/m², intravenously every 3 weeks. The major efficacy outcome was OS.

Based on the efficacy results of the CM017 study, in which a statistically significant and clinically meaningful improvement in survival was demonstrated for nivolumab compared with docetaxel, the FDA committed to an expeditious review (<4 months) of the BLA compared with both the standard (10-month) and priority-designated (6-month) BLA review times.

Table 1. Currently Available FDA-Approved Second-Line Chemotherapeutic Agents for Metastatic Squamous NSCLC

<table>
<thead>
<tr>
<th>Drug</th>
<th>NSCLC Refractory Indication</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy</td>
<td>Docetaxel vs best supportive care with primary end point OS (TAX317): mOS, 7.5 vs 4.6 mo; HR, 0.56; (95% CI, 0.35-0.88); P = .01; mTTP, 2.8 vs 1.6 mo; ORR, 5.5% vs NA</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen</td>
<td>Erlotinib vs placebo with primary end point OS (BR.21): mOS, 6.7 vs 4.7 mo; OS HR, 0.73 (95% CI, 0.61-0.88); P &lt; .001; mPFS, 2.3 vs 1.8 mo; PFS HR, 0.59; ORR: 8.9% vs 0.9%</td>
</tr>
<tr>
<td>Ramucirumab + docetaxel</td>
<td>In combination with docetaxel for metastatic NSCLC with disease progression or after platinum-based chemotherapy</td>
<td>Docetaxel + ramucirumab vs docetaxel + placebo with primary end point OS (REVEL): mOS, 10.5 vs 9.1 mo; OS HR, 0.86 (95% CI, 0.75-0.98); P = .02; mPFS, 4.5 vs 3.0 mo; PFS HR, 0.76; ORR: 23% vs 14%</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; NSCLC, non–small-cell lung cancer; ORR, objective response rate.

Table 2. Survival Data From Study CM017*

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Deaths, No. (%)</th>
<th>OS, Median (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 135)</td>
<td>86 (64)</td>
<td>9.2 (7.3-13.3)</td>
<td>0.59 (0.44-0.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Docetaxel (n = 137)</td>
<td>113 (82)</td>
<td>6.0 (5.1-7.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; OS, overall survival.

* This study is described by Brahmer and colleagues.
FDA Approval of Nivolumab for Lung Cancer

Box. Benefit-Risk Assessment for Nivolumab in the Treatment of Patients With Metastatic Squamous NSCLC With Progression During or After Platinum-Based Chemotherapy

**Disease**
Patients with metastatic squamous NSCLC that has progressed during or after front-line platinum-based doublet chemotherapy have a serious and life-threatening condition with historic median survival rates of 8 to 10 months and minimal available therapies.

**Unmet Medical Need**
Patients with metastatic squamous NSCLC that has progressed after front-line therapy have few options and are usually treated with standard cytotoxic chemotherapy. The FDA-approved available therapies are docetaxel, with or without ramucirumab, and erlotinib, which yield modest response rates (ORR, 5%-22%) and improvement in survival only compared with placebo or as add-on therapy rather than active-controlled, head-to-head trials.

**Clinical Benefit**
In a randomized trial comparing nivolumab with docetaxel, nivolumab treatment resulted in a 3.2-month increase in median survival and a 41% reduction in risk of death. The survival curves continued to separate after the median. In a second, single-arm study, nivolumab treatment resulted in a 15% IRC-determined ORR, with 59% of responders maintaining responses for 6 months or longer.

**Risk**
The most common adverse reactions and laboratory abnormalities of nivolumab (>30%) were fatigue, lymphopenia, dyspnea, decreased appetite, and cough. The most frequent grades 3 and 4 adverse drug reactions and laboratory abnormalities of nivolumab (>5%) were dyspnea, fatigue, lymphopenia, and hyponatremia. Clinically significant immune-mediated adverse reactions included pneumonitis, colitis, nephritis/renal dysfunction, hypothyroidism, and hyperthyroidism. Immune-mediated adverse reactions were managed with high-dose corticosteroids and interruption of nivolumab dosing.

**Uncertainties**
The randomized trial demonstrated an improvement in overall survival. However, further studies will be needed to identify better predictive biomarkers and to explore the utility of PD-L1 testing to predict clinical benefit. Additional data are also needed to assess the long-term outcomes of the immune-related adverse events and their management.

**Conclusions**
Nivolumab meets the criteria for traditional approval based on a favorable benefit-risk profile for the treatment of patients with metastatic squamous NSCLC that has progressed during or after treatment with a first-line platinum-based doublet regimen. Nivolumab demonstrated an improvement over currently available therapies with a risk profile acceptable relative to the clinical benefit offered.

**Benefit-Risk Assessment**
A summary of the FDA’s benefit-risk assessment is presented in the Box. After observing the magnitude of the survival improvement over an active treatment, docetaxel, from the CM017

Safety

To expedite the submission of the BLA, the FDA did not wait to receive or review safety data from CM017. However, the approval was contingent on a postmarketing requirement for formal submission of the CM017 data within the year. Therefore, the FDA relied primarily on safety data in patients with SQ NSCLC from the single-arm CM063 trial, supported by safety data obtained in other disease settings. The most common (>30%) adverse reactions and laboratory abnormalities in the 117 patients receiving nivolumab in CM063 were fatigue, lymphopenia, dyspnea, decreased appetite, and cough. The most frequent (greater than or equal to 5%) grades 3 and 4 adverse reactions and laboratory abnormalities were dyspnea, fatigue, lymphopenia, and hyponatremia. Immune-mediated adverse reactions in CM063, defined as cases requiring use of systemic corticosteroids with no clear alternative cause, were immune-mediated pneumonitis (6.0%), hypothyroidism (4.3%), hyperthyroidism (1.7%), motor dysfunction (1.7%), rash (1.7%), adrenal insufficiency (0.9%), vasculitis (0.9%), colitis (0.9%), and renal dysfunction (0.9%). Immune-mediated adverse reactions were managed with administration of high-dose (2- to 4-mg/kg prednisolone equivalent) corticosteroids followed by a taper and interruption of nivolumab therapy. No patients administered corticosteroids were rechallenged with nivolumab following corticosteroid taper. The FDA has mandated a postmarketing requirement to submit the results of the randomized CM017 trial to better characterize the incidence, severity, and outcomes of nivolumab-induced immune-mediated adverse reactions in patients with NSCLC.
The FDA believed that it was critical to incorporate the data from CM017 into the BLA and include these findings into the product label to support an indication for second-line treatment of SQ NSCLC, a disease with unmet need. Rapid dissemination of this data would ensure timely access to nivolumab for patients and physicians as well as a reevaluation of control arms for ongoing and planned trials in SQ NSCLC.21

The information from the CM017 trial submitted to the FDA was the survival and demographic data analyzed by the DMC under a prespecified interim analysis. The safety data from the single-arm CM063 trial, which in combination with the safety data from the prior approval in melanoma, provided sufficient basis to characterize risks to inform prescribers of safe use and confirm a favorable benefit-risk analysis, considering the magnitude of OS effect, to support approval. A conventional submission that included all the data (including safety) from the CM017 trial would have delayed the BLA submission. On average, sponsors require 6 months or more to clean, prepare, and standardize data sets, perform quality control and assurance, write clinical study reports, and submit elements from other disciplines, including chemistry, manufacturing and controls, nonclinical toxicology, and clinical pharmacology modules. As a condition of the approval, Bristol-Myers Squibb must submit a more comprehensive report and data from the CM017 trial.

Discussion

This application was noteworthy for a number of reasons. It is the first head-to-head trial against an active control in second-line squamous NSCLC to demonstrate a large survival benefit and is the first immunotherapy approved for treatment of a histologic subtype of NSCLC. Survival is the gold standard for clinical benefit because it is objective and not influenced by potential bias that may occur with progression-free survival. The 15% ORR in the CM063 single arm study,26 though durable, was modest. Absent the data from the CM017 randomized trial, it is uncertain that the ORR data alone would have supported an accelerated approval, which would have required substantial discussion including advice obtained during an advisory committee meeting. Importantly, in CM017, the docetaxel control arm performed similarly to other recent studies in terms of OS; for example, in REVEL,31 the median OS was 9.1 months (Table I). It is unclear if ORR and duration of response fully capture the clinical benefit of immunotherapy; further research is needed to explore novel end points for activity estimation and assessment of clinical benefit.22

In both the CM017 and CM063 studies, patients were entered irrespective of tumor PD-1 ligand 1 (PD-L1) status,16,18 and further trials with PD-1/PD-L1 inhibitors will need to address the value of predictive biomarkers in NSCLC. In addition, pre-competitive collaboration and cross-validation is needed for the various PD-L1 assays in clinical development.23

Conclusions

The FDA’s approach to reviewing and incorporating the OS results from the CM017 study into product labeling ensured rapid access to patients with SQ NSCLC that progressed during or after platinum-based chemotherapy. Specifically, 6 months was saved by not waiting for formal preparation of the data by the sponsor, and an additional 2.5 months was saved by the FDA expedited review. Studies are ongoing to evaluate the role of PD-1/PD-L1 inhibitors in other NSCLC histologic types and disease settings.

REFERENCES

Balancing Benefit, Risk, and Time to New Cancer Therapies

Howard (Jack) West, MD

The US Food and Drug Administration (FDA) is charged with the task of thoroughly assessing the benefit vs risk of novel therapies. While its representatives may seek greater clarity with more data and longer follow-up, there is a competing challenge of delivering potentially dramatically beneficial new opportunities in the most timely way possible, this pressure perhaps being most acute in the setting of a terminal illness such as advanced non-small-cell lung cancer (NSCLC).

In this issue of JAMA Oncology, Kazandjian and colleagues1 review the process by which the FDA evaluated the immune checkpoint inhibitor nivolumab for patients with chemotherapy-pretreated advanced squamous NSCLC. This summary includes thoughtful discussion of objective response rate (ORR) vs overall survival (OS) as end points potentially sufficient for approval. While very high response rates that far exceed prior benchmarks have led to the admirably rapid approval of crizotinib for anaplastic lymphoma kinase-positive NSCLC based on high response rates in phase II studies,2 the authors note that the ORR of nivolumab in the CheckMate 063 trial was a modest 15%,3 a result that may underestimate the incremental value of immunotherapies owing to the unique response patterns of this class of agents. In contrast, OS provided a more meaningful primary end point for the subsequent randomized CheckMate 017 trial.4

The report also highlights the steps taken to bring nivolumab to commercial availability as readily as possible once the efficacy and safety of this agent were determined in patients with previously treated advanced squamous NSCLC. This included the FDA decision to defer on formal submission of all safety data from the randomized CheckMate 017 trial and consider prior safety data with nivolumab as well as the expedited review process by the FDA; together, these efforts shortened the time to approval by approximately 6 months. For many appropriate candidates for this agent based on the rapid approval of nivolumab in this setting in early March 2015, this enabled an opportunity to experience a dramatic and prolonged response against a disease for which that time interval is critical.

As the shared enthusiasm of patients and cancer care specialists leads us to complete exciting clinical trials of more immunotherapies and targeted therapies, we remember that our ability to translate the potential benefits to a broader cancer community reaches a potential bottleneck at the doorstep of the FDA. It is very helpful to understand more of the decision-making process and know that the FDA is striving to balance a thorough adjudication of the benefits and risks of these novel strategies with the acute needs of the patients with cancer who cannot afford to wait for them.