Immunotherapy for Lung Cancer: Many Questions Yet to Be Answered

David S. Ettinger, MD

I have been treating patients with lung cancer for more than 40 years, and since the first publication of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer (NSCLC) in 1996,1 significant progress has been made in the systemic therapy for advanced NSCLC. However, the latest advance and most hopeful therapy for patients with lung cancer is immunotherapy. With immunotherapy, we can say, “the future is now!”

We can look at a number of milestones that have brought us to this point and will inform the future:

• In October 2015, Vice President Joe Biden announced his Cancer Moonshot initiative, which describes increased funding from both the government and private sector to combat cancer.
• In January 2016, billionaire Patrick Soon-Shiong announced an industry-led moonshot program aimed at testing combinations of cancer immunotherapy drugs in clinical trials.
• In March 2016, Johns Hopkins announced the formation of the Bloomberg-Kimmel Institute for Cancer Immunotherapy with a $125 million investment.
• In April 2016, billionaire Sean Parker, cofounder of Napster and first president of Facebook, announced he’s giving $250 million to form the Parker Institute for Cancer Immunotherapy. This institute will bring together immunologists from 6 cancer centers nationwide, including Memorial Sloan Kettering Cancer Center, Stanford University, The University of Texas MD Anderson Cancer Center, University of California Los Angeles, UCSF Helen Diller Family Comprehensive Cancer Center, and the University of Pennsylvania, to develop immunotherapy to fight cancer.

Of course, there is a need to improve therapy for all cancers, but this is especially true for lung cancer because it is the most common cause of cancer mortality globally. In 2012, there were 1.59 million deaths (19.4% total) worldwide from lung cancer.2 Further, it is the leading cause of cancer death in men and women in the United States, with an estimated death rate of 158,080 (85,920 men; 72,160 women) in 2016.3

The use of immune checkpoint inhibitors is a promising immunotherapy approach to treat patients with lung cancer. Although T cells in the body can recognize and kill cancer cells, the cancer cells can evade immune attack by the T cells by expressing PD-L1, which dampens the antitumor immune response. By blocking PD-1 and PD-L1, we can reactivate the immune system to kill the cancer cells.4

In March 2015, the FDA approved the PD-1 checkpoint inhibitor nivolumab, which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, for the treatment of advanced squamous cell lung cancer that progressed on first-line platinum-based chemotherapy. This approval was based on the results of a phase III trial (CheckMate 017) in which 272 patients were randomized to receive either nivolumab, 3 mg/kg intravenously every 2 weeks or docetaxel, 75 mg/m² intravenously every 3 weeks.5 For nivolumab versus docetaxel, the overall response rate (ORR) was 20% versus 9%, and progression-free survival (PFS) was 3.5 versus 2.8 months, respectively (hazard ratio [HR], 0.62; P<.001). Overall survival (OS) was 9.2 versus 6.0 months (HR, 0.59; P<.001) and 1-year survival rates were 42% versus 24%, respectively.

The ideas and viewpoints expressed in this editorial are those of the author and do not necessarily represent any policy, position, or program of NCCN.
The most common side effects of nivolumab were fatigue, musculoskeletal pain, decreased appetite, cough, and constipation. Eighty-three patients had tumor samples suitable for PD-L1 expression analysis. Across the prespecified expression levels (≥1%, ≥5%, and ≥10%), PD-L1 expression was not prognostic or predictive of any of the efficacy end points.

The FDA also approved the PD-L1 IHC 28-8 pharmDx test (Dako, Carpinteria, CA) to detect PD-L1 expression levels to help physicians determine which patients may benefit from treatment with nivolumab, but the testing was not mandatory before treatment initiation. Also supporting the FDA approval were the results of a large phase I experience (117 patients) with nivolumab. Although the ORR was 15% at the time of analysis, 10 of 17 patients who showed a response (59%) had response durations of 6 months or longer. At publication, 3-year survival was 18%.

In October 2015, the FDA approved nivolumab to treat nonsquamous cell carcinoma of the lung based on the results of a phase III trial (CheckMate 057) in which patients with nonsquamous carcinoma of the lungs received either nivolumab or docetaxel. In this study, the ORR was 19.2% for nivolumab versus 12.4% for docetaxel, and PFS was 2.3 months for nivolumab versus 4.2 months for docetaxel (HR, 0.92; *P* = .31). OS was 12.2 versus 9.4% (HR, 0.73; *P* ≤ .0015) and 1-year OS rates were 51% and 39%, respectively.

Also in October 2015, the FDA approved the PD-1 checkpoint inhibitor pembrolizumab to treat patients with metastatic NSCLC whose tumors expressed the PD-L1 protein in the companion diagnostic. The approval was based on results of a phase I trial (KEYNOTE-001), in which various doses—2 or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks—were given across several cohorts of patients who underwent pretreatment or were treatment-naive. PD-L1 expression was evaluated using immunohistochemistry on fresh tissue specimens, and only patients with membranous staining greater than 1% were eligible for the study.

The FDA approved pembrolizumab based on a subgroup analysis of 61 patients whose tumor overexpressed PD-L1 on a companion diagnostic test called PD-L1 IHC 22C3 pharmDx (Dako). After treatment with pembrolizumab, tumor size decreased in 24 patients (41%), and the effect lasted up to 9.1 months. In the overall patient population, the ORR, PFS, and OS were 19.4%, 3.7 months, and 12 months, respectively. The PD-L1 expression rates were grouped according to 1% or lower, between 1% and 49%, and 50% or greater; 23% of patients had a high ORR and longer PFS and OS. The most common side effects were fatigue, pruritus, and decreased appetite.

A phase II/III study was conducted of pembrolizumab versus docetaxel for PD-L1—positive NSCLC after failure of platinum-based chemotherapy (KEYNOTE-010). This study compared pembrolizumab, 2 mg/kg intravenously every 3 weeks versus 10 mg/kg intravenously every 3 weeks versus docetaxel, 75 mg/m² intravenously every 3 weeks. The primary end points were PFS and OS, looking at the end points related to PD-L1 expression in the 50% or greater stratum and the 1% or greater population.

Among patients with PD-L1 expression of 50% or greater, OS for pembrolizumab at 2 mg/kg was 14.9 months (HR, 0.54; *P* = .0002) versus 17.3 months for pembrolizumab at 10 mg/kg (HR, 0.50; *P* < .0001) and 8.2 months for docetaxel. PFS was significantly longer with pembrolizumab at 2 mg/kg and pembrolizumab at 10 mg/kg than with docetaxel (5.0 and 5.2 vs 4.1 months, respectively; HR, 0.59; *P* < .0001). In patients with PD-L1 expression of 1% or greater, OS for pembrolizumab at 2 mg/kg was 10.4 months (HR, 0.71; *P* = .0008) versus 12.7 months (HR, 0.61; *P* < .0001) for pembrolizumab at 10 mg/kg and was at 8.5 months for docetaxel. PFS was 3.9, 4.0, and 4.0 months, respectively. Comparable efficacy was seen for pembrolizumab, 2 and 10 mg/kg intravenously every 3 weeks. The data also validated the PD-L1
Immunotherapy for Lung Cancer

expression in advanced NSCLC. The current approved dose of pembrolizumab is 2 mg/kg intravenously every 3 weeks.

Currently, only nivolumab and pembrolizumab are approved for the treatment of lung cancer in the second-line setting. However, studies are ongoing evaluating nivolumab in the first-line setting and in combination with other agents. CheckMate 012 is a multi-arm phase I trial evaluating nivolumab versus nivolumab plus ipilimumab in chemotherapy-naïve patients with lung cancer.

Other checkpoint inhibitors are being evaluated in the treatment of patients with lung cancer. Atezolizumab (MPDL3280A) is an antibody targeting PD-L1 rather than PD-1. A phase III study is underway to include the agent with combination chemotherapy in chemotherapy-naïve stage IV nonsquamous NSCLC. Another, similar study includes the addition of bevacizumab; other phase III studies are atezolizumab versus chemotherapy for patients with PD-L1–positive chemotherapy-naïve stage IV nonsquamous cell NSCLC and 2 other similar separate studies involving patients with squamous cell NSCLC; one study includes PD-L1–positive disease.

Another checkpoint inhibitor, durvalumab (MED14736), a PD-L1 antibody, is being evaluated in 3 phase III studies: (1) alone in patients with completely resected NSCLC, (2) alone in patients with locally advanced unresectable (stage III) NSCLC who have not experienced progression after chemoradiation therapy (PACIFIC), and (3) alone or with tremelimumab, a CTL-4 checkpoint inhibitor, versus standard of care therapy in patients with locally advanced or metastatic NSCLC who had received prior therapy and have no known EGFR and ALK mutations (ARTIC).

Several additional phase III studies are evaluating the 2 CTL-4 checkpoint inhibitors ipilimumab and tremelimumab:

- A phase III study of nivolumab versus nivolumab plus ipilimumab versus chemotherapy in patients with stage IV NSCLC (CheckMate 227)
- A phase III study of durvalumab with and without tremelimumab versus standard-of-care chemotherapy for patients with NSCLC (Mystic)
- A phase III trial of durvalumab plus tremelimumab versus standard-of-care chemotherapy for patients with NSCLC (NEPTUNE)

Other immunotherapies include the development of (1) monoclonal antibodies, (2) therapeutic vaccines, and (3) adoptive cell therapy.

Because serious immune-related adverse events are different from the toxicities associated with the administration of chemotherapy, physicians, nurses, and other health care providers must understand what the toxicities are and how to treat them.

These toxicities include issues in numerous systems. Adverse events in the endocrine system include thyroiditis, hypothyroidism, hyperthyroidism, hypophysitis, hypopituitarism, and adrenal insufficiency. In the pulmonary system, they can include pneumonitis and respiratory failure. In the gastrointestinal system, they include nausea, emesis, diarrhea, colitis, perforation, and pancreatitis. Neurologic adverse events include neuropathy, meningitis, and Guillain-Barré syndrome; ocular events include iritis, uveitis, and conjunctivitis; cardiac events include pericarditis; dermatologic events include mucositis, rash, and vitiligo; hepatic concerns include transaminitis; and renal toxicities include nephritis and renal insufficiency.

Significant progress has been made with the use of immunotherapy in the treatment of lung cancer. Much work is still needed to develop optimal doses and combinations for different stages of lung cancer. A reliable predictive biomarker of the therapy's effectiveness needs to be established. Is the PD-1 expression according to proportion score reliable? The various pharmaceutical companies that have one
of these checkpoint inhibitors and abnormalities of PD-L1 expression should work together to achieve this goal.

The cost of immunotherapy is high and the issue of cost-effectiveness must be addressed by all the parties affected—patients, health insurers, pharmaceutical companies, and government. Stay tuned. The future is now! It is important that we succeed for the improved health of patients with lung cancer.

References