

LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Selecting Patients for Immune Checkpoint Inhibition in Lung Cancer



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H&O Which patients are currently considered eligible for immune checkpoint inhibition in lung cancer?

EG The only US Food and Drug Administration (FDA)–approved indication for immune checkpoint inhibition in lung cancer is the use of nivolumab (Opdivo, Bristol-Myers Squibb) in previously treated, metastatic squamous non–small cell lung cancer (NSCLC).

H&O Could there be more FDA-approved indications in the near future?

EG Yes, there could be—this is a very rapidly moving field. Data presented at the most recent American Society of Clinical Oncology (ASCO) annual meeting showed that nivolumab also benefitted patients with metastatic nonsquamous NSCLC. In addition, the FDA has granted priority review to pembrolizumab (Keytruda, Merck) for use in NSCLC.

H&O Are checkpoint inhibitors being studied for use in nonmetastatic NSCLC?

EG Yes, several studies are underway or beginning to enroll patients that are looking at immune checkpoint inhibitors as adjuvant therapy in early-stage disease. In the international PACIFIC study, researchers are randomly assigning patients with locally advanced, unresectable NSCLC after chemoradiotherapy to receive either the experimental programmed cell death

ligand 1 (PD-L1) inhibitor MEDI4736 or a placebo (NCT02125461).

H&O What other patients are being looked at as potential candidates for treatment with immune checkpoint inhibitors?

EG Data recently have been presented on use in a number of different patient types. For example, Dr Evan Alley presented data at the American Association for Cancer Research (AACR) conference on the use of pembrolizumab as second-line treatment for patients with advanced mesothelioma that is positive for PD-L1. These data encompassed 25 patients with mesothelioma enrolled in the KEYNOTE-028 trial, which evaluated pembrolizumab as a treatment for several solid tumors. The researchers found that 76% of the patients had a partial or complete response, compared with a response rate of 10% for second-line chemotherapy in other studies. In addition, the FDA granted orphan drug designation to AstraZeneca in April for the experimental anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) monoclonal antibody tremelimumab as a treatment for mesothelioma.

We also saw 2 very interesting, high-profile studies at this year's ASCO meeting on the use of immune checkpoint inhibitors in SCLC. For the first study, which was presented by Dr Patrick Ott, the response rate to pembrolizumab was 35% among 20 patients with SCLC that was positive for PD-L1. For the second study, which was presented by Dr Scott Antonia, researchers evaluated nivolumab as a single agent or with ipilimumab;

tumor PD-L1 status was not a condition of enrollment. The overall response rate was approximately 15% with nivolumab alone vs approximately 30% with nivolumab plus ipilimumab.

H&O Could you talk about the data from the CheckMate trials?

EG These were the most important new data with respect to checkpoint inhibitors in lung cancer at this year's ASCO meeting, and both of those were called out as Highlights of the Day in lung cancer during the meeting. In the CheckMate 017 trial, which was presented by Dr David Spigel at the meeting and also published in the *New England Journal of Medicine* with Dr Julie Brahmer as the first author, 272 patients with squamous NSCLC that had progressed despite treatment with chemotherapy were randomly assigned to receive either docetaxel or nivolumab. The study found that median overall survival was significantly better in the nivolumab group than in the docetaxel group: 9.2 months vs 6.0 months. This finding led to early closure of the study.

In the CheckMate 057 study, nivolumab and docetaxel were compared in 582 patients with nonsquamous NSCLC that had progressed on platinum-based chemotherapy. This study also found that median overall survival was significantly better in the nivolumab group than in the docetaxel group: 12.2 months vs 9.4 months. One of the interesting findings from CheckMate 057 is that, based on looking at archival samples, the level of PD-L1 expression by the tumor was predictive of outcome. The overall survival curve was much better for patients in which at least 10% of the tumor cells were positive for PD-L1. Among patients who did not have staining in at least 10% of their cells, nivolumab did not offer any advantage over docetaxel in overall survival.

H&O How do doctors decide which immunotherapy agents to use in which patients?

EG Right now it is very easy, because there is just one approved indication—for nivolumab in squamous NSCLC after prior chemotherapy. The CheckMate 017 trial certainly supports the idea that nivolumab is the standard of care in patients with previously treated squamous NSCLC. The overall survival results shown by nivolumab in this setting are profound enough that without additional data, it is hard at this point to justify not using nivolumab as the standard second-line therapy in this setting. Another option would be the monoclonal antibody ramucirumab (Cyramza, Lilly) plus docetaxel, which is approved for use in both squamous and nonsquamous NSCLC.

There were also data presented by Dr Jean-Charles Soria at the most recent ASCO meeting looking at the tyrosine kinase inhibitor afatinib (Gilotrif, Boehringer Ingelheim) in advanced squamous cell carcinoma. In the LUX-Lung 8 trial, 795 patients with advanced squamous cell carcinoma who had received prior chemotherapy were randomly assigned to receive one of 2 epidermal growth factor receptor (EGFR)-directed agents: afatinib or erlotinib (Tarceva, Genentech/Astellas). Overall survival, progression-free survival, and disease control all were better with afatinib than with erlotinib.

Although the second-line results were clearly superior with afatinib compared with erlotinib, it is hard to recommend this agent over nivolumab based on available data outside of those rare squamous cell carcinoma patients who have an *EGFR* mutation and did not receive an EGFR inhibitor in the frontline setting.

H&O What is the role of biomarkers in predicting who will respond to immunotherapy?

EG There are no approved biomarkers for use at this time, although Merck has submitted for an approval for a diagnostic assay that measures PD-L1 expression. This assay was designed to be used as a companion to pembrolizumab. The assay is based in large part on the KEYNOTE-001 trial. This trial, which I presented at AACR meeting in April (it was simultaneously published in the *New England Journal of Medicine*), included 495 patients. We used a training/validation set approach. First we looked at 182 patients to determine what level of PD-L1 expression might be predictive of superior clinical outcome, and then we evaluated an additional 313 patients to determine the predictive ability of that biomarker. There were clear differences based on the level of PD-L1 expression, with the best results for objective response rate, progression-free survival, and overall survival in patients who had staining for PD-L1 in at least half of their tumor cells.

Other studies have looked at patient selection. Dr Roy Herbst and colleagues published a study in *Nature* that looked at the role of PD-L1 expression on immune cells in predicting response to the PD-L1 inhibitor atezolizumab. At this year's ASCO meeting, data from the POPLAR study demonstrated improved outcomes in those positive for their biomarker, which included both tumor PD-L1 staining as well as PD-L1 staining in the immune infiltrating cells.

There have been intriguing data from multiple groups looking at previously untreated patients. In these patients, it is very possible that those with high levels of staining for PD-L1 should receive a checkpoint inhibitor prior to receiving chemotherapy. That is still investigational, and

is the subject of multiple clinical trials from multiple different sponsors. The frontline setting, however, is a situation in which patient selection, such as with a biomarker, will be particularly important.

H&O What role does cost play in decisions about immunotherapy?

EG That is a very big issue. I think that when one looks at the results with nivolumab in squamous NSCLC, the cost—although high—can be justified. I also think that based on the data from this CheckMate 057, the cost of using this in patients with nonsquamous NSCLC who have high levels of staining for PD-L1 is quite reasonable. The question of what to use in patients with nonsquamous NSCLC who do not have a high level of staining for PD-L1 is quite difficult. As I mentioned earlier, it performed no better than docetaxel with regard to overall survival. On the other hand, the side effect profile is better.

As I stated in my Highlights of the Day talk at the ASCO meeting, if the patient were my own family member, I would prefer the use of nivolumab based on the better side effect profile. On the other hand, does it make sense for our tax dollars and Medicare payments to be going toward this agent for all patients with nonsquamous NSCLC? This is an issue that we as a society are going to have to grapple with. More and more immunotherapy drugs will be rolled out, presumably for use in a variety of cancers beside melanoma and squamous NSCLC, and they are very expensive agents.

H&O Is there anything else that you would like to add?

EG It is extraordinarily exciting to see how quickly these immunotherapy agents are becoming pillars in the management of lung cancer. It is going to be very interesting

to see what happens in the coming months as these drugs presumably become clinically available.

Although this is an exciting time for patients, it is important to remember that even with the spectacular responses we are seeing, the great majority of patients do not respond to these agents. We need to continue doing high-level research in order to move quickly to improve patient outcomes further.

Suggested Readings

Alley EW, Molife LR, Santoro A, et al. Clinical safety and efficacy of pembrolizumab (MK-3475) in patients with malignant pleural mesothelioma: preliminary results from KEYNOTE-028. Presented at: American Association for Cancer Research Annual Meeting; April 18-22, 2015; Philadelphia, PA. Abstract CT103.

Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer [published online May 31, 2015]. *N Engl J Med*. PMID:26028407.

Garon EB, Rizvi N, Hui R, et al. Efficacy of pembrolizumab (pembro; MK-3475) and validation of PD-L1 expression as a biomarker in patients (pts) with non-small cell lung cancer (NSCLC): findings from KEYNOTE-001. Presented at: American Association for Cancer Research Annual Meeting; April 18-22, 2015; Philadelphia, PA. Abstract 9109.

Garon EB, Rizvi NA, Hui R, et al; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028.

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515(7528):563-567.

Luis Paz-Ares, Leora Horn, Hossein Borghaei, et al. Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC) [ASCO abstract LBA109]. *J Clin Oncol*. 2015;33(suppl).

Ott PA, Fernandez ME, Hiret S, et al. Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): preliminary safety and efficacy results from KEYNOTE-028 [ASCO abstract 7502]. *J Clin Oncol*. 2015;33(suppl).

Antonia SJ, Bendell JC, Taylor MH, et al. Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032 [ASCO abstract 7503]. *J Clin Oncol*. 2015;33(suppl).

Soria JC, Felip E, Cobo M, et al. Afatinib (A) vs erlotinib (E) as second-line therapy of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following platinum-based chemotherapy: overall survival (OS) analysis from the global phase III trial LUX-Lung 8 (LL8) [ASCO abstract 8002]. *J Clin Oncol*. 2015;33(suppl).