Immunotherapeutic Approaches to the Treatment of Squamous Non-Small Cell Lung Cancer

Dates of Certification:
April 20, 2015- April 20, 2016

Medium: *Print with online posttest, evaluation, and request for credit*

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Disclosure: *No relevant financial relationships with commercial interests to disclose.*

The American Journal of Hematology/ Oncology Editorial Board

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Disclosure: *Grant/research support from Genentech/Roche, Pfizer, Puma Inc, and Novartis (clinical trial support contracted to the University of Southern California and MD Anderson Cancer Center); consultant for Eisai, Oncoplex Diagnostics, Merck, and Novartis.*

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Overview

This activity is designed to aid physicians in assessing new data in immunotherapy for lung cancer, including patient-specific treatment regimens and monitoring for adverse events during therapy, and applying these data to their practices.

Target Audience

This activity is directed toward medical oncologists who manage and treat patients with lung cancer. Surgical oncologists, radiation oncologists, pathologists, pulmonologists, fellows, nurses, nurse practitioners, physician assistants, and other healthcare providers interested in the treatment of lung cancer are also invited to participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

- Identify current treatment challenges in the treatment of squamous cell lung cancer.
- Describe the currently available immunotherapy options for the treatment of squamous cell lung cancer.
- List the most frequent adverse events associated with available immunotherapy agents for squamous cell lung cancer.

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Immunotherapeutic Approaches to the Treatment of Squamous Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death, accounting for about 27% of all cancer deaths each year.[1] A total of 221,200 new cases of all types of lung cancer and over 158,000 deaths are expected in 2015.[1]

Non-small cell lung cancer (NSCLC) makes up about 85% to 90% of lung cancers, with 3 main subtypes: squamous cell (epidermoid) carcinoma (25%-30% of cases), adenocarcinoma (40% of cases), and large cell (undifferentiated) carcinoma (10%-15% of cases).[1] The overall survival (OS) for patients with NSCLC is low, with a 5-year OS of only 4% to 6% in advanced stages of the disease.[2] Epidermal growth factor receptor (EGFR) overexpression is most commonly encountered with squamous (84%), large cell (68%), and adenocarcinoma (65%).[3] The increased vascular endothelial growth factor (VEGF) expression in squamous NSCLC can lead to resistance to anti-EGFR drugs (independent of EGFR signaling) and bevacizumab (**Table**). With a limited number of immunotherapy options for lung cancer to begin with, squamous NSCLC becomes even more challenging to treat.

Traditional chemotherapy agents for the treatment of lung cancer are associated with severe adverse effects (AEs) on the patient's immune system. Immunotherapeutic agents enhance the immune response to tumors with hopes of avoiding immunosuppressive AEs, as well as prolonging responses and improving survival compared with chemotherapeutic agents.[4,5] Immunotherapeutic agents for lung cancer fall into 4 main categories: monoclonal antibodies, checkpoint inhibitors, therapeutic vaccines, and adoptive T cell transfer (**Table**).[6] These agents treat lung cancer via passive immunotherapy (eg, cytokines or immunomodulating monoclonal antibodies) or active immunotherapy (eg, antitumor vaccines or cellular therapies).[7]

This article will focus on checkpoint inhibitors approved for use in advanced NSCLC.

Checkpoint Inhibitors

Patients with advanced, refractory squamous cell NSCLC have poor outcomes. With the scarcity of approved or efficacious treatments for refractory squamous NSCLC, up until recently, supportive care or clinical trials were the primary treatment options for patients with this disease.[8] Immune checkpoint inhibitors (including CTLA-4, PD-1, and PD-L1) have become the focus of research for NSCLC, particularly the squamous cell type.[9] Nivolumab, a PD-1 checkpoint inhibitor, was recently FDA-approved for the treatment of metastatic squamous NSCLC with progression on or after platinum-based chemotherapy.[10,11]

Nivolumab's approval followed results of a phase III trial (CheckMate-017), an open-label, randomized trial comparing nivolumab with docetaxel in 272 pretreated patients with advanced, squamous NSCLC. The trial excluded patients with active autoimmune disease or symptomatic interstitial lung disease, and all patients received ≥2 prior systemic treatments.[10] The study was stopped early once the primary endpoint of improved OS was reached.[11] The results of this trial showed that patients who received nivolumab for their squamous cell NSCLC lived 3.2 months longer (41% reduced risk of death), on average, than patients receiving docetaxel.

Checkpoint inhibitors are associated with immune-related toxicities not encountered with established chemotherapy treatments for lung cancer, including pneumonitis, colitis, hepatitis, thyroiditis, rashes, neuropathies, and other less-common immune-mediated toxicities. Many of the toxicities associated with these agents are low grade. However, for AEs such as pneumonitis, there is a potential for serious or fatal outcomes if not recognized promptly.[10,12] Nivolumab was discontinued in 27% of patients in the nivolumab arm of the CheckMate-017 trial due to AEs, and 29% of patients had a drug delay for an AE. Serious AEs occurred in 59% of patients receiving nivolumab. Serious AEs occurring in at least 2% of patients were: dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.[10]

Dr. Roy Herbst, Chief of Medical Oncology, Yale Cancer Center, New Haven, Connecticut, shares his clinical insight into the approval of nivolumab, and how it can change the landscape of squamous NSCLC treatment:

Moderator: What are the clinical implications of the data from the nivolumab trials for NSCLC?

Dr. Herbst: I think the data on nivolumab are quite impressive. With 40-plus percent improvement in survival in refractory squamous cell lung cancer, I think it's likely to become the standard of care in the second-line setting in squamous cell lung cancer. At this point, we've seen median improvement in survival of over 3 months, even without yet incorporating biomarker work, which is still ongoing. So I think it's going to change the way we treat squamous cell lung cancer.

Moderator: What can we take from any clinical experience with nivolumab in melanoma? How similar or different would your expectations be for a patient with lung cancer?

TABLE. Antibodies and Immunotherapeutic Agents Approved or in Phase III Trials for Lung Cancer[6,13]

Agent Name	Category	Target	Approval Status/Indication(s) FDA-Approved: A Clinical Trial: C
Bevacizumab	Monoclonal antibody	VEGF	A: first-line advanced/metastatic nonsquamous NSCLC
Bavituximab	Monoclonal antibody	Phosphatidylserine	C: advanced/metastatic nonsquamous NSCLC
Cetuximab	Monoclonal antibody	EGFR	C: advanced NSCLC
Patritumab	Monoclonal antibody	HER3	C: recurrent advanced/metastatic NSCLC
Rilotumumab	Monoclonal antibody	HGF	C: second-line therapy for advanced/metastatic squamous NSCLC
Ipilimumab	Checkpoint inhibitor	CTLA-4	C: metastatic squamous NSCLC; extensive-stage SCLC
Nivolumab	Checkpoint inhibitor	PD-1	A: squamous NSCLC that has failed chemotherapy C: advanced/metastatic NSCLC
Pembrolizumab	Checkpoint inhibitor	PD-1	C: PD-L1$^+$ NSCLC
MEDI4736	Checkpoint inhibitor	PD-L1	C: NSCLC
GV1001	Therapeutic vaccine		C: inoperable stage III NSCLC
INGN	Therapeutic vaccine		C: extensive-stage SCLC
Tergenpumatucel-L	Therapeutic vaccine		C: second-line advanced/metastatic NSCLC
TG4010	Therapeutic vaccine		C: first-line metastatic MUC1$^+$ NSCLC

CTLA-4 indicates cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; HGF, hepatocyte growth factor; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1; SCLC, small-cell lung cancer; VEGF, vascular endothelial growth factor.

Dr. Herbst: Well, I think we're seeing equally strong data in melanoma, though given the unmet need and the large number of patients in lung cancer, this will benefit an even larger number of patients. I believe the drug has shown itself to be well tolerated in patients with lung cancer; there were some early issues with severe pneumonitis have been dealt with via early treatment with steroids and other initiatives. So I think it's really a paradigm shift now for lung cancer. Immunotherapy is here to stay in lung cancer treatment. Who would have thought this 10 years ago? It is great for patients!

Moderator: When evaluating an individual patient, how should the clinical team define response—is the evaluation of response and progression different than other types of systemic therapy for lung cancer?

Dr. Herbst: Only a little different. In immunotherapy, you will usually allow patients who are clinically stable to progress through one assessment because sometimes the tumor grows before it shrinks (we call this pseudo progression). That only occurs about 10% to 15% of the time, but that's one thing that's a little bit different, and you might wait a little bit longer to see a benefit. But still, if someone is progressing with symptoms, they have to come off the therapy.

Moderator: Could you go into a little more detail about that? Would you let it go for any case or only if the patient was asymptomatic?

Dr. Herbst: Only if a patient had few, if any, symptoms of clinical significance. One also has to carefully evaluate the presence of any immune-related toxcities.

Moderator: How does nivolumab differ from other checkpoint inhibitors, such as anti-CTLA-4 agents and/or alternative anti-PD-1/PD-L1 agents?

Dr. Herbst: Nivolumab is a PD-1 inhibitor. There are a couple of other drugs that are similar but slightly different. There's another PD-1 inhibitor that is still in clinical trials. There are also several PD-L1 agents, too. PD-L1 is thought to be theoretically, less toxic, as it targets PD-L1 only, leaving PD-L2 intact to interact with PD-1, which is thought to be involved in normal inflammatory responses. It's still too early to say that PD-L1 is less toxic than PD-1 inhibitors, but that's a different approach. Most feel that the agents are all quite similar in efficacy. Some of the biomarker work and selection criteria might separate them, but there aren't any data for that yet. Perhaps the data will be coming at future meetings.

Moderator: Do the responses and progressions of those agents seem very similar to ipilimumab?

Dr. Herbst: Not really. Ipilimumab never showed that much single-activity in lung cancer, so that's one thing to separate the 2 drugs. Ipilimumab works more in T-cell early development, the priming of T-cells, that is, the T-cells as they're developing in the lymph node, whereas PD-1 and PD-L1 checkpoint inhibition function more in the tumor microenvironment. They specifically work at the site of the tumor cells, in the primary or metastatic site. I think the combination of the two offers some promise, though we will need to dose carefully and monitor for combined immunotoxicity (increased autoimmunity).

Moderator: Are there any data you can give us about patient selection for nivolumab? Are there any criteria you use to identify a patient who might be more appropriate, or less appropriate, for this?
Dr. Herbst: This is the million dollar question! This is an amazing advance in patient care, but we're not where we need to be yet. Still only 15% or so of patients respond, and the median survival is still only 9 months, so there's still a lot of room to go. So many patients still don't benefit. Some patients don't benefit and have some side effects, so that's certainly even worse than nothing at all. Some patients benefit and then they become refractory, so I feel there is room to raise the bar further. Clinical trials with biomarker endpoints will help this process.

Moderator: Are there any patient or tumor characteristics that make nivolumab an agent of choice?
Dr. Herbst: No. I think there are some data that are emerging that the number of mutations in these patients' tumors makes a difference, and we're more likely to see activity in smokers versus nonsmokers—but it is still very early.

Moderator: What are the clinical data for other immunotherapeutics in lung cancer? Is nivolumab likely the beginning of the trend?
Dr. Herbst: All of the agents have about a 15% to 20% response rate, similar to nivolumab in the unselected population. I think they'll generate similar data, some a little bit better, and some a little bit worse. But I think the whole class is looking like it's going to be a winner. Biomarker discovery and their use could differentiate among the agents.

Moderator: Is there anything that a clinician who doesn't have experience with nivolumab might need to know in order to successfully adopt this drug into their practice?
Dr. Herbst: Primarily, it's to understand that the toxicities are a little bit different from standard chemotherapy. You don't see neurotoxicity and neutropenia with nivolumab, but we're dealing with more unique inflammatory situations—pneumonitis, hepatitis, gastritis, colitis, dermatologic rashes, and endocrine issues, such as thyroid, pituitary, adrenal. For the most part, if recognized early, they're all manageable and treatable, but they're rather new to lung cancer.

Moderator: What should clinicians tell their patients to be aware of when taking nivolumab, and how can they successfully monitor their patients for toxicities?
Dr. Herbst: Patients should know to report any possible side effects with nivolumab, as with any drug. Clinicians should check thyroid hormone levels and adrenal function and think about consulting either a pulmonologist or an endocrinologist for advice and management.

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