Checkpoint Inhibitors: Where Have We Been and Where Are We Going in Advanced NSCLC?

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Overview

This activity is designed to inform physicians about the current availability and use of checkpoint inhibitors in advanced non–small-cell lung cancer (NSCLC).

Target Audience

This activity is directed towards medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with advanced non–small-cell lung cancer. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other health care providers are also invited to participate.

Learning Objectives

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

- Describe the biologic function of the PD-1/PD-L1 pathway and the rationale behind targeted inhibition in NSCLC
- Explain the development history leading to the approval of immune checkpoint inhibitors in NSCLC
- Discuss emerging treatment strategies and new indications in FDA-approved PD-1 or PD-L1 inhibitors

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Introduction

Lung cancer is the second most common cancer diagnosed in men and women in the United States, behind prostate cancer and breast cancer, respectively, and it is the most common cause of cancer-related mortality.[1] While the incidence rate has been decreasing and overall survival (OS) rate increasing over the last 2 decades, there are still more than 222,000 new cases of lung cancer expected in the United States in 2017, accounting for more than 13% of all new cancer cases.[2] Moreover, upwards of 155,000 people are expected to die from this disease, accounting for 25% of all cancer-related deaths in 2017. Overall, an estimated 525,000 people are living with lung cancer in the United States as of 2014; of those, 420,000 are living with NSCLC.[2] The incidence of lung cancer is highest in people aged 65 to 74 years, with a median age at diagnosis of 70, but it is observed commonly in people aged 45 to 84 years or older. In the past 40 years, the 5-year survival rate has nearly doubled; as of 2009, it was nearly 20%.[2]

The 2 main types of lung cancer are small cell lung cancer (SCLC), which accounts for approximately 10% to 15% of lung cancers, and non–small cell lung cancer (NSCLC), which accounts for the vast majority of lung cancer cases, between 80% and 85%.[1] NSCLC is further subcategorized into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, depending on the origin of the cancer cell. All histologic subtypes are seen in current and former smokers. However, small cell and squamous cell histology are more strongly associated with smoking, and adenocarcinoma is the predominant histology seen in nonsmokers. The distinctions between different histologic subtypes are critical in making treatment decisions, especially with respect to molecular testing and selecting the optimal platinum doublet therapy for patients without driver mutations. With the advent of immune checkpoint inhibitors in the treatment of all histologic subtypes, and the approval for their use in a select cohort of patients with NSCLC for first-line therapy, and in all patients as second-line therapy, immunotherapy has become increasingly prominent in the armamentarium of treatment options for patients with metastatic disease.

PD-1/PD-L1 Checkpoint Inhibitors

Checkpoint inhibitors, specifically of programmed cell death protein 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1), have been a focus of immunotherapy strategies in lung cancer. The PD-1/PD-L1 axis works primarily to mitigate the action of effector T cells as part of the body's defense against itself. The transmembrane protein and its ligand function to limit autoimmune responses of T cells, preventing potentially destructive self cannibalism.[3]

PD-1, a type 1 transmembrane protein, is a member of the immunoglobulin superfamily.[4] It is composed of an extracellular N-terminal immunoglobulin-variable-like domain, a transmembrane domain, and a cytoplasmic tail that contains an immunoreceptor tyrosine-based inhibitory motif as well as an immunoreceptor tyrosine-based switch motif.[5,6] Numerous splice variants of PD-1 have been identified, but have not been thoroughly studied.[3] In healthy individuals, PD-1 is minimally expressed in cells of the immune system including T cells, B cells, natural killer (NK) cells, NK T cells, and macrophages.[3,7] In specific tissues of individuals with an infection or inflammatory event, PD-1 is activated to limit immune-mediated tissue destruction.[3]

PD-1 binds 2 specific and distinct ligands: PD-L1 and PD-L2. While PD-L2 expression is limited to cells of the immune system, PD-L1 is constitutively expressed on hematopoietic and nonhematopoietic cells throughout the body.[8] PD-L1 is further induced by inflammatory cell signals, including interferons and TNF-α, regardless of cell type. PD-1/PD-L1 interactions promote downstream T-cell inhibition and T-cell apoptosis.[3] PD-L1 is also able to bind B7-1 and inhibit T cells independently of its interactions with PD-1, making the PD-1/PD-L1 axis a more complicated inhibitory receptor with a coinhibitory-ligand system.[3,9]

PD-L1 is primarily expressed on antigen-presenting cells and on tumor cells, including lung cancer.[3] Paired with the expression of PD-1 on tumor-invading lymphocytes, tumor cells are able to utilize the feedback inhibitory loop of the PD-1/PD-L1 axis as similarly observed in inflamed tissue. In addition, multiple oncogenic signaling pathways exist to increase the expression of PD-L1 on malignant cells following a host immune response.[3]

PD-1/PD-L1 Blocking Antibodies

The blocking of either PD-1 on immune cells or PD-L1 on cancer cells has the potential to restore normal host immune response and allow the body to fight the cancer itself. Immunotherapeutic options have become standard of care in the treatment of NSCLC with the approval of PD-1–targeted nivolumab in March 2015,[10] pembrolizumab in October 2015,[11] and PD-L1–targeted atezolizumab in October 2016.[12]

Nivolumab

Nivolumab is a human immunoglobulin G4 monoclonal antibody that targets and binds the PD-1 receptor on activated T cells; it completely blocks the interaction of the PD-1 receptor with both its ligands.[13] Nivolumab has a high affinity and specificity for PD-1 and is able to maintain a plateau of 70% PD-1 receptor occupancy, while serum nivolumab concentrations are nearly undetectable.[13,14]

The antitumor activity of nivolumab was first established in a phase I trial including 76 patients with advanced NSCLC; the response rate was 33% in squamous and 22% in nonsquamous NSCLC.[15] The randomized phase III CheckMate trials later led to the approval of nivolumab in advanced NSCLC following prior chemotherapy with a platinum doublet.

The phase III CheckMate 017 trial assessed nivolumab versus docetaxel in advanced squamous cell NSCLC.[16] A total of 272 patients were randomly assigned to the 2 treatment arms. Nivolumab was associated with a median OS of 9.2 months (95% CI, 7.3-13.3 months) compared with 6.0 months (95% CI, 5.1-7.3 months) with docetaxel,

resulting in a 41% lower risk of death while on nivolumab (HR, 0.59; 95% CI, 0.44-0.79; *P* <.001). At 1 year, the OS rate was 42% versus 24% for nivolumab and docetaxel, respectively. In this trial, expression of the PD-L1 was not a predictive factor of benefit from treatment.[16]

Simultaneously, the phase III CheckMate 057 trial assessed nivolumab versus docetaxel in patients with advanced nonsquamous NSCLC.[17] A total of 582 patients were assigned to receive either nivolumab or docetaxel. Nivolumab was associated with a median OS of 12.2 months (95% CI, 9.7-15.0 months) compared with 9.4 months (95% CI, 8.1-10.7 months) for docetaxel. OS at 1 year was 51% versus 39% for nivolumab and docetaxel, respectively. Patients with tumors that were PD-L1–positive had a higher response rate and improved OS with nivolumab compared with docetaxel, while those patients with tumors that were PD-L1–negative had a similar benefit.[17]

Since nivolumab's approval, CheckMate 017 and 057 have announced 2-year survival rates. For patients with nonsquamous NSCLC nivolumab was associated with a 2-year OS of 23%, compared with 8% with docetaxel. For patients with squamous NSCLC, nivolumab was associated with a 2-year OS of 29%, compared with 16% for docetaxel.[18]

Nivolumab has also been investigated as a first-line treatment option for patients with PD-L1–positive (1%) advanced NSCLC in the phase III CheckMate 026 trial. Regarding PD-L1 status, PD-L1–positive patients had expression on at least 1% of their tumor cells (TC) or tumor-infiltrating immune cells (IC). PD-L1–negative patients had >1% expression on their TC and IC. This trial did not meet its primary endpoint and nivolumab has not been approved for this indication.[19] Nivolumab has also been approved for use in melanoma, renal cell carcinoma, Hodgkin lymphoma, and head and neck cancer.[20]

Atezolizumab

Atezolizumab is a human immunoglobulin G1 monoclonal antibody that targets PD-L1 and has been shown to be effective in reinitiating an antitumor response. Atezolizumab was approved for use in NSCLC in October 2016, based on results from the OAK and POPLAR trials.[21]

The phase II POPLAR trial compared atezolizumab with docetaxel in patients with NSCLC who had progressed after receiving platinum-based chemotherapy.[22] A total of 287 patients were randomly assigned to the 2 treatment arms. Atezolizumab was associated with an improved OS of 12.6 months (95% CI, 9.7-16.4 months) compared with an OS of 9.7 months (8.6-12.0) with docetaxel. The benefit with atezolizumab was higher in patients with tumors that were PD-L1 positive, but was seen regardless of PD-L1 expression.[22]

Following the results of the POPLAR trial, 1225 patients were randomly assigned to receive either atezolizumab or docetaxel in the phase III OAK trial.[23] Patients receiving atezolizumab received 1200 mg every 3 weeks. OS for patients receiving atezolizumab was 13.8 months (95% CI, 11.8-15.7 months). OS for patients receiving docetaxel was 9.6 months (8.6-11.2 months). Similar to nivolumab, a more robust response was seen with atezolizumab in patients with tumors that were PD-L1 positive, a benefit was seen regardless of PD-L1 expression.[23] Atezolizumab has also been approved for use in urothelial carcinoma and advanced bladder cancer.[24]

Atezolizumab also showed clinical efficacy in chemotherapy-naïve patients with NSCLC in the phase II FIR trial,[25] and an ongoing phase III trial is comparing atezolizumab with platinum-based chemotherapy in patients with tumors that are PD-L1 positive. Also, multiple phase III trials are comparing platinum-based chemotherapy with or without atezolizumab in patients with treatment-naïve NSCLC with advanced stage disease.

Pembrolizumab

Like nivolumab, pembrolizumab is a highly selective immunoglobulin G4 monoclonal antibody that inhibits PD-1.

The phase I KEYNOTE-001 trial investigated pembrolizumab at multiple doses across multiple tumor types, including 495 patients with advanced NSCLC.[26] The overall response rate (ORR) was 19.4% across all NSCLC cohorts and correlated with PD-L1 expression levels. Dose and schedule did not dramatically affect ORR. Median duration of response was 12.5 months across all cohorts, but was lower (10.4 months) in previously treated patients and higher (23.3 months) in treatment-naïve patients. Current or former smokers had an ORR more than twice the rate of nonsmokers—a trend observed in nivolumab treatment as well.[26,27]

Pembrolizumab has also been approved for use in patients with advanced melanoma, head and neck cancer, Hodgkin lymphoma, and urothelial cancer. In October 2016, pembrolizumab was approved in the first-line setting, based on results from the KEYNOTE-024 trial.[28] In that study, patients received either pembrolizumab or physicians' choice of platinum-based chemotherapy. Median progression-free survival (PFS) was 10.3 months in the pembrolizumab arm compared with 6.0 months for chemotherapy; 6-month OS rates were 80.2% and 72.4%, respectively.[29] In May 2017, pembrolizumab was also approved as a first-line combination therapy for patients with nonsquamous NSCLC irrespective of PD-L1 expression.[30] This approval was based on results from the KEYNOTE-021 trial, cohort G1, in which pembrolizumab plus chemotherapy was associated with an ORR of 55% compared with 29% for chemotherapy alone; median PFS was 13.0 months for patients receiving pembrolizumab and 8.9 months for patients receiving chemotherapy alone.[31]

Durvalumab

Durvalumab, currently under investigation, is an immunoglobulin G1 monoclonal antibody that targets PD-L1. The phase II ATLANTIC trial demonstrated durvalumab's clinical benefit in patients with advanced or metastatic NSCLC. ORR increased with PD-L1 expression level.[32] Following these results, the phase III PACIFIC trial is now investigating durvalumab in patients with unresectable NSCLC who have not progressed following chemotherapy. In May 2017, it was announced that the trial reached its primary endpoint of improvement in PFS.[33] These data have not yet been presented. Durvalumab is also

being evaluated with or without tremelimumab versus platinum-based chemotherapy in patients with NSCLC in the phase III MYSTIC trial (NCT02453282)[34] and as a single-agent in the second- and third-line settings in advanced NSCLC in the phase II Abound2L+ trial (NCT02250326).[35] Both of these studies have completed enrollment and are awaiting follow-up.

The Future of Immunotherapy in NSCLC

The currently approved checkpoint inhibitors in NSCLC are nivolumab and pembrolizumab for PD-1 and atezolizumab for PD-L1. Investigations continue into additional agents, including durvalumab and avelumab. Other indications and combinations for these drugs are also being investigated, including in the first-line setting. Combinations with platinum-based chemotherapy, and combinations with ipilimumab—a checkpoint inhibitor of CLTA-4, a type 1 immunoglobulin protein that primarily functions to limit T cell activation and clonal expansion—are also being investigated. Leora Horn, MD, MSc, discussed the past and future of checkpoint inhibitor treatment in NSCLC.

Leora Horn, MD, MSc, is associate professor of medicine in hematology and oncology, and Ingram Associate Professor of Cancer Research, at the Vanderbilt Ingram Cancer Center, where she is also the clinical director of the Thoracic Oncology Research Program. She is the co-leader of the Schaffner Society and assistant vice chairman for faculty development at Vanderbilt University Medical Center, Nashville, TN.

Can you speak briefly about the mechanism of PD-1 and PD-L1 pathways?

PD-1 is expressed on T cells, and PD-L1 is expressed on tumor cells as well as on other cells in the body. In their normal interaction, they bind together to dampen an immune response. It is actually a negative regulator, acting so that if you get exposed to a virus or bacteria and your body is mounting an immune response, the immune response does not get out of control. PD-1 and PD-L1 bind together to act as a negative regulator.

It Is thought that by exploiting this negative interaction, you can actually make the body aware of cancer cells present within the body and make your own immune system fight against the cancer. The new agents, those that are currently in clinical development or are FDA-approved, block this negative interaction so that the immune system becomes activated and, as a result, can cause death of cancer cells and tumor shrinkage.

Can you discuss more specifically the roles of PD-1 and PD-L1 in NSCLC? What role do targeted therapies play in treating NSCLC?

The initial trials with both the anti–PD-1 and then anti–PD-L1 agents were conducted in patients both as first-line and second-line or beyond. When drugs are traditionally developed, we are often evaluating them first in patients who have exhausted all current standard therapies. Nivolumab was the first immune checkpoint inhibitor in the lung cancer space to enter clinical trials, and it was evaluated in patients who had progressed on multiple different prior lines of therapy regardless of PD-L1 expression status.

What we are still learning is how dynamic PD-L1 is as a biomarker. While there is fairly good concordance, it appears there is about 20% to 30% discrepancy between a fresh and an archival tissue sample. Many of the patients enrolled on the nivolumab study had PD-L1 expression assessed on archival tissue samples. And if you were using an older sample—such as an archival specimen—and treating a patient second- or third-line, there may have been a discrepancy calling a patient PD-L1–positive or PD-L1–negative, based on some of the data that have emerged.

Now what we do not know is this: is that discrepancy because there is a change in PD-L1 expression as a result of therapy, or are those expression data different because of where the patient was biopsied? For example, if you biopsy the primary site versus the metastatic site, we do not really know how good the concordance is between the 2. We also know tumors are heterogenous and we may see a positive result just because of where in the mass the tumor was sampled.

A lot of research is also being done in lung cancer patients in terms of targeted therapies and molecular testing. Generally, if a patient has a mutation, they are only going to have a single mutation. So, for example, if a patient is *EGFR*-mutation positive or has an *ALK* fusion, that is most likely to be the mechanism driving the growth of their tumor. PD-L1 is not necessarily a mutation, although it is something that we are testing for. For example, a patient can be EGFR-positive or *KRAS*-positive and PD-L1–positive.

Moving on to some of the checkpoint inhibitors and landmark trials that resulted in the original approvals, can we talk about the nivolumab data and its original indications? There was a 2-year follow-up of CheckMate 017 and CheckMate 057 presented at ESMO last year; can you comment on those findings as well, and the impact it may have on your use of nivolumab?

Both CheckMates 017 and 057, and for completeness 063, were the trials that led to the approval of nivolumab. CheckMate 063 was actually a third-line study for patients who had progressed following at least 2 lines of chemotherapy; it was not a randomized trial. CheckMate 017 and 057 had identical trial designs. Both were randomized phase III trials comparing nivolumab every 2 weeks until progression versus docetaxel in patients who had progressed on platinum-based therapy. The reason that nivolumab, unlike atezolizumab and pembrolizumab, was evaluated in 2 separate trials based on histology was due to data gleaned from a phase I trial, where it was thought that there was a difference in the benefit in squamous versus nonsquamous NSCLC.

Both studies met their primary endpoint with a significant improvement in OS for nivolumab compared with chemotherapy. Both had about a 3-month improvement in OS. There have been some discussions that the docetaxel arm in the CheckMate 017 underperformed, where the median OS of docetaxel was only around 6

months. Nevertheless, both trials led to approval for nivolumab in the second-line setting.

We had seen updated data presented twice. We saw data on 18-month survival at ESMO 2015, and then we saw data on 2-year survival at ASCO 2016, showing that this benefit is sustained, with a continued benefit for patients treated with nivolumab and a clear separation of the survival curves.

Now what is interesting about these trials is that the PD-L1 appears to have a differential role in squamous versus nonsquamous. What I mean by that is that in the CheckMate 017 trial, patients with squamous cell histology appeared to have a benefit with nivolumab regardless of level of PD-L1 expression. There was no differential if they were positive or nonexpressive, and there was no differential at 1%, 5%, or 10%.

Compare that with the CheckMate 057 trial, where there was a difference. Patients who were PD-L1–positive appeared to have a greater benefit with nivolumab, with a higher response rate and OS, whereas the benefit in OS was not seen for patients who were considered PD-L1–negative. That is not to say that nivolumab didn't work in the patients who were PD-L1–negative—it just was not better than chemotherapy. It was actually equal in terms of OS.

Now when you look at the difference in response to nivolumab between patients with tumors that were PD-L1 1%, 5%, and 10%, you do not really see a significant difference in terms of response rate. Responses range from 30% to 38% as the PD-L1 percentage increases. You also do not see a large difference in terms of OS, where it was between 17 and 19 months for patients treated with nivolumab. This was an improvement compared with OS of about 10 months with docetaxel in the PD-L1 expressers. Given that the trial was positive overall, nivolumab, similar to atezolizumab, is currently approved in the second-line setting regardless of PD-L1 expression.

CheckMate 026 was the first-line trial that ran at the same time as KEYNOTE-024. It compared nivolumab with platinum-based chemotherapy as first-line therapy for NSCLC patients with tumors that were *EGFR* and *ALK* wild type. Based on the data from CheckMate 057, the primary endpoint initially looked at patients with tumors that were greater than 5% PD-L1 positive. This trial did not meet its primary endpoint; there was no significant improvement in PFS for nivolumab compared with platinum-based chemotherapy. The response rates were low, around 28% for patients treated with nivolumab. We also saw that even in the patients who were strongly PD-L1–positive (>50%), if you used the pembrolizumab endpoint, then there was not a survival benefit.

There has been a lot of hemming and hawing about this subject. Even some patients who are on nivolumab at my institution, and doing well, have said, "Well, I want to switch over to pembrolizumab because it is a better drug," even though nivolumab is working. I think it was just an unlucky trial. There was some thought that maybe some of the nivolumab patients in the trial were sicker; there were maybe more patients with liver metastases in the nivolumab arm, more females in the chemotherapy arm, and more patients who were strongly PD-L1 positive in the chemotherapy arm. Regardless, it was a negative study and nivolumab remains an option only as a second-line therapy.

Atezolizumab was approved last year for the treatment of patients with metastatic NSCLC following progression from platinum-based chemotherapy based on results from the OAK and POPLAR clinical trials. Can you comment on these trials and how the approval of atezolizumab may be practice changing?

Atezolizumab was the third immune checkpoint inhibitor to receive approval for patients in NSCLC. We did see some indication from the phase I study that atezolizumab was an effective treatment in patients with NSCLC, particularly in patients with tumors that were PD-L1–positive. The first randomized study investigating atezolizumab was a small phase II trial, the POPLAR trial, a second-line trial that randomized patients who had progressed on platinum-based chemotherapy. If patients were *EGFR*- or *ALK*-positive, they also had to have progressed on a prior EGFR or ALK inhibitor. Patients were randomized to the flat dose of atezolizumab or docetaxel. The trial did show a significant improvement in OS by about 3 months for patients treated with atezolizumab compared with docetaxel.

This trial also looked at differences in benefit based on level of PD-L1 expression. Atezolizumab is being developed slightly differently than some of the other checkpoint inhibitors, in that we looked at not only PD-L1 expression within the tumor cells, but also at the immune infiltrate. The study also demonstrated that in patients with higher PD-L1 expression, there was an even greater benefit in terms of OS compared with patients who had lower PD-L1 expression or were PD-L1–negative.

The approval of atezolizumab did not come from the POPLAR trial, but from the phase III OAK trial. The OAK trial, again, randomized patients with similar criteria. They had to have progressed on a platinum-based chemotherapy regimen. If they were *EGFR*- or *ALK*-positive they had to have progressed on an EGFR or ALK inhibitor. And this trial randomized patients regardless of PD-L1 expression to atezolizumab or docetaxel. The primary endpoint of this study, again, was OS.

The OAK trial met its primary endpoint with a significant improvement in OS with patients treated with atezolizumab compared with docetaxel; the improvement was about 4 months. You do not often get a phase III trial looking better than the phase II, but the OS was 13.8 months for patients treated with atezolizumab and about 9.6 months for patients treated with docetaxel. This trial also looked at survival based on PD-L1 expression level and again found that in the patients who were PD-L1–positive, be it tumor-infiltrating immune cells (IC) 1, 2, or 3, that the stronger PD-L1–positive the patients were, the greater benefit they seemed to derive.

The OAK trial also showed that in patients whose tumors were considered to be PD-L1–negative, that there was an OS benefit with atezolizumab. This was not seen in the CheckMate 057. As a result of this trial, atezolizumab received FDA approval in the second-line setting for patients who have progressed on platinum-based chemotherapy regardless of a PD-L1 expression.

One thing to keep in mind when you are looking at the data from these different studies with atezolizumab, nivolumab, and pembrolizumab, is that the FDA Blueprint Project compared the PD-L1 expression with the different antibodies: SP142 with atezolizumab, 28-8 with nivolumab, and 22C3 with pembrolizumab. It found that there was fairly good concordance between the assays used to measure PD-L1 expression for therapy with nivolumab, pembrolizumab, and durvalumab, but found that the 1 outlier was the SP142 assay, which was used to assess PD-L1 expression for treatment with atezolizumab. This assay did not appear to be as sensitive. What that means is that in this trial, where we found that in patients who are PD-L1–negative, there was an OS benefit with atezolizumab compared with docetaxel, that might have been actually underreporting. And some of those patients who were called PD-L1–negative may actually have been PD-L1–positive, if the tumor had been measured with a different assay.

Nevertheless, atezolizumab at this time is FDA approved in the second-line setting for patients who progressed on chemotherapy.

In the frontline setting, atezolizumab is also being evaluated as a first-line therapy in the phase II FIR and BIRCH trials and the phase III IMpower trials. Can you provide us with a brief overview of the findings from these studies and what to expect in the future?

Yes. The FIR trial had multiple arms: there were patients who had prior treatment, patients who were previously untreated, and patients with brain metastases. This measured PD-L1 expression with the SP142 assays. The FIR trial did show us a nice response rate to atezolizumab and a fairly good PFS; OS data in this trial are still immature and pending.

BIRCH had 3 cohorts: first-line, second-line, and third-line. Patients who were enrolled were PD-L1–positive either on the immune infiltrate IC 2/3 or tumor cell (TC) 2/3. The assay used was SP142. Patients with brain or central nervous system metastases were excluded. The response rate was similar regardless of line of therapy, higher in the TC/IC groups compared with TC 2/3 or IC 2/3. The 6-month PFS and OS rates were higher in the untreated/first-line cohort.

Based on these data, the IMpower 110 trial was launched comparing atezolizumab as a single agent with platinum-based chemotherapy. The trial initially was restricted to TC/IC 3 but amended to included 1/2/3 patients. Enrollment in this trial is ongoing. The trial is excluding patients who are *EGFR*- and *ALK*-positive, partly because—from what we have seen from some of the phase III trials in the second-line setting, and other data—these agents do not appear to be as effective as targeted therapies in those specific patient populations.

In addition to the first-line single-agent trial, several IMpower trials are comparing chemotherapy to chemotherapy plus or minus atezolizumab or chemotherapy plus bevacizumab to chemotherapy plus or minus bevacizumab and atezolizumab in the first-line setting. Those studies are not restricting patients by PD-L1 expression but, again, they are excluding *EGFR*- and *ALK*-positive NSCLC patients. These trials are the IMpower 130, 131, 132, and 150 trials.

We are likely going to see a readout of many of these studies in the next 1 to 2 years. The primary endpoint of the majority of these studies is PFS, and the key secondary endpoint is OS. We've seen some long-term data presented at AACR earlier this year that looked at the 5-year OS of patients enrolled in the phase I study with nivolumab. And in that study we saw that the OS at 5 years was around 16%. That is pretty remarkable, when you consider that about a decade ago, the median OS for all of lung cancer patients—stage I through IV—was 16%. Now, we are saying the 5-year survival for stage IV disease alone is 16%, so we are definitely making progress.

With these trials we may see that PFS is better, but we do not yet know if OS is going to be improved. For example, if you look in the EGFR space, we know that with the EGFR TKIs PFS is improved if you get a first-line EGFR TKI, but OS is not improved, suggesting that it is just important that a patient gets a TKI at some point during their treatment course. We do not yet know if that is the same with the immune checkpoint inhibitors. We are seeing PFS is improved, but we do not know if OS is going to be improved if you use those agents first-line versus second-line.

Can we discuss pembrolizumab and durvalumab? Pembrolizumab has been approved based on the KEYNOTE trials. Can you comment on your usage of pembrolizumab and sequencing strategies you may employ?

Pembrolizumab initially got approval in the second-line setting for patients who were strongly PD-L1–positive (>50%). That was based on data from KEYNOTE-001 that showed a high response rate as well as durable response. There are 2 additional trials with pembrolizumab that have been reported to date, KEYNOTE-010 and KEYNOTE-024.

KEYNOTE-010 was a second-line registration trial. It was different from nivolumab and atezolizumab; this trial required patients to have tumors that were at least 1% PD-L1–positive. It randomized patients to pembrolizumab or docetaxel. Interestingly, the PFS was not dramatically different between the 2 arms. However, the OS was clearly better with pembrolizumab. Based on these data, pembrolizumab has been approved in the second-line setting for patients with tumors that have 1% or greater PD-L1 expression.

For a period of time, many providers were not necessarily testing for PD-L1 in the second-line, because nivolumab was available regardless of level of PD-L1 expression. In lung cancer, even *EGFR* and *ALK* testing are not performed in about 30% to 40% of patients in the United States. So adding another test like PD-L1 was unlikely. However, after ESMO 2016 we saw KEYNOTE-024, which looked at patients who were strongly PD-L1–positive (≥50%). The results showed a significant improvement in response rate and PFS, and a trend toward increased OS for patients treated with first-line pembrolizumab compared with platinum-based chemotherapy. Again, patients in this first-line trial had to be *EGFR*- and *ALK*-negative.

Based on these data, PD-L1 testing has become standard of care in the first-line setting. Pembrolizumab as a single agent, in my opinion, should be the preferred agent of choice in patients with tumors that are PD-L1 ≥50%. There was also a phase II trial that looked at combi-

nation carboplatin, pemetrexed, and pembrolizumab compared with chemotherapy alone that demonstrated an improvement in response rate and PFS regardless of PD-L1 expression but no improvement in OS. This was a small trial with response rate as the primary endpoint. Results of this study led to FDA approval of the combination of carboplatin, pemetrexed, and pembrolizumab in patients with nonsquamous NSCLC. I hope it does not stop people from testing for PD-L1 expression because what we do not know is this: do the patients who are strongly PD-L1–positive even need chemotherapy? Is pembrolizumab all that they need in terms of treatment to derive benefit? Which patients benefit from combination therapy? What is the long-term survival and toxicity from combination therapy?

The response rate for first-line pembrolizumab in patients who are strongly positive is around 50%. The response rate for the carboplatin/pemetrexed/pembrolizumab combination was 54%, so it is not dramatically improved. What we do not know is what was driving that response in the combination patients. Personally, I do not think that that trial was practice changing. I do not think that we should suddenly adopt carboplatin, pemetrexed, and pembrolizumab for all nonsquamous NSCLC patients. I think PD-L1 should still be tested. I think that if patients are strongly PD-L1–positive (≥50%) by the 22C3 assay, that they should get single-agent pembrolizumab.

I am waiting for the readout of the multiple phase III trials before I stop testing for PD-L1 and just routinely prescribe a checkpoint inhibitor plus chemotherapy. When you combine a checkpoint inhibitor with chemotherapy you are going through 2 lines of therapy upfront, so there is then not a lot for those patients when they progress. The standard of care, your next line of therapy, becomes docetaxel and ramucirumab. We do not know exactly which patients are going to benefit. With the larger ongoing phase III trials, if we see an overwhelming benefit, especially in the direction of OS, I think that that would be practice changing. To change treatment based on a response rate without OS data, especially a treatment that is significantly cost toxic, gives me pause prior to just blanket prescribing of this drug.

So what about durvalumab? Durvalumab has been investigated as a first-line or subsequent therapy for patients with advanced NSCLC. Can you comment on the role durvalumab may play in treating NSCLC going forward?

There was a press release of the PACIFIC trial investigating concurrent chemoradiation therapy for patients with locally advanced disease followed by 1 year of durvalumab compared with placebo. The PACIFIC trial had an announcement that the primary endpoint of PFS had been met for the study. The 1 cautionary tale I have is that PFS is not a good enough endpoint in patients where the goal is cure. So unless we see an improvement in OS, I do not think that that should become a standard of care treatment following concurrent chemoradiation therapy.

We are also waiting eagerly for the results of the MYSTIC trial. The MYSTIC trial is similar to KEYNOTE-024 and CheckMate 026, looking at first-line durvalumab or durvalumab and tremelimumab compared with platinum-based chemotherapy; it does not require patients to be PD-L1–positive. The primary endpoint is PFS, and the secondary endpoint is OS. We are expecting to see data from that trial potentially at ESMO 2017.

The big thing with these drugs is they are all fairly similar. Nivolumab and pembrolizumab are PD-1 inhibitors. Durvalumab, atezolizumab, and avelumab, which I haven't really talked about, are PD-L1 inhibitors. The big distinguisher in my mind between these drugs is frequency of administration. Even though they are similar, there are some patient convenience factors. For example, in the second-line setting if you are prescribing nivolumab versus atezolizumab, a patient may prefer atezolizumab because you only have to come in once every 3 weeks. If the MYSTIC trial is positive, durvalumab is only given once a month, which is even less frequent. Imagine with stage IV disease you only have to come to the cancer center 12 times a year for therapy. That can really have an impact on patients' quality of life and what they are able to do in between therapies, as we continue to look at lung cancer as a chronic disease.

How important of a role does PD-L1 expression play as an effective biomarker that will predict response to anti–PD-1 therapy?

Is PD-L1 the correct biomarker to use in selecting these agents? There was nice analysis that was preplanned for patients treated in the CheckMate 026 trial that looked at tumor mutation burden and how well that predicts response to nivolumab. What you saw from the data that was presented at AACR by Solange Peters, MD, PhD, is that high mutation burden was a better predictor of benefit from nivolumab than was PD-L1 expression. I think that the role of PD-L1 as a biomarker will continue to be explored and potentially in the next 5 to 10 years, hopefully sooner, PD-L1 may be replaced as the biomarker for selecting treatment.

This is the first time where we've seen a single class of drugs transcend so many tumor types. Lung cancer is the 1 tumor type where PD-L1 expression is required to be positive prior to administration of certain agents. These agents are approved in bladder cancer, melanoma, head and neck cancer, renal cell cancer, and lymphoma, and pembrolizumab just got approval in MSI-high [microsatellite instability] cancers. In my opinion, nobody knows exactly what the right biomarker is to screen for the optimal patient selection. A biomarker that predicts response in 30% to 50% of positive patients, but still has a 10% response in negative patients, is not a great biomarker, as opposed to an EGFR TKI, where if you are positive, you have a 70% chance of response, and if you are negative you have a 1% chance. And so I think a lot of research needs to be done in figuring out the appropriate and optimal biomarker in selecting patients for single-agent therapy as well as potentials for combination therapy.

It seems that the future of immuno-oncology (IO) is going to be in combination therapies. Is that how you see it? Will these therapies become the standard of care across multiple settings? What do we need to be aware of in managing treatment-related toxicity with these combinations?

There is clearly a group of patients who very much derive benefit from single agents, and we still are trying to figure out exactly who those patients are. Right now we are using PD-L1 expression as our best biomarker for benefit. The reality is, though, these drugs only benefit about 15% to 20% of patients when you look at the different ongoing studies. When you look at the long-term survival data, especially, you see they are similar among all trials. So combination therapies are definitely where we are headed.

The melanoma data that looked at nivolumab/ipilimumab compared with nivolumab alone showed that the combination was better initially, but now with longer-term follow-up, the OS is not that different. If you are combining nivolumab and ipilimumab, we are potentially subjecting patients to a higher level of toxicities, particularly with the CTLA-4 inhibitor, as opposed to using single-agent therapy.

Now some of the interesting results that are coming out are the combinations with the indoleamine-(2,3)-dioxygenase (IDO) inhibitors, as well as the histone deacetylases inhibitors and OX40 agonists. There were nice data at ASCO 2017 with pembrolizumab and an IDO inhibitor in NSCLC. There were also nice data with nivolumab and epacadostat in patients with melanoma where none of the patients in the phase I trial had progressed, which is pretty amazing. Further, what's interesting is the toxicities do not appear to be as significant as in previous combinations; for example, pembrolizumab combined with ipilimumab.

Hopefully, some of the new combination treatments will have less toxicity than those that combined a PD-1 or PD-L1 inhibitor with a CTLA-4 inhibitor. When you look at ipilimumab as an agent on its own—not to pick on that one, but it is the only CTLA-4 inhibitor that is approved—it is more toxic than nivolumab. When you look at epacadostat on its own, it is not as toxic as ipilimumab, so maybe that is a rational combination when you are combining it with atezolizumab or nivolumab or pembrolizumab. Then it is a matter of figuring out who the patients are who should receive those combinations versus a single agent. I'm still not excited about the combinations with chemotherapy. I do wonder if there is a group of patients who can be spared chemo and should never have received chemotherapy to begin with—if an IO/IO would make more sense for those patients.

When patients develop these toxicities, they have them sometimes for life. We do not know if there is a group of patients whom we are potentially harming with a checkpoint inhibitor because they are going to develop pneumonitis or colitis, which never completely goes away. If we could find the optimal biomarker in selecting patients for therapy, perhaps we could also potentially figure out some biomarkers that can predict for toxicity.

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