Newer Options on the Horizon for Non-Small Cell Lung Cancer

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Overview
This activity is designed to aid physicians in assessing patients with non-small cell lung cancer (NSCLC), including the applicability of testing for mutations and the use of emerging treatments for both squamous and nonsquamous NSCLC.

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

Learning Objectives
After participating in this CME activity, learners should be better prepared to:
- Cite current challenges associated with using PD-L1 as a predictive marker in the setting of advanced NSCLC
- Summarize findings of recent clinical trials that focus on immuno-oncology agents for use in patients with NSCLC
- Identify emerging agents for the treatment of brain metastases in patients with NSCLC
- Describe current data on the role of third-generation EGFR TKIs in the frontline setting of NSCLC

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The treatment options for patients with non-small cell lung cancer (NSCLC) are finally expanding into the realm of immunotherapy as well as with newer growth factor receptor pathway inhibitors. For those patients with squamous cell NSCLC, a tumor type with genetic alterations that are difficult to target, newer treatment options have not been available since the approval of docetaxel for second-line treatment almost 15 years ago.[1] As a result, advanced, refractory squamous cell NSCLC has been associated with poor outcomes.

Research on the interaction between the immune system and tumor has focused on pathways where the host–immune response can be augmented by blocking the natural "checkpoints" that keep the immune system from attacking host antigen-bearing cells: CTLA-4, PD-1, and PD-L1. Further discussion of squamous cell NSCLC and checkpoint inhibitors has been covered earlier this year in *The American Journal of Hematology/Oncology*.[2]

Nivolumab, a PD-1 antibody checkpoint inhibitor, was FDA-approved for the treatment of metastatic squamous cell NSCLC with progression on or after platinum-based chemotherapy.[1,3] The drug's approval followed results of the phase III CheckMate-017 trial,[1] 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 or more prior systemic treatments. The study was stopped early once the primary endpoint of improved overall survival (OS) was reached. Results showed that patients who received nivolumab for squamous cell NSCLC lived 3.2 months longer (41% reduced risk of death) on average than patients receiving docetaxel.

Nivolumab "is the first immunotherapy to demonstrate a survival advantage in lung cancer," according to the lead investigator in the CheckMate-017 trial, Julie Brahmer, MD, of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University.[4] The use of nivolumab as frontline therapy versus platinum-based chemotherapy in both squamous and nonsquamous cell NSCLC is an exciting area of research.

In NSCLC, nivolumab is currently approved only for second-line treatment of squamous disease, but has shown promising clinical results (CheckMate 057[5]) for nonsquamous NSCLC. CheckMate 057 was conducted in patients with advanced nonsquamous NSCLC who were previously treated with platinum-based chemotherapy. Patients were randomized to either nivolumab (3 mg/kg every 2 weeks; n = 292) or docetaxel (75 mg/m^2 every 3 weeks; n = 290) until disease progression or unacceptable toxicity. The primary endpoint, median OS, was 12.2 months in the nivolumab group and 9.4 months in the docetaxel group (HR, 0.73; 95% CI, 0.59-0.89; *P* = .0015). This translated into a 27% reduction in death for patients receiving nivolumab.[6] This study, as with the CheckMate 017 trial in patients with squamous NSCLC, did not indicate that the PD-L1 biomarker should be used at this time for nivolumab patient selection; however, PD-L1 expression was associated with varying degrees of benefit from nivolumab, with stronger OS outcomes (60% reduction in risk of death) seen in patients with the highest PD-L1 levels in the CheckMate 057 trial.[7]

Data on other immune-oncology agents for NSCLC were presented prior to or during the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting. Heather Wakelee, MD, of the Stanford Cancer Institute shares her clinical insights about what is on the horizon for both squamous and nonsquamous NSCLC and what various mutations can tell us about which patients may benefit from up-and-coming agents for NSCLC.

Moderator: Based on what we heard at the 2015 ASCO meeting, do you consider nivolumab to be the new treatment standard for second-line squamous NSCLC?

Dr Wakelee: Based on the data for nivolumab in squamous NSCLC from the publication that came out in *The New England Journal of Medicine*, as well as the presentation at ASCO, nivolumab was superior to docetaxel, with a 3-month OS benefit, which clearly exceeds what we've seen before with other second-line trials in the squamous setting. In this particular trial, in squamous NCSLC, expression of PD-L1 was not a prerequisite for patients to be enrolled, although it was looked at. There was a trend toward more benefit in patients who had PD-L1 expression, but there was still benefit seen in those without it. So, with that in mind, nivolumab does become the standard as second-line treatment for patients with squamous NSCLC. There are, of course, going to be patients who from a safety standpoint wouldn't be able to get the drug, and those are primarily patients with underlying autoimmune disease. But that's a relatively small subset, and other than that, there really isn't a group where you would think about giving docetaxel before nivolumab.

Moderator: Based on what we now know about nonsquamous NSCLC in previously treated patients, where do you see nivolumab playing a role?

Dr Wakelee: The data in the nonsquamous, randomized phase III trial, CheckMate-057, showed that the magnitude of benefit from an OS standpoint was very similar to what we saw in the squamous cell study, CheckMate-017, where nivolumab was superior to every-3-week docetaxel for OS, with a survival benefit of approximately 3 months. That was also very striking. The difference between the nonsquamous versus the squamous cell data with nivolumab was in the PD-L1 expression data. So, with the nonsquamous disease, in patients who did not have the PD-L1 expression noted, the benefit over docetaxel was not as apparent as it was in the squamous setting. How much we make of that is of course debatable, because the toxicity

profile of nivolumab is so much better than that of docetaxel, but it's still something we need to think about. We also need to put that into context, though. PD-L1 expression is not something that is straightforward to measure. It is a protein, and with immunohistochemistry methods it's not always easy to detect varying protein levels.

The difficulty we're running into is that PD-L1 expression is measured differently by each of the companies looking at drugs that target either PD-1 or PD-L1. There are different thresholds for positive or not positive. There are different cells that are being looked at, as well. And so this whole PD-L1-positive or not remains very confusing. So one of the issues with nivolumab in nonsquamous NSCLC is the PD-L1 expression. The other issue is that with nonsquamous disease, it's a much more heterogeneous population than squamous because within nonsquamous we have patients with actionable driver mutations. In a patient with an actionable driver mutation, it's not so clear that nivolumab is the standard second-line treatment. I think in patients who do not have an actionable driver mutation, nivolumab is now the standard treatment for second line over docetaxel.

Moderator: Where are we with molecular markers, PD-L1 specifically, as a predictive marker in lung cancer?

Dr Wakelee: PD-L1 as a predictive biomarker is still very confusing. It's confusing for those of us who are dealing with a lot of these different drugs, it's confusing for practitioners out in the community, and it's very confusing for patients because they're hearing about this PD-L1 marker. With all of our other markers, there are fairly standardized tests. When we talk about the driver mutations, you either have the mutation in your tumor or you don't, and the tests are fairly consistent across the different platforms as to whether it's positive or not. With the PD-L1 expression, it's a protein that theoretically could be in any cell, and to more or less of a degree in various tumors. Practitioners and patients who know about the HER2 story know that expression of HER2 can be variable and can be somewhat difficult to measure by immunohistochemistry. So that idea is not foreign, but when we talk about PD-L1 in lung cancer, it's become a difficult topic to wrap your head around, and part of that, as I mentioned before, is that the antibodies used to detect PD-L1 are not the same when you look at the assays used by the different companies. So everybody has their own favorite antibody that they think is a little bit better, but there's no consensus as to which is the best for detecting PD-L1 expression. And then there are various levels of expression: Is it 1%, 5%, 50%? Different cut points have been used to determine whether it's positive or negative, so that's also confusing.

Most of the companies are looking just at the tumor and expression on the tumor of PD-L1, but PD-L1 on the infiltrating lymphocytes is also being looked at by some of the groups. That in turn makes it even harder to really understand what it means for a tumor to be PD-L1-positive or -negative. And the last confusing part is that it's a dynamic marker, meaning that the PD-L1 expression can change over time and with different treatments. So if a tumor is read as PD-L1-negative by one assay, the same tissue could be read as positive by a different assay. And then the same tumor over time could be negative and then become positive. It's difficult to understand what it means to be PD-L1-positive in that context. Discussions are ongoing to try to standardize the testing further, but that has not happened yet.

Moderator: What about other immune-oncology therapies for NSCLC, such as pembrolizumab, MEDI4736, and MPDL3280A (atezolizumab)?

Dr Wakelee: Let's start with small-cell lung cancer. With small-cell, pembrolizumab data were presented, and there were also nivolumab-plus-or-minus-ipilimumab data presented. To focus on the study with pembrolizumab in patients with small-cell disease, they screened almost 160 patients, of whom one-third who were tested were positive by Merck's proprietary assay for PD-L1. Keeping in mind that with that particular assay, the Merck assay, about two-thirds of patients with NSCLC are positive, but only one-third of patients with small-cell cancer on this trial. And then of the groups that were positive, which was just over 40 patients in this trial, half of them never went on the trial because they had progressed in the time that it took to get that assay, which was only a few weeks.

It's important in this context to mention that patients with rapidly progressive disease weren't included in any of these trials that required PD-L1 testing, because any trial that required upfront PD-L1 testing was going to require a few weeks before patients could actually start treatment. As a result, there were a lot of patients who never went on these trials because their cancer progressed too quickly. So, in small-cell cancer, we saw that very clearly on the pembrolizumab study. In total, they had only about 20 patients who got treated, but 7 of those responded. Seven out of 20 is a pretty high response rate, but it has to be put into the context that they initially started with nearly 160 patients. So I think that was really striking that they were able to talk about all of those numbers so clearly to help people really think about these drugs in the right way, as opposed to saying, "Look, there were 7 patients who responded out of 20; everybody should get it."

Moving on to atezolizumab, formerly known as MPDL3280A, there was a presentation of a randomized phase II study versus docetaxel, the POPLAR trial, in patients with previously treated NSCLC. Spira and colleagues screened 287 patients and stratified patients based on PD-L1 expression. PD-L1 expression was not required and was scored as 0, 1, 2, or 3. The OS HR didn't reach statistical significance, but for patients who had a high expression of PD-L1, the HR was .46, almost statistically significant, but not quite.

Moderator: It looks like OS was the primary endpoint?

Dr Wakelee: Yes, that's correct. When they looked at the PD-L1 expression in either level 2 or 3+, then OS was statistically significantly favoring atezolizumab. The HR was 0.56, with *P* value of .03. So when you look at the whole group, there was not a clear OS difference. But when you look at those who had PD-L1 expression, whether it was 1, 2, or 3, there was statistically significant improvement in OS with atezolizumab versus docetaxel, and it was more so with higher expression of PD-L1. But due to the smaller numbers, the

significance was lost. In the group without any expression, there's no difference. For each subgroup that had expression, there was a difference. That means that in the group that didn't, it's the converse. And in that setting, while there was no statistical significance, the docetaxel appeared numerically better. So one would think that it makes sense that the focus with this drug will be in patients who have the biomarker.

Moderator: Was there anything new on anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK TKIs) from either the ASCO meeting or just before?
Dr Wakelee: Yes, there are new data in ALK. We had data on alectinib, and we had data on ceritinib. They both look very encouraging by showing activity in patients with brain metastases, which was the emphasis by both groups in the presentations.

Moderator: What evidence is there so far regarding the use of the third-generation EGFRs? What did we learn in previously treated patients, and what sort of frontline trials are being planned based on what we learned about the 2 compounds so far?
Dr Wakelee: We had *The New England Journal of Medicine* publications with both rociletinib (CO-1686) and AZD9291. Both of them are showing response rates now in the 50% to 60% range for patients with previously treated *EGFR*-mutant lung cancer who have progressed after treatment with a first- or second-generation EGFR TKI, and have the T790M resistance mutation. That number has been pretty consistent. That's exciting because it was a struggle for years to find anything that worked in the patients with T790M. For patients without the T790M mutation as their mechanism of resistance, both drugs are showing some activity. It is going to be interesting to watch how well the drugs truly perform in that setting in larger studies. Clearly, these drugs are working well in the T790M-positive tumors but still have some activity in T790M-negative tumors. Those numbers fluctuate a lot because the numbers are still small, so it only takes 1 or 2 responses to make those numbers move up or down quite a bit, even as high as in the mid-30s. It also depends on how you define *T790M-negative*.

The drugs are both going into phase III studies, comparing them versus chemotherapy as next-line treatment for patients who've already failed first- or second-generation EGFR TKI therapy. They are also both going head to head with a first-generation EGFR TKI first-line. We don't have any first-line data with rociletinib yet. A little bit was presented with AZD9291, which looked encouraging, but it had small numbers of patients, so hard to say too much about it. What we really need to see are progression-free survival (PFS) data. For the length of PFS for both drugs, the numbers are fluctuating, and it's probably not going to be substantially longer than a year. The numbers have moved a lot, going from around 8 months to 12 months to 13 months, back to 8, depending on what time point you're looking at. In both cases, we haven't really hit a median yet because they're still dealing with less than half of the patients in these trials actually hitting progression. So those numbers are very immature in both settings. What's going to be important is to see whether or not either of these drugs has a first-line PFS that exceeds 18 months. That's really the number they're going to need to hit to move into first line. If you're going to get a PFS with a first- or second-generation EGFR TKI that's going to be, say, 9 to 10 months, and then with either of these drugs you're going to get a PFS that's another, let's say, 10 months, you're at 20 months sequentially. Compare that scenario with using a third-generation EGFR TKI upfront when you don't really have the opportunity to then go to the first-line drug because we don't think it will be likely to work well after resistance develops to a third-generation drug. The resistance to the third-generation EGFR TKIs is a really interesting evolving story, and at least with the AZD9291, a lot of the patients develop another resistance mutation, the C797S mutation, and that one so far has been resistant to everything we know. With the rociletinib, the resistance mechanisms are more varied and potentially more treatable, but, again, it's still in the early days of trying to sort all that out.

So we have a lot of exciting trials ongoing trying to figure out how well these drugs work first-line and how they really compare with each other, and what can we do to make them work better or longer, or what do we combine them with? Lots of questions still, but those both have been clearly active as a second drug for patients who have had a first- or second-generation EGFR TKI. The toxicities with both are there. The hyperglycemia with the rociletinib at the 500-mg dosing is actually not too bad, and it's pretty manageable with oral hypoglycemics, but it is something people have to get used to because we're not used to having to manage that issue. And whether hitting that insulin growth factor receptor is going to be a good thing or a bad thing, I think is still to be determined.

Moderator: It sounds as if it's going to be awhile before we work out the perfect sequence for these agents?
Dr Wakelee: Yes, it will be.

Moderator: How about testing for the T790 mutation? Is there actionable information that tells us it's worthwhile to test for that mutation before initiating frontline therapy?
Dr Wakelee: Well, for first-line therapy, for patients who've never had an EGFR TKI, the probability of finding T790M is very, very low. It rises up to about 60% for patients who have progressed on a first- or second-generation EGFR TKI, but de novo is incredibly rare. So testing before you start any first-line treatment doesn't make sense. Testing after progression makes sense, and there's been a lot of progress in doing the plasma testing so that we're not having to do repeat biopsies, and that's looking pretty encouraging. It was part of the rociletinib update, and there's more and more literature on those mechanisms of testing and sensitivity of that.

Moderator: What's next in NSCLC? What are the most anticipated trials coming up within the next 6 months to 1 year?
Dr Wakelee: One thing that's worth following very closely is that several of the PD-1/PD-L1 drugs are being looked at in combination

with first-line chemotherapy, and those are actually looking quite promising, especially with platinum/pemetrexed combinations. The response rates of a couple of the drugs have been well over 60%, and so I think that's worth following very closely.

Other interesting areas of research are related to the combinations with the checkpoint inhibitors, such as the CTLA4 and PD-1/ PD-L1 combinations. Those look encouraging, but with toxicity. The combinations with the targeted agents in patients with targetable mutations are also being watched closely, but are mostly still early and with very preliminary information. The radiation combinations are going to be interesting, as are the chemotherapy combinations with the PD-1/PD-L1 agents. Those are really going to be exciting to see, because while there's so much enthusiasm for these drugs, we're still only seeing response rates of about 20% of patients at most with the single agents. You might think the numbers are much higher with some of the PD-L1-targeting drugs, but that's only in highly selected patients. If you look at all comers, we're only helping maybe 20% of patients with these drugs, and the PFS with them alone is mostly under a year. Yes, there are a few longer-term responders, but most patients aren't getting any benefit, and those who are getting some benefit are certainly not getting a long-term response, which is what we need.

So the future is going to be looking at how we get the immune system working even better, what we add to these drugs to help them work better, and also how we better select patients. But we want to figure out a way of having these work for all people, because it's not necessarily a tumor-specific issue the way it is with actionable mutations. We want these drugs to be something we could use for all patients.

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