Transcript Details

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Keeping Pace in Lung Cancer – All About Antiangiogenics and TKIs: Current Roles and Future Directions in EGFR-Mutant NSCLC

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Keeping Pace in Lung Cancer – All About Antiangiogenics and TKIs: Current Roles and Future Directions in EGFR-Mutant NSCLC" is provided by Prova Education.

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Dr. Socinski:
Welcome to the Lung Cancer Education Series. Lung cancer is the third most common cancer in incidence; however, it causes the highest number of cancer-related deaths per year. With earlier availability of lung cancer screenings and more advanced genetic testing, we are now able to stratify lung cancer into non-small cell versus small cell, along with biomarker-specific subsets. So let's dive right into one of the subsets, EGFR mutation-positive non-small cell lung cancer.

This is CME on ReachMD, and I'm Dr. Mark Socinski.

Dr. Garon:
And I'm Dr. Edward Garon.

Dr. Socinski:
Let's get started. There are many treatment options available for patients with non-small cell lung cancer. However, it is imperative to know if the patient harbors a potential oncogenic driver mutation that would allow for a targeted treatment approach. Dr. Garon, can you talk about the different EGFR mutations we see in non-small cell lung cancer and how they may influence current combination regimens in the frontline setting?

Dr. Garon:
The FLAURA study was a large, international effort looking to test osimertinib versus either erlotinib or gefitinib. The control arm included either agent as in different parts of the world, the other agent was commonly used, so they wanted a control that would be appropriate for multiple different locations. And the reason for this study was that, at the time it was launched, we knew that patients who progressed with one of these agents and developed the T790M mutation had a better outcome if they then received osimertinib as opposed to, for instance, chemotherapy. And so the question was, if you were to take these patients earlier and potentially even prevent the development of this T790M-resistance mutation, could you improve outcomes, further? And the answer was that you could. There was a striking signal with respect to progression-free survival. Part of this due to improved outcomes in the central nervous system, but part of it being from outside of the central nervous system, with progression-free survival being clearly better with osimertinib as opposed to either erlotinib or gefitinib.

There is another approved frontline regimen. This is the combination of erlotinib and ramucirumab. This is based on the RELAY study. The RELAY study was a large international study that – looking at erlotinib versus erlotinib plus ramucirumab. And as part of this study, an international group of patients were randomized to this question. Again, the outcomes were clearly better when ramucirumab was

added to erlotinib. The median progression-free survival exceeded a year and a half, and this study is a little earlier along in its life cycle as compared to FLAURA. We do not have survival data from this study, but one of the other sort of important questions from this study is whether or not the T790M mutation, which is a common resistance mutation with agents such as erlotinib, would be seen at a similar frequency if patients had ramucirumab added to erlotinib, and the answer was that they did. This is important because there is always the potential that osimertinib could be used as a salvage therapy in patients who received non-osimertinib-based frontline therapy.

So, Dr. Socinski, do you have any additional thoughts about combinations in these patients based on the mutational status?

Dr. Socinski:
Yeah, I think the take-home message is that all EGFR mutations are not created equal. As Dr. Garon pointed out, the 2 common sensitivity mutations, exon 19 and exon 21, comprise probably around 80% or so of all the mutations, so those are by far what we see most commonly. But as he mentioned, there were some other sensitivity mutations in which afatinib is approved for, and then also, I think, the latest development being the exon 20 insertion drugs that you mentioned before. And I do agree with your comment. There seems to be a difference with the current TKIs in terms of how they do with regard to exon 19 and exon 21. The exon 19 has always seemed to be more sensitive to currently available TKI options, and so I think the exon 21 is one of the subsets where you may consider using an anti-VEGF agent in combination with, in this case, one of the first-generation drugs. And we'll talk about some of that data in the next question. So speaking of that, let's kind of move on to that.

You know, we know right now, Eddie, there are, I think, 5 TKIs currently FDA-approved in this setting. Can you talk a little bit about the evolving landscape in this area and who you might use a TKI in and who you think you might use a combination with an antiangiogenic strategy in?

Dr. Garon:
Sure, so there are obviously multiple approved agents. The original agents that were approved were gefitinib and then erlotinib. I always think it's important for an audience that doesn't follow this as closely to sort of recognize why some of the trials that we have seen look the way they do. In general, in the United States, erlotinib has been the agent of choice among first-generation EGFR inhibitors. That has also been true in much of western Europe, but in Asia, gefitinib was frequently used. And so many of the studies, in fact, will use as a comparator arm for some of these studies either gefitinib or erlotinib. There are, in addition to these, a class of second-generation agents, afatinib and dacomitinib, and these are certainly available agents. As I mentioned, afatinib is approved for some rarer mutations. However, the one that has sort of become a standard frontline option for many practitioners is osimertinib. Osimertinib has been associated with good tolerability but also has improved progression-free survival and even overall survival as compared to either gefitinib or erlotinib.

There are now also several data sets that have showed improvement in progression-free survival when erlotinib is given along with an antiangiogenic agent as opposed to erlotinib as monotherapy. And the magnitude of benefit in progression-free survival has been very similar to what has been seen in studies looking at osimertinib. The combinations include either erlotinib and bevacizumab – there are multiple studies out of Japan that have tested this regimen, and it is an approved regimen in some parts of the world, including in Europe. And in the United States, there is an approval for erlotinib and ramucirumab based on the RELAY study showing superiority of erlotinib plus ramucirumab as compared to erlotinib alone. So those are options that are currently available. There, of course, are ongoing studies looking at adding antiangiogenic agents to osimertinib, and I think how those studies pan out, we still have yet to see.

Dr. Socinski, do you have any additional insights in this setting?

Dr. Socinski:
No, I think you summarized it well, Eddie. I think that the data has, for the most part, been pretty consistent with anti-VEGF agents added to the first-generation drugs. There may be one exception, and that's a US-based study that Dr. Stinchcombe reported relatively recently, but certainly the weight of the data suggests that there is some benefit, and that benefit may be significantly important for the exon 21s versus the exon 19. I'd like to get your perspective. I think one of the big questions is, will we see a benefit when it's added to osimertinib? We know from the FLAURA data that osimertinib outperformed the first-generation drugs, so will there be additional benefit from the addition of, say, either bevacizumab or ramucirumab to osimertinib? Your thoughts on that?

Dr. Garon:
I think one of the appealing approaches of the EGFR inhibitor plus antiangiogenic approach is that it does preserve – in those patients who develop a T790M mutation at the time of progression – the potential for using osimertinib at a salvage point in order to be an additional effective EGFR inhibitor. There have now been a couple of readouts that have looked at adding antiangiogenic therapy to osimertinib. There was the ETOP BOOSTER study that was looking at a salvage study, and recently at ESMO, there was a study out of Japan that looked, again, to add bevacizumab to osimertinib, this time in a frontline setting. What I would say is that, in general, the data, which had been very consistent, that adding an antiangiogenic agent to erlotinib led to a benefit in progression-free survival, has been

harder to show with osimertinib, and I think that the reasons for that are unclear. There are, in addition, multiple studies ongoing. But it is not clear that adding an antiangiogenic to osimertinib is going to be as effective as what we have seen with adding an antiangiogenic to frontline EGFR inhibition with, let's say, erlotinib.

One thing that has been seen that is of interest in those studies is that the smokers actually have appeared to have disproportionate benefit. Patients who have a history of smoking have had a greater benefit when there was the addition of an antiangiogenic to osimertinib. And this has been seen in some studies as well of antiangiogenics plus erlotinib. And I don't know that we think smoking status in and of itself is the issue, but the issue may be co-mutations, and there's been a particular focus on the role of TP53 and its potential role in making tumors more sensitive to antiangiogenic therapy along with EGFR inhibition as opposed to tumors that are TP53 wild-type.

So, Mark, is there anything you want to add to that?

Dr. Socinski:
Well, not to add to that, but that's kind of where I was going to evolve the conversation. You know, this is a situation where individual patient characteristics do play a big role in treatment selection, and so when you start to look at the whole picture from the patient's performance status, comorbidities, you brought up the issue of co-mutations and that sort of thing.

So kind of talk me through your approach to how you personalize treatment selection. Now that we have a number of different options, how does this all kind of roll out in your mind, and what is some of the patient or co-mutational factors that influence what you may do first line in this setting?

Dr. Garon:
So I think that this is certainly an evolving area. I think that the way that we use co-mutations in general is something that we still have a lot of work to do. One thing that has been shown early on is having, for instance, a TP53 mutation across targeted therapies is associated with inferior outcomes with targeted agents. This was, I know, shown as part of the original Lung Cancer Mutation Consortium. That group of patients that had TP53 mutations just did not have as good of outcomes, in general. How that translates to osimertinib – I don't know that we have all of the data yet, but the assumption would be that is a more difficult group across targeted therapies. And that's one group in which, I think, there has been a focus on looking at antiangiogenic therapy. And I think that's going to be particularly important now that we have seen what initially may have looked like a sort of a fishing expedition, trying to find a subset that benefited, but now is starting to look more like a consistent signal: patients who have a history of smoking doing better with antiangiogenic therapy along with EGFR inhibitor-based therapy.

Also, I think that there is certainly interest in looking, as well, at the 2 different mutations that are commonly associated with sensitivity to EGFR inhibitors: the exon 19 deletions as well as the L858R point mutation in exon 21. Again, targeted therapy on its own has appeared to be more effective in those who have exon 19 deletions, and also, we've started to see some similarity in the improvement for at least erlotinib and ramucirumab in those patients who have an L858R mutation as compared to an exon 19 deletion. So I think that's an intriguing set of data that will lead to more investigation. Also, we know that at least in terms of survival, the benefit with osimertinib really was not in the Asian population; it was in non-Asian patients. And there is some disproportionality with L858R being seen more commonly in Asian populations.

Dr. Socinski:
Well, Eddie, this has certainly been a fascinating conversation. Before we wrap up, can you share just one take-home message with our audience?

Dr. Garon:
I think the take home message is that we have really improved a great deal in terms of what we have to offer our patients with EGFR mutation-positive non-small cell lung cancer. And I think this is really exciting. We have to remember that it was only about a dozen years ago that we were able to demonstrate that the EGFR mutation was associated with efficacy of these agents in the first place. And now, we have a multitude of different therapies where we really are trying to balance the issues of toxicity plus efficacy. We are starting to be in a position where there are new ways of approaching which patients are most likely to benefit from different potentially personalized regimens for their disease, and I think it's an exciting time in the field.

Any additional thoughts that you would have?

Dr. Socinski:
Something we haven't mentioned, which seems obvious, but test, test, test. We still know that there are sections of our country that are getting undertested or not tested for EGFR mutations as well as other oncogenic drivers. I think that my take-home message is all of this data we've talked about today is irrelevant unless you test for and diagnose patients with EGFR mutations. So that's my take-home

message is we must test all newly diagnosed patients with a non-squamous and in selected squamous non-small cell lung cancer.

Well, unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Garon, for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Garon:
And nice speaking with you as well. Thank you very much.

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