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### Keeping Pace: Advances in First-Line Therapy for EGFR-mutated NSCLC

Announcer:

Welcome to CME on ReachMD. This activity, entitled “Keeping Pace: Advances in First-Line Therapy for EGFR-mutated NSCLC” is provided by Prova Education and is supported by an independent educational grant from Bristol Myers Squibb, Lilly, and Merck.

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Dr. Socinski:

Scientific and clinical data are emerging on the role of targeted therapies and epidermal growth factor receptor, or EGFR, mutation-positive non-small cell lung cancer. So, how will this new information be utilized in everyday clinical practice? This is CME on ReachMD, and I'm Dr. Mark Socinski.

Dr. Yu:

And I'm Dr. Helena Yu.

Dr. Socinski:

So, Helena, let's get started. Could you walk us through and explain to us the rationale for testing for driver alterations, specifically EGFR?

Dr. Yu:

Sure. I think that this is an important point to start out on because of the critical importance of testing for these driver mutations. So we know in non-small cell lung cancer, more than half of the time when we do this molecular testing, we are able to identify a driver mutation, the first of which was initially identified in 2004 was, as you said, the EGFR mutation. We know when we find these mutations that targeted therapy is superior to our standard of care, chemotherapy and immunotherapy treatments, so it really is critical to detect these. What has been really exciting in lung cancer over the last decade is the identification of more and more of these molecular targets. So now we have EGFR, ALK fusions, RET fusions, MET exon 14, BRAF, ROS1, and with this plethora of different mutations that we hope to identify, it is really important – and important with limited tissue resources – to use some sort of comprehensive molecular panel to look for these mutations. And so I tend to use a next-generation sequencing panel that would be able to identify all of those targetable mutations, many of which either have FDA-approved targeted therapies or really interesting and already demonstrated efficacious clinical targeted therapies in clinical development.

Dr. Socinski:

Yeah, I've been saying for quite some time that the greatest thing we do as a medical oncologist is to diagnose a driver alteration because it opens up the – as I call it – the closet of targeted therapies, which we can't get into unless we make a molecular diagnosis. And I'm completely comprehensive and rather compulsive in that I see value in adding plasma next-gen sequencing to tissue. This can sometimes be very helpful with getting results quickly and identifying additional patients where tissue may have its limitations in certain patients or be difficult to obtain, so very important points.

So now that we have kind of established that testing is important in this population – again, you mentioned, you know, kind of our first

driver alteration that was targetable was the EGFR mutation-positive population – discuss the current standard of care of these patients in your practice.

Dr. Yu:

Sure. I'm excited to report that there are currently five approved EGFR tyrosine kinase inhibitors as first-line treatment. We have the earlier-generation EGFR TKIs, and more recently we have osimertinib, which is a third-generation EGFR TKI that actually targets both the sensitizing EGFR mutations as well as the common resistance mutation to earlier-generation EGFR TKIs, EGFR T790M.

So the most recent study is the FLAURA study, and that was a randomized phase III study that looked at osimertinib versus standard of care EGFR inhibitor – so either erlotinib or gefitinib – worldwide and did demonstrate both an improved progression-free survival as well as overall survival with osimertinib compared to the earlier-generation TKIs. And I think two additional important points is that osimertinib, because it is more mutant-specific in its inhibition, does have less EGFR wild-type toxicity, specifically rash and diarrhea, and also has better CNS, central nervous system, penetration. This population of patients with EGFR-mutant lung cancer has a very high cumulative incidence of brain metastases, and so it is really important to select a targeted therapy that has good brain penetration.

Dr. Socinski:

So I want to transition and talk a little bit about the biology, specifically as it relates to vascular endothelial growth factor and the role that anti-VEGF therapy may play in treating EGFR-mutated non-small cell lung cancer. We've seen a number of trials combining both ramucirumab and bevacizumab with TKIs, and I'd like to get your perspective on this.

Dr. Yu:

I think this is a really interesting space and an important space. I think now that we've established the TKIs that are standard of care as monotherapy, of course, as oncologists we want to do better for our patients and figure out how we can have patients respond for longer and live for longer, and I think one important way are combination treatments in the first-line setting. And so there are several studies, as you mentioned, using the earlier-generation TKIs in combination with VEGF inhibitors. And so one of the most robust studies was the RELAY study which looked at erlotinib in combination with ramucirumab and really showed a very impressive improvement in progression-free survival with the addition of ramucirumab. And this was added to earlier data from several Japanese studies that looked at the combination of erlotinib and bevacizumab that, again, showed an improved progression-free survival.

So, based on these studies, I think that one of the natural sort of subsequent studies to think about is combining osimertinib with bevacizumab. So here at MSK, we did have a phase 1/2 study of the combination and did demonstrate safety and potential early efficacy signals. And there will be a randomized phase 3 study of osimertinib versus osimertinib-bevacizumab that will be in the ECOG-ACRIN cooperative group, so we look forward to those results as well.

Dr. Socinski:

Yes, it certainly does have great interest in the field. It does change the playing field a little bit from once-a-day, oral, well-tolerated drug to introducing an IV anti-VEGF, whether it's ramucirumab or bevacizumab. So we'll see, but if the efficacy is there, you know, as you pointed out in the RELAY trial, that data led to a first-line approval for the combination of erlotinib and ramucirumab. Have you used it yet in your practice?

Dr. Yu:

I was really excited about that. I think we have been waiting for either an NCCN guideline or FDA approval of these combinations for some time now. I have used it in several patients because we had those random bevacizumab study open that I certainly have more experience with that. But I do think that patients are motivated, and ultimately, they want to do better for longer and live longer. And I think if we can clearly demonstrate that with these combinations, I do believe they will be taken up as standard of care. And I think one important thing to think about is – as we design these studies and implement these studies – is trying to understand which patients are high risk and, you know, perhaps select those patients for these escalation-of-care combination treatments, and allow patients that are lower risk or who would do well with EGFR TKI monotherapy to be on monotherapy alone. So I think that'll be an important way to look at these future studies.

Dr. Socinski:

Yeah, so keeping all of this in mind, what really drives your treatment selection for EGFR-mutated non-small cell in terms of patient selection preference? And then I'd also like, you know – because I think you're going to say that the vast majority of your patients, you use osimertinib in a first-line setting. What do we know about resistance mechanisms for osimertinib?

Dr. Yu:

Sure. I think there is some talk about potential sequencing and trying to, you know, kind of sequence the TKIs to allow for longer time on treatment. But I think, you know, even though this a really healthy, well population, some of these patients don't get to second-line

treatment, so I think we need to use the evidence that we have to pick the best treatment. But I am really interested in these different combinations as a way to move forward as well. In regards to resistance, I think that we don't know the data are emerging. I think that what seems most interesting to me is that with the earlier-generation TKIs, we saw a lot of EGFR on-target resistance, which really means, kind of, secondary EGFR mutations that lead to resistance, such as EGFR T790M. With osimertinib, we are seeing some amount of EGFR second-site mutations, such as EGFR C797S, but it's with much less frequency, and I think that might attest to the fact that osimertinib is a better EGFR inhibitor. But as a result, we are seeing more off-target resistance, and specifically, that is acquired alterations in bypass signaling pathways. And then, very interestingly, we're seeing lineage plasticity or transformation from adenocarcinoma to either small cell or squamous cell lung cancer. And I think that's something that we're really going to need to take note of, because we really have no idea the best way to treat those patients. And so I think as we get more plasma samples as well as tissue biopsies, we're going to learn a lot more about these resistance mechanisms and figure out the best way to treat these patients.

Dr. Socinski:

I'd like to get your opinion on one other issue and that is where do you see the RELAY regimen fitting in to everyday practice? Is there a patient type where you would consider it in your practice?

Dr. Yu:

Sure. I think that our patients are increasingly more and more motivated and more and more educated, and so I do have patients that come to me, you know, with ideas or thoughts or questions already. And I do think it is a valuable regimen where we have seen really good progression-free survival data. And so I do think that maybe for patients that have one of those atypical mutations, that would really make sense to utilize the combination.

Dr. Socinski:

So Helena, this has been great. It's certainly been a valuable conversation. Before we wrap up, could you share with our audience the one take-home message you would want them to remember from the discussion today?

Dr. Yu:

Sure. It'll be a two-part one. I think what – first, you know, test, test, test. Because I think testing, molecular testing, allows as you said, opens up so many treatment options for our patients that it would just be a shame if we weren't able to use them. And then, I think, what I said just recently about using your best treatment first. I think we have to do what the data suggest is best kind of at every line of treatment.

Dr. Socinski:

Yeah, and I agree. I've been saying this, and you heard me say it on this podcast earlier. The greatest thing we do as medical oncologists is identify an oncogenic driver because, again, that opens up the – as I call it, the closet of targeted therapies. And that closet is getting fuller and fuller as we get new approvals for new targets, and so I think your point is exactly right: test, test, test. You can't use any of these drugs unless you make the diagnosis from a molecular standpoint.

Dr. Yu, this has been fantastic. Your insights have been incredible. Unfortunately, that's all the time we have for today, so I want to thank our audience for your participation and thank you, Dr. Yu, for joining me and for sharing all your valuable insights. It was great speaking with you today.

Dr. Yu:

Absolutely. My pleasure.

Announcer:

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