Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Keeping Pace in Lung Cancer: Applying the Right Therapy to the Right Patient in RET-Positive NSCLC

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Keeping Pace in Lung Cancer: Applying the Right Therapy to the Right Patient in RET-Positive NSCLC” is provided by Prova Education.

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Dr. Socinski:
Over the last decade, the treatment of patients with metastatic non-small cell lung cancer has clearly been transformed. With the evolution of genetic testing, treatment options now revolve primarily around the presence or absence of an actionable biomarker. To date, RET fusions as an oncogenic driver account for about 1% to 2% of patients diagnosed with metastatic non-small cell lung cancer.

So let’s jump right into this *Keeping Pace in Lung Cancer* educational activity where we’re going to delve deep into the right treatment for the right patient with RET-positive non-small cell lung cancer.

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

Dr. Gainor:
And I’m Dr. Justin Gainor.

Dr. Socinski:
Molecular profiling and next-generation sequencing play integral roles in the diagnosis and treatment of patients with metastatic non-small cell, particularly, non-squamous. Dr. Gainor, can you give us an overview of how you approach NGS for your metastatic non-small cell lung cancer patients, specifically in the terms of fusion testing?

Dr. Gainor:
Yes. I think this is absolutely critical when seeing a new patient with advanced-stage disease. All these patients need to have broad molecular testing. We now have 9 distinct therapeutic targets with FDA-approved therapies, including RET fusion. So fusion testing should be a part of that in all of our non-squamous patients with newly diagnosed advance disease.

So in my own practice, I send off both tissue-based next-generation sequencing using a broad panel. My particular panel is a homegrown institutional panel, but that covers 500 genes. In addition, I have been sending off a liquid biopsy right away. Part of that is now we have several liquid biopsies that are FDA-approved, and the turnaround time on liquid biopsies is simply faster. The turnaround times in some liquid biopsies are 5 to 7 days. So if I find something on the liquid biopsy, I think that’s something I can act on. It’s got that degree of specificity. But if I don’t see something on liquid biopsy, I would view that as a nondiagnostic test and then wait for the tissue-based testing.

Dr. Socinski:
That’s a great point. I do exactly what you do. We have an internal next-gen sequencing platform. Ours is only about 55 genes. It’s very

clinically oriented across solid tumors. But I also do a liquid biopsy at the time of this. We know from studies on liquid biopsy that 15% to 20% of the time you might find something in plasma that you don't find in tissue and vice versa, so I think the important thing is to find something. And to your point, getting the answer can be, actually, quite speedier with plasma-based testing.

Justin, comment on the issue of DNA and RNA platforms, particularly as they relate to fusion testing.

Dr. Gainor:
It's an important point, and it actually varies depending on fusion. RNA assays are more sensitive for detection of fusions, and I think that's something that you can say across the board. The differences in sensitivity between DNA and RNA goes up even more the different fusion partners. So for example, ROS-1 fusions, where there's so many different fusion partners, DNA-based testing is not as sensitive. So an RNA-based platform is going to be more sensitive for detection of fusions.

Dr. Socinski:
It's my impression that most commercial labs are doing both at this point?

Dr. Gainor:
That's my impression, as well. In my own institution, we certainly do both. As an aside, I know we're talking about RET today, but both is also really important for MET exon 14 skipping. That's another alteration where RNA certainly beats DNA in detection.

Dr. Socinski:
Let's talk about once you identify a patient that does indeed have a RET fusion, whether it's in tissue or whether it's in plasma, how do you go about approaching them therapeutically in the treatment-naïve setting?

Dr. Gainor:
Fortunately, this field has evolved a lot in the last several years. And we now have 2 FDA-approved selective RET inhibitors. I make sure to use the term "selective" because early on when RET fusions were identified, we were using more multi-kinase inhibitors that had a lot of off-target effects, and we saw a lot of toxicity and not great activity. So the selective RET inhibitors are pralsetinib and selpercatinib, and both of these agents have shown a very high response rate, approximately 80% in treatment-naïve RET fusion-positive lung cancer. And we're seeing median progression-free survival around 18 months. That's in the platinum-resistant setting. We're waiting on longer-term follow-up for the treatment-naïve patients since many of them were enrolled at a later point. So for me, this goes in the category of a no-brainer that these patients should be treated with targeted therapy, and we now have 2 very good options, both of which also have CNS penetrants, which we've come to recognize is crucial when using targeted therapies in lung cancer.

Dr. Socinski:
I think it's impressive, when you look at the waterfall plots for both of these drugs, particularly in the treatment-naïve patients, almost everyone has a profound degree of tumor reduction in this setting. And that's been my experience clinically.

Any pearls in terms of how you decide between selpercatinib and pralsetinib? Or is it really kind of the Coke/Pepsi argument?

Dr. Gainor:
I think it's the Coke/Pepsi argument. I think these drugs are a lot more similar than they are different, especially with respect to efficacy. In the toxicity side, they have slightly different toxicity profiles. Both have some degree of hypertension. For selpercatinib, you tend to see more dry mouth. You also have – on the FDA label, there's QTC prolongation. By contrast on the pralsetinib side, you see more neutropenia and also pneumonitis. So both have slight differences in toxicity profile. But again, I think a lot more similar than they are different.

Dr. Socinski:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mark Socinski and here with me today is Dr. Justin Gainor. We're just about to discuss the role of RET fusions in metastatic non-small cell lung cancer and how they factor into selecting the right treatment.

You raised the point about the hypertension. These are relatively selective RET inhibitors, but there is some VEGF receptor inhibition as well as FGFR. But compared to the prior generation of multi-kinase inhibitors, these are far superior in activity as well as tolerability.

It's also helpful to know the patient's mutational status up front. However, there are times when that's not an option. So, Dr. Gainor, how do you select an appropriate treatment option for patients who present with a RET fusion but who have also been previously treated with chemotherapy with or without immunotherapy in the first-line setting?

Dr. Gainor:
You're right. This is something that comes up not infrequently when a patient's being referred to me in this setting. In those situations,

what I tend to do is if they're on chemo alone and responding, I'll generally treat just the 4 cycles and then switch. If they are on chemo/IO, what I'll generally do is stop the PD-1 inhibitor, give 2 more cycles of the platinum doublet, just to let the PD-1 inhibitor wash out of the system, and then switch to a selective RET inhibitor. Part of that is we know that the PD-1 inhibitors in targeted therapies don't mix very well. That's a general statement in lung cancer. There have been some reports of some hypersensitivity reactions in patients starting selpercatinib after PD-1. In my practice, I generally don't like starting any targeted therapy with IO on board, and so that's why I generally prefer to have a couple cycles of chemo alone before switching. Both of these agents, pralsetinib and selpercatinib, have shown very robust activity in the platinum-resistant setting, as well, and so that would be my preferred go-to option in someone who was started on chemo plus or minus IO.

Dr. Socinski:
That's a very important message that you just touched on and that this was a concern initially raised by osimertinib following pembrolizumab in the risk of pneumonitis, so certainly, take caution. My advice to physicians: If you feel like you need to treat for medical reasons before you know the genomic profile, it's okay to give a cycle or 2 of chemo without IO until you know. Particularly in those patients who clinically might be enriched for finding a driver like this, you know, a never-smoker or a younger patient.

Let me ask you this, Justin: Patients with metastatic non-small cell with a RET infusion, how quickly do they respond? What are your concerns about brain mets and these sorts of things? You obviously have treated a large volume of these patients, so I think our listeners would like to hear kind of how the typical experience goes.

Dr. Gainor:
I think you touched on a number of key points there, the first being how quickly do these therapies work? And these really are reminiscent of our other targeted therapies for other drivers, so ALK and EGFR, where patients can respond within days to therapy. We see really rapid responses. Median time to response is generally the first scan.

A second is that patients with RET fusion-positive lung cancer do have a high lifetime incidence of brain metastases approaching 50%, and so you're going to come across patients with brain metastases who have more underlying RET fusions. Just as my patients with EGFR, ALK, I really try to avoid doing radiation, particularly whole brain. I would avoid that at all costs because I know these drugs can work really fast and in the brain. A majority of patients in both LIBRETTO-001, which is the selpercatinib study, and ARROW, which was the pralsetinib study, that patients with measurable intracranial brain metastases, most of those patients had tumor shrinkage, and it can also be very fast. So if I was seeing a patient with a brain met, I would think about starting first with targeted therapy. If you're concerned about the location or the size of the brain met, then I would get a very short interval brain MRI, but I would favor that over pursuing radiation.

Mark, do you do anything differently?

Dr. Socinski:
No, but just to relate the most recent patient I treated with a RET fusion, a young guy, 34 years old, who was really having such chest pressure he couldn't lay flat and he couldn't really go up a flight of stairs. He had a very large pleural effusion, lots of bulky mediastinal disease. And literally I see these patients 2 weeks after they start just for a toxicity check and check their routine labs, and he related the story that within 24 to 48 hours his chest pressure was gone, and 2 weeks later, our elevators were on the blitz, so he actually walked up to my clinic, which is on the sixth floor. So not being able to go up a flight of stairs prior to selpercatinib, which is what I treated him with, now going up 6 flights of stairs to get to see his doctor was very reassuring.

You made the point that when you look at the studies, the median time to response is the time you get the first CT scan, but symptomatically, these patients can really respond quite quickly.

Justin, we're getting, toward the end of our time. I wanted to ask you what do we know about resistance to these drugs?

Dr. Gainor:
We're just starting to scrape the surface of that. What we've learned so far is that on-target resistance, that is additional mutations in RET, are relatively infrequent here. So about 10% of patients will have on-target resistance. We do see some off-target resistance mutations, such as MET amplification, in about 10% to 15% of patients. But the remaining, we don't know, and so I think that's an area of intense interest is trying to understand how resistance is emerging. And I think this is a prime example of how far drug development has come, because essentially, what we've done is we've taken all of the lessons that we've learned for ALK, EGFR, ROS1 and have already built them into pralsetinib and selpercatinib. These agents were selected because they already overcame the RET gatekeeper mutation. They already were seen as penetrant. And so I think that speaks to one of the reasons why we're not seeing a lot of on-target resistance is because these agents were really optimized to try to overcome as much of resistance in the target before they even enter the clinic.

Dr. Socinski:
This has been a fascinating conversation. Before we wrap up, Justin, can you share just a take-home message with our audience?

Dr. Gainor:
The take-home message is that the last 20 minutes is irrelevant if you don't test. So you absolutely need to test for these alterations, and we now have really good therapies for these patients.

Dr. Socinski:
And I would echo that message: test, test, test. It's so gratifying to be an oncologist when you identify these patients; we have such effective therapies. It really makes a big difference, and we're still learning about the survival endpoints with these patients, so I remain optimistic.

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

Dr. Gainor:
Great speaking to you and thanks so much for having me.

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