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TRANSCRIPT

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The Expanding Value of Biomarkers in NSCLC Treatment

Opening Announcer:
This is ReachMD, and you're listening to Closing the Gaps in NSCLC, sponsored by Lilly.

Dr. Johnson:
Medicine is continually evolving toward a more personalized targeted approach to care, and nowhere is this more evident than within the oncology field. At the heart of these great strides are ongoing research efforts to better identify predictive and prognostic biomarkers for numerous cancer types. On today's program we'll examine the current and emerging roles of biomarkers in the clinical management of non-small cell lung cancer.

This is *Closing the Gaps in Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Shira Johnson, and joining me today is Dr. Ross Camidge, Director of the Thoracic Oncology Program at the University of Colorado Cancer Center.

Dr. Camidge, welcome to the program.

Dr. Camidge:
Thanks for having me.

Dr. Johnson:
So, just to start, can you get us caught up to speed on the clinical biomarkers specific to this cancer type that are currently in use by oncologists, such as yourself?

Dr. Camidge:
Well, so let's try and clarify what exactly we're talking about here. Mostly we're talking about predictive biomarkers, so tests that you do on somebody's tumor, either directly—although, nowadays we can actually do some in the blood to predict whether you're likely to respond to a specific therapy or not. Now, that's different from prognostic biomarkers, which just tell you what the future holds regardless of the information, and they have much less actual role, particularly in lung cancer—we don't really use those. So, in terms of predictive biomarkers, we really have 5 in routine use for licensed therapies. There's PD-L1 immunohistochemistry. And what are you using that for? You're using that to determine if the patient with advanced non-small cell lung cancer in front of you has single-agent pembrolizumab as a first-line option as opposed to chemotherapy and pembrolizumab, essentially. So there's a chemo-free option for the 30% of people that have high tumor proportion score, which is defined as 50% or greater cells expressing PD-L1. And then all the rest are genetic biomarkers, not inherited but acquired genetic changes in the cancer that are really what are called driver oncogenes, things that you can look for that say this is the ring leader in that cancer. And if you could somehow shut it up with a targeted therapy, that would be your first choice over and above all those chemotherapies that we talked about. And the 4 licensed ones are EGFR mutations, ALK gene rearrangements, ROS1 gene rearrangements, and BRAF V600E mutations. And so those are the things that, at the bare minimum, should be tested, because those are FDA-approved therapies.

Dr. Johnson:
So this practice of utilizing biomarkers compared to what we did 5, 10, 20 years ago has taken off exponentially. We didn't have anything like this back then. What has this done to our current state of practice?

Dr. Camidge:
I mean, it's really transformed it. And I think one of the really interesting things is, if you go back barely 10 years, the first truly predictive biomarkers we had were EGFR mutations. And it's interesting because at that point in time, we didn't know what we didn't know. So people would talk about EGFR mutant, and everything else was called EGFR wild type, which now seems ridiculous, because EGFR wild type wasn't a uniform population. It contained all of these other groups. And I think we have to very much get into the habit of where defining what somebody has… And when we say they don't have any abnormalities, the first question you need to ask is: Well, what haven't they looked for? And so, one of the questions that I like to ask is: Okay, if the patient sitting in front of you has had the

testingdecisionand they're ALK, EGFR, ROS1, BRAF negative, do you say, "Oh, there's no point in doing any further testing if you sent off these individual tests?" Well, the question to ask is: If that was your mother, would you be happy with that, or would you say, "Well, hold on. What if that abnormality could say you had a 70% response rate from a drug in a clinical trial that you should travel for?" I would want to know. And so I think very much the move has gone towards broad panels of testing. And you don't even have to think about this. You don't have to say, "Do I check the ALK box and the EGFR box?" You just say, "I'm going to send off the lung panel."

Dr. Johnson:
So, what about guidelines? Do we have guidelines that have kept up with the best practice for utilizing the biomarker assessments in the patient population the way you described?

Dr. Camidge:
Well, I suspect from that question you're expecting the answer no, and the answer is, of course, no, because guidelines are written by human beings, and they have to meet, and they take time to be processed and eventually published, so the guidelines are always a little bit out-of-date. Now, the NCCN is very rapid. I mean, it does multiple updates a year, so they tend to be a little better. So, if you look at the NCCN guidelines, they certainly say a broad panel of testing is appropriate. There's also one of the appendices in the back where they start to list some of the other abnormalities, that when you're trying to decide in your practice, do I use this panel or that panel, you should say, "Well, does it include these abnormalities?" Not all panels are the same, and knowing what is or isn't in our panels is going to become important. If you go to a few academic centers that are leading this—and I would modestly include our own center in this—then what we're doing is we're doing a DNA- and an RNA-based next-generation sequencing platform. So, why the two? Well, there are some abnormalities that you can best pick up by looking at the RNA, because it's hard to see with the DNA, and so that includes many of the gene fusions and also the MET exon 14 skip mutations. So these things happen in about 4% of lung cancer, and many of the next-generation sequencing panels pick up some of them but not all of them. So you think, "Gosh, I found one last week; therefore, it's in the panel." What you don't know is the variance that you're missing. And so, certainly, with our own practice, when we added in the RNA, we doubled our detection rate of MET exon 14 skip mutations.

Dr. Johnson:
So, for those just tuning in, this is Closing the Gaps in Non-small Cell Lung Cancer on ReachMD. I'm Dr. Shira Johnson, and I'm speaking with Dr. Ross Camidge from the University of Colorado Cancer Center. So, Ross, let's focus on treatment impacts. How do these biomarkers contribute to your overall decision-making for the treatment of this disease?

Dr. Camidge:
So let's say you find one of these mutations. And if there's a drug out there that has a response rate that's more than about 60%, then that becomes a first-line treatment decision, because in your mind you're thinking this is it compared to either platinum doublet or platinum doublet immunotherapy, for example. That's why EGFR and ALK and BRAF and ROS1 are there already, because they already have these very high response rates, and we know that that would be something that you would go to first keeping the kind of more doubled down therapies in reserve. Now, not all of them do. So MET exon 14 would be a great example. That has about a 30% response rate with a MET inhibitor. So, what does that mean for MET exon 14? That's a useful thing to have as a second-line option. So I use it to sort of to want to know is there something that I really want to give instead of chemotherapy as my first-line choice. People are now developing agents that work when you initially respond and then develop acquired resistance, so knowing that you have that abnormality might also push the chemotherapies down to third line. This isn't one size fits all anymore. It's not just about the first-line. Increasingly, it's about multiple lines of therapy. And you still keep the radiotherapy and the chemotherapy in your back pocket as needed. It's kind of a little hard to prove, but if I give you an example, so earlier this year we had a celebration that was impossible to have a few years ago. This was a celebration for people with stage IV lung cancer who had survived more than 5 years. Now, that nationally is about 2% of the population, but we had enough… We sent out 400 invitations. We had enough to fill a room, because there are people who you can control their disease for years now—not decades yet, but suddenly we've gone from taking what is essentially a death sentence for some patients and turning it into a life sentence. You have to be vigilant, you have to work very aggressively, you have to keep up with the cancer that's trying to evolve around your treatments, but we're starting to turn some subtypes of lung cancer into chronic diseases.

Dr. Johnson:
That's incredible, because stage IV, whether it was a substage after that, always had a certain death sentence for patients, and what you're telling us is all those rules are changing.

Dr. Camidge:
Yes. I mean, nobody is resting on their laurels. So these driver oncogenes are still—if you add them all up, maybe we can find a driver oncogene in 30%, 40% of non-small cell lung cancer. I think the immunotherapy has defined another group of people who we can get prolonged control on. Our challenge has been we don't have such a great biomarker to say exactly who they are, but we kind of know them when we see them. So there are subgroups of people that we can turn this into a long-term condition. It's still a condition that's going to change your lifespan. So think about it as kind of like poorly controlled diabetes. You can go on medications, you can work very hard and you can get

someone's glucose into the normal range, but it will still affect their lifespan even though they're going to live for years.

Dr. Johnson:
So, as we look even further ahead, are there ongoing or future investigations that are exploring potentially new biomarkers that may lead to even more individualized treatment paradigms that you can share with us?

Dr. Camidge:
I think what we're starting to see is defining new elephants in the room that we didn't quite know were there. And so one of the things we've started to see is, if you have a group of people and they go on a targeted therapy, and they have an amazing response, and then 2 years later they start to grow, okay, we can rebiopsy; we can figure out what went wrong. But here is the question. If you have an amazing response and they're not progressing for 2 years, what's the cancer doing at that point? So, one of the elephants in the room is: How does the cancer enter a dormant state where it's essentially still sensitive to the drug… You know, you can take the drug away and the cancer will grow up, put them back on the same drug and it will go back down again. How does it enter a dormant state when only a fraction of the cells are still alive and then that's the incubator from which these later-acquired resistance mechanisms pop up? And that persistent state, I think, is very hard to study because the patients are doing great and their scans look great and people have to do kind of biopsies about 2 weeks after you start the therapy, but that to me is one of the ultimate elephants in the room, because if we can't address that, we're never going to cure anybody.

Dr. Johnson:
It's really fascinating how far we've come. Ross, before we close, are there any additional takeaways or points that you want to reiterate for our audience that's listening regarding this topic, and really the field as a whole?

Dr. Camidge:
Well, I think the key thing is you have to know what you don't know, and it's very hard. If you're a busy oncologist and you're trying to treat all of these different cancers, and the field is exploding in so many different directions, I mean, first of all, is just check that you're doing the basics. So every patient that walks through the door should be getting ALK, EGFR, ROS and BRAF. It's amazing how many people aren't even getting the BRAF tested and PD-L1 testing. But if they are negative on all of that, and particularly if they have a light smoking history or they're adenocarcinoma or they're young, don't tell the patient they don't have a driver. Say, "We didn't find anything on the basic panel. Let's go do a more advanced panel." Or touch base with whoever your local expert is to find out what else you can

test it for, because again, if that was your mom or your brother or your sister, you would push really hard to say, “I’ve taken this to the limit of human knowledge,” because it can change people’s lives dramatically.

Dr. Johnson:
Well, Dr. Camidge, I’d really like to thank you for sharing these perspectives on the entrance and the impact of molecular biomarkers in clinical cancer care. It was a real pleasure speaking with you today.

Dr. Camidge:
My pleasure, thank you.

Dr. Johnson:
I’m Dr. Shira Johnson, and thank you for listening.

Closing Announcer:
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