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Exploring Advancements in RET Diagnostics: Improving Outcomes Through Accurate Molecular Typing

Announcer:
You're listening to ReachMD, and this episode of Project Oncology is sponsored by Lilly. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to Project Oncology on ReachMD. I'm Dr. Charles Turck, and here with me today to talk about advances in RET diagnostics and the non-small cell lung cancer arena is Dr. Balazs Halmos, who's the Director of Thoracic Oncology in Clinical Cancer Genomics at Montefiore Medical Park at Eastchester in the Bronx, New York. Dr. Halmos, welcome to the program.

Dr. Halmos:
My pleasure. Thank you for having me.

Dr. Turck:
Now, Dr. Halmos, over the last decade, molecular testing has led the charge in developing personalized or precision medicine. So to start us off, would you talk about the role of molecular testing in the non-small cell lung cancer patients healthcare journey?

Dr. Halmos:
Absolutely. I would love to. As you mentioned it's happened only like the last 10 or 15 years. When I started in oncology, really, thoracic oncology especially was about giving chemotherapy to patients with advanced cancer without much understanding who would benefit, particularly from treatment A versus treatment B. And we've seen a major, major transformation since. First with the discovery of the EGFR targeting agents identifying a subset of non-small cell lung cancers, on average about 10 to 15 percent, harboring actionable changes in the EGFR gene that we could target, very, very efficiently, with excellent results. For our patients with , EGFR tyrosine kinase inhibitors that the current lead agent being osimertinib, also called Tagrisso. And since that original discovery, there's been a series of other discoveries now to make a list of eight to nine actionable targets that each and every clinician taking care of patients with advanced lung cancer need to remember and make sure to test for to make sure that our patients can achieve the best outcomes. You can go on the most effective cancer treatment journey to get good results in terms of cancer remissions and a longer survival, but also the highest level of functionality. With agents nowadays that actually have a very favorable toxicity profile for a particular patient subset. So it's very important to get this done right. And we're definitely fully committed to do that for our patients.

Dr. Turck:
And specifically for non-small cell lung cancer patients with RET alterations, what are the optimal diagnostic tools to use from the point of initial diagnosis?

Dr. Halmos:
Yes, that's an excellent question. And of course, our diagnostic tools are rapidly evolving and getting better and better by the day.

The bottom line is that RET alterations occur in a small but important percentage of non-small cell lung cancers. Typically in non-squamous non-small cell lung cancer, lung adenocarcinomas, about 0.5 to 2 percent will harbor RET fusions. Fusions of the RET protein with another partner gene, partner protein, creating a constitutively active molecule. And then cancerous harbored as RET alterations, they can be targeted with RET inhibitors.

And just the last year we've seen a revolution with the development and ultimately approval of two agents, selpercatinib and pralsetinib, for the management of RET fusion positive lung and thyroid cancer, as well as RET mutation, positive medullary thyroid cancers. So now that we have, great molecules to treat our patients better, it's definitely super important to test for these alterations.

What we've learned is that immunohistochemistry is not the best tool. That's a traditional tool in pathology, but not the right tool for this particular situation. PCR testing also has a number of deficiencies.

So what emerged as really the leading tool has been next generation sequencing, which allows really a very detailed analysis of the RET gene, its fusion partners, as well as the introns of these genes, where many times the breakpoints actually occur, making it more difficult to find it with other technologies.

I also have to say that when we say NGS, that's the technological platform, it's very important to know what we put on the NGS. Is it just DNA, or do we test RNA as well? The breakpoints occur in introns, which are challenging even for the best NGS technologies. And it turns out that if we add RNA testing with NGS or other methodologies, to our testing platforms, we can enrich the number of patients we can identify with RET fusions. And as I mentioned, this is really critical ultimately for the patient.

So it's really important to remember that, especially for the right patient profile, it's not enough just to ask for NGS, but you might want to make sure that you order NGS for a provider that's able to add RNA testing as well, if the DNA testing is not informative.

Dr. Turck:
Along that same line, Dr. Halmos, are there any other best practices that you use to select the most appropriate detection technology for your patients with RET alterations?

Dr. Halmos:
I have to also say that tissue-based technology, of course, is the traditional way of completing molecular testing. But lately we've seen really again, just a dramatic transformation in terms of our practices with the introduction of CT DNA technology as well. And as it turns out, CT DNA-based NGS testing can be very helpful to complement tissue-based testing for both the upfront detection of alterations, as well as for the detection of emerging resistance alterations. So CT DNA technology can be added in day-to-day practice to make sure that both up front and through their treatment continuum, we optimize therapy for patients with RET alterations.

Why did I mention the resistance setting? Well, as we're starting to learn, similar to other actionable alterations, when we use very effective targeted therapies, resistance mutations can occur over time. And now we've learned with RET as well, that alterations in the RET kinase can occur at the time of resistance. Learning about those mutations will inform science and possibly will inform proper switch to second-line treatment strategies as well.

So it's important to remember that molecular testing is not useful only at the time of diagnosis, but can be very helpful later on in the treatment continuum as well. A critical juncture such as a disease progression.

Dr. Turck:
For those just tuning in, you're listening to Project Oncology on ReachMD. I'm Dr. Charles Turck. Today I'm speaking with Dr. Balazs Halmos about advances in RET diagnostics.

Now, Dr. Halmos, if we shift our focus over to outcomes, what impact has RET diagnostics made in the lives of your patients with non-small cell lung cancer?

Dr. Halmos:
Molecular diagnostics, per se, has made a dramatic transformation as to how we manage our patients and how patient outcomes have improved. And RET, diagnostics have added the same way. So for the right patients where RET fusion is identified, the patient's treatment course is drastically different from patients who do not harbor such alterations. Now a patient with a RET fusion positive non-small cell lung cancer can benefit from one of the two front-line RET inhibitors, selpercatinib or pralsetinib. They can enjoy a chance for a 60 to 70 percent major response rate, a very small percentage of early progression.

And at a time of progression, that can be guided potentially towards experimental therapeutics or some other, targeted agents as well. So they gain a number of other lines of therapy that they might not have otherwise without understanding the molecular underpinning of the cancer, the cancer harboring RET, translocation RET fusion.

And let me add to that that they also have a better quality of life. These very specific potent RET targeting agents are very safe and their side effect profile is really favorable. For a reason being that the RET protein is not that important for the adult human being. So blocking it doesn't lead to a lot of side effects. Only 2 to 4 percent had to stop taking these medicines due to side effects. And the large majority of side effects are mild and in the range of grade 1 to 2 side effects that can be appropriately managed. These are really, really just so welcome changes in a field when in the past we were facing toxic and largely ineffective treatment strategies.

Dr. Turck:
And as we look ahead to the future testing techniques for RET alterations, what sort of advancements do you think might be on the

horizon to help improve patient outcomes?

Dr. Halmos:
I think I got to say that the current diagnostics are starting to be quite good. I think if we look hard enough, they'll find the large majority of our patients currently with the NGS-based techniques, especially if we add the RNA platform as I mentioned. CT DNA as a technology helps, but I think it could still be improved as the sensitivity, as to our ability to figure out how to use it. For example, CT DNA dynamics, CT DNA changes, clear-outs can be potentially early dynamic biomarkers to adjust treatments, optimize outcomes. Of course, there will be new technologies to look at minimal residual disease for earlier stage patients, and that's also likely CT DNA-based. So we'll see some improvements, I think. But very specifically, in terms of RET diagnostics, I think we've got a quite powerful set of assets currently available. We just need to remember to use them properly.

Dr. Turck:
Then lastly, Dr. Halmos, let me open up the floor to you for the final word. Any takeaways or lessons learned that you'd like to pass along to our listeners?

Dr. Halmos:
I think the key lesson here is that, you know, identifying RET fusions, RET alterations is critical for your patient. But not just that, understanding the entire molecular set of changes that your patient with advanced lung cancer might harbor will be so important to optimize their journey. So don't just focus on a single gene, focus on the paradigm, on the idea that up front we need to invest into molecular testing. That needs to include a whole set of actionable markers. That includes RET transfusions. But of course, it includes EGFR, ALK, ROS, BRAF, METex14, NTRK alterations, energy alterations, and now KRAS has been added to that mix as well. With KRAS, you treat while targeting age. And so if you do it right, maybe about a third of your patients could benefit from a targeting agent as opposed to a more conventional chemotherapy. And of course, we also have the benefit of immunotherapy making a big impact in the management of our patients as well. That's guided by biomarkers too. So early on biomarkers to make sure that long term your patients can do the best.

That's the message and that will be the best journey for your patients.

Dr. Turck:
Well it's becoming increasingly clear that there are many developments in the works to help improve the lives of our patients with non-small cell lung cancer. And I want to thank you, Dr. Halmos, for sharing your insights with us today. It was really great having you on the program.

Dr. Halmos:
Thank you so much for inviting me.

Announcer:
This program was sponsored by Lilly. To revisit any part of this discussion and to access other episodes in this series, visit ReachMD.com-slash-ProjectOncology where you can Be Part of the Knowledge. Thanks for listening.