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Keeping Pace in Lung Cancer: Improving Outcomes for Patients with RET-Positive NSCLC

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Keeping Pace in Lung Cancer: Improving Outcomes for Patients with RET-Positive NSCLC” is provided by Prova Education.

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Dr. Socinski:
Welcome to the Lung Cancer Education Series. Today we will be discussing RET rearranged non-small cell lung cancer. We’ve made some exciting progress about this subset of non-small cell lung cancer, so we have a lot to discuss today.

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

Dr. Subbiah:
Hi, I’m Dr. Vivek Subbiah from MD Anderson Cancer Center.

Dr. Socinski:
So RET rearrangements occur in about 1% to 2% of non-small cell lung cancers. So, Vivek, what and when and how should we be testing for RET alterations?

Dr. Subbiah:
Thank you, Mark, for this question. Since lung cancer has become a poster child for precision oncology with at least 9 targeted therapy options, I would recommend a comprehensive genomic panel. Again, different diagnostic methods have been used to test for the presence of RET genomic alterations such as IHC, FISH, RNA, and DNA-based next-gen sequencing [NGS] assays. However, the sensitivity and specificity of different tests are different. And patients with RET fusion-positive non-small cell lung cancer have seen in 1% to 2% are younger, more likely to have non-squamous lung cancer, and more be nonsmokers. Interestingly, these patients have a better performance status than other oncogene-driven patients with lung cancer. So with increasing availability of next-gen sequencing testing, we are finding more patients with RET fusion.

So let’s go through a couple of scenarios. A patient affected by non-small cell lung cancer with available formalin-fixed paraffin-embedded specimen, if we need to screen for detection of RET fusion, if NGS is available, we would go for that. If NGS is not available, FISH or RT-PCR is indicated in non-small cell lung cancer depending upon the local availability, cost, and turnaround time. In case of a negative test result, it is recommended still to perform a comprehensive next-gen sequencing panel.

Let’s go to scenario 2. For patients affected by non-small cell lung cancer whose FFP specimens are not available or are exhausted, again, we suggest performing a liquid biopsy, which is a cell-free nucleic acid next-gen sequencing panel to detect for RET alteration. It is important to note that if a RET alteration is not detected by liquid biopsy, then tumor tissue testing is still required to definitely exclude the possibility of a RET fusion. In none of these above cases are RET immunohistochemistry testing is recommended.

Dr. Socinski:

Thank you for that. That's exactly my thinking. And in fact, you know, Vivek, in my practice, I tend in almost every patient to do both tissue and liquid biopsy at the same time. I think it's so critically important that we test comprehensively for all of this. You mentioned the FDA has 9 targets in which we have approved therapies for. And then certainly in the case of RET, and we'll talk about this with the trials that have been done to date with the 2 recently approved agents, these agents are highly effective, so you never really want to miss this diagnosis. And again, I would endorse the concept of NGS, both DNA/RNA-based, both in tissue and blood to make sure that you've left no stone unturned.

So historically, in the past we've had some non-selective RET inhibitors. You know, drugs like cabozantinib, vandetanib, lenvatinib, even sunitinib has some RET activity. Certainly the initial results with those, there are a lot of off-targets effects, so there were toxicity issues; they weren't that active. But now we have very highly selective RET inhibitors. And how has this changed the care of our patients?

Dr. Subbiah:
So as you know, historically, patients with RET fusion-positive non-small cell lung cancer had very few selective options beyond standard of care chemotherapy. Again, as you mentioned, vandetanib, cabozantinib, sunitinib are – any of the, you know, small molecule kinases also target RET. They are multi-kinase inhibitors with non-selective RET activity. Again, they were approved by the FDA for medullary thyroid cancer, and they did not have specific lung cancer indication. So they were originally designed to target other kinases such as VEGFR2 and MET. But they were repurposed because of the discovery of their immunity actions on RET gene. So this off-target, multi-kinase activity leads to significant and sometimes prohibitive off-target clinical side effects such as nausea, vomiting, diarrhea, rash, hypertension, QT prolongation, and hemorrhage that limit the use in some patients or limit the dose that the patients can tolerate, leading to drug discontinuation or dose reduction. Together with the non-selectivity for RET, an inferior profile, and the pharmacokinetic properties of these multi-kinase inhibitors, these prevented potent RET inhibition. So it was so welcome to have these customized, designer, highly potent, selective RET inhibitors approved for patients with RET fusion-positive non-small cell lung cancers.

Dr. Socinski:
So you were very involved in the ARROW study, which led to the approval of pralsetinib. Tell us what we should know about this study.

Dr. Subbiah:
ARROW is a first prospective study to investigate pralsetinib for the treatment of RET-altered solid tumors that included RET fusion-positive non-small cell lung cancer and the second study to report on the outcomes with the selective RET inhibitor following the study of selpercatinib. The data showed that pralsetinib has clinical activity in patients with RET fusion-positive non-small cell lung cancer with a response rate of 61% in patients with previous platinum-based chemotherapy and 70% in treatment-naïve patients who are not candidates for available standard of care. The adverse events were predominantly grade 1 to 2 severity and rates of dose reductions and treatment discontinuations were low when you compared them with the multi-kinase inhibitors. In fact, in the 233 patients in the RET fusion-positive, non-small cell lung cancer, the data that was published, the common grade 3 adverse events were neutropenia, hypertension, and anemia. Overall, pralsetinib had a manageable safety profile and short clinical activity in patients with RET fusion-positive non-small cell lung cancer regardless of previous treatment history of fusion partner.

Again, interestingly, there was shrinkage of intracranial metastases in all 9 patients with measurable intracranial metastases at baseline. And at least one post-line baseline measurement. 5 of the 9 patients had an intracranial response, including 3 complete responses. Initially, all treatment-naïve patients with advanced RET fusion-positive non-small cell lung cancer were required per protocol not to be candidates for standard platinum-based therapy generally due to age, comorbidities, or other poor prognostic factors. In fact, given the promising activity – fantastic activity that was seen in the early phase of the study, the eligibility criteria were expanded by a protocol amendment in July of 2019 allowing enrollment of treatment-naïve patients who were candidates for standard platinum-based therapy to provide a study population more representative of the real-world population. In this update, interestingly, the objective response rate was 88% in the post-eligibility revision subset, which included treatment naïve patients who are otherwise eligible for standard platinum-based therapy, providing support that selective RET inhibitors, such as pralsetinib, can be offered as first-line standard of care therapy. In fact, after FDA approval recently, pralsetinib is a first and only precision medicine approved in the European Union for first-line treatment of people with RET fusion-positive advanced non-small cell lung cancer.

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. Vivek Subbiah. We're discussing RET inhibitors for non-small cell lung cancer.

And we have an ongoing phase 3 trial, the AcceleRET trial in lung, that's comparing pralsetinib to platinum-based chemotherapy in this population. You know, we've established the paradigm, certainly in EGFR mutation-positive disease and ALK fusions, that targeted

therapies are superior treatments. I would go out on a limb here and predict that we'll see the same in the RET fusion population.

You know, we have a second agent. You mentioned pralsetinib was the second drug approved. Selpercatinib was approved several months before pralsetinib, and this was based on the LIBRETTO-001 trial. Again, this had cohorts of RET fusion-positive patients, 105 of which were previously treated. There were 39 previously untreated patients in the LIBRETTO-001. In the previously treated patients, the overall response rate was 64%, very similar to the pralsetinib ARROW trial, with a median duration of response of about 17.5 months. And impressively, in the 39 previously untreated patients, an overall response rate of 85%. We don't yet have a median duration of those responses yet. And you mentioned the CNS activity of these drugs. The reports that we saw from LIBRETTO, I think there was a recent update of about 22 patients with approximately about an 80% response rate with measurable disease. As you mentioned, these are extremely well-tolerated drugs. The most common adverse reactions with selpercatinib were hypertension and LFT [liver function test] abnormalities; hypertension grade 3 or higher was about 14% and grade 3 or higher AST or ALT was about 10% or so. But only 2% of patients discontinued due to a drug-related adverse event. So, you know, to your point, these are highly effective, extremely well-tolerated drugs.

One comment I'd like you to just briefly touch on is, you know, this issue of hypertension. Is this a VEGF effect? Because we know there is some inhibition of VEGF with these agents.

Dr. Subbiah:
I think although these drugs are, you know, designed to go after RET, I think, you know, that is a homology between RET and VEGF/KDR2. And at a higher dose, especially at the highest dose level in some patients, I think it could tickle the VEGF receptors as well, especially as these drugs are dosed continuously. So I think that is probably the reason why we see the hypertension from these agents.

Dr. Socinski:
So now that we have these 2 agents, how do you go about selecting treatment for individual patients?

Dr. Subbiah:
I think that's a great question. In the world of oncology, I think, you know, for especially a rare subset of population, it is always good to have 2 drugs or even more drugs, and it is better than 1. And, you know, the good thing is that we have 2 drugs and, you know, both of them seem to be well tolerated, and they have a high response rate. Since these are approved in a line-agnostic manner, regardless of treatment line, we should start treating patients with RET-positive tumors as soon as we find out about the RET fusion, again, ideally in the first line. And, you know, 2 of them have different side effect profiles. Again, as you said, the most common adverse event of grade 3 or higher in the selpercatinib LIBRETTO study was hypertension and increased AST/ALT in 10% and 12% of patients and lymphopenia in a subset of patients. And in the pralsetinib study, we saw anemia low-count and pneumonitis. And they did not see a problem with LFTs. Again, these are different classes of agents with different side effects. And, you know, we will see. Since we don't have head-on-head studies, the real-world data will inform us in the future.

Dr. Socinski:
Yeah, I completely agree with you. Well, this has, certainly been a fascinating conversation, but before we wrap up Dr. Subbiah, can you share your one take-home message with our audience?

Dr. Subbiah:
The last 5 years has been amazing for lung cancer precision oncology. The continued implementation of molecular screening strategies like comprehensive next-gen sequencing panels, both tissue and liquid biopsy, that include the ability to detect RET fusions will be critical for identifying patients with non-small cell lung cancer who may benefit from these selective RET inhibitors. Thank you.

Dr. Socinski:
Yeah, I couldn't agree more. I mean, the management of advanced non-small cell lung cancer has become very complicated. It is the poster child for targeted therapy, as you mentioned. My take-home message would be comprehensive, genomic testing, try to wait for the results before you make your therapeutic decision. If you feel you have to treat, it's okay to give a cycle of chemotherapy alone. And I think that's the proper strategy in the day-to-day management today.

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

Dr. Subbiah:
Thank you so much.

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