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Keeping Pace: Advances in RET Fusion-Positive NSCLC

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Keeping Pace: Advances in First-Line Therapy for RET Fusion-Positive 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:
There are now multiple biomarker-defined patient subgroups, including RET rearrangements with evidence showing that treatment with targeted therapies has significantly improved clinical outcomes. With such rapid changes in the field of NSCLC, how can we translate the updated recommendations into clinical practice? This is CME on ReachME, and I’m Dr. Mark Socinski.

Dr. Drilon:
And I’m Alexander Drilon.

Dr. Socinski:
So, Alex to get us started can you walk us through and explain the frequency of RET rearrangements in non-small cell lung cancer? And how, how are you testing patients? How often are you testing patients?

Dr. Drilon:
Sure. RET fusions are found in about 1 to 2 percent of unselected non-small lung cancers, and knowing that the landscape of oncogene-driven lung cancers has really exploded over the last decade, our approach to testing is a comprehensive one, and so whereas in the past we might have done single gene testing or a more focused panel, now with several analytes that you’re looking at, it actually becomes much more cost effective to do one big test, and so, at our institution, we do next-generation sequencing with a broad, hybrid capture approach that is able to identify RET fusions, other recurrent gene rearrangements, and also other copy number changes and mutations you may be looking for.

Dr. Socinski:
So I assume, I mean, to me this seems like it should be the standard of care – comprehensive testing – particularly in adenocarcinomas of the lung.

So, we’ve heard some recent issues with regard to this issue between DNA and RNA testing. Could you give us the perspective on that, p-particularly with regard to these fusions?

Dr. Drilon:
Absolutely. So, you know that DNA-based NGS tests, even our best ones – the hybrid capture type assays – do have their limitations in – no pun intended – fishing out these recurrent gene fusions, and that’s because of the structure of how these are formed and the fact that it’s not easy to catch the so-called breakpoints where the fusions occur because sometimes those occur in long intronic regions. So, long story short when you get to the RNA level where you actually have the fusion product, it becomes much easier to interrogate

that and find fusions. So, for a practical perspective, we looked at this in our DNA NGS-negative cases and found that in about 15 percent of cases we found a fusion or a MET exon 14 alteration that was not identified on DNA when we did something called anchored multiplex PCR, and now we're routinely doing that in driver negative DNA-based testing. So, I think as we move into the future, as long as cost isn't prohibitive, an optimal approach that would maximize the likelihood of detecting these fusions or exon skipping alterations might be to do double extractions for DNA and RNA and run both assays in parallel.

Dr. Socinski:
Any barriers or any issues with regard to access to molecular testing in non-small cell? I think one of them might often be limitation of tissue.

Dr. Drilon:
And that's exactly right, and I think that the solution there, of course, is to talk to the surgeons, pulmonologists, interventional radiologists, and really just stress the fact that it's important that we find these things because it can match a patient to a very active therapy and as, because we've done that at our center they've really focused on getting us as much tissue as possible for testing. So, as opposed to doing something like an FNA, they might do several FNA passes if a needle, a small needle biopsy is the only thing that can be done or actually go in and get us two or three good cores but, yeah, having solved that issue, the other thing of course, is cost, so payers will have to recognize that this is really a more optimal approach even from a cost perspective.

Dr. Socinski:
Can these rearrangements be found with plasma-based testing?

Dr. Drilon:
They can, although I always say that if you find a positive test, it's something that you can trust. However, because of factors such as shedding and the fact that you're only really looking at DNA and not RNA in blood, um, it's important that if you have a negative test, not to give up on that patient and make sure you pursue tissue-based testing.

Dr. Socinski:
So, what, what can you tell us about the biology of these patients? Is there any t- particular type of patient that you get more suspicious of a RET fusion? Or is it pretty much like the driver population we see in general?

Dr. Drilon:
Yeah, it's, it's the latter, really, which makes it fairly easy. We tend to see these fusions in patients with a younger median age, of course, never smokers, predominantly lung adenocarcinomas, so not different at all from what we've come to expect from EGFR and ALK and ROS1. However, as with those populations, we do occasionally see these fusions as well in patients who are older or who have a heavy smoking history. So, our approach isn't biased towards a particular demographic, but we try to screen really widely and I think that if you do that you're poised to capture these rare events in a population or demographic where you might not think an oncogene-driven lung cancer might be.

Dr. Socinski:
Yeah, so let's switch gears a bit. You alluded to this earlier on, and the importance of detecting the RET fusions really centers around the recent approval of a drug for RET fusion-positive non-small cell lung cancer patients in the first-line setting. So, could you discuss the most recent approval of selpercatinib and tell us your thoughts on this new drug?

Dr. Drilon:
Right, so we've seen a wave of what we're calling selective RET inhibitors which are clean drugs. I use that in the sense that they hit RET very powerfully but don't really hit much else apart from RET but can give patients things like side effects, and selpercatinib, or formally LOXO-292, is one of these drugs. It was tested in the LIBRETTO trial which is a global multicenter phase I/II study that looked at this in RET fusion-positive lung cancers, and, as a sidebar, also in other RET-driven tru-tumors like papillary thyroid cancers and RET-mutant MTCs. So, moving back to lung cancer, the high level results are that in platinum pretreated patients, and there were about 105 cases, the objective response rate was 64 percent with an intracranial response rate of 91 percent and they also looked at the treatment-naïve patients where the response rate was even higher at 85 percent. Now speaking about durability, we do need much more mature follow-up because the median PFS has still not been reached I think just the signal that we're seeing very long-term disease control here, and that was for both populations, so very encouraging. One last thing I'll throw in is that this drug is much more tolerable compared to older RET inhibitors so it's a win both on the activity front and the safety front.

Dr. Socinski:
Yes and you mentioned briefly, I think, the CNS activity. That, that was fairly impressive. We saw some updates at ASCO this year.

Dr. Drilon:

That's right. The good thing about the selective RET inhibitors is that they can get into the brain very well. I'll call out an interesting case that we published recently of a patient of mine who unfortunately couldn't get onto the LIBRETTO trial because of symptomatic leptomeningeal disease. We thankfully got her compassionate use on a single patient program of selpercatinib, knowing that it can work in the brain very well, and she had a complete response in her leptomeningeal disease sort of harking back to what we've seen for osimertinib and EGFR and, again, another win for patients.

Dr. Socinski:
Yeah, so you mentioned before there – this has been a busy space. We, we have another drug I'll refer to as BLU-667 that, again, we saw some updated data at ASCO this year. I wonder if you could tell us a little bit about this agent.

Dr. Drilon:
Right. It's another selective RET inhibitor that's now called pralsetinib, and that was explored on the ARROW study – again, a global multicenter phase I/II effort. The number of patients that were interrogated was about the same as in the LIBRETTO study with 92 patients who were platinum pretreated and 29 patients who were treatment-naïve with RET fusion-positive lung cancers and the top line outcomes were that the objective response rates in those populations were 55 percent and 66 percent respectively. For that program, we do have an early readout on the median PFS and that's in the treatment-naïve population where the median was 17 months.

Dr. Socinski:
We still don't know the overall survival of this population on the newer drugs. The one thing that was impressive to me at ASCO was an update of the ALEX trial, where even on the control arm of crizotinib, the median survival on the drug that we don't think is the best drug was almost five years and had not yet been met with alectinib. So, I guess the point here is it's so important to identify these patients and to get them the right drug because they can live for years.

Dr. Drilon:
Absolutely, and I have very high hopes for the RET space.

Dr. Socinski:
Yes, there should be great enthusiasm for screening for RET fusions because of the activity of these drugs and certainly a step up from what we did historically. You know, there's an old saying – all good things must come to an end. So, I want to ask you about resistance mechanisms. What do we know about how these tumors become resistant and do patients have options in that space?

Dr. Drilon:
Patients do have options, for sure, and I'll first highlight that our knowledge surrounding resistance in the selective RET inhibitor space is quite early, particularly since most patients remain on treatment and are still going strong but in the patients that have progressed on a selective RET inhibitor we have reports of what we call on-target resistance meaning not different from what we see with ALK and ROS1, for example, where the cancer will learn to outsmart the selective RET inhibitor by acquiring a kinase domain mutation. The one reported recently has been the solvent front G810 substitutions but thankfully the field is very forward-looking, and now we have at least one company making a next-generation drug, and that's called TPX-0046. It's currently in phase I testing and that drug was designed to hit the solvent front substitutions while also very potently hitting the fusion itself.

Dr. Socinski:
Well, Alex, this has certainly been a valuable conversation. Before we wrap up Dr. Drilon, can you share with our audience the one take-home message you would want them to remember from this discussion today?

Dr. Drilon:
Yeah, I think it goes back to the first thing we discussed. Testing is really critical and for that, make sure that you get a decent amount of tissue because even though the frequency of these oncogenes might seem low when you find it, it can be very meaningful for an individual patient.

Dr. Socinski:
Yeah, I would, I've been saying for several years now that I think the greatest thing an oncologist can do in the lung cancer patient is diagnose an oncogenic driver because it opens up what I call the closet of targeted therapies. You can't use these therapies unless you make the molecular diagnosis, and to the point you made drugs are only going to get better with time, particularly as we understand the resistance mechanisms. So, with that message I want to thank Dr. Drilon and I want to thank our audience for your participation today. Alex, thanks for joining me, sharing these valuable insights. It was great talking to you today.

Dr. Drilon:
Thanks, Mark. It was my pleasure.

Announcer:
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