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Released: 12/07/2022
Valid until: 12/07/2023
Time needed to complete: 1h 03m

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Selecting and Managing *RET*-Targeted Therapy in mNSCLC

Announcer:
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Dr. Gainor:
Hi, my name is Dr. Justin Gainor from the Massachusetts General Hospital and it's my pleasure to be joined by Dr. Alex Drilon for Memorial Sloan Kettering where today we'll be focusing on some of the practical aspects of treating patients with advanced fusion-positive non-small cell lung cancer. So, hi Alex. Great to be joined by you today.

Dr. Drilon:
Good to be here.

Dr. Gainor:
Maybe a place to start is really on the diagnostic front and perhaps you could just tell us, you know, at your institution, how do you approach molecular testing in patients with advanced non-small cell lung cancer?

Dr. Drilon:
Yeah, I think that the overarching strategy is obviously to look for a bunch of things that includes RET. So, we have many targeted therapies such as ALC, Ross1 TKIs that are matched to those fusions plus EGFR mutations, braf v600e, et cetera. So, the first point is it's usually a comprehensive approach. We do next-generation sequencing of tumor, and in cases where there are issues with acquiring a good enough sample, we also send a liquid biopsy to look for plasma CT DNA. And that's also comprehensive. It doesn't only look for it, it looks for a number of mutations and potentially fusions as well with a caveat that sometimes it's hard to really find these in plasma. If it's there, you believe it, but if it isn't make sure you look to tumor sequencing to see if you've missed something on blood.

Dr. Gainor:
I think that's a great point about, you know, CT DNA, you know, that there, it's certainly a complimentary test, but there are, you know, some weaknesses to it. So, we take a very similar approach. I've actually gotten to taking the approach of sending both off right away just because CT DNA generally has a faster turnaround time.

Dr. Drilon:
That's wonderful. And talking about sending complimentary tests, what do you generally do if you do a great DNA-based test and that's negative for a fusion or a driver?

Dr. Gainor:
Yeah, you raise a great point, which is, you know DNA based sequencing is, you know, less sensitive than RNA based next generation sequencing when it comes to fusions, particularly fusions that have lots of fusion partners because the DNA-based test you have to tile along the introns, and you may be missing a break point. Whereas RNA-based sequencing, you know, you're looking for the fusion

transcripts and you can identify novel transcripts. So, our practice is to jump to an RNA-based sequencing platform to begin with. But you're right, when you have a high index of suspicion that this person may have a driver and the DNA-based assay comes back, if that's what you're using, and it doesn't show something, I would certainly reflex to an RNA-based approach.

Dr. Drilon:
Yeah, and that's certainly something that we do as well. So, let's assume that we've found a RET fusion. I guess an important question on a practical front is how do we pick between the approved drug Selpercatinib and Pralsetinib? What are your thoughts?

Dr. Gainor:
Yeah, I first I'd say this is really a great place that we're in where, where we have options. You know, I, know you and I back seven years ago when we were finding RET fusions, we didn't have approved options. We were really repurposing older drugs with some degree of anti-re-activity. And, and the response is while we had some, they were relatively modest. Now with the selective inhibitors both Pralsetinib and Selpercatinib, both of these agents are FDA-approved line agnostic.

These should be the first-line therapy. So that, that's like the main point is that we should be using retroactive therapies as our first-line therapy. Both agents have shown high response rates. We're talking 60, 70% response rates in the first line setting. Both agents have CNS penetrance, so we're talking about intracranial objective response rates in the 70, 80% range.

And we're seeing impressive progression-free survivals ranging anywhere from, you know, 18 months to 25 months. I think if we put this all together I think Selpercatinib has a slight edge in terms of just looking at the numbers, but, you know caution always in terms of, you know, cross trial comparisons and you know, I don't think we can be dogmatic about it but if I had to reach for one drug, cause that's ultimately what we're going to treat patients with, right? We can only choose one. I think it has a slight edge. What about your practice? I know you were involved very much so in the development of Selpercatinib.

Dr. Drilon:
Yeah, and, and so the caveat there is that I'm biased that I treated many, many more patients with Selpercatinib. I'm trying to be very objective about this. I share the same viewpoint. I do feel like with the progression-free survival that we're seeing numerically looking across the aisle it does seem like Selpercatinib has an advantage. But we'll see what happens with more long-term data. Perhaps it's a good segue to also talk about other ways to pick drugs. And of course, that relates to side effects, and I'll mention that there are some common side effects between the drugs, including increase in liver function tests, we can see that with other TKIs.

There's a lower frequency of high blood pressure, but it does happen, you know, certainly not like with Cabozantonib or Vandetanib, but if again, looking across the trials there are some things that might be a little more unique with one drug versus the other. For example, Pralsetinib because it inhibits jack, jack kinaseses, you do see more frequent myelosuppression. So low white blood cell counts, red blood cell counts, et cetera. So, if I have someone that already doesn't have a great bone marrow, perhaps our counts are borderline, I may not choose Pralsetinib. And then there are other things which are more common with Selpercatinib, like the dry mouth of course is something that's been described. It's one of the most frequent related side effects. And there are other things as well that have been described with Selpercatinib like these kyllis effusions that can occur. And I think one thing to think about as well is if you've identified a fusion late, Justin, do you want to talk about what we see in terms of a potential increase in side effects with these drugs if you

Dr. Gainor:
Yeah, had therapies?

Dr. Gainor:
Yeah, a great point. So, you know, it, there's always an urge to treat patients right away. I think there's that, that tension of, you know, this patient's newly diagnosed, they wanted to start treatment yesterday and we know for patients without drivers PD1 pathway inhibitors are, you know, standard of care and but we know from our experience across many, many different drivers that in general targeted therapies and PD1 inhibitors don't mix well. And I think that is a, obviously, it's a generalization, but I think it is one that that's largely held up in lung cancer and you know, there are reports of hypersensitivity reactions with Selpercatinib you know, particularly after PD1 pathway blockade. So that is one of those like more unusual side effects that that clinician should be aware of. I think you highlighted, you know, the adverse events that differentiate the drugs. I think they're a lot more similar than they are different, obviously, you know, we're forced to make comparisons because patients, you know, clinicians need to decide on one. But I think they're a lot more similar than they are different. You know, we see hypertension with both drugs even though they are selective. So, you know, I think the good news is, you know, if you do have a patient who runs into one of these adverse events, say for example, the chylothorax, you know, which, you know, you and I have both had experiences with that where it can be tough to treat and I would feel perfectly comfortable in that patient, you know, who's experiencing adverse event that we're having difficulty managing, switching to Pralsetinib, in that patient knowing that it's another good option. And I think that that then leads to an important point which is, you know, in your patients say you started someone on Pralsetinib and they develop disease progression, how are you approaching them at the time of progression? Are

you switching to Selpercatinib or are you moving onto something else?

Dr. Drilon:
Yeah, it's great that we've talked about how these drugs are similar and I think that we consider them a sort of cousins in terms of design and structure and that applies also to when cancer is developed true resistance to therapy. I would be worried that the drugs are similar enough that there would be cross-resistance to the other drug. So, on that practical front, I would not switch to the other drug. If I start, let's say with Pralsetinib, I wouldn't do Selpercatinib. There are things that we can do of course, like switch to chemotherapy, which we've shown can be very effective if their adenocarcinomas, platinum pemetrexed, inclusive regimens can be helpful. We discussed trying to avoid immunotherapy for these patients, especially if they're gonna get another therapy, targeted therapy down the line. But maybe to ask you, Justin, so there are newer therapies like Loxo 260, HMO6, et cetera, that are called next-generation drugs. These are available on clinical trials. But is there sort of a practical point to bring out in terms of if you resequence someone's cancer who's more appropriate for these versus not appropriate?

Dr. Gainor:
Yeah, good question. So, I agree with you. You know, generally, if someone develops true resistance on either Selpercatinib or Pralsetinib, I'm not switching to the other drug. But the question is, you know, what happens, you know, should we switch to one of these next-generation drugs? In my mind, in someone who's chemotherapy naive, I would feel most enthusiastic if they have an on-target RET resistance mutation, specifically one of these solvent front mutations in G-810. We think those are going to be the patients most likely to benefit from further RET inhibition. I worry about patients who don't have RET resistance mutations that they may have some bypass signaling pathway and you know, for those individuals, you know, if I don't see a clear bypass pathway and they don't have a RET resistance mutation, I would direct them first to platinum doublet chemotherapy cause these patients can really respond well to chemotherapy and then perhaps consider the trial down the road. So, I know we're, we're about at time but this has been a fun conversation. I know we can go on and on, but I wanted to thank Alex for joining me today and having this great discussion.

Dr. Drilon:
Absolutely.

Announcer:
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