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Personalizing NSCLC: The Optimal Applicability of NGS and Liquid Biopsy

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Dr. Socinski:
There has been a transformation in the diagnostic approach for advanced non-small cell lung cancer, or NSCLC. We now have 8 or 9 biomarkers that have FDA-approved therapies. How can you be sure you're selecting the most appropriate agent for your patient?

This is CME on ReachMD, and I'm Dr. Mark Socinski from the AdventHealth Cancer Institute in Orlando, Florida.

Dr. Suga:
And I'm Dr. Marie Suga. I'm a thoracic medical oncologist from Kaiser Permanente in Northern California.

Dr. Socinski:
We have a lot to cover, so let's jump right in. To start off the conversation today, Dr. Suga, what are your thoughts about genomic testing in non-small cell lung cancer?

Dr. Suga:
So genomic testing is oftentimes utilizing next-generation sequencing testing, or NGS. I think it's now an essential test that really should be obtained in all advanced lung cancer patients. I think before, when we only had to look at EGFR or ALK testing, it was really much easier just to test for those mutations. But now we have 8 mutations that have FDA-approved therapies for lung cancer, and I know many more are coming. So I think we need to use a test that will broadly look at multiple mutations at once so we really don't miss these mutations and the opportunity to offer additional targeted therapy for these patients.

Dr. Socinski:
Quick question for you, and maybe you're going to address it now, is the issue of tissue versus liquid.

Dr. Suga:
Yeah, you know, I think that for the most part, I think they're complimentary, and I think you can use both tissue or liquid next-generation sequencing. But I think that there are some advantages to liquid NGS testing. Blood-based testing can really result in much quicker results than tissue-based testing. And it's also very useful, I think, when there's just not that much tissue available, which can be a challenge, I think, for many of us in the in the community when we're testing for these.

I think there are a couple different ways that you can utilize both liquid and tissue testing. Some oncologists really sent both at the same time. And if the liquid biopsy, say, shows an actionable mutation such as EGFR, then cancel the tissue-based testing. My practice is that I tend to use the tissue-based testing for the most part. But you know, I do think that if I need the results quicker because the patients are symptomatic or there's just limited samples and I don't think that I'm going to get a result from the tissue-based testing or I'd have to

send them for another biopsy, I will definitely utilize blood-based testing in that situation.

But I think one thing that I would say is that I probably wouldn't substitute liquid biopsies for tissue-based testing in all situations, as I think liquid biopsies can miss some important rearrangements, especially. So I think if it's negative and you really suspect that patient's cancer might have a driver mutation, that you should still try to obtain tissue-based testing as well, in addition, so that you're not missing anything.

Dr. Socinski:
Yeah, I think that's the issue is the false negativity we may see in liquid biopsies. Of course, tumors have to be shedding enough circulating tumor DNA for it to be detected. But I tend to do both in my practice. I'm very influenced by the NILE trial where, you know, it showed the clinical utility of adding the liquid biopsy to the tissue biopsy. We know there are lots of issues with tissue in terms of the robustness of biopsies, the samples getting exhausted, and you end up 2 weeks later not having enough to do the testing that we need to do. And as we both pointed out, there are 8 or 9 different things we need to know about: half of them are mutations; half of them are fusions.

And I think your comment about the fusions is important because you can maximize the detection of fusions with RNA in addition to the DNA-based next-gen sequencing. So I think we all endorse a very broad platform that covers at least these 8 or 9 things, if not more things; more things will probably be coming down the line. But I think it's the standard of care much akin to where we insist on knowing ER [estrogen receptor] and PR [progesterone receptor] as well as HER2 [human epidermal growth factor receptor 2] status in breast cancer. I think you have to know all of these 8 or 9 biomarkers in lung cancer so we make the right decision.

Dr. Suga:
Absolutely. I totally agree with that.

I think one thing that I would want to just point out is that, I think, while we all, you know, I think, accept that next-generation sequencing testing is absolutely essential, I think in practice, the rates of obtaining next-generation sequencing testing in the community are much lower than ideal. You know, I think at ASCO 2021, there was a report from the US oncology practices that next-generation sequencing testing rates for metastatic lung cancer patients were less than 50%. And I think it can be very challenging to get the tests ordered and resulted in a timely manner. And it does require a lot of coordination with other specialties to make sure that it's done at the right time.

Dr. Socinski:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mark Socinski from the AdventHealth Cancer Institute. And here with me today is Dr. Marie Suga from Kaiser Permanente. We're discussing the role of NGS and liquid biopsy in treatment selection for patients with non-small cell lung cancer harboring EGFR exon 20 insertions.

I mean, I couldn't agree more with you. I've said many times in public that it is malpractice not to know all these things, because we have FDA-approved therapies that are incredibly useful. And when you identify these mutations in fusions, these are groups of patients that get much more benefit from targeted therapy than either chemo; they tend not to get benefit from IO therapy, many of these subsets. So again, our job as oncologists are really to get the right treatment to the right patient at the right time.

But as you point out, the testing rates are not where they need to be for the majority of our patients, not to mention some of the disparities that were reported at ASCO that you alluded to before. So we have to make sure that all patients get tested.

So now that we've had some background knowledge on genomic testing, let's turn to really have some discussion about what you do when you identify these patients. You find an actionable fusion or mutation. What do you do with that information?

Dr. Suga:
Yeah, I think once we get the information for genomic testing, I think it's really important that we make sure that the patients are getting the appropriate treatment for that targeted mutation. I think, you know, one of the things that could be challenging, I think, if you're in a busy practice, you know, and you may not be treating lung cancer patients all the time, is that you may not be comfortable necessarily, you know, interpreting a next-generation sequencing test. And I really do encourage that everyone consider utilizing a genomic tumor board or your lung tumor board for guidance if you're really not sure how to interpret the results of a next-generation sequencing test.

Just for example, I think, you know, MET mutations, there's exon 14 skipping mutations that we know are extremely sensitive to MET-targeted drugs. However, there's other alterations like MET amplifications. While they do have activity, definitely, with the newer generation of MET inhibitors, I think their definition of what even a MET amplification is and their role of how we treat is not fully established. So I think it's important to know what type of mutation that you might have.

Dr. Socinski:
Yeah, and it still is astonishing to me, when you look at some reports, that even there are patients who are identified, for instance, with

an EGFR-sensitizing mutation, either the exon 19 deletion or the exon 21 substitution, and never get exposed to an EGFR TKI [tyrosine kinase inhibitor]. So, you know, if you find it, you must act on it, and that's when patients get the real benefit.

Dr. Suga:
Yeah, I think, you know, EGFR, just to even say a little bit further, I think you can't just stop at knowing that the patient has an EGFR mutation. You have to know what type of EGFR mutation because EGFR exon 20 insertions, they're de novo resistant to traditional EGFR drugs, such as erlotinib and afatinib. So, you know, really, now there are a new class of drugs that are specifically designed to target the EGFR exon 20 insertions. So really, it's important to recognize that your patient has an EGFR mutation, but also what type of mutation they have and know what type of treatments, you know, might be appropriate for that patient.

Dr. Socinski:
Yeah, and to your point before, the one thing we do know about the exon 20 insertions is that there's great heterogeneity. There are a number of different insertions that have been identified. And if you do kind of hotspot to PCR-based testing, you're going to miss many of those. So that's the importance, and you stressed this before, Marie, that, you know, a broad-based NGS platform is best for identifying all of these mutations because we do have new therapies.

And so that really leads us to our third and final topic. And that's, you know, once you've interpreted the results of the NGS and/or liquid biopsy, you know, it should be guiding your treatment selection. So can you share your thoughts about specifically how we accurately select therapies for these patients with EGFR exon 20 insertions?

Dr. Suga:
Yeah, I think this is a space where there's just a lot of activity and new drug development. It's really quite exciting to see. So I think once a patient's tumor is found to have an EGFR exon 20 insertion, you know, first thing just to stress is that the data that we have for these new drugs for exon 20 is really in the post-platinum setting. So I would start with systemic doublet chemotherapy first.

However, once the patient has progressed on chemotherapy, there are several options to consider in terms of targeting the EGFR exon 20 insertion. So I think there's 2 FDA-approved drugs currently on the market, which one is amivantamab, and that's a fully humanized bispecific IgG antibody that's targeting both EGFR and MET receptors, and it induces the EGFR MET internalization and degradation.

So they studied this in the CHRYSALIS phase 1 expansion cohort. And in 81 patients, they showed an overall response rate of 40% of progression-free survival at 8.3 months and a duration of response of 11 months. And I think some of the common side effects for this particular drug include skin toxicities and infusion-related reactions that really occur in the first infusion and then also some MET type of side effects including peripheral edema.

The other FDA-approved drug is mobocertinib. That's approved currently for the EGFR exon 20 insertion patients. It's an oral EGFR TKI. And so in the phase 2 platinum-pretreated cohort in the EXCLAIM trial, the overall response rate was about 28%. Progression-free survival is 7.3 months, and duration of response of 17.5 months. So the main side effects of the mobocertinib tend to be GI toxicity, mainly, actually, specifically diarrhea, but other side effects, including rash and perionychia, was also observed.

And then there are other drugs that are being developed – really quite exciting. At the recent ASCO 2022, they reported on a new drug, CLN-081, which is showing a very promising phase 1 or 2 trial response rate of approximately 40% and a progression-free survival of 10 months, and really, it seemed to be relatively tolerable with grade 1 to 2 toxicities, mainly.

And then there's another agent, sunvozertinib, which is another oral TKI in development that's showing very similar promising activity with overall response rates around 40%.

So, I mean, I think there's just so many new drugs that are in development for these particular mutations. I think that that's really quite exciting.

Dr. Socinski:
If we have both amivantamab and mobocertinib approved in the space that's post platinum-based therapy, how do you choose which one to use in the second-line setting for these patients?

Dr. Suga:
I think that's a great question. And I think it's one that, unfortunately, we don't have a lot of information about. I think right now, the NCCN [National Comprehensive Cancer Network] basically lists both amivantamab and mobocertinib as options and does not necessarily have a preference between the 2. So I think some of that may depend on certain situations about the side effects perhaps of both of the drugs or even, you know, one is an IV and one is an oral agent. So perhaps, depending on the patient preference, you know, you might want to choose one or the other. But right now, I think we have limited information to know which one we should be using first.

Dr. Socinski:
And of course, that gets back to do we know which patients are going to be best served with one versus the other? And we've got a little bit of work to do to figure those sorts of things out. And as you pointed out, we have more drugs coming. So that's the good news. And so we have a lot to learn in this space moving forward.

Well, Marie, this has been a fascinating conversation. But before we wrap up, I do want to give you a chance to share your one take-home message with our audience.

Dr. Suga:
I think my take-home message is really, you know, there's such new, exciting targeted drugs in lung cancer. We really just need to make sure that all the metastatic lung cancer patients' tumors are tested broadly with next-generation sequencing so we're really not missing the opportunity to provide effective drugs to our lung cancer patients.

Dr. Socinski:
Yeah. You know, my message is the 3 Ts of lung cancer: test, test, test. Do it with both plasma-based as well as tissue-based. Know your pathologist, collaborate with your pathologist, know your tissue procurers, those interventional radiologists and pulmonologists that we rely on for getting adequate samples for these sorts of test procedures, but they're all vitally important in the management of lung cancer patients 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. Suga, for joining me today and sharing your valuable insight. It was great talking with you today.

Dr. Suga:
Thank you so much.

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