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Targeting Oncogenic Drivers in NSCLC: Opportunities & Challenges

Announcer:
Welcome to *Closing the Gaps in Non-Small Cell Lung Cancer* on ReachMD, sponsored by Lilly.

Mr. Nacinovich:
In addition to conventional treatments, targeted therapies for oncogenic mutations are emerging as a promising way to manage patients with non-small cell lung cancer. But just like any other therapeutic approach, it's not without its challenges. So, which currently outweighs the other in the case of targeted therapies? The opportunities or the challenges?

This is Closing the Gaps in Non-small Cell Lung Cancer on ReachMD. I'm Mario Nacinovich, and joining me is Dr. Lyudmila Bazhenova, a board-certified medical oncologist and Professor of Medicine at the University of California San Diego.

Dr. Bazhenova, welcome to the program.

Dr. Bazhenova:
It's my pleasure to be here and speak on a very exciting topic of molecular alterations in lung cancer.

Mr. Nacinovich:
So, to start us off, Dr. Bazhenova, can you walk us through the different oncogenic drivers that have been discovered in non-small cell lung cancer?

Dr. Bazhenova:
Absolutely. Lung cancer has enjoyed tremendous progress in the last couple of years. Just in May of this year the FDA has approved 2 targeted therapies and moved 1 targeted therapy from second-line to first-line. Currently, as it stands now, all patients with nonsquamous non-small cell lung cancer need to be tested for the EGFR, ALK, ROS, BRAF, NTRK, RET and MET exon 14 skipping mutation. Patients with squamous cell lung cancer only require testing if they are nonsmokers or the diagnosis is made on a small tissue sample. In case of a small tissue sample, testing is important because you can be missing a mixed pathology, so-called adenosquamous histology, and patients with mixed histologies can also have molecular abnormalities, which are now proven to be targetable.

Mr. Nacinovich:
And what kind of testing techniques are available to identify these oncogenic drivers?

Dr. Bazhenova:
If one looks at the testing, there are several ways of doing it. The most tissue-efficient, meaning you're saving the tissue, is next-generation sequencing. In some institutions you can do initial immunohistochemical testing, which tests an expression of the protein of the surface of the cell, or you can start with FISH testing where some oncogenic drivers can be fished out by a FISH test while you're preparing for tissue. In addition, we also have an ability to do next-generation sequencing from liquid. Liquid cell-free DNA assays have faster turnaround time, and they are less invasive to the patient, but the most important thing to remember is that liquid cell-free DNA assays have a false-negative rate of approximately 30%. So the way you approach that, if you started with a liquid biopsy and you found an abnormality on a liquid, then you know this is present in tissue, so your specificity is 100%, and it's okay to be treated for that specific molecular abnormality if you found it on a liquid. However, if you did a liquid biopsy and your liquid biopsy is negative, just remember that there is about 30% false-negative rate, and you have to follow negative liquid with the tissue.

There is also some increased encouragement from us from using RNA-based next-generation sequencing. Many of our oncogenic-driven patients have fusions—for example, ALK, ROS, RET, NTRK—and we know that fusions are very difficult sometimes to find on DNA-based NGS, and RNA-based NGS can find some of those fusions which are missed on the DNA. There's also a recent publication at ASCO showing that a very rare mutation called MET exon 14 skipping mutation also can be missed on DNA-based NGS, and RNA-based NGS will uncover some of those abnormalities that were missed on DNA.

Mr. Nacinovich:
So, with that being said, Dr. Bazhenova, how do you determine which test to use?

Dr. Bazhenova:
I think as a practicing physician you need to decide individually what works for you and your institution. We are being held to a very strict goal of no more than 14 days from the time the decision is made to send the tissue until you have the result. Currently, at the time of the diagnosis of stage IV lung cancer, all patients need to get a PD-L1 expression and next-generation sequencing. You can start with liquid NGS as long as you understand the limitation that we just discussed. Also you need to remember is that your PD-L1 testing will come first, because the turnaround time for PD-L1 testing in majority of institutions is about 48 to 72 hours, and your molecular testing will take at least 2 to 3 weeks if you are using tissue-based NGS.

It is very important to wait for the NGS results before initiating therapy. This is recommended because patients with oncogenic drivers commonly have high PD-L1 expression but immunotherapies are not very effective for them, and there's also a risk of increased ALK-immune complication if you first give immunotherapy and then give patients tyrosine kinase inhibitors. We now have 2 publications showing that immunotherapy followed by EGFR tyrosine kinase inhibitors can have increased risk of pneumonitis, colitis as well as hepatitis, and there is also evidence that combining immunotherapy without some of the ALK tyrosine kinase inhibitors can also increase immunotherapy adverse events. So, don't jump on positive PD-L1. Wait until you have molecular testing.

There is a small proportion of patients where you just can't wait. (The patient is becoming rapidly symptomatic; they have a lot of disease.) And in this situation, if you have to start something, I think it's appropriate to start on a platinum doublet and then decide once your molecular testing comes back if you want to add immunotherapy or if you want to switch the patient to a targeted agent. Those patients are actually quite rare, the ones that we can't wait for the molecular testing, but they do happen.

Mr. Nacinovich:
For those just joining us, this is Closing the Gaps in Non-Small Cell Lung Cancer on ReachMD. I'm Mario Nacinovich, and today I'm speaking with Dr. Lyudmila Bazhenova about targeting oncogenic mutations in non-small cell lung cancer.

So, Dr. Bazhenova, the targeted therapies have shown a lot of potential tailoring systemic treatment strategies to more specific tumor types and mutations, but just like traditional approaches, these options aren't beyond the risk of drug resistance either. So, how common is this issue of resistance for patients receiving targeted therapies, and how do you manage it?

Dr. Bazhenova:
Mario, you correctly stated that patients who receive targeted therapy will eventually develop resistance. Even though our targeted therapy in stage IV lung cancer is very effective and across the board response rate to our targeted drugs are ranging between 60–80% and responses are very durable, eventually patients will develop resistance. If you have a patient in front of you who is faced with resistance to your targeted therapy, clinically those patients can be separated into 3 groups: 1) if the recurrence is only in the CNS or the brain, 2) when your patient has an oligo-progression—so, for example, they start with a lot of disease in the body and then they responded beautifully, and now you see 1 or 2 sites of the disease that are growing, and the third and the most difficult to manage is when you have a rapid, diffuse progression in all sites of the disease.

I personally believe that post-progression biopsy is very important for 2 reasons: 1) We are increasingly seeing something that's called a small-cell transformation, or the scientific term for it is cell plasticity, where your patients which started with non-small cell lung cancer and have an oncogenic driver responded beautifully to a targeted therapy, when they progress they actually turn into a small cell. We now have evidence of small-cell transformation in EGFR patients and ALK patients. And treatment for small-cell transformation and prognosis of small-cell transformation is different, and your chemotherapy options are different, so it would be very important for you to make sure that you ruled out small-cell transformation. The second thing which is important is to understand what exactly has happened and if you developed any acquired oncogenic drivers. We have examples of patients who were having an EGFR mutation, and upon resistance to an EGFR TKI, they could require a BRAF mutation or they could acquire a RET mutation. The challenge with those patients -unfortunately we do not have any standard of care approaches to manage those patients, but we do have several case reports that have reported successful addition of a new targeted therapy to recurrent targeted therapy or switch. For example, the same patient that I mentioned before, there's a BRAF-acquired mutation. There are some cases where patients would continue them, let's say, on osimertinib and add BRAF-targeted therapy with responses or switch to the BRAF-targeted therapy.

At this point, as I already mentioned, this is just anecdotes. We do not have any comprehensive prospective trials to answer the question, but those trials are either ongoing or being planned.

Mr. Nacinovich:
Are there any other considerations we should keep in mind when it comes to addressing this particular barrier encountered for non-small cell lung cancer patients?

Dr. Bazhenova:
I strongly believe in trials, because the only way we can improve our patients' outcome is to learn from our patients, so please consider referring your patients to clinical trials if they develop acquired resistance to a targeted therapy.

Mr. Nacinovich:
And lastly, Dr. Bazhenova, when it comes to addressing other potential barriers encountered for non-small cell lung cancer patients, what else should we keep in mind?

Dr. Bazhenova:
Number one is to make sure that you test. You really don't know what your patients have until you perform the molecular testing. There has been some controversy as to what type of testing you should do. There are some institutions that do sequential single-gene testing and some institutions who do next-generation sequencing. It's a personal belief of mine that next-generation sequencing is preferred because A) it's safe tissue, and B) it is a bit faster to do NGS versus sequential tissue. But I think the most important thing is not what you use for testing, what specific laboratory, what specific assay you use for testing. The most important thing is not to forget to test our patients with stage IV disease for the 7 oncogenic drivers for which we have an FDA-approved drug. There are also a couple of oncogenic drivers which are still in development. We don't have FDA-approved treatment strategies yet, but there are several compounds that look very promising in their initial clinical test.

Mr. Nacinovich:
Well, it certainly seems like there is a lot to look forward to in lung cancer research based on our discussion today. And I want to thank my guest, Dr. Lyudmila Bazhenova, for joining me to discuss the opportunities and challenges involved in the treatment of oncogenic mutations in non-small cell lung cancer.

Dr. Bazhenova, it was great having you on the program.

Dr. Bazhenova:
Thank you, Mario. It was my pleasure to be here.

Announcer:
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