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Liquid and Tissue Biopsy in the Treatment of NSCLC: Focus on MET Gene Aberrations

Announcer:
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Dr. Paik:
Lung cancer remains the most common cancer in the United States and Europe and second most common in Japan. The majority of lung cancer is characterized as non-small cell lung cancer, or NSCLC, out of which approximately 3% to 4% of tumor samples harbor MET exon 14 skipping mutations. These mutations result in increased MET kinase protein levels and a constitutively active pathway. Patient subsets of NSCLC with MET exon 14 skipping mutations face a worse prognosis. So timely diagnosis and access to effective targeted therapies are essential.

This is CME on ReachMD, and I'm Dr. Paul Paik. Today, I'm talking with Dr. Jyoti Patel about the value that liquid biopsy brings to patients with non-small cell lung cancer, and specifically those patients with MET exon 14 skipping mutation. Dr. Patel, welcome to the show.

Dr. Patel:
Thanks, so much, Dr. Paik.

Dr. Paik:
Dr. Patel, there is a good deal of discussion about the emerging value of liquid biopsy compared with standard tissue biopsy as part of the NSCLC diagnostic workup. Could you take us through the advantages and disadvantages of tissue biopsy versus liquid biopsy, including the types of information one obtains from each? Also, how can we increase the uptake of liquid biopsy in clinical laboratories so we can expand upon the genetic information that is so critical to the selection of therapy for our patients with NSCLC?

Dr. Patel:
Thanks so much. There has been tremendous innovation in the development of liquid biopsy, and we now have validated datasets that show good concordance between tissue and liquid biopsy. Tissue biopsy of a tumor remains the gold standard; it's been clinically validated. But for people who take care of lung cancer in particular, often patients present with metastatic disease, and finding a diagnosis and tissue confirmation needs to be as less invasive and minimize potential risks to patients as possible. Often, we can get a good sample, but it's difficult to repeat these biopsies. We understand that in tumor evolution, that there can be tumor heterogeneity, there can be different clonal populations, and so tissue biopsy only samples one area of tissue. It can also be impractical to suggest that patients undergo the risk of having biopsy at multiple time points in their disease course.

Liquid biopsy using NGS is really the dominant platform in what we use. It's got increased depth of coverage. You are able to do multi-gene sequencing and detect all modes of genomic alterations. We're able to detect dominant clones of cancer cells that may shed light on how we want to treat a patient. And we can also look, sort of, in real time. Important biomarkers that we measure by liquid biopsy for

patients with non-small cell lung cancer are certainly EGFR, ALK, ROS1, RET fusions, and, importantly, MET exon 14, HER2 mutations, KRAS – and that list continues to grow. The problem is that we have not fully validated or engrained it into routine clinical practice. The advantages are certainly that it's noninvasive, so patients in clinic can undergo their liquid biopsy, and results can turn around fairly quickly.

Dr. Paik:
I think that's a great summary, Jyoti, about the advantages of liquid biopsy and the role with tumor biopsy.

Jyoti, in your discussion, you mentioned that MET gene aberrations can be detected using liquid biopsy. Could you explain what exactly MET exon 14 skipping mutations are and why they've become such an important genetic marker to identify for patients with NSCLC? And today, how widespread is the use of liquid biopsy to identify this important aberration?

Dr. Patel:
We know that MET dysregulation can occur through two main mechanisms. One is loss of a transcription of exon 14 in MET, and that can come from point mutations, insertions or deletions, or whole exon deletions. As a result of MET exon 14 skipping mutations, essentially the binding site is deleted and this leads to impaired MET ubiquitination which leads to decreased MET turnover. These kind of MET alterations are primary oncogenic drivers in about 3% to 4% of patients with non-small cell lung cancer, and these can be easily detected in liquid biopsy.

We know that these are distinct drivers, and they usually are singular, so they don't occur with other known oncogenic drivers, such as ALK, EGFR, and ROS1. The age of patients with MET exon 14 clinically is a little bit older than some of these other mutations like EGFR, ALK, and ROS1, so there isn't really a clinical profile. I would say that every patient who is diagnosed with non-small cell lung cancer needs to be investigated, and up to 4% of these patients will have MET exon 14 mutations. You can detect it, again, both with tissue and with blood with good confidence that you can pick it up with either modality.

Dr. Paik:
I think that last point in particular is great to point out, that unlike some other driver alterations where there are distinct patterns of clinical characteristics happening, for example, in never-smokers, it is in fact the exact case as you point out, that we really don't have that for MET exon 14 skipping. So the recommendation really is exactly as you said, to try to test everyone. And I would note, also, we do find these in other histologies, and the NCCN guideline includes that now for squamous cell lung cancers, for example, and also sarcomatoid carcinomas. So I think this was a great summary of the biology and the characteristics.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Paul Paik, and here with me today is Dr. Jyoti Patel. We're discussing the value of liquid biopsy in patients with non-small cell lung cancer, specifically those patients with MET exon 14 skipping mutations.

So we've discussed the importance of identifying MET exon 14 skipping mutations in patients with NSCLC and that liquid biopsy appears to provide some real advantages in doing so, compared with traditional tissue biopsy. That said, is there proof of concept that liquid biopsy identification of the exon 14 mutation can lead to a targeted therapeutic intervention with improved outcomes?

Dr. Patel:
So I think we have good data. In particular, I think the data around that supports the approval of tepotinib is worth considering in this context. So the data comes from a phase 2 study called the VISION study that Dr. Paik was the lead author for, and that was published in the *New England Journal of Medicine* and had been presented at ASCO as well as World Lung. So in the study, there were 152 patients who had received tepotinib, and the primary endpoint was really response rate, and at least 99 patients had been followed by 9 months. The response rate in this population of people receiving tepotinib, despite line of therapy and who had known exon 14 mutation either by tissue or blood or both, was 46%. Interestingly, the response rate was almost the same. In the liquid biopsy group, it was 48% and 50% in the 60 patients that were in the tissue biopsy group. Based on this data that was initially presented, the FDA granted breakthrough designation for tepotinib back in September 2009.

Further data has been analyzed, and we now know that there is also not a significant difference in line of therapy for patients receiving tepotinib. So patients who had had prior therapy, the response rate was 44.6% with a median duration of response of 11.1 months. For patients who were treatment naïve, the response rate was 44.9% and median duration of response of 10.8 months.

Just recently, February 3rd this year, the FDA granted accelerated approval to tepotinib for adult patients with MET exon 14 skipping mutations. The thing this study really demonstrated that either modality is effective in looking at these patients. If you think about a Venn diagram, some patients will have tissue, some patients will have liquid, and we were able to, again, demonstrate that good concordance between the two.

Dr. Paik:
Right, I think it's a continuing, sort of, evolution of how we've been practicing, I think dating back to the use of liquid biopsy testing in a very limited fashion for EGFR T790M mutations. We do this in other malignancies in other fields, and I think increasingly we're beginning to do this. And so it's been a nice proof of concept for the use of this, but I think one that influences really all targets that we now have for non-small cell lung cancer. So again, I think hopefully we'll provide further rationale for increased utilization of liquid biopsy because of its advantages in our patients.

Dr. Patel, let's take a look at another aspect of MET gene activation in NSCLC. I'd like to discuss patients with an EGFR mutation who are being treated with an EGFR TKI. Many of these patients develop resistance to EGFR TKI therapy, and there's evidence that MET pathway participates in that resistance. Can you briefly touch upon that and also how MET pathway inhibition may play a role in preventing or overcoming EGFR TKI resistance?

Dr. Patel:
So, I think this is a great opportunity to really discuss the use of liquid biopsy over the course of disease of the patient who's been treated with an EGFR tyrosine kinase inhibitor. So we know that that patients will eventually develop acquired resistant to really potent drugs like osimertinib, and we've learned a lot in the past several years about what that resistance looks like. We know that there's some on-site resistance, which is within the EGFR gene, but we've also learned there can be a lot of off-target resistance. And one method of developing resistance to osimertinib is MET amplification. And often, that can be sort of one of the main drivers. And so if there's MET amplification, there are multiple trials that are ongoing and combining MET TKI to osimertinib, and clinically we've seen some really good response rates in early trials. There are 3 MET-inhibitors that are approved, too, that are MET specific, so tepotinib and capmatinib that have phase 2 data. Certainly, I think traditionally we've used crizotinib in many of these patients and, again, seen some nice clinical responses.

Dr. Paik:
Yeah, it's fascinating sort of seeing the development of therapeutics in the EGFR TKI now, the sort of third-generation resistance setting along with some of these newer alterations, because they're good examples of cross-fertilization in the field where, you know, if we didn't have selective MET TKIs that were being developed, then we would neither have very good therapies to try to test in the acquired resistance setting for those patients who have MET amplification and also would not have a really great selective therapies for those with MET exon 14 skipping. So a wonderful example of how people doing work in different fields is important in that all of this information is useful even in ways that we might not be able to anticipate down the road.

Well, this has certainly been a fascinating conversation, but before we wrap up, Dr. Patel, can you share your one take-home message with our audience?

Dr. Patel:
Sure. So there is incredible heterogeneity in lung cancer, and we know oncogenic drivers can be targeted with great efficacy in clinical impact for patients and so it's absolutely essential that we get appropriate testing. So that's likely tissue and blood, in my practice, to really make sure that I've interrogated all options for patients because we see these great results that are clinically impactful when we get the right drug to the right patient.

Dr. Paik:
I agree. I was sort of a latecomer in utilizing and really, I think, understanding the clinical utility of liquid biopsy. But it really has come to the fore now, I think, with all of the different targets and with all of the testing that's now required, that liquid biopsy really is a critical part and will become a critical part of how we take care of our patients with non-small cell lung cancers.

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

Dr. Patel:
Great. Thanks so much for the invitation. I really enjoyed it.

Announcer:
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