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Exploring the Role of MET Aberrations in NSCLC: Pathways to Personalized Care

ReachMD Announcer:
Welcome to *Project Oncology* on ReachMD. This medical industry feature, titled "Exploring the Role of MET Abberations in NSCLC: Pathways to Personalized Care," is sponsored by AbbVie US Medical Affairs.

MET amplification is an emerging biomarker and is currently under investigation in clinical research as a potential therapeutic target.

There are no FDA-approved tests for MET amplification.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. In our program today, we're going to explore the role of the MET pathway in non-small cell lung cancer. And joining me for this discussion is Dr. Paul Paik, who's the Clinical Director of the Thoracic Oncology Service at Memorial Sloan Kettering Cancer Center in New York. Dr. Paik, welcome to the program.

Dr. Paik:
Thanks for having me.

Dr. Turck:
Well, to start us off, Dr. Paik, how has the treatment landscape for non-small cell lung cancer shifted with the rise of targeted therapies?

Dr. Paik:
The rise of targeted therapies was indicative of a sea-change in both the way we conceptualize non-small cell lung cancer and the way we approach treatment of these diseases. It's probably most accurate to talk about the identification of molecular alterations, largely based on mutational events in DNA, as the novel trigger for these changes. And so the discovery of alterations in genes like *EGFR, ALK, MET, ROS1, RET, HER2,* etc. These all allowed us to concretely define non-small cell lung cancers into a disease of many different types of cancers driven by these specific alterations, opening the door to targeted therapy development.[1,2]

As a result, targeted therapies have allowed us to personalize treatments for patients based on their tumor's genetic profile. Now testing for these genetic alterations, even if the frequency of some of these is small, is important, and our sincere hope is that we find one of these in every patient we encounter.[1]

Dr. Turck:
Now let's now zero in on the MET pathway. What role does it play in the pathogenesis of non-small cell lung cancer?

Dr. Paik:
The MET pathway includes the *MET* gene, which encodes for the c-Met protein, a transmembrane tyrosine kinase receptor involved in signal transduction. Under normal circumstances, the MET receptor is activated when hepatocyte growth factor, or HGF, binds to it. This binding triggers several downstream pathways, including MAPK, PI3K/AKT, and JAK/STAT, which regulate critical cellular processes like proliferation, survival, and motility.[3,4]

But, in non-small cell lung cancer, dysregulation of MET can lead to uncontrolled cell growth and resistance to other therapies.[4] The aberrant MET signaling can drive uncontrolled tumor growth, metastasis, and even resistance to certain therapies, and so this dysregulation is often seen in advanced or aggressive forms of non-small cell lung cancer with a poor prognosis.[3,4]

Dr. Turck:
Now with that in mind, let's break down some of the more common MET aberrations we see with non-small cell lung cancer. Dr. Paik, would you tell us more about them?

Dr. Paik:
Sure. There are broadly three aberrations that we've focused on as markers for MET dependency.[3]

MET exon 14 skipping alterations have been the most successfully targeted to date. These mutations result in alternative mRNA splicing that deletes out exon 14. This is important because exon-14 encodes for a portion of the MET receptor that controls its turnover. When exon 14 is deleted, MET stabilizes and accumulates, promoting tumor growth, which leads to dependency on the MET pathway that we can target with therapies. There are targeted therapies known as MET tyrosine kinase inhibitors, or TKIs for short.[2,3,5]

Next, *MET* amplification functions by ramping up signaling through multiple copies of the gene, leading to overexpression of the c-Met receptor protein.[3] There are generally two contexts in which *MET* amplification is present. The first is *MET* amplification as a primary driver, meaning that there are no other co-alterations and that targeting *MET* alone can be effective.[3] The second is *MET* amplification as a driver of resistance to other therapies, such as EGFR-TKIs.[2,3,6]

Now it's important to note that although there are no FDA-approved therapies yet for *MET* amplification, it's a promising target under clinical investigation.[1]

Dr. Turck:
Now if we move on to c-Met protein overexpression, how does it differ from MET exon 14 skipping and MET amplification?

Dr. Paik:
c-Met protein overexpression is the oldest biomarker of interest in this space. We've known for quite some time that non-small cell lung cancer tumors can harbor higher levels of c-Met protein expression.[3,4,7,8] c-Met protein overexpression is also different because it is, to an extent, a more general biomarker that can be present as a result of other MET aberrations. *MET* exon 14 skipping and *MET* amplification can, for example, both lead to tumors that have high levels of c-Met protein expression. Conversely, c-Met protein overexpression can occur even when these other alterations are absent.[3,8]

As with *MET* amplification, the context for c-Met protein overexpression probably matters as well. We do know, for example, that some non-small cell lung cancer patients with certain actionable genomic alterations can have high levels of c-Met protein overexpression at the time of diagnosis.[7,9] This likely means something different than when we see c-Met overexpression in the acquired resistance setting.[8]

Dr. Turck:
For those just tuning in, you're listening to Project Oncology on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Paul Paik about MET aberrations in non-small cell lung cancer.

So, Dr. Paik, can you tell us how these MET aberrations are detected in clinical practice?

Dr. Paik:
Yes, so we have a few tools at our disposal, and each of these aberrations requires different testing methods.

First, next-generation sequencing, or NGS, is the preferred method for detecting *MET* exon 14 skipping mutations. This allows us to look at the genetic level for these specific alterations, and so it's essential for selecting patients who are likely to be treated with MET-targeted therapies.[2,10,11] For *MET* amplification, fluorescence in situ hybridization, or FISH for short, is the standard method.[2] FISH detects increased *MET* gene copies, helping us assess whether MET is being overexpressed due to amplification.[12] NGS can also be useful for identifying amplifications.[2,13,14] As for c-Met protein overexpression, immunohistochemistry, or IHC, is a standard testing method.[15,16] Unlike NGS or FISH, which detect genetic changes, IHC measures protein levels directly in tumor tissue, making it the gold standard to assess protein overexpression. And so each method is highly specific for what it can or cannot test, and together they provide a comprehensive picture of a patient's MET status.[17]

Dr. Turck:
And what do these MET aberrations mean for patient care? How do they impact treatment decisions and resistance to therapy?

Dr. Paik:
Well MET aberrations are becoming increasingly important for guiding treatment decisions in non-small cell lung cancer.[4] Identifying

MET exon 14 skipping mutations, for example, allows us to offer patients MET-targeted therapies, such as TKIs, which are designed to block MET signaling. This can offer a personalized therapeutic approach in patients whose tumors harbor these mutations.[3] On the other hand, *MET* amplification and c-Met protein overexpression are associated with resistance to EGFR-TKI therapies.[3] Comprehensive biomarker testing is vital to inform how to best approach treatment, especially in patients with advanced or metastatic disease.[1]

Dr. Turck:
With all this in mind, let's discuss the biomarker landscape with MET aberrations. What's currently established, and what's still emerging?

Dr. Paik:
At this point, *MET* exon 14 skipping mutations are well-established as actionable biomarkers, and we have MET-targeted therapies that we can offer patients who have non-small cell lung cancer tumors that harbor these mutations.[3] We're also starting to explore the role of *MET* amplification as a potential biomarker, and c-Met protein overexpression as an actionable biomarker.[1,7,17–19] And while we don't have approved therapies for all of these yet, they're being investigated in clinical trials. So, this is definitely an evolving area.

What's also promising is the idea of using these biomarkers not only to guide MET-targeted therapies, but also to predict resistance to other treatments, such as EGFR TKIs. As more data emerge, we could see even more independent biomarkers come to light, which may help us refine treatment options that we can offer patients.[3]

Dr. Turck:
And if we look ahead for a moment before we close, Dr. Paik, what do you see as the future for MET-targeted therapies and MET biomarker testing in non-small cell lung cancer?

Dr. Paik:
Though we've studied MET as a target for a while, it's only recently that we've successfully targeted it through*MET* exon 14 skipping alterations.[3] And so the future with this lies in the identification of resistance mechanisms to guide the next steps in drug development, as we've seen in other oncogene contexts.[20]

Although there are no FDA-approved therapies for *MET* amplification in non-small cell lung cancer, we know that *MET* amplification can be targeted both as a primary driver and a driver of resistance to other therapies.[1,7,17,18] Here, research is focused on therapeutic approaches such as antibody or antibody drug conjugates.[6] c-Met protein overexpression is a target of interest in clinical trials and real-world studies as well.[2–4] In terms of biomarker testing, we may see a broader adoption of testing, particularly in advanced non-small cell lung cancer where precision medicine is becoming the standard of care.[3,4] The great hope for me is in better understanding the intrinsic biology of MET-aberrant disease, which may provide windows of opportunity in other therapeutic directions.

Dr. Turck:
Well, you've certainly given us a lot to consider as we wrap up our program. And I want to thank my guest, Dr. Paul Paik, for sharing his insights on MET aberrations and their role in non-small cell lung cancer. Dr. Paik, it was great speaking with you today.

Dr. Paik:
Thanks for having me.

ReachMD Annoucer:
This medical industry feature was sponsored by AbbVie US Medical Affairs. If you missed any part of this discussion or to find others in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge.

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