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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Meeting Future Global Challenges: Case-Based Presentations in the Management of NSCLC

Announcer:
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Dr. Paik:
Lung cancer is the most common cancer in the United States and Europe and second most common in Japan. While there are numerous oncogenic drivers in non-small cell lung cancer, or NSCLC, for the 3% to 4% of patients who harbor a MET exon 14 skipping mutation, the prognosis is grave. And for patients with EGFR-mutated NSCLC, MET pathway dysregulation may play a role in the emergence of resistance to EGFR TKI therapy.

This is CME on ReachMD, and I'm Dr. Paul Paik. Today, I'm discussing case scenarios with Dr. Joshua Sabari. We'll be focusing on the importance of identify MET gene aberrations and understanding the implications of synergies between the MET and EGFR activation pathways in non-small cell lung cancer. Dr. Sabari, welcome to the show.

Dr. Sabari:
Thank you, Dr. Paik. Looking forward to a great discussion.

Dr. Paik:
Dr. Sabari, let's start with the case of a 47-year-old man diagnosed with advanced metastatic NSCLC. He was found to not have an EGFR mutation and his PDL-1 status was less than 1%. The patient received first-line chemotherapy at a regional/community hospital. He achieved a partial response and was stable for 6 months, but has since relapsed. He is referred to you and is in your office seeking next steps in treatment. What information is critical when making this second-line choice?

Dr. Sabari:
Yeah, so I'd want to know the molecular status of the patient's tumor. So both tissue NGS as well as plasma NGS, next-generation sequencing, also known as liquid biopsy, would be critical to identify a driver alteration so the patient could be matched to targeted therapy. There's key differences between tissue-based NGS, particularly DNA-based, versus liquid NGS, or liquid biopsy, and the difference being that tissue-based NGS, the turnaround time is oftentimes weeks, on average. You know, 3 weeks or so to get a result. Whereas liquid biopsy, the turnaround time is quite robust, about 3 to 5 days or 7 days, on average. For liquid biopsy, you can also identify the heterogeneity of patient's tumor. Whereas, with tissue biopsy, you're only identifying the mutations in the actual sample itself. So I'm often using both liquid biopsy as well as tissue biopsy in the up-front setting to identify driver alteration to then match the patient to a targeted therapy.

And the reason it's so important to do next-generation sequencing in our patients is because there are multiple targets that have FDA-approved matched targeted therapy, such as EGFR, ALK, ROS1, RET, MET, and NTRK fusion. And understanding whether a patient has this driver alteration not only predicts potential response to therapy but correlates with survival. So these are critical.

Dr. Paik:
Right. It's such a great thing to mention all of these different targets. The fact, I think, that we have 7 different targets to go after with matched therapeutics that have developed, really, over a relatively short period of time is pretty astounding and really underscores the importance of having done this testing for this particular patient.

So, Dr. Sabari, in this particular case, the full genetic analysis revealed that the patient harbored a MET gene aberration, more specifically a MET exon 14 skipping mutation. He was negative for other mutations, such as ALK, ROS, and RET. So knowing that, what would be your approach for the second line? And further, had the genetic profile of his tumor been available prior to chemotherapy, could it have changed this patient's first-line intervention?

Dr. Sabari:
So MET exon 14 skip alterations are relatively common, right? Reported in frequency between 3% and 7%, depending on what literature you read. You know, it's interesting, in patients who have sarcomatoid carcinomas or sarcomatoid cancers, the frequency is significantly higher, 20%, 30% of the population will identify to have a MET exon 14. And yes, I think knowing this data up front would have guided therapy for a MET-specific targeted drug.

So there are 2 currently approved FDA therapies for MET exon 14, so capmatinib as well as tepotinib. And both of these are MET-specific inhibitors. And, you know, it's really important, again, to understand the driver alteration in patients because it not only changes the outcome for patients – and also very important, you know, why not do this in the second-line setting for our patients? You know, we want to use our best drugs first. We want to use our therapeutics that have the best possibility of activity up front. So most patients actually, unfortunately, are not able to get a second-line therapy in non-small cell lung cancer. So yeah, knowing the information up front, I would've matched this patient to either capmatinib or tepotinib in the frontline setting.

Dr. Paik:
Right. It's interesting how quickly this space developed from some of the first reports, I think, back in 2015, identifying MET exon 14 skipping as actionable. And the data certainly do look quite promising in both studies with response rates that are sort of, on average, about 50% and median PFS values that are around 9 to 10 months.

The one thing I'll note in this case is that it's a little unusual for this patient to be this young, at 47, with a median diagnosis for MET exon 14 skipping now around 72 to 73. Which is important to note since, of course, patients who are older have questions as to whether or not standard first-line therapies like chemotherapy, for example, might be well tolerated in this population.

Dr. Sabari:
I agree completely. And one controversy here is whether immunotherapy is as effective as targeted therapy in the frontline setting, and we don't have any prospective data to support this. But the current FDA recommendation, as you stated, is to use a MET TKI in the frontline setting.

Dr. Paik:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Paul Paik, and here with me today is Dr. Joshua Sabari. We're discussing the importance of identifying MET gene aberrations and understanding the patient management implications of the relationship between the MET and EGFR activation pathways in the subset of patients with non-small cell lung cancer.

So, let's switch gears, a bit. A 54-year-old woman is diagnosed with advanced metastatic NSCLC. She undergoes a full genetic assessment and is found to harbor an EGFR mutation. She begins treatment with a third-generation EGFR TKI and responds well. We know that many of these patients develop resistance to EGFR TKI therapy, and our patient is no different. Could you discuss the basis of EGFR TKI resistance in NSCLC and perhaps also evidence for the role of the MET pathway in this resistance?

Dr. Sabari:
Yeah, so acquired resistance to targeted therapeutics is universal, not only in lung cancer but in most solid tumors. And thinking about, sort of, how acquired resistance comes about is a complicated one and, you know, most patients who have a third-gen EGFR inhibitor up front will no longer develop the classic resistance mutations that we've seen from first- and second-generation inhibitors, such as the T790M solvent for resistance, or I should say resistance mutation. So with third-generation EGFR TKI, the most common resistance mutations that we see are C797S and MET amplification. But again, compared to what we were seeing with first- and second-generation inhibitors, where 60% of patients had T790M, it's a lot less common in the third-generation EGFR TKI population. So, you know, MET amplification may occur only in about 15% of patients and in C797S also in a similar number, about 15% of patients. So it's critical to re-sequence our patients post-progression on osimertinib to try to then understand novel pathways in therapeutics. So we know that MET is targetable, right? We talked about MET exon 14 with MET-targeted TKI. Potentially we can target MET in third-generation EGFR-TKI resistance, as well.

Dr. Paik:
It is pretty astounding how quickly fields shift. Josh, you and I, I think, remember the days when patients were still being treated with first-gen TKIs, and that decision about testing was pretty straightforward, with about half having a T790M mutation after that. And I think, as you pointed out, things have gotten a lot more complicated in the resistance testing scenario after osimertinib. But it remains important to perform that kind of extensive testing for reasons of therapeutic selection afterwards.

MET gene overexpression or amplification can participate in the emergence of EGFR TKI resistance, as in the clinical case situation we're discussing. Dr. Sabari, what evidence exists to support the rationale for using MET inhibitors as an approach to delaying or possibly reversing resistance to EGFR TKI therapy in NSCLC?

Dr. Sabari:
So there are a couple of prospective studies, mostly phase 1/2 studies, looking at adding a MET inhibitor to a third-generation EGFR TKI in patients with MET-directed resistance. And, you know, although the responses are not phenomenal, there clearly is activity for MET inhibition in patients with MET-mediated resistance. More recently, there is a compound JNJ-372 or amivantamab that is a bi-specific EGFR and c-MET inhibitor that has shown activity, about a 30% response rate in patients who have MET as a possible resistance mutation. So I think this is a very novel sort of niche area to study and understand. The question is, are we going to use targeted therapies in this space and sequence each individual patient, or are we going to use more broad approaches in targeting potential resistance mechanisms as a whole? I think it's too early to tell. But again, understanding whether a patient has MET-mediated resistance is critical in offering the patients further lines of therapy.

Dr. Paik:
It will be interesting to see how these trials end up progressing and reading out. I think, as you mentioned, there have been a number of different approaches here spanning antibody-drug conjugates to selective MET inhibitors, data have been reported out for tepotinib and savolitinib, also. But it is interesting that the response rate in general is not as high as we were expecting to see for reasons that are not entirely clear. Perhaps this has to do with sub-clonal heterogeneity, but I think it is one of the areas that I think has gained the most traction in the acquired resistance setting to targets. So it will be interesting to see again how it unfolds in the short term.

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

Dr. Sabari:
Sure. I think at the end of the day, sequencing patients up front is critical in order to identify a driver alteration so patients can be matched to the best possible therapy. I think another, sort of, take-home message here is that MET is actionable. MET exon 14, MET amplification, as well as MET-mediated resistance clearly has potential activity and should be further studied.

Dr. Paik:
I agree. I think the key here is testing, and it is broadly testing for the different things, I think, Josh, that you had mentioned, as well as the different scenarios that have been mentioned in terms of resistance to EGFR TKI therapy as well as frontline diagnosis. At the end of the day, I've said this before, but a rising tide lifts all ships, and so doing testing basically for all of these different targets is going to be quite important with the hope of finding one of them, at least for the patient that's sitting in your office.

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

Dr. Sabari:
Thank you, Dr. Paik. It was a pleasure talking to you, as well.

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