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Therapy Gaps: Identifying New Targets in the Management of NSCLC

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CHAPTER 1

Dr. Paik:
Dysregulation of MET signaling has been widely described in oncogenic processes across numerous tumor types. It's notable that all 3 types of MET dysregulation have been documented in non-small cell lung cancers, or NSCLC, thus MET gene aberrations provide excellent insight from which to develop new therapeutic agents.

This is CME on ReachMD, and I'm Dr. Paul Paik. Today, I'm talking with Dr. Viola Zhu about c-MET gene aberrations and their relevance in the management of NSCLC, especially in those patients with MET exon 14 skipping mutations. In this first chapter, we'll be discussing the MET proto-oncogene in NSCLC.

Dr. Zhu, welcome to the show.

Dr. Zhu:
Thank you for having me here, today.

Dr. Paik:
Dr. Zhu, the MET proto-oncogene has been implicated in a number of cancers, including NSCLC. Can you describe for us the various types of MET gene dysregulations that occur in NSCLC? How has their identification led to therapeutic approaches for a subset of patients with NSCLC with a very poor prognosis?

Dr. Zhu:
Absolutely. So MET, M-E-T, this is a proto-oncogene that can encode a receptor tyrosine kinase with its ligand known as HGF, hepatocyte-growth factor. The binding of MET to its ligand induces downstream signaling through the RAS, RAF, and PI3K pathways. Aberrant MET signaling can drive tumor growth through increased cell proliferation, survival, invasion, and metastases. Now, in non-small cell lung cancer, aberrant MET signaling can occur through a number of mechanisms, including MET or HGF protein over-expression, MET gene amplification, MET gene mutations, such as exon 14 skipping alterations, or MET gene fusion/rearrangement. Particularly, MET exon 14 skipping alterations are primary oncogenic drivers that can occur in approximately 3% to 4% of patients with non-small cell lung cancer. Now, these mutations can be detected in either tissue or liquid biopsy samples.

Speaking of MET exon 14 skipping alterations, these genomic alterations spatially disrupt distinct splicing sites at the acceptor or donor site flanking the MET exon 14. So as a result, the MET juxtamembrane domain is deleted, which can lead to impaired MET ubiquitination, decreased MET turnover, and increased signaling.

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Dr. Paik:
Before we wrap up, Dr. Zhu, can you provide us with one key takeaway from this chapter?

Dr. Zhu:
Yeah, sure. So, I would say the take-home message for this chapter is that MET dysregulation is a very important molecular alteration, particularly seen in non-small cell lung cancer, and we really need to test everybody to look for a MET dysregulation, particularly the exon 14 skipping alterations, in order to treat them with effective therapeutic agents.

Dr. Paik:
In Chapter 2, we'll be discussing recently approved and emerging therapies in NSCLC harboring MET gene aberrations. Stay tuned.

CHAPTER 2

Dr. Paik:
Welcome. In the first chapter, we covered the MET proto-oncogene in NSCLC. In Chapter 2, we're looking at recently approved and emerging therapies for patients with NSCLC harboring MET gene aberrations. I'm Dr. Paul Paik.

Dr. Zhu:
I'm Viola Zhu.

Dr. Paik:
Dr. Zhu, let's get started by taking a closer look at recently approved and emerging therapies that are likely to improve outcomes for patients with NSCLC harboring MET gene aberrations.

Dr. Zhu:
Sure. So before I get into 2 effective TKIs [tyrosine kinase inhibitors] for MET exon 14 skipping alterations in non-small cell lung cancer, I'd like to just briefly mention various therapeutic ways to try to block MET dysregulation. This includes anti-MET receptor monoclonal antibodies; anti-HGF, the ligands; monoclonal antibodies such as ficlatuzumab; or selective tyrosine inhibitors such as selumetinib, capmatinib, tepotinib; lastly, the various multi-kinase inhibitors such as crizotinib, cabozantinib, merestinib, glesatinib, and sitravatinib. I also like to point out that when you look at MET inhibitors, they can be sort of placed into 2 categories, type 1 versus type 2 MET inhibitors, depending on how they bind to the MET tyrosine kinase. For type 1, there's also type 1a and b. Generally speaking, perhaps the type 2 MET inhibitors can potentially rescue some solvent from mutations.

Now I do like to focus on 2 MET TKIs that have been approved for patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. The first TKI is capmatinib. This drug received its accelerated FDA approval in May 2020, and the approval is based on the landmark GEOMETRY study, which was published by *The New England Journal of Medicine* in September 2020. Now, GEOMETRY, this is a multi-cohort, phase 2 study evaluating capmatinib at 400 mg twice daily in patients with MET dysregulated events, non-small cell lung cancer. The trial's primary endpoint was objective response rate by independent review committee. Secondary endpoint included duration of response, again, by independent review committee. So for a total of 69 patients who had received only 1 or 2 lines of therapy, ORR was 41%; DOR was 9.7 months. In comparison, for 28 patients who had not received previous treatment, ORR was higher at 68%; DOR was longer at 12.6 months. I also like to point out that this trial also allowed other MET-dysregulated non-small cell lung cancer patients. For example, for MET amplification defined as a gene copy number of 10 or higher, the ORR was actually 29% for patients that had been previously treated versus 40% that were treatment naïve.

So coming to another TKI, which is tepotinib, this drug was initially approved in Japan in March 2020, followed by its accelerated FDA approval in February of this year, 2021, also for patients with non-small cell lung cancer harboring MET exon 14 skipping alterations. The approval was based on the landmark VISION study that was published in *The New England Journal of Medicine* in May 2020. This is an open-label, phase 2 study evaluating tepotinib at 500 mg once daily in patients with MET exon 14 skipping alterations. The primary endpoint was ORR by independent review committee among patients who had undergone at least 9 months of follow-up. So there were a total of 99 patients that fit into this category. ORR was 46% and duration of response, DOR, was 11.1 months.

Now, this trial also looked at patients with this molecular alteration detected by either liquid biopsy or tissue biopsy. So for liquid biopsy group among 66 patients, ORR was 48%. For the tissue biopsy group, among 60 patients, ORR was quite comparable at 50%. Again, peripheral edema was the most common toxicity; it was 7% for all treatment-related peripheral edema. This continuation rate due to AE [adverse events] was roughly around 11% or so.

Now, in terms of tepotinib, there were some updated data presented at WCLC 2020. In this presentation, for 69 patients who were treatment naïve, ORR was 45% and DOR was 10.8%. Looking at 83 patients who were previously treated, the data were quite comparable. ORR was 45% and duration of response was 11.1 months. So, that's pretty much my summary.

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Dr. Paik:
Well, this has been great. Before we wrap up, Dr. Zhu, can you provide us with one key takeaway from this chapter?

Dr. Zhu:
Yes, so my take-home message is obviously MET exon 14 skipping alterations are a very powerful primary oncogenic driver in non-small cell lung cancer. We really need to test,you know, if we find these patients, either capmatinib or tepotinib presents a very effective and tolerable therapeutic option.

Dr. Paik:
In Chapter 3, we'll be discussing the emerging therapeutic landscape and c-MET inhibitors. Stay tuned.

CHAPTER 3

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. Viola Zhu. We're discussing c-MET gene aberrations and their relevance in the management of NSCLC, especially in those patients with MET exon 14 skipping mutations.

Welcome. In the second chapter, we covered recent and emerging therapies for patients with NSCLC harboring MET gene aberrations. In Chapter 3, we're considering the therapeutic landscape in a broader view of the value proposition for c-MET inhibitors. I'm Dr. Paul Paik.

Dr. Zhu:
I'm Viola Zhu.

Dr. Paik:
Dr. Zhu, while substantial attention has been directed to c-MET dysfunction as an oncogenic driver in NSCLC, the landscape of the MET activation pathway has taken on new importance. Of particular interest is this pathway's role in the acquired resistance to EGFR TKIs in patients with NSCLC expressing EGFR activating mutations, such as exon 19 deletions or exon 21 point mutations like L858R. Could you put that into perspective for us?

Dr. Zhu:
MET dysregulation can also be seen as a resistance mechanism in patients with EGFR-positive non-small cell lung cancer after failing EGFR TKI therapy. So it is very important when you see a patient after disease progression on EGFR TKI, to look for resistance mechanisms by doing repeat biopsy. You can attempt with either a tissue biopsy or a repeat liquid biopsy. When you detect MET amplification, for example, it might be important to try to use a combination TKI approach to block the original founder mutation, in this case EGFR mutations, and the acquired resistance mutation, in this case MET amplification.

So such a concept has actually been tested in clinical trial. There is a trial known as the INSIGHT study which is an open-label, phase 1b/2, multicenter, randomized trial conducted in 6 Asian countries. So this trial enrolled EGFR-positive patients without the acquired T790M mutation but with acquired MET overexpression or amplification. These patients were randomized to either gefitinib plus tepotinib, versus platinum doublet chemotherapy. The trial's primary endpoint was PFS by investigator assessment. Secondary endpoints included overall survival and safety. I like to mention that for this trial, only 31 patients were enrolled into the combination TKI group, and the PFS was 4.9 months. And for patients enrolled into the chemo group, PFS was 4.4 months. There were about 24 patients in the chemo group. In terms of overall survival, the data were quite similar. OS was 17.3 months for the combination TKI group versus 18.7 months for the chemo group.

So the trial's outcomes were essentially negative; however, if you focus on 34 patients with MET overexpression, defined by IHC of 3+, the PFS and OS data favored the combination TKI group: PFS was 8.3 months [gefitinib + tepotinib] compared to 4.4 months for chemo; OS was 37.3 months as compared with 17.9 months for the chemo group. Also, if you look at 19 patients with MET amplification, defined as a gene copy number of 5 or higher or ratio of 2 or higher, again, both PFS and OS data favored the combination TKI approach. PFS was 16.6 months as compared to 4.2 months for the chemo group; OS was 37.3 months as compared with 13.1 months for the chemo group. So this trial really triggered designing of many current ongoing trials to look at this combination approach to try to rescue resistance mechanisms of MET amplification or MET overexpression in patients with EGFR-positive non-small cell lung cancer after disease progression on EGFR TKI therapy.

So briefly, there are a couple of ongoing trials. The first one is the INSIGHT 2 study which is the combination of osimertinib and tepotinib. The second trial is the osimertinib plus savolitinib trial; savolitinib is another MET TKI. The third one is osimertinib plus TPX-0022, which is a next-generation TKI for MET alterations. And lastly, I like to mention a trial of JNJ-372 known as amuvatinib. This is a

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human bispecific EGFR c-MET antibody, so from a mechanistic standpoint, you could potentially think of this treatment as an option for MET alteration in EGFR-positive non-small cell lung cancer.

Dr. Paik:
In this sense, I think, the work that's been done trying to target these MET pathway alterations in EGFR-mutant lung cancers has been encouraging because in a relatively short period of time, we've been able to do a number of different trials that have shown some promising signals, which have led on to additional trials in this space. And so more to come on that, as well as, I think, targeting other pathways in the context of EGFR-mutant lung cancer and acquired resistance to drugs like osimertinib.

Well, this has been great. Before we wrap up, Dr. Zhu, can you provide us with one key takeaway from this chapter?

Dr. Zhu:
So my take-home message is that it is very important to look for resistance mechanisms in patients with EGFR-positive non-small cell lung cancer. This concept, perhaps, should be applied to patients with all oncogenic drivers among disease progression and existing TKIs. So when you do identify MET dysregulation as a resistance mechanism, perhaps we should consider a combination approach to block the original founder mutation as well as MET dysregulation.

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

Dr. Zhu:
So thank you very much for having me here today. Goodbye.

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