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MET Inhibition in Metastatic NSCLC “In the Spotlight”

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Dr. Paik:
Today we will be recapping the recent MET inhibition in metastatic non-small cell lung cancer symposium from WCLC [World Conference on Lung Cancer] 2023 and highlighting the clinical pearls that were discussed at that event.

This is CME on ReachMD and I’m Dr. Paul Paik. Here with me today are Drs. Keith Kerr and Ross Camidge.

Dr. Kerr:
Hi there.

Dr. Camidge:
Hello.

Dr. Paik:
Let’s get started with detecting MET gene aberrations. Dr. Kerr, can you please give us a brief overview of testing considerations for MET exon 14 skipping mutations?

Dr. Kerr:
Sure. Thanks very much Paul, for the introduction. So MET exon 14 skipping mutations are one of the number of different aberrations that we can find in non-small cell lung cancers, which may have clinical relevance. The other alterations are MET gene amplification and overexpression of the protein.

The unusual location and the size of the mutations does lead to some problems with testing and identification of these mutations. Now, we’re all used to using DNA and sequencing DNA, most likely in the context of a next-generation sequencing [NGS] approach, and yes, sequencing DNA will work. Certainly the hybrid-capture-type approaches of DNA sequencing are better than amplicon-based approaches for finding this kind of mutation, but this technology will miss some MET exon 14 skipping mutations. It’s actually better – the yield is better if we use RNA sequencing, again, usually in the context of next-generation sequencing. RNA sequencing appears to be better at picking up these alterations. It avoids some of the complications around the intronic involvement by the mutation, and rather like the success using RNA with fusion genes, MET exon 14 skipping is better identified using this particular technique.

Now, tissue is definitely the preferred medium for identifying these mutations, but you can also identify them in the blood. But there are issues, as we all know, about identifying any mutation that may be tumor-derived in the blood around issues with sensitivity because of the huge dilutional effect that any mutant alleles might have in the context of large amounts of DNA derived from non-tumor cells. So there is a sensitivity issue. And also bearing in mind what I just said about RNA being the preferred moiety, you can’t really work with RNA in the blood; you’re stuck with DNA. So you are going to miss even more, I guess, of the mutations. But if you find one, it’s good and it’s fine and it’s specific for the purposes of treatment. It’s just that tissue is better overall.

Finally, there are issues here around communication. It's really, really important that the lab knows that it's a MET exon 14 skipping mutation that the oncologist might be interested in, rather than one of the other alterations. And finally, the lab needs to communicate in discussion with the oncologist around any MET mutation that is identified as to whether or not we predict it's likely to cause mutations. So overall, communication really important in this arena.

Dr. Paik:
So, Keith, I appreciate the fact that pathologists are mindful of sort of synthesizing that and communicating over the fact that it is an exon 14 skipping alteration that's present, depending on what's found in the DNA.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Paul Paik, and here with me today are doctors Keith Kerr and Ross Camidge. We're highlighting the key takeaways and clinical pearls from the recent MET inhibition in non-small cell lung cancer symposium from WCLC 2023.

Dr. Kerr:
So next we need to move on to your presentation, Paul, which was describing the key clinical trials and the data from them around the use of MET inhibitors. Would you like to give us some of the highlights from that presentation?

Dr. Paik:
Oh, sure. So the presentation really was broken into, I think, 3 or 4 different parts. One of the parts was talking about the structure of the pivotal phase 2 trials that led to approval for MET inhibitors, particularly against MET exon 14 skipping. And the second part was about the clinical efficacy data. The third part was about certain important safety signals, particularly peripheral edema. And the fourth part, which was much more brief for the sake of time, had to do with taking a look at new emerging targets, and that really was MET amplification both in a primary and acquired-resistance setting.

Most of the discussion was about the FDA-approved indications for tepotinib and capmatinib. So the studies that led to their approval were called VISION and GEOMETRY, respectively, and they were fairly similar. They were both signal-finding, phase 2, non-randomized studies that were taking a look at overall response rate as a primary endpoint to really see what the signal of efficacy was in the population. Everyone had to have MET exon 14 skipping, though the way that this was detected differed between the 2 trials. For VISION, both tissue and liquid biopsy detection were allowed. For the GEOMETRY study with capmatinib, it was only tissue or tumor testing detecting MET exon 14 skipping that was allowed. Tepotinib ended up treating over 300 patients in a couple of different cohorts that were essentially identical. Capmatinib treated a bunch of patients, but parsed out by very specific lines of therapy cohort as the rehab, and these would be things like cohort, you know, 5b47 which was reported.

And I did present sort of the very specific details about the efficacy, but I think for this purpose, it's useful to say that if you take a look at the data, they're more similar than different. If you just lumped everything together, what you end up seeing is an overall response rate of between, really, sort of 50% to 60% depending on the particular drug and the line of therapy. For both tepotinib and capmatinib, it did look like the efficacy was a bit higher, in the 60% range in the frontline setting, a little bit lower for response rate in the second-line setting and beyond. Median PFS overall was around 12 months. Median overall survival, importantly, was between 20 to 21 months for both drugs. So as it stands, very good efficacy data from both drugs, which led to line-agnostic approvals for both in the United States.

The other thing we talked about was that peripheral edema seemed to be somewhat of a unique side effect in terms of kinetics. It takes about 2 months on average for the edema to develop and can take quite a long time for it to resolve. That in the end, it tends to be more like a lymphedema where drug cessation for upwards of 4 weeks, along with dose holds, are really the mainstays for management of the edema. Things like diuretics really don't work, and things like compression stockings and other lymphedema techniques have really mostly modest impact on the peripheral edema.

The updates at WCLC 2023 for MET inhibition really did focus on INSIGHT 2, which took a look – it was a randomized study of osimertinib and tepotinib versus tepotinib as a monotherapy in patients with MET-amplified non-small cell lung cancer in the acquired-resistance setting following treatment with a third-generation TKI [tyrosine kinase inhibitor]. And so there's been, against this backdrop, a wealth of other information from TATTON, et cetera, that suggests that this approach can be successful. Things like savolitinib combined with osimertinib, and so this is a formal way to test efficacy in a randomized study against a control arm of just tepotinib. And they were taking a look at overall response rate. One of the things to know about that I don't have time to talk about, but there is a particular definition for MET amplification that you'll have to take a look at, because those definitions do change depending on what trial you're looking at, and those things can feed into the efficacy data.

What I'd say is that the update does sort of demonstrate and reaffirm the fact that it's an effective therapy, that the response rate was quite good, in excess of 50%.

But I think one of the key questions that the data raised, and I think may be an issue from a regulatory standpoint, is how this is

perceived relative to what the standard of care might be. In this case the standard of care is chemotherapy. And so I think there's going to be some amount of discussion in the wake of this, along with some other data as to where this fits within the setting of MET-amplified lung cancer as an acquired-resistance mechanism relative to chemotherapy and sort of how one positions these things.

The other was a presentation taking a look at other biomarkers from the VISION study to try to see if we could tease anything out with regards to resistance mechanisms and things along those lines. Some of the data, our data that we had presented before when it came to the molecular characterization by liquid biopsy for responders and non-responders, but I think the more interesting part of this were some novel data that took a look at biomarkers in the blood. So these would be taking a look at ligands like HGF, which is the ligand for MET in the blood, to see whether or not those dynamics played into sensitivity to MET inhibition. And the takeaway message from that is that there did appear to be a signal that was there when it came to things like HGF ligand expression and resistance and sensitivity to therapy. So I think it's intriguing from a hypothesis-generating standpoint. I think the real trick here though is that we can't really do anything about these things, right? We don't have treatments that target ligands, and it's not entirely clear how we might be able to take advantage of this. And I think it's also not entirely clear as to whether or not we can use these biomarkers to stratify patients in terms of what they should receive.

So these updates were really, I think, important updates. They were very interesting updates, and hopefully we'll be able to build on top of these things with some other data and studies to really, at the end of the day, increase the efficacy that we're seeing with these drugs, but also really circumvent acquired resistance as a next step for our patients who need to move on to a next line of therapy.

Dr. Kerr:
Excellent, thank you. And that's really quite a nice segue into asking Ross to give us a summary on his experience and his presentation while actually using MET inhibitors in the clinic in the context of patients with MET exon 14 skipping mutations.

Dr. Camidge:
Yeah. Thanks. That was really a gift, Paul, for you setting me up for that. So I presented a case to illustrate a number of different points. So a woman in her middle 50s, never-smoker, who develops metastatic disease. No brain metastases at diagnosis and has a MET exon 14 skip mutation and a PD-L1 of 90%.

So she goes on MET TKI, has the peripheral edema, and Paul and I talked about, you know, some of the existing management but also the theoretical pathophysiology, that you get a sort of feedback loop, and part of that feedback loop liberates ligands that cause capillary leak, and Paul certainly has a theory that if we add in an anti-angiogenic, that might suppress things, and that's going on in some ongoing clinical trials now. The patient tolerated the treatment reasonably well apart from the peripheral edema, but then developed brain metastases and that opened up the discussion about which of the MET tyrosine kinase inhibitors has good or bad CNS [central nervous system] penetration. Obviously, crizotinib very poor, but there is data on both capmatinib and tepotinib having responses in the brain. It's a retrospective analysis, so they tend to have, like, more patients that have brain metastases than those with measurable brain metastases, but there is some evidence that both of these next-generation MET TKIs can have activity in the brain. And then when this patient progressed extracranially, we illustrated the point that she pushed very hard to have immunotherapy, and she completely blew through it, despite a PD-L1 of 90%. No benefit whatsoever. And that kind of picks up on what Paul just said, which is, you know, it's not about the PD-L1; it's not just about the MET exon 14. Maybe smoking status might be the differentiator. You know, that a high PD-L1 in somebody with a reasonable smoking history might mean a lot more in the setting of a MET exon 14 skip mutation than somebody with a never-smoking history, and that's what we kind of used the case to illustrate.

Dr. Paik:
One of the things that we didn't get to talk about that we did sort of cover during the Q&A is MET amplification in the EGFR-acquired resistance setting and whether or not this is something that you're routinely testing for, Ross, and if you do detect MET amplification in whatever RASi [renin-angiotensin system inhibitors] you're using, whether or not at this point you're comfortable treating with a MET inhibitor or if there are other alternatives to consider in these particular cases.

Dr. Camidge:
So we do rebiopsy for, you know, many of the drive oncogenes that had a specific targeted therapy, and we do include MET FISH [fluorescence in situ hybridization] testing. And it's interesting, you brought it up earlier, the FISH testing, we think, allows us a better call for MET amplification than next-generation sequencing because your amplified relative to something in the next-generation sequencing. Keith, maybe you want to comment on this. It's a bit of a black box because it might vary depending on your assay. So we do MET FISH testing, and yes, if we see it we do act on it probably initially by adding in a MET TKI. But, you know, I think some of the MET ADCs [antibody-drug conjugates] are going to be interesting in that setting.

So, Keith, one issue regarding FISH in the acquired-resistance setting is we have some data that the level of perceived MET copy number gain in whatever form appears lower than in the primary driver state of MET amplification. And, you know, the hypothesis is that

it's a subclone, and so your denominator might be all of the cells, not all of which you've got acquired resistance, and your numerator is just the acquired-resistance ones which have MET amplification. And I really think FISH probably allows you to make that call better than next-generation sequencing, which just takes everything together. But what do you think?

Dr. Kerr:
It would certainly allow you to make that call provided, of course, that you have a sufficient number of cells to appreciate what might be heterogeneity in the number of copies in particular in individual tumor cells. You would be relying, then, on your biopsy having enough tumor cells that are assessable, but also a reasonable representation of what's in the patient's disease. And given that I suspect in patients who've got this kind of subclonal heterogeneity, it may be localized within the context of 100 or 1,000 tumor cells rather than there being an intimate admixture of cells with different copy numbers in them. So it might be a bit of blind luck when it comes to the biopsy, but for sure you're not going to get the kind of averaged assessment that you would through NGS. And bearing in mind that NGS doesn't make the distinction between amplification and polysomy, and polysomy is extremely common in lung cancer. And given the fact that we know that with MET exon 14 alterations we see sometimes phenomenal nuclear irregularity, polysomy, I think, is particularly common in those particular patients. So I would certainly advocate using FISH where I could.

Dr. Paik:
I think the discussion has pulled this out, that FISH is kind of the poor man's single-cell, you know, testing. In this case, it's still DNA testing. But it provides that level of granularity and can then reveal really parts of the heterogeneity of biology that something integrative like NGS really does miss. And I think that's a really important thing to highlight as part of this discussion.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Keith and Ross, as ever for joining us and for sharing all of your valuable insights and expertise. It was great speaking with you today.

Dr. Kerr:
Thank you very much.

Dr. Camidge:
Thanks for having us, Paul.

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