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The Changing Landscape of NSCLC: MET Inhibitors

Dr. Vokes:
When looking at the non-small cell lung cancer patient population as a whole, approximately 3–4% harbor MET exon 14 skipping mutations that result in increased MET kinase protein levels and a constitutively active pathway. And although this patient subset does not yet have a licensed therapy in the United States, the good news is that there is a lot of excitement that these changes may be targetable with MET-directed approaches, which is what we'll be focusing on today.

Welcome to CME on ReachMD. I'm Dr. Everett Vokes, and joining me today is
Dr. Ross Camidge. Welcome to the program, Dr. Camidge.

Dr. Camidge:
Thanks for having me.

Dr. Vokes:
So let's get started. There's increasing discussion about MET exon 14 skipping mutations and MET gene amplifications in non-small cell lung cancer. What exactly are they, and why have they become such an important genetic marker to identify?

Dr. Camidge:
So we've known about MET, which is the receptor for the hepatocyte growth factor, as a contributor to oncogenesis for many years, and I think what we're starting to define is some subgroups of non-small cell lung cancer where MET is the primary driver of their—of their state. The ways we can define that are variable. Perhaps the easiest one is these things called MET exon 14 skip mutations, which are a range of different mutations which alter the splicing of the RNA such that you lose the coding for exon 14, which encodes something called the CBL-binding domain, which is essentially the expiry date the of the protein, and when that's not there, the protein has a longer half-life on the surface of the cell; it's felt to auto-aggregate or together with its ligand and cause signaling.

In addition you can get a MET-addicted state through other means. A high copy number of the gene, which can be defined in different ways, can also sometimes produce a primary MET-driven state. And finally, there are rare examples like MET fusions which behave a little bit like ALK, and Ras1 gene fusions can also be described as another means of primary MET-driven status.

Dr. Vokes:
Great. So there are several different inhibitors of MET pathway activation including anti-hepatocyte growth factor, MET receptor antibodies, as well as small molecule MET kinase inhibitors in development. So let's look at the anti-hepatocyte growth factor MET receptor antibodies first. Could you describe some of them for us, Dr. Camidge?

Dr. Camidge:
Yes. So we actually have a lot of tools in the armamentarium for attacking the MET pathway. Some of the earlier attempts, many of which were unsuccessful, were developing monoclonal antibodies either against the ligand, HGF, or against the MET receptor itself. To be honest, most of those have fallen by the wayside partly, you could argue, because of the drug but probably a lot because of not quite knowing who to give it to. But most of the excitement I think is relating to the small molecule inhibitors, and crizotinib, which was, perhaps, the first workhorse MET inhibitor—it's well-known as an ALK and Ras1 inhibitor but is also a MET inhibitor—has shown some

interesting activity, but the other drugs, such as capmatinib and tepotinib, have also, I think, really taken over that mantle. They also have CNS activity, which crizotinib does not.

One of the things we're starting to realize is that there are different classes of MET inhibitor. It becomes a little complex in terms of the biochemistry, but most of it relates to where these drugs bind on the kinase domain of the MET, and it matters because sometimes the acquired resistance mechanisms will leave the MET vulnerable to something in a different class. Crizotinib is a type 1A. Capmatinib and tepotinib are both type 1Bs, which means they have a slightly different binding site. And the type 2s, there's the rather dirty drug cabozantinib, but some of the other drugs such as glesatinib and merestinib are type 2 inhibitors, but they're not the ones which are the focus of most clinical development at present.

Dr. Vokes:
Great. So, for those just tuning in, you're listening to CME on ReachMD. I'm Dr. Everett Vokes, and today I'm speaking with Dr. Ross Camidge about the role of MET kinase activation in non-small cell lung cancer, and we are currently addressing some of the therapeutic implications and available currently-under-investigation drugs.

And, Dr. Camidge, Could you also discuss a little bit the importance that some of these are very specific and some of them are what we call a little bit more dirty, multi-kinase inhibitor in terms of what that would mean for their toxicities as we think about treating patients with these various drugs?

Dr. Camidge:
Well, with any kinase inhibitor, there are all varying levels of dirtiness in terms of other kinases that they hit. Now, in terms of their effect on toxicity, that depends on how much of the toxicity is due to on-target activity in terms of the target you're concerned with. So, for example, peripheral edema is an on-target effect of MET inhibition, so all of these will produce that, but the drugs which also hit a bunch of other kinases… So crizotinib hits ALK and Ras1, which doesn't give it a lot of extra toxicity, but cabozantinib hits a large range of other kinases and certainly is a fairly tough drug to give. Anyone who's trying to give it for thyroid cancer will recognize that dose reduction is very common for mucositis or diarrhea. So, when you want to hit MET, having a cleaner MET drug means you'll take on board the MET-related toxicities, but you can jettison some of the unnecessary baggage, and cabozantinib would be a great example of a drug with a lot of unnecessary baggage.

Dr. Vokes:
So, Dr. Camidge, what can you tell us then about the clinical data so far that have been generated with these more specific drugs targeting MET exon 14 mutations?

Dr. Camidge:
Well, there's a lot of interesting data that's coming out. If you look… And let's focus on capmatinib and tepotinib as the 2 furthest advanced in-development drugs. If you look at their data, they seem to routinely have objective response rates in the 40–50% range. Now, there's an exception. There's a 28-patient study of capmatinib in the first-line which showed a 68% response rate by the independent radiology review committee, 61% by the investigator—interesting, that's the opposite way around from the way we would normally do it—but that's really the exception. And if you look at capmatinib in the second or third line, it's still running in about a 40% response rate. Tepotinib, regardless of line of therapy, is running at about a 40–50% response rate. And median PFSs are sort of running in the 12- to 9-month range.

Now, certainly this shows activity of these agents in MET exon 14 skip-mutant patients—and on the basis of this, for example, we've recently heard that tepotinib has just got licensed in Japan for MET exon 14 skip-mutant-positive patients—but I think there's something hiding in plain sight here. I think the fact that we're used to with ALK and EGFR to get response rates in the 70–80% range and we're really not seeing that with the exception of that first-line study of capmatinib, maybe what we're really seeing is some underlying biological heterogeneity. And if you get lucky, your study happens to have more of those patients and your response rate is higher, and if you're unlucky, your study has fewer of those patients and your response rate is lower, and that introduces A) a question as to what is that relevant heterogeneity, and secondly, it introduces a challenge in comparing the activity of different drugs when you don't know if it's the drug effect versus who actually went into the studies.

There's only one clue. So clearly, if there's our kind of true MET-addicted population and some who are either less or not addicted who go into the study, that can mess around with your response rate; it can mess around with your PFS; but it introduces the idea that duration of response might be our only clue to allow us to compare between drugs. And what I mean by that is if you responded, you've kind of defined yourself as being in the true MET-addicted state, and, therefore, a difference in the duration of response could actually reflect a difference in the effects of the drugs. And it's interesting that tepotinib tends to have durations in response running about 14 or 15 months, whereas there are about 9–11 months for capmatinib. The one caveat here is you have to assume that the duration of follow-up is actually the same. I think that's definitely going to be something to watch.

Dr. Vokes:
Really interesting information. Is there anything you can tell us about the patients with brain metastases? This is something that commonly happens in this population of patients. Do the drugs work? Do they help these patients best as we know today?

Dr. Camidge:
So that's a really great question, and I think we've certainly seen in the last few years a maturation in our thinking in terms of how to address brain metastases in clinical trials. Capmatinib I think did a somewhat better job in terms of allowing patients in with untreated brain metastases and capturing that data, and they certainly have generated some data that they have CNS efficacy. Tepotinib took a more conservative approach. They tended to exclude those patients from getting into their study, but they had an expanded access program or single patient IND for 1 patient actually with a MET fusion who had brain metastases and they clearly responded, so I think tepotinib is playing catch-up. Both of them believe they have activity in the brain, but we have a slightly tighter dataset for capmatinib than tepotinib at present.

Dr. Vokes:
Great. And, Dr. Camidge, can you also comment on the other class of patients—or group of patients better—where EGFR is… The EGFR-mutant population that becomes resistant to an EGFR inhibitor with MET amplification, is that a group of patients that could benefit or is benefitting best as we know to date from this class of drugs?

Dr. Camidge:
Yes, I think MET is certainly going to be in the running for Best Supporting Actor Oscar because it can be the mechanism of acquired resistance. We now know for EGFR-mutant cases on both first-, second- and third-generation EGFR inhibitors. Recently, we saw it was also a mechanism of acquired resistance in ALK-rearranged patients. And so the excitement is these classes of drugs, these more specific MET inhibitors with CNS penetration, may have an additional life as something that is added in in those patients who are manifesting MET as their mechanism of acquired resistance. EGFR is the group that is furthest advanced. The challenge there is that they are using MET often by MET amplification, which goes back to the idea that it's a continuous variable. Where do you put the cutpoint to say this is the group that needs MET added in and this is the group that doesn't. There are conflicting demands. The higher you put the cutpoint, the more you're going to show activity but the smaller your patient population that might benefit.

Dr. Vokes:
Thank you. And as we come to the end of our program, Dr. Camidge, what are the key take-home messages from this discussion? And could you also offer a glimpse of how you think these agents will be used in the near future to improve outcomes for subsets of patients with non-small cell lung cancer?

Dr. Camidge:
I'm excited that MET, which has really hung around for quite a long time, is now going to have its moment in the sun. I think MET exon 14 will be the first group that we will start to routinely test for. We are going to have useful tools which are going to get this disease under control, but that is the beginning of the journey, not the end. As mentioned, maybe there's going to be relevant heterogeneity in MET exon 14 to truly define the sensitive population. We're going to see acquired resistance mechanisms which may still be addicted to MET, and maybe we need to change the class of drug. Maybe those antibodies or antibody drug conjugates are going to come in there. And then those same agents are going to have a separate life where MET is a mechanism of acquired resistance in other driver oncogenes. So this is the beginning of MET's time as a relevant biomarker in lung cancer.

Dr. Vokes:
Great. Thank you for sharing that, Dr. Camidge. And for me, I agree with these conclusions. I think the biggest take-home message is, 3–4%, that is a large number of patients where non-small cell lung cancer is concerned with a MET exon 14 mutation, and then an additional group of patients coming from the EGFR-mutated cohort of patients, so this is a potentially large group of patients for which there's now increased hope that in the future we will have better treatments available.

Unfortunately, that's all the time we have for today, so I want to thank my guest, Dr. Ross Camidge, for joining me today to discuss MET kinase pathway activation in non-small cell lung cancer. It was great speaking to you today, Dr. Camidge.

Dr. Camidge:
It was my pleasure.