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Recognizing the Role of Capmatinib for METex14 in NSCLC

Dr. Sands:
For patients with metastatic non-small cell lung cancer, MET exon 14 skipping mutations can occur in three to four percent of patients. MET amplification can also occur in other patients. With the recent approval of a new selective inhibitor of the MET receptor capmatinib, another treatment option may be available for patients.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands. And joining me to talk about the role of capmatinib for metastatic non-small cell lung cancer is Dr. Edward Garon, a thoracic medical oncologist and Professor of Medicine at the David Geffen School of Medicine at the University of California, Los Angeles.

Dr. Garon, thank you for joining me today.

Dr. Garon:
Thank you very much for having me.

Dr. Sands:
So, to start, Dr. Garon, can you discuss the typical treatment options that existed for patients with a MET exon 14 skipping mutation?

Dr. Garon:
Sure. So, in patients who were diagnosed with non-small cell lung cancer and MET exon 14 skipping mutation was identified, those patients were traditionally eligible for chemotherapy. Over time, most patients with who do not have contraindications received both chemotherapy and immunotherapy, although there's some data to indicate that the outcome of this group of patients is not particularly good with those approaches. At the time of progression on front-line chemotherapy or chemoimmunotherapy, options were more like second-line docetaxel, which has a reasonable toxicity profile, but fairly difficult and a somewhat modest overall benefit, and so that's the sort of situation into which these MET inhibitors were coming when they were in clinical development.

Dr. Sands:
And now let's take a look at the GEOMETRY Mono-1 study. But before we get into some of the details of that trial, can you give us a little background to the study itself?

Dr. Garon:
Sure. So the study that you're referring to is the study that led to the approval of capmatinib, and this is a study that was designed to really comprehensively evaluate MET as an oncogene and treatments that would be effective in treating sort of MET-driven non-small cell lung cancer. So, MET is an oncogene that has been studied for decades now. It is the receptor for hepatocyte growth factor. And many of those efforts really had not been successful to date.

One of the groups that we had looked at historically with MET were patients who had amplification of the gene. Now, there are a relatively large percentage of patients with non-small cell lung cancer who have some increase in the number of copies of the MET gene, but very high copies are fairly uncommon.

So, interestingly, in sort of the early days of defining oncogenes in non-small cell lung cancer, we were often looking, for instance, at whole exome sequencing, looking at all of the DNA that codes for an eventual protein, because our sense was that if you were going to have an abnormality that would be druggable, of course you would have to have a mutation or genomic abnormality in the coding region of a gene. But MET exon 14 skipping is a little bit different in that a portion of the DNA doesn't end up making it into the eventual protein, whereas typically it would. And the reason this is an issue is that the missing portion is integral in the destruction of MET. So basically,

there's then an impeded ability to get rid of MET, and over time, that emerged as a potential vulnerability that's seen in probably somewhere near four percent of patients with non-small cell lung cancer.

Dr. Sands:
Okay. So, within the background you had mentioned that these patients maybe have a worse prognosis in general when treating with what had been the standard of care options, particularly chemotherapy, and then more recently also with immunotherapy, and now looking at next line and the consideration of docetaxel, which in many cases, although, had been the standard for a long time, I know in many cases we are now not as enthusiastic about having to go to docetaxel in the second-line setting.

Let's turn to some of the results now of the GEOMETRY Mono-1 trial. Can you maybe give us an overview of the findings from the trial? And then we can dive into some of the details.

Dr. Garon:
Sure. So the GEOMETRY Mono 1 study was really a study that looked at MET sort of across the board. We looked at some patients who had, for instance, low-level amplification, some patients who had medium-level amplification, some patients who had high-level amplification. Interestingly, the drug does have activity, particularly in patients who have high-level amplification of MET, but that activity was not sufficient to get the drug approved, where the activity was greater was among patients who had MET exon 14 skipping. That was a group that approximately 40 percent of patients who were previously treated, responded.

Again, as you mentioned, certainly when compared to the risk-benefit profile of docetaxel-based chemotherapy, which certainly has its tolerability difficulties, that that was considered quite good. And the response rate in the patients who were treatment-naive was more in the 70 percent range. The progression-free survival was reasonable in that group, and many of these patients had good duration of response, which obviously is something that we look at more over time, as we sort of hope in the era of targeted therapy that not only will patients, respond to therapy but that that response, will be long-lasting.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Edward Garon about the GEOMETRY Mono-1 trial and the role of capmatinib for metastatic non-small cell lung cancer.

Now, Dr. Garon, so we've gone over kind of the overview of some of the details of the trial, and, of course, this did lead to FDA approval, as you've mentioned. Let's dive into some of the nuances of it. Is there anything about this that you think is worth pointing out as far as subpopulations? And how will this impact, or how does this impact, your perspective on standard of care and when to utilize this?

Dr. Garon:
Sure. So one thing that is different about MET exon 14 skipping as opposed to some of the driver mutations that have been more traditional, the patients with MET exon 14 skipping mutation are more similar to lung cancer patients in general. They are older. The median age is in the early 70s, right around the median age of lung cancer in general perhaps partly because smoking prevalence was higher when these patients were younger. They are a little more likely to be smokers than patients who have, for instance, EGFR or ALK genomic abnormalities.

Other things to know is that because the testing is a little more complicated, you know, good molecular tests will certainly test for MET exon 14 skipping, but there are tests, unfortunately, that will return a MET result that is not assessing for MET exon 14 skipping, which is the targetable mutation here, and I think that's something for which we have to be watchful. The other thing to know is that in some of your patients who maybe a couple years ago or more did have genomic testing, it is certainly possible that they had what at the time was comprehensive testing for genomic abnormalities, and were sort of considered to be "pan-negative," but now, in fact, do have a MET exon 14 skipping mutation and can be offered a targeted therapy, and that fact, is something that I have certainly seen in my practice.

Dr. Sands:
And to add to that, let's say you're meeting a new patient, you're sending testing, and prior to any therapy you're now noting a MET exon 14 skipping mutation. How would that alter your treatment at that time?

Dr. Garon:
Under most circumstances, I have been using capmatinib as my front-line option in these. There is an additional issue that we know that capmatinib, like other tyrosine kinase inhibitors has been somewhat both difficult to combine with a PD-1 or PD-L1 inhibitor. And, actually, there is some data to indicate that patients are going to be likely to have an increased risk of toxicity if they got a prior PD-1 or PD-L1 inhibitor or other immunotherapy. So, in totality, when going through all of that, in most cases when I know they have a MET exon 14 skipping mutation, I started with capmatinib rather than the combination for instance, chemotherapy and immunotherapy.

So one thing I would certainly want clinicians to know is that they should remember that this tends to often be an elderly population and that although capmatinib is in general well-tolerated at the 400 mg twice-a-day dose that is approved, especially in patients who are in their late 80s or early 90s, I often will start at a reduced dose. Some of the toxicities like lower extremity edema can be difficult. Particularly in this quite old patient population, I have reduced the dose prior to starting.

Dr. Sands:
So I imagine that's very encouraging for many to hear as patients in their late 80s, early 90s, still a treatment option that can benefit one's quality of life. I find that to be a surprise to many, and so it's really important that these patients end up seeing their oncologist to discuss these options because if patients don't go in to be seen, then these things can't be looked for, and options are not known in that setting.

Dr. Garon:
Yes, and I'd like to follow up on that point because I think that, historically, there has been a sense among primary care physicians and even pulmonologists that for patients in this age range, that you almost want to protect them from the oncologist. You want to prevent them from having the toxicities of traditional chemotherapy. And I think that with a drug like capmatinib, that becomes somewhat silly. The disease itself has significant toxicities, and to be able to treat a patient and have better disease control for a longer period of time is likely to both allow a person to live longer, but also should be helpful from a quality perspective rather than harmful.

Dr. Sands:
Yeah, such an important statement. When you are seeing a new patient, how are you ordering genomic testing and just talking from the beginning what everybody should know about the importance of genomic testing and how you do that?

Dr. Garon:
The gold standard is still tissue. MET exon 14 skipping can be picked up on liquid biopsy, but the accuracy to date remains better with a tissue-based biopsy. I think that I would caution the listeners. There are somewhat limited regulations with respect to diagnostic companies, and I certainly would want to know if I get a result on that to see specifically that they test for MET exon 14 skipping.

Dr. Sands:
Well, I appreciate that excellent overview of MET exon 14 skipping mutations, MET amplification, and capmatinib in particular. Dr. Garon, I'd like to leave you with the last word. Any final takeaways that you'd like to leave with our audience today?

Dr. Garon:
Yeah. I think that it's exciting that there are new options. Both capmatinib and tepotinib are approved in patients with MET exon 14 skipping. There is an additional drug, savolitinib, which has also been extensively developed as a potential approach in patients with EGFR mutations at the time of progression. Some of those patients do have MET amplification, and that is a very active area of research. And so, if you do get data on patients, for instance, who have other driver mutations and have subsequent testing showing MET amplification, consider referring them for clinical trials in your area. If you have patients who have received the approved agents with MET exon 14 skipping mutations, just to know that there are clinical trials looking to improve on the currently available approaches. And finally, that in terms of amplification, although there are no approved agents for MET amplification, to know that can be a true driver for patients and that to consider a referral of patients like those for clinical trials. And as I say, there is some data to indicate efficacy, particularly in patients with high-level MET amplification, at least in the GEOMETRY study that was defined by patients who had a gene copy number of 10 or greater.

Dr. Sands:
Well, with those final words about the increasing options with MET exon 14 skipping mutation and the importance of clinical trial enrollment, I want to thank my guest, Dr. Edward Garon, for joining me today to share his insights. Dr. Garon, it was wonderful having you on the program.

Dr. Garon:
Thank you very much for having me.

Dr. Sands:
I'm Dr. Jacob Sands. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology where you can be Part of the Knowledge. Thanks for listening.