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https://reachmd.com/programs/cme/evaluating-your-current-options-in-the-treatment-of-nsclc-with-metex14-skipping-mutations/14089/

Released: 11/02/2022
Valid until: 01/17/2025
Time needed to complete: 15 minutes

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

Evaluating Your Current Options in the Treatment of NSCLC with METex14 Skipping Mutations

Announcer:
Welcome to CME on ReachMD. This activity, entitled **"Evaluating Your Current Options in the Treatment of NSCLC with METex14 Skipping Mutations"** is provided by **AGILE**.

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Dr. Paik:
MET exon 14 skipping is observed in 3% to 4% of all non-small cell lung cancer cases. We now have 2 FDA-approved therapies to consider for our patients with non-small cell lung cancers harboring MET exon 14 alterations. So it's becoming increasingly important to use broad molecular profiling to ensure patients receive the appropriate targeted therapy. Do you have the tools you need to select the right therapy for the patient in front of you?

This is CME on ReachMD, and I'm Dr. Paul Paik.

Dr. Shu:
And I'm Dr. Catherine Shu.

Dr. Paik:
So let's dive right into a case study. We have a 74-year-old man with a 15 pack-year history of smoking, who was recently diagnosed with stage IV adenocarcinoma of the lung through a tissue biopsy. Sites of metastatic disease include the liver and the bone, but he's not terribly symptomatic from his disease. His ECOG performance status is zero.

Dr. Shu, what initial steps do you take in the management of this patient?

Dr. Shu:
So now that we have so many great targeted treatment options, I think it's more important now than ever to perform reflex testing with a comprehensive molecular panel. At my institution, we test all lung adenocarcinomas with a reflex panel. And I think this is important because, even though we have some stereotypes for which types of mutations we find in which patients, it's still not a complete "typical" patient, and we don't want to miss any patients. The stakes are just so high. And I think that even a low pretest probability is not zero.

So at our institution, we perform a reflex test. And then if that reflex DNA test is negative, we go on to do an RNA-based test. I think the RNA-based tests, we know can capture a higher proportion of these MET exon 14 skipping patients, because the RNA result of the MET exon 14 skipping is constant regardless of the underlying genomic event.

So for this patient, I would start with making sure that he has a comprehensive molecular panel pending. And the other thing that I would say is I often do order a liquid biopsy, because if it turns out that the tissue biopsy can't, you know, doesn't have enough tissue to make it through testing, then at least you have a liquid biopsy pending. So I think for this patient, we make sure that he has some sort of NGS [next-generation-sequencing]-based panel going and I would also perform a liquid biopsy.

Dr. Paik:
No, I think that's a great point, especially the reflex nature of the testing. Generally speaking, when we meet a patient, we really have no idea what alteration they're going to have, so whether or not they have an EGFR mutation or an ALK fusion or a MET exon 14 skipping alteration, any of those things would be great. But like you said, we can't a priori predict who's going to have one of those things. So really the only reliable way to find one of these things is to actually order the test on everyone in an indiscriminate manner. And so I think that's actually one of the most important points.

Dr. Shu:
Molecular testing in our patient confirms a MET exon 14 skipping mutation. As far as treatment, we now have 2 FDA-approved targeted therapies to consider.

Dr. Paik, what can you tell us about the first option, tepotinib?

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. Catherine Shu. We're discussing current options in the treatment of non-small cell lung cancer patients with MET exon 14 skipping mutations.

So tepotinib is a selective MET inhibitor that was FDA-approved in 2021 for patients with stage IV or advanced non-small cell lung cancers whose cancers do harbor MET exon 14 skipping alteration. VISION was a signal finding, single-arm, phase 2 study of tepotinib in a non-randomized fashion in this specific population.

There are a couple of points that are worth highlighting, I think, for the VISION study. The first is that there were 2 ways that patients could get onto the study. One way was through, as we talked about in the case before, standard tumor testing through next-gen sequencing. The other was actually through liquid biopsy. And so the data, the efficacy data that's been presented is parsed out in that fashion, patients who were liquid biopsy positive, patients who were tissue biopsy positive.

In addition to that, while there were no prespecified or cohort numbers for analysis, patients were – 50% of patients accrued or treated in the first-line setting, 50% in the second line setting and beyond. So the data that's been presented sort of hews to that first-line efficacy for the second-line and beyond efficacy. And it was a positive study, which is why it was FDA-approved in 2021. By lines of therapy, first-line therapy patients had an overall response rate as of the latest data update that was presented at World Lung just a couple of months ago, about 60% with a median PFS [progression-free survival] of around 16 to 17 months, which is pretty good as a first-line therapy. The second-line therapy and beyond had an overall response rate of about 47% with a median PFS of 12 months.

So I think overall, most of us would consider this a great option for our patients, particularly our patients who tend to be elderly. And we really did reach that bar for what would be classified as adequate results to give in that frontline therapy.

I think the last thing to talk about were the safety, sort of, adverse events features of the study. And there's a fingerprint for safety for MET inhibitors, which I sort of think about as a vascular leak phenomenon. Most of this is peripheral edema, about 60% of patients will develop peripheral edema. Most of these are grade 1 or 2 events; very few of these are grade 3 events. But when you're older, and you're not as mobile and your feet are swelling, you can't put your shoes on, it's still something of a quality of life issue to be aware of. Again, it's something that tends to be unique for MET inhibition.

Dr. Shu, can you discuss the other FDA-approved therapy for this driver mutation, which is capmatinib?

Dr. Shu:
Sure. So this is about the GEOMETRY trial, which was a multiple cohort phase 2 study evaluating capmatinib in 2 populations, in the MET exon 14 skipping population as well as the MET amplification population. Patients received capmatinib at 400 mg BID, and the primary endpoint was overall response. In the patients with MET exon 14 skipping, the overall response was seen in 41% of the previously treated patients but as high as 68% in the treatment-naïve patients, which goes to what you were saying before with the higher response rate in the treatment-naïve patients. The median duration of response was 9.7 months and 12.6 months, respectively.

The efficacy seen in the MET amplification arm was much lower, although the response was 29% in the previously treated and up to 40% in the treatment-naïve patients and patients with a gene copy number of 10 or greater.

The most frequent adverse events are similar to what you had discussed earlier. They were really peripheral edema, which we saw in 51% of patients, but only 9% of those were grade 3 to 4. So even though seen in many patients, really a much smaller proportion that were significant. And also nausea, which was seen in 45% of patients. And there was also 1 death from pneumonitis that was thought to be related to the capmatinib.

Dr. Paik:

Now that we've outlined the clinical data for tepotinib and capmatinib, let's talk about any key distinctions between the 2 and have a bit of a friendly debate, keeping in mind, the patient we discussed earlier.

So I think I'll start by adding a bit of a suppositional in the case. One of the things I did not mention was the PD-L1 TPS [tumor proportion score] status, which of course we also recommend is done in a reflex fashion for all non-small cell lung cancer patients. Let's say the PD-L1 TPS comes back at 50%. One of the questions is differences between tepotinib and capmatinib, but this is not in isolation. We do know that standard frontline therapy is also in the realm of immunotherapy. And so I guess the first question I have for you is, would you treat that patient with a MET inhibitor or with immunotherapy, for example, like pembrolizumab, and why?

Dr. Shu:
That's a great question, Paul. I think if you ask, you know, several oncologists, you may get many different answers. However, I would still start with a MET inhibitor myself. I think that there is really great efficacy. The side effects profile, as we mentioned, is somewhat limited. And it's a PO pill. So tepotinib is a once-daily and capmatinib is a twice-daily pill. So there is some difference there. But really, between the 2 drugs, I find them fairly similar. And I think that most physicians who prescribe them maybe prescribe whichever one they're more comfortable with or have been prescribing more often. But back to the kind of the immunotherapy versus the targeted therapy question, if I were a patient, and I could get a great response just by taking a pill versus coming into an infusion center every few weeks, I think that that would be still my choice. How about yourself?

Dr. Paik:
No, I think that's right. And I think the data tend to support that insofar as we have any kind of data, which is important to note that we don't have any kind of prospective data. It really is retrospective data that our institution did and some others have done that demonstrates that patients with MET exon 14 skipping alterations, even with high PD-L1 expression in their tumors, do tend to be resistant to single-agent immunotherapy. So there is a concern, as with other oncogenic cancers, that these are more resistant to immunotherapy. So that's the first thing, I think, that leads us to have a little bit of a pause in terms of recommending that.

The other is that in elderly patients – and again, patients with MET exon 14 skipping alterations tend to be elderly. Many of these patients are in their 80s when we meet them, as you know. They're not actually well represented in these pivotal randomized phase 3 studies of immunotherapy, even in the frontline setting, so we actually don't know what the results are in that population. So I think I tend to agree with you that most of us would end up prescribing a MET inhibitor for that reason.

And like you, I think it's very difficult to make comparisons, cross-trial comparisons between tepotinib and capmatinib, because they have not been randomized and studied in that fashion. I think one of the things that we tried to do to overcome that was to perform what's called a matching-adjusted indirect comparison [MAIC] analysis where we take data from 2 separate single-arm studies, 1 of which at least we have sort of granular patient-level data, and try to sort of align the patient populations between the 2 and then redo an efficacy analysis to see whether or not, in a more balanced fashion, differences emerge. So we published this earlier this year, this MAIC analysis where we sort of confirmed that in the up-front setting, the treatment-naïve setting, there are no differences for overall response rate or PFS between capmatinib and tepotinib. The 1 difference that we did see emerge in the MAIC analysis was in the second-line and beyond PFS, where there was a difference, which is also evident on cross-trial comparison, actually, where the median PFS for tepotinib was 11 months and for capmatinib it was 5.5 months. Why that difference exists when there are otherwise fairly similar drugs, no one really knows. But that difference does, in fact, exist on MAIC, even on cross trial comparisons. So I think that's one of the differences that's there.

I think the last thing that I'll mention is that, you know, dosing does tend to matter in the elderly population. Polypharmacy is an issue for these folks. And so capmatinib is a number of pills taken twice daily, tepotinib is 2 pills taken once daily, and that tends to simplify the regimen for these patients with dose modifications.

Dr. Shu:
Well, this has been a great discussion, Dr. Paik. but before we wrap up, can you share your one take-home message with our audience?

Dr. Paik:
My take-home message is that the, sort of, advances we make in non-small cell lung cancer haven't stopped; they continue to march on. MET exon 14 skipping alterations are found in 3% to 4% of patients. This is something that's pretty new, I think, at a time when we thought, many of us, that we'd exhausted finding any new actual alterations. And I find that terribly encouraging. I think it's particularly important for patients with these alterations, because as we said before, they tend to be elderly; they are often left out of the pivotal trials. So we don't really know what the best treatment options are for these patients. And they do have a unique set of circumstances, comorbidities that we have to take into consideration. And so, this is, you know, this set of drugs is really a great option for these folks.

Dr. Shu:

Absolutely. Well, those were great points, Dr. Paik. I think my main takeaway is probably around detection, because as we know, if you don't find it, you can't treat it. so for me, I would say test all lung adenocarcinomas with some sort of next-generation sequencing test. And if the DNA-based test is negative, I would encourage you to look onwards with an RNA-based test.

Dr. Paik:
Right. I'd like to thank our audience for listening in and thank you, Dr. Shu, for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Shu:
My pleasure and same to you.

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