Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/how-approach-liquid-biopsy-treatment-nsclc/11275/

Released: 04/30/2020
Valid until: 04/29/2021
Time needed to complete: 15 minutes

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

How to Approach Liquid Biopsy in the Treatment of NSCLC

Dr. Socinski:
Lung cancer remains the most common cause of cancer-related mortality. This outcome is often related to its advanced stage at diagnosis as well as the challenge to obtain sufficient initial or sequential tissue biopsy material to guide therapy. Recently, liquid biopsy has emerged as a less invasive approach than tissue biopsy, and its application in non-small cell lung cancer continues to grow.

This is CME on ReachMD, and I'm Dr. Mark Socinski. Joining me today is
Dr. Ming Tsao to discuss the role of liquid biopsy in non-small cell lung cancer.

Dr. Tsao, welcome to the show.

Dr. Tsao:
Thanks for having me. It's great to be here.

Dr. Socinski:
So, for many years, Ming, we have always looked at tissue as kind of the gold standard for not only histopathologic diagnosis but also for molecular testing, and I wonder if you could just explain to us kind of the advantages and disadvantages of liquid biopsy compared to tissue biopsy in patients with advanced non-small cell lung cancer .

Dr. Tsao:
As you just said, that the standard is tissue biopsy, and we can do a lot of molecular testing on the tissue biopsy, but tissue biopsy does take some time. Sometimes it takes some time to arrange to do the procedure, and there is some sort of risk with it, but with the liquid biopsy, of course, it's much simpler to take blood from patients, and then it can be done much more—sort of a shorter turnaround time to get the results. But there are some pitfalls with the liquid biopsies, and particularly I think there is some data, good data, showing that in fact it has less sensitivity. That means that for some genes it can only have a sensitivity of approximately 80%—for example, T790M, EGFR T790M mutations. On the other hand, also, there is some advantage with liquid biopsy because it can cover tumor heterogeneity. For example, if you biopsy, you only biopsy one of the lesions, but if that lesion does not have the mutation, then you will miss it. And liquid biopsy, basically, cell-free DNA, in circulating DNA it collects the whole tumor, so DNA coming from the tumor, the whole body, and so sometimes you can detect in the blood better than in the tissue .

So I think considering between whether you do a liquid biopsy or the tissue biopsy, you have to actually consider the setting where you want to do it. For example, in the initial diagnosis, or molecular testing, or in the setting of patient recurrence.

Dr. Socinski:
Yes, so we have NCCN guidelines and other guidelines that tell us what we should be measuring. I wonder if you could comment on the use of liquid biopsies.

Dr. Tsao:
I think that the one that is the most sort of used right now for detecting in the liquid biopsy is the point mutation. For example, the T790M are resistant mutation when patients progress on EGFR TKI. So, for example, the other biomarker—for example, ALK and ROS1 and

RET—I think the clinical utility as a resistant mechanism I think is still not clear.
That's why I say I think the clinical utility or the evidence that in fact using the liquid biopsy results for the other type of mutations and to guide treatment is not as, I think, not robust at this time.

Dr. Socinski:
For instance, in the ALK population we make our first-line choice, and then when patients become resistant to this, it's controversial as to how informative retesting is, whether it's a tissue biopsy or whether it's a liquid biopsy. And, of course, when we go to conditions like ROS1 and BRAF and others, I think, as you point out, the data seems to be in evolution. We've seen some recent liquid biopsy results in patients who have progressed on osimertinib, and it's interesting that, unlike the first second-generation agents where we had a dominant T79DM-acquired resistance mechanism, the patterns of resistance, at least in the early studies from osimertinib, are much more complex. One of the things that has emerged from that is that the MET amplification seems to be a bit higher in frequency, but then it's only probably roughly 25–30% of the patients in that setting. And then the other point mutation has been this C797S mutation—although, we don't necessarily have a good clinical strategy if we detect that at the current time.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mark Socinski, and today I'm speaking with Dr. Ming Tsao on the growing role of liquid biopsy in non-small cell lung cancer.

One of the interesting things is the MET alteration or amplification that we see, and there have been some interesting trials incorporating various MET inhibitors in this setting. And again, I don't know that I would consider it a standard of care, but certainly there is some degree of optimism about potentially that being a strategy that could be defined based on molecular testing.

Do you have any comments about retesting in this space?

Dr. Tsao:
Yes. At this time I think we don't know that there are 2 kind of MET genes, alterations that appear to be sensitive to the small molecule MET inhibitors that have been developed. One is the MET amplifications, MET gene amplifications. The other one is the MET Exon 14 splice site mutation that give rise to an alternate splice form, which actually missing the protein actually receptor, missing domain or an amino acid sequence that actually is involved in the degradation of the MET, so the MET becomes very high level at the expression level. Those are the 2 situations that actually MET inhibitors appear to be having an activity in either—in the treatment-naive patients or after the progression from EGFR TKI . In the (inaudible)*14:42 sort of situation, I think it's more a MET amplification.

Dr. Socinski:
Yes, yes, not so much the mutations but the amplification.

Dr. Tsao:
Yes, yes.

Dr. Socinski:
Historically, there was some early data looking at the MET inhibitor that is on the market now. That is crizotinib. And there was some (inaudible... skip in audio)*15:55 activity, but at ASCO this year we saw some early data on 2 MET inhibitors, both capmatinib as well as tepotinib. These were first-line as well as second-line studies. They were phase II trials. Patients were selected for MET Exon 14 deletion mutations, and they were selected both by tissue biopsy as well as by liquid biopsy. We saw in this setting with these drugs response rates of in the 60-70% range, some durability of response both in first- as well as second-line setting. And these drugs, like most of the TKIs, they do have toxicity, but most of the toxicity is related to or is grade 1 or 2 with very low rates of grade 3 or 4 toxicity. I think, again, MET Exon 14 should be included in the initial testing .

Dr. Tsao:
I think from testing point of view, I think one has to be careful using what is the platform or the testing platform. For example, next-generation sequencing was the panel that one used, that it should include the MET and, in fact, includes the (inaudible)*17:34 before the Exon 14 so you can detect the mutations. The other thing is that, in terms of the Exon 14 splice site mutations, there is some evidence, in fact, that suggest it's more frequent in these called sarcomatoid carcinoma. From the pathologist point of view, that's very interesting, because when we see that diagnosis, we definitely would like to do the testing .

Dr. Socinski:
I still think—obviously, as a pathologist you probably agree—that histopathology is still important.

Dr. Tsao:
Yes, yes. I was just going to raise something else about the liquid biopsy versus the tissue biopsy even in the post EGFR TKI or post

ALK inhibitor, ALK TKI therapy progression, that in fact we see this small-cell transformation and that at this time we can only detect by tissue biopsy, by histology.

Dr. Socinski:
Yes, clinicians should be aware of the possibility of small -cell transformation, particularly in the EGFR mutation positive population. We always think that if you have rapid progression, which is typical of small cell, then liquid biopsy testing is not adequate. You need to do a tissue biopsy for histopathology and then act accordingly in that setting, so I think that's a very good pearl . And then the other pearl from a histopathology point of view is that there seems to be a higher rate of ALK fusion and signet ring adenocarcinoma in the lungs, so that's another kind of pearl that we talk a lot about in our tumor boards and those sorts of things.

So, this has been a fascinating discussion. Dr. Tsao, is there anything you'd like to revisit or key takeaways you'd like to leave with the audience?

Dr. Tsao:
Yes, I think that we are moving into the era where liquid biopsy is gaining not only a foothold but also, I think, becoming more and more sort of mainstream in terms of biomarker testing. There are still some issues with the liquid biopsy in terms of compared to the tissue biopsy, in terms of sensitivity and also standardizations of the assays, but it has many advantages also—for example, less invasive and faster turnaround time and also covering the heterogeneity.

Dr. Socinski:
Yes, but as you well know—that's a great point—lung cancer has become very complicated, and comprehensive genomic testing is part of our standard workup nowadays, and I think it's important that clinicians understand the limitations and pitfalls of both tissue biopsy as well as liquid biopsy so they can make sure that if a patient has an oncogenic driver, that they make that diagnosis either from tissue or blood.

Well, as we wrap up our discussion, I'd like to thank my guest, Dr. Tsao, for helping us better understand the growing world of liquid biopsy in non-small cell lung cancer.