

Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: <https://reachmd.com/programs/project-oncology/treatment-after-alk-tki-progression-mnslc/49182/>

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Guiding mNSCLC Treatment After ALK-TKI Progression

Announcer:

Welcome to *Project Oncology* on ReachMD. Joining us to discuss how we can use treatment history and molecular testing to guide therapy after ALK TKI progression in ALK-positive metastatic non-small cell lung cancer is Dr. Alice Shaw. She's the Chair of the Department of Medical Oncology at Dana-Farber Cancer Institute and a Professor of Medicine at Harvard Medical School. Here's Dr. Shaw now.

Dr. Shaw:

There are still many patients who've actually started on second-generation inhibitors, such as alectinib or brigatinib, and then gone on to lorlatinib at progression. And that's what we refer to as sequential TKIs. And I wanted to highlight this; it seems like a subtlety, but it's not. It's a very common situation in the clinic. Resistance is actually very different when patients receive sequential TKIs, such as alectinib followed by lorlatinib, compared to resistance that develops to first-line lorlatinib. And in particular, when patients receive first-line alectinib or brigatinib, actually, about 40 or 50 percent of them will become resistant due to a secondary ALK mutation, such as G1202R. And then when that patient goes on to lorlatinib and resistance develops again to second-line lorlatinib, these patients can develop yet another ALK resistance mutation. And the bottom line is that these patients can remain highly ALK-dependent. And that's a very different situation than when patients receive lorlatinib first line, because then, as I mentioned, they become resistant due to ALK-independent mechanisms.

And so this is a very important distinction because there is a fourth-generation ALK inhibitor that's been developed called neladalkib, and we expect neladalkib to be approved by the FDA very soon for patients who've received prior ALK TKIs. But the previously treated patients who've been shown to derive the most benefit from neladalkib are the ones who've received sequential ALK TKIs, such as alectinib followed by lorlatinib, and not so much the patients who have received first-line lorlatinib, because these patients progressing on first-line lorlatinib mostly have ALK-independent resistance, and they're just unlikely to respond to another ALK inhibitor, such as neladalkib.

Now, in terms of molecular monitoring, I think it is really critical for patients to undergo repeat biopsy at the time of progression on any ALK-targeted therapy. And at the minimum, a liquid biopsy should be sent, and if it's safe and feasible, a tumor biopsy can also be really helpful in identifying an actionable mechanism of resistance. And the most common genetic alterations that we identify in patients progressing on ALK inhibitors are on-target ALK resistance mutations, including double or triple compound mutations. Also, we frequently detect alterations in MET, and this can be MET amplification or sometimes rare MET fusions. And these really are actionable. For the ALK mutations, we have our newest next-generation ALK inhibitor I just mentioned, neladalkib, and also novel investigational approaches to targeting ALK, such as an ALK molecular glue degrader called TRI-611. And then for MET-mediated resistance, we actually have MET-targeted therapies such as tepotinib or capmatinib, which we can safely add to ALK tyrosine kinase inhibitors, and these combinations have been shown to be really effective in inducing responses.

Now, in addition to DNA sequencing, tissue biopsies also are really helpful and important to allow us to do what we call immunohistochemistry studies. These results could really impact selection of next line therapies as well. So for example, with a repeat tumor biopsy, we can check for expression by immunohistochemistry of MET, HER2, and MTAP, since each of these is actionable.

As an example, we fairly commonly detect high-level expression of MET by immunohistochemistry, and that meets criteria for the MET antibody-drug conjugate telisotuzumab vedotin, and that's now FDA-approved, and there are other MET antibody-drug conjugates in development as well. So really important to be able to do not just DNA sequencing, but also looking for expression of certain proteins on the tumor cells themselves.

Announcer:

That was Dr. Alice Shaw discussing how treatment history and molecular testing can help guide care for patients with ALK-positive metastatic non-small cell lung cancer. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!