Transcript Details
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Beyond ALK Inhibition: Addressing Unmet Needs in Non-Small Cell Lung Cancer

Announcer:
Welcome to *Project Oncology* on ReachMD. On this episode, Dr. Urs Weber, Assistant Professor in the Division of Medical Oncology at the University of Colorado Anschutz Medical Campus, will discuss unmet needs in ALK-positive non-small cell lung cancer management. Here's Dr. Weber now.

Dr. Weber:
Essentially, what you're doing when you're treating a mutation-driven lung cancer with a targeted treatment is applying a selective pressure to that cancer to figure out a new way to grow or to die. It's like you're inducing evolution in real-time by applying that selective pressure. So broadly, what we see are three different types of resistance mechanisms. We see on-target resistance, where the target—in this case, ALK—develops additional mutations that render it resistant to whatever targeted treatment you're giving, usually by altering the binding site on the protein that actually prevents the drug from sticking to the protein. And that was a big problem with the earlier generation ALK TKIs, so crizotinib, and then the second line or second-generation TKIs as well—alectinib and brigatinib. Those were drugs where we were seeing a lot of on-target resistance. And a lot of the design of drugs like lorlatinib was around trying to build a drug that was not going to be affected by those on-target resistance mechanisms. That was really successful, and I think it's a really great example of taking what we're seeing in clinic, taking it back to the lab, doing structural modeling, and really figuring out how to get around some of these things that the cancer was doing.

Now, with long-term follow-up of lorlatinib—even in patients who are having disease progression on lorlatinib—we really don't see on-target resistance all that much. It's much less than with the earlier-generation ALK TKIs. So the newer, third and fourth-generation ALK TKIs are so effective at inhibiting ALK that it's really running out of ways to mutate that can get around these inhibitors. And so that moves some of the other resistance mechanisms into the forefront.

Off-target resistance is the second big one that we deal with, where you are successfully blocking the original driver—in this case, ALK—but the cancer cell figures out some other protein that can activate but also works on these same cell growth pathways that push that cancer cell to be able to grow and make more cancer cells. And so that gets a lot trickier because we try to figure out what that off-target mechanism is. But even if we can figure it out, oftentimes, we don't have the right tools to block it. And then it gets really challenging in terms of, how do you block all those things? And oftentimes the disease is heterogeneous at this point, where you have different sub-clones of your cancer that are all sort of behaving differently, and that gets really tricky.

And then the third one is histologic transformation, where your non-small cell lung cancer turns into a small cell lung cancer. It doesn't happen that often in ALK-positive disease; it happens a lot more in EGFR-mutated disease. But that's a really challenging entity to deal with and often requires switching to more of a small cell lung cancer treatment paradigm with chemo and such.

And so those are the biggest areas of need—the off-target and then the histologic transformation. We don't really have reliable strategies to address those, and I think that's definitely an area of future need to try to address those things.

Announcer:
That was Dr. Urs Weber explaining current unmet needs in ALK-positive non-small cell lung cancer. To access this and other episodes in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!