

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/progression-resistance-patterns-alk-positive-mnslc/49180/>

ReachMD

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

Patterns of Progression and Resistance in ALK+ mNSCLC

Announcer:

This is *Project Oncology* on ReachMD. Today, we'll hear from Dr. Alice Shaw, who's the Chair of the Department of Medical Oncology at Dana-Farber Cancer Institute and a Professor of Medicine at Harvard Medical School. She'll be discussing patterns of progression and mechanisms of resistance in metastatic ALK-positive non-small cell lung cancer. Let's hear from her now.

Dr. Shaw:

There are multiple next-generation ALK inhibitors. We have second-, third-, and even fourth-generation ALK inhibitors that are really transforming the course of disease for our patients. And I would say in particular, just to focus for a moment on the third-generation ALK inhibitor lorlatinib, it really has set a new benchmark for efficacy in the first-line setting. The median progression-free survival with first-line lorlatinib is now exceeding seven years, which is really phenomenal.

But if you look closely at the actual data, you'll see that patients are still relapsing due to resistance. And at one year, about 20 percent of patients progress on lorlatinib. At two years, about 30 percent of patients progress, and then by five years, about 40 percent of patients have progressed. And so resistance, I would say, is still a major challenge for a significant fraction of patients.

Now, the largest data set we have on mechanisms of resistance to first-line lorlatinib comes from the CROWN trial, and here we actually did have paired baseline and end-of-treatment samples for about 23 patients who were treated with first-line lorlatinib. And as predicted, based on lorlatinib's broad coverage of single ALK resistance mutations, we actually didn't detect any new ALK mutations at the time of progression, and so there was no what we call "on-target resistance." But instead, what we found is a number of putative bypass pathways, or ALK-independent mechanisms of resistance. And I think those will almost certainly require combination approaches to overcome.

And then I'll just note that in the literature very recently, there's one case report of a patient who progressed on first-line lorlatinib and was found to have an acquired ALK resistance mutation. This is a duplication of a lysine at residue 1150. So it's possible that on-target resistance could develop in rare patients, but in general, I think that most resistance to first-line lorlatinib is going to be off-target, and for that, we need combinations.

Now, in terms of patterns of progression on first-line lorlatinib, I think it's really worth emphasizing that in the seven-year follow-up of the CROWN trial, we showed that median time to intracranial progression had still not been reached, and even more importantly, 92 percent of patients remained free of intracranial progression at seven years. And what's also important is that after about two and a half years of lorlatinib treatment, there were no further progression events in the brain. So the progression events were all extracranial. So it really speaks to, again, lorlatinib's ability to treat the brain and prevent metastases from developing in this one specific site.

Announcer:

That was Dr. Alice Shaw discussing mechanisms of resistance and progression in metastatic ALK-positive 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!