Ceritinib and Other Second Generation ALK Inhibitors for Acquired Resistance in ALK-Positive NSCLC

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TRANSCRIPT & FIGURES
One of the exciting things about the ALK field is that in a relatively short space of time, we've gone from defining a molecular subtype of lung cancer that responds very nicely to a first generation drug, crizotinib, that we've actually not got more choices. More specific, more potent ALK inhibitors have been developed: ceritinib, alectinib, brigatinib to name a few. Ceritinib is already licensed – the other two drugs have got what's called FDA breakthrough approval. That means the FDA is very keep to look at the results, and hopefully if they're good, will license the drug fairly quickly.

What they're showing is, one: because they tend to be slightly cleaner drugs, they have a different side effect profile from crizotinib. For example they tend to not have the swelling of the ankles and other areas of swelling which is associated with an off target effect of crizotinib called anti-MET activity. However they're not completely free from side effects. Ceritinib for example has a lot of gastrointestinal side effects – a lot of nausea, a lot of vomiting and diarrhea, and nearly 60% of people need a dose reduction. The alectinib and brigatinib are looking relatively cleaner in terms of the side effects.

In terms of whether they work: after the crizotinib has stopped working, people have progressed in one of two ways. Either their cancer is growing in their brain because crizotinib doesn't penetrate into the brain very well, or the cancer has evolved and changed its biology in the presence of the crizotinib.

The good news is these next generation drugs work on both of those mechanisms. Either more is getting into the brain or the drug is just more potent, and therefore we're seeing responses in the brain, and also they work
on some of the known resistance mechanisms to crizotinib. We're seeing 50-70% of people responding in their body after initially progressing on crizotinib.

So very rapidly we now have a clearly defined next line of therapy for ALK-positive patients progressing on crizotinib.