



Timing of Second Generation ALK Inhibitors: First Line vs. Treatment after Acquired Resistance



TRANSCRIPT & FIGURES

One of the long-standing philosophies in oncology is you use your best drugs first. To be honest that goes back to a mindset that maybe people weren't going to survive for you to try a treatment in a second line or third line setting, so you were just trying to get in your best drug in whilst you had a chance. Now we've seen with the next generation ALK inhibitors, they have better activity in the brain, they have activity after crizotinib has stopped working, so the logical question is, what if you come in with these drugs first instead of crizotinib? Could they displace the recently crowned king of ALK crizotinib by being the new pretender? Well, maybe.

The only direct head to head study is with alectinib and that's the so-called ALEX study – alectinib, ALE, compared to crizotinib which is also called Xalkori and that's where the X comes from – ALEX. There's a very similar study run in Japan which is called the J-ALEX study. Both of those have finished accrual, so we should see those results in the near future.

Now, when we get that data it's going to be very interesting to look at. Does the alectinib just have to be better than the crizotinib? Well, sure, it probably has to be and it probably will be. The real question is, how much better? If it's just a little bit better, sure that's a positive study, they'll get a license for the drug, but you could still use crizotinib followed by alectinib, or followed by any other second generation ALK inhibitor, and maybe that sequential benefit may be more than if you use your best card up first.

What if it's the same as the sequential therapy? Well that might change people's prescribing if the drug is better tolerated, more convenient, or cheaper, and new drugs tend not to be cheaper. Perhaps what we're hoping

for is that by suppressing some of the dominant mechanisms of resistance from the get go, we'll actually change the natural history of the disease. Every time resistance occurs, more cells divide, they grow up, and they're generating the next and the next mechanism of resistance.

So the more you can suppress cell turnover from the get go, the more maybe you can extend out the overall duration of control – but we have to wait for those results to come out and until they come out, I wouldn't start using second generation inhibitors in the first line setting without that data.

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