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First-Line Targeted Therapies for *ROS1* Fusion-Positive Lung Cancers

Announcer:
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Dr. Drilon:
Hi there. I'm Dr. Alexander Drilon from Memorial Sloan Kettering Cancer Center, and today we're going to talk about first-line targeted therapies for ROS1 fusion-positive lung cancers.

We'll start by showing you that there are three different tyrosine kinase inhibitors, or TKIs, that are approved in the first-line setting. This is for patients with advanced or metastatic ROS1 fusion-positive non-small cell lung cancers. And the three TKIs are shown here: crizotinib, entrectinib, and repotrectinib. And these are arranged in the order that they were first introduced in trials and later approved, with crizotinib being the oldest drug and repotrectinib being the newest drug. Crizotinib is a multi-kinase inhibitor that inhibits ROS1 and other kinases, like ALK and MET, as many of you know. Entrectinib is also a multi-kinase inhibitor that inhibits ROS1 and NTRK; in fact, it has an approval for NTRK fusion-positive cancers. And finally, repotrectinib is also a multi-kinase inhibitor that likewise inhibits ROS1 and NTRK. And while the drug is approved for ROS1 fusion-positive lung cancers, it has also been explored on clinical trials for NTRK fusion-positive cancers.

What are the differences between these three agents? We'll start here with the response rate. And in the graphs, you'll note that the response rates are pretty high across all tyrosine kinase inhibitors. Starting from the left, you'll see there are two bars representing two different trials, the PROFILE 1001 trial, and the OxOnc trial showing response rates for crizotinib north of 70%. You'll also see ceritinib, a drug which we haven't discussed thus far, which is only in the NCCN guidelines but does not have approval. The data that you see here is from a Korean trial, where the response rate is north of 60%. And then finally, you have the other two drugs, entrectinib explored, you have the STARTRK trial, and repotrectinib in the TRIDENT-1 trial, again with response rates that are high. So, across the board, you'll see response rates in the order of 60 to almost 80%. So, a very high likelihood of shrinking your patient's cancer.

And then in the orange bars, we have the intracranial objective response rate. And you'll note that with crizotinib, those programs really did not put out a lot and patients with baseline brain metastases, and so we have a read only from the other trial shown here. But the punchline is that response rates in the CNS are also high. And for entrectinib and repotrectinib, you'll see these qualitatively approximate the systemic responses that we're seeing, maybe numerically, a little bit better. So, these will get into different compartments in the body, including the CNS.

And these are just the nice waterfall plots from all of the trials we had already discussed showing that many patients will have disease regression, you'll see complete responses to therapy, and there are very few patients who have primary progressive disease. In fact, for repotrectinib, everyone had a downgoing bar, as you see on the lower left.

So, if all of these TKIs have a high likelihood of response, what are the potential differentiating features? Well, there's one thing to pay attention to, and that's durability. Here, we have progression-free survival across the different trials. And in the blue bars, you'll see

moving from left to right, the progression-free survival medians for crizotinib, ceritinib, and entrectinib are in the order of almost 60 in the north of 19 months, while with repotrectinib, we see a big jump where the median progression-free survival is almost 3 years. And we've seen this pattern before, where if you use a next generation drug, which repotrectinib is, compared to the older drugs, you can see meaningful improvements in how long patients are on targeted therapy. And the progression-free survival curve from the TRIDENT-1 trial is shown on the right for repotrectinib.

So, putting that all together, in the first-line setting, targeted therapy is preferred for patients with advanced ROS1 fusion-positive lung cancers. There are several ROS1 TKIs that are approved for TKI-naïve ROS1 fusion-positive non-small cell lung cancers, and these achieve higher response rates but differing progression-free survivals with, so far in the absence of randomization, repotrectinib showing the highest median PFS.

Thanks for your attention.

Announcer:
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