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

Announcer:
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Dr. Drilon:
Hi, this is Dr. Alexander Drilon from Memorial Sloan Kettering Cancer Center, and we are going to talk about later-line targeted therapies for ROS1 fusion-positive lung cancers.

Here, we just show a schema of patients with advanced or metastatic ROS1 fusion-positive lung cancers who have already gotten a tyrosine kinase inhibitor, or a TKI. And before repotrectinib was approved, the later-gen drug which we're going to go into more detail on, we had crizotinib and entrectinib. And many patients are currently on these TKIs. And while patients can be on these TKIs for a long time, eventually resistance will develop, at which point we do recommend getting either a tumor and/or liquid biopsy in order to determine the resistance mechanism. And that will divide patients into those who have cancers that are possibly still dependent on the ROS1 fusion, or the second group as shown on the right, where they may have acquired bypass resistance, meaning activated another gene or protein that's not a ROS1, and thus may not be amenable to ROS1-targeted therapy by itself anymore.

So, what characterizes the first group, those cancers that still maintain dependence on the ROS1 fusion despite progression on crizotinib or entrectinib? Well, while some cases might not have an obvious culprit when you do tumor or plasma sequencing, in many cases a resistance mutation can emerge. And a common one is the solvent-front mutation, or ROS1 G2032R. And as you see in the diagram on the right, what happens is these mutations very conveniently occur at the site where the drug binds and makes it much more difficult for crizotinib or entrectinib to engage the ROS1 kinase and shutdown cancer signaling.

Fortunately, there are therapies which may work after patients have progressed on a priority TKI. And so, to remind you, these are patients who have come off crizotinib and entrectinib for progression. But if you assume that they have ROS1 fusion dependence that persists, then there are two options: lorlatinib, which is not approved but currently in the NCCN guidelines, and repotrectinib, which is the only TKI that has FDA approval for patients who have progressed on a prior TKI. Now, lorlatinib, you know well, not just in the ROS1 world but also in ALK where it's approved as a third generation TKI. However, it isn't as expansive in terms of its coverage of resistance mutations unlike repotrectinib, which is the only drug which can meaningfully inhibit G2032R, that's of course approved by the FDA.

Now, here you'll see the activity of lorlatinib and repotrectinib in the trials that established this data where you see response rates are in the order of about 1 out of 3 patients. Intracranial response is good, anywhere from almost 40 to 50% of patients for both drugs. And the median progression-free survival is in the order of 8.5 and 9 months.

But what again is the major differentiating factor between lorlatinib or repotrectinib? Well, that's shown here on this slide, and it goes back to the solvent-front ROS1 G2032R mutation. This is a mutation that only repotrectinib has meaningful activity against. If you look at the lorlatinib data thus far, we have not observed great responses to cancers with the resistance G2032R mutation. But in contrast here, you're seeing in the repotrectinib data that many patients with these mutations will have regression with therapy. As you'll see in the

table on the left, the objective response rate is almost 60%, showing that the drug is highly active.

Now, we previously said that some cancers might not be a ROS1 dependent anymore, and if they acquire, say, KRAS or MET or another gene alteration, then I would not recommend doing a single-agent TKI, either lorlatinib or repotrectinib, but I would do chemotherapy, which can skirt the issues of bypass resistance that you're seeing.

So, to put all of that together, in someone that's progressive, crizotinib or entrectinib. If you think the cancer is ROS1 dependent, give the repotrectinib or lorlatinib, with repotrectinib for the solvent-front mutation. If they can bypass resistance, give them platinum doublet chemotherapy. If they have had repotrectinib in the first-line setting, then there's no other agent that's approved and you would do platinum doublet chemotherapy.

So, to end, ROS1 fusion-positive lung cancers develop different types of resistance to TKI therapy. The use of sequential TKI therapy is appropriate for ROS1-resistant mutations or without bypass resistance, highlighting the need to sequence these cancers. And when bypass resistance is identified, consider the use of chemotherapy.

Thanks for your attention.

Announcer:
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