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Zidesamtinib for ROS1-Positive Non-Small Cell Lung Cancer

Announcer:

You're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan Quigley:

This is *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Ryan Quigley, and today, we'll be learning about an investigational drug for ROS1-positive non-small cell lung cancer, zidesamtinib. We're lucky enough to speak with an investigator on the ARROS-1 trial, Dr. Alexander Drilon. Dr. Drilon is a thoracic medical oncologist and Chief of the Early Drug Development Service at Memorial Sloan Kettering Cancer Center in New York. Dr. Drilon, thanks so much for being here today.

Dr. Drilon:

Oh, it's my pleasure.

Ryan Quigley:

So let's start with some background about the drug itself, Dr. Drilon. What is zidesamtinib, and how is it different from the ROS1-targeted therapies that came before it?

Dr. Drilon:

There are many ROS1 TKIs that are already approved, including this drug, but we'll get to that in a second. However, the design intent here was to make a better drug than the other TKIs that preceded it. So that's in terms of inhibiting ROS1's resistance mutations and activity in the brain, and, importantly, trying to make the drug safer by avoiding or minimizing the inhibition of TRK that, with other drugs like repotrectinib, for example, can cause neurological side effects such as dizziness, weight gain, etc.

Ryan Quigley:

Now, with that in mind, could you briefly walk us through the design and key findings from ARROS-1?

Dr. Drilon:

This is the ARROS-1 trial. It's a global, multicenter, phase 1/2 trial of zidesamtinib for advanced ROS1-positive lung cancer and other solid tumors. And this is a registrational data set that already resulted in the drug's U.S. FDA approval for patients with TKI-pretreated ROS1-positive lung cancers.

But of course, if you have a very good drug in the later-line setting, the question is, can we move it up to the first-line setting and see if we can improve outcomes in TKI-naïve patients?

We are going to focus on the ROS1 TKI-naïve population of the phase 2 portion really briefly. By the data cutoff date of April 2026, more than 600 patients were enrolled. There was a large safety population of more than 530 patients. But the ROS1 TKI-naïve efficacy population was comprised of 94 patients with measurable disease and enough follow-up time. And, as you can imagine, the patient characteristics were similar to what we've seen for other ROS1-positive lung cancers: a younger median age, many never smokers. There's good geographic distribution across Asia, Europe, and North America. And patients had baseline CNS metastases 17 percent of the time, and were also allowed to have prior chemo plus/minus immunotherapy. And that occurred in 27 percent of patients, and that was specifically platinum-based chemotherapy.

And this really takes a page from what we've seen with EGFR and ALK-positive lung cancer, where we've moved later-gen drugs like osimertinib or lorlatinib into the first-line setting, and we've seen improvements in activity. So that was the intent of exploring the TKI-

naive population here.

Ryan Quigley:

Now, before we come to the end of our program, Dr. Drilon, let's look ahead for a moment. How do you see zidesamtinib potentially fitting into the treatment landscape for ROS1-positive non-small cell lung cancer?

Dr. Drilon:

The results of the trial were highly encouraging. The objective response rate was 94 percent. Complete response rate was 15 percent. We don't have medians yet, but the one-year DOR was 86 percent, and the one-year PFS was 90 percent. Great CNS activity. All patients that were evaluable, 10 patients, had intracranial responses to treatment. Seven of them had complete responses to treatment. I think the hope is that—if the FDA does approve this—with more mature data, we will see, fingers crossed, an improved median PFS compared to prior agents, again, following that paradigm we've seen with EGFR and ALK. And that will be one big win for patients.

The other win is that, in the safety data set of more than 530 patients, the most common AEs were edema, CPK increase, constipation, and weight increase. And those were, really, mostly low-grade. There were few severe side effects. And what was remarkable to me was that the dose reduction and discontinuation rates due to treatment-emergent AEs were 12 percent and 4 percent respectively—so lower, historically, than several other ROS1 TKIs.

So what I'm trying to say here is that we may have another win on the safety front. And if that's the case, then it's perfect that we have a drug that's not only more active but is also safer. And this kind of echoes what we've seen with EGFR, where osimertinib was not only more active and had many good features but also had a better AE profile relative to older drugs like afatinib, for example, or even gefitinib.

Ryan Quigley:

It'll be very exciting to see what the future holds there. Thanks so much to my guest, Dr. Alexander Drilon, for sharing his expertise and research on zidesamtinib. Dr. Drilon, it was great having you on the program. Thank you so much for doing this.

Dr. Drilon:

Oh, this was wonderful. Thank you for the invitation.

Announcer:

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