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Released: 03/01/2024
Valid until: 03/01/2025
Time needed to complete: 1h 06m

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Overcoming Acquired TKI-Resistance with Next-generation ROS1-TKI Agents

Announcer:
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Dr. Drilon:
Hi there. I'm Dr. Alexandra Drilon, and I am joined today by Dr. Charu Aggarwal to discuss overcoming acquired TKI resistance with next-generation ROS1 TKIs.

So, Charu, first question for you, does resistance eventually develop in a ROS1 fusion-positive lung cancer patient who's on their first TKI?

Dr. Aggarwal:
Yeah, I think as in all things in oncology, I think resistance is inevitable. You know, we've certainly learned a lot about resistance over time in oncogene-addicted tumors, and ROS1 is the exception. I think, especially with the use of first generation TKIs we are seeing clear distinct emergent patterns of resistance in patients with ROS1 TKIs – sorry, in ROS1 non-small cell lung cancer. And, you know, thankfully, now we have some options to come in to possibly treat the resistant clones.

What is your preferred method to identify the specific type of ROS1 mutation? And how do you guide TKI selection?

Dr. Drilon:
Yeah, I do believe that it's important whenever you have coverage, and it's safe and feasible, to try to do another biopsy of a growing area to interrogate resistance, so tumor next generation sequencing. But you've done a lot of work on this, Charu. We know that liquid biopsies can serve as complementary approaches to tumor biopsies, particularly when it's tough to reach a particular lesion that's growing, you may be able to collect circulating tumor DNA sequence of that. And these resistance mechanisms that pop up, many of them are mutations, which are actually easier to find a DNA-based liquid biopsies. And so, there's a chance if the tumor is shedding substantially, free to capture some of this resistance in plasma. We know that a common way of developing resistance that we call on-target, quote unquote, is to acquire a new ROS1 mutation that prevents drug binding, one of the most common ones is ROS1 G2032R.

Is there anything we can do about these resistance mutations?

Dr. Aggarwal:
Yeah, so I think there are newer drugs. Repotrectinib is certainly engineered to be able to overcome the binding issues and attack or still target cells in the presence of this alternation. So, I think this is definitely something that we can come in with in patients who may acquire this resistance. And also, I think important to recognize that, as we have done in other situations, for example, osimertinib was being used only in patients with T790M until they actually moved it up based on both better intracranial activity but also longer median PFS, eventually leading to a survival benefit. I think we can follow a similar practice here, where we could come in with an agent such as repotrectinib in the first-line setting to really overcome many of the issues involving PFS and emergence of resistance.

Alex, is this how you're thinking about treating your patients in the future as well?

Dr. Drilon:
Yeah, so with repotrectinib, it's actually the only approved drug that we know can work clinically against G2032R. And the response rate in the G2032R mutant population is approximately 60%. So yes, if I have someone who, say, has been on crizotinib or entrectinib for a very long time, develops resistant, I find a resistance mutation. And it's amenable to repotrectinib, meaning it's G2032R, I would give repotrectinib, which is approved for this indication.

There are other agents like cabozantinib that also inhibit ROS1 that bind differently, and so those drugs may abrogate some mutations like ROS1 D2033N, for example. But in addition, there is off-target or bypass or resistance, meaning that if another kinase is activated, receptor tyrosine kinase like MET, and cabozantinib inhibits both ROS1 and MET, then presumably on trial, if that were available, you could try something like cabozantinib. However, in the absence of that, if you have someone that progresses and there's a KRAS mutation or high-level MET amplification, I think my choice, rather than doing a next generation TKI or even a clinical trial, if they're chemo naïve, would be the new platinum doublet-based chemotherapy.

Dr. Aggarwal:
This has been amazing insight. Thank you for sharing your suggestion and all the knowledge that has been generated on clinical trials. Thank you for watching.

Announcer:
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