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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Treatment Strategy of *ROS1*-Rearranged NSCLC in TKI-Naive Patient

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Dr. Aggarwal:
Hello, and welcome to this roundtable discussion. I'm Dr. Charu Aggarwal, and I'm joined here today by Dr. Alexander Drilon. Today, we will talk about treatment strategy for ROS1-rearranged lung cancer in a TKI-naïve patient. So, Alex, can you comment on your approach and initial selection for ROS1 TKI agents, given the availability of newer agents that are both NCCN recommended and approved?

Dr. Drilon:
Yeah, this is a great topic, Charu. And it is worth calling out that ROS1 fusions are found in 1 to 2% of lung adenocarcinomas. And so, it's not the most common oncogene, and running randomized trials, where you do head-to-head comparisons has not been possible. So, what we're going to talk about today is based on looking across the aisle at the different single-arm trials, to look at activity. And what you'll note is that all of the TKIs that are available, crizotinib was the first, and then entrectinib, there was the ceritinib trial, and then finally repotrectinib, do have comparable response rate. So, the likelihood of response is in the order of 60 to 80%. So, for me, that's not a primary deciding factor.

Where things start to differ a little bit, are when we get to durability. And if you look at progression-free survival, the median progression-free survival across all of the trials for the earlier-gen agents, like crizotinib, entrectinib, ceritinib, you're getting a median of about 16 to 19 months across the different trials. And again, in the absence of a head-to-head comparison, if you look at the repotrectinib data, this is the most recently approved TKI, you're seeing a big jump in the median progression-free survival to almost 3 years. And for me, if you're talking about only activity, I think that patients deserve a chance at being on their first targeted therapy for as long as possible. And on the activity front, I think that trumps things, meaning that I would always choose repotrectinib over the other agents.

Does the presence of brain metastases, or even say leptomeningeal disease, if someone has that diagnosed upfront, does that influence your choice of TKI?

Dr. Aggarwal:
I think you raise such interesting points and questions about management of these patients. I think CNS metastases remains a matter of morbidity for our patients. So, I think there are two things, right; there is the treatment of a patient who doesn't yet have brain metastases but has the possibility of developing them. And secondly, in a patient who presents with brain metastases, how do we obtain our treatment there. And I think both aspects are important.

As we have seen with other treatment subsets in non-small cell lung cancer, I think with availability of newer agents, we are actually able to do both; that is, prevent the emergence of brain metastases as well as treat the brain metastases that may be present. My preference has been just like yours, Alex, where you want to come in with a TKI that will give you the longest median PFS, my preference is to come in with a TKI that can provide the most meaningful CNS penetration. And this may be either protection or even

treatment. We both see enough of these cases in our clinics where untreated brain metastases or treatment with inefficient TKIs may actually eventually lead to leptomeningeal disease. So, I have been using brain-penetrant drugs as first-line agents in my practice both for ALK and now for ROS1, with the availability of drugs such as repotrectinib and also entrectinib, which have higher CNS activity than crizotinib.

Do you tend to agree? And do you have any other suggestions for the management of such cases?

Dr. Drilon:
I agree. So, entrectinib and repotrectinib are definitely better than crizotinib at reaching into the central nervous system but paired with the overall activity of the much longer median progression-free survival with the repotrectinib versus entrectinib. I tend to choose repotrectinib upfront, recognizing very quickly for our viewers that you do need to watch out for a particular side effects of repotrectinib and entrectinib that are mediated by TRK inhibition like the dizziness, weight gain, etc.

Thank you for joining us for this section on treatment strategies for ROS1-rearranged non-small cell lung cancers in the TKI-naive setting.

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