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## Reacting to RET Inhibitors: A Look at Progression & the Future

Dr. Sands:

Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and on this episode, Dr. Ross Camidge, who's the Director of the Thoracic Oncology Clinical and Clinical Research Programs at the University of Colorado, joins us to discuss progression on RET inhibitors in non-small cell lung cancer. Here's Dr. Camidge now.

Dr. Camidge:

Let's imagine that you start on one of these RET inhibitors, and then you progress. Then what do you do? Well, let's break it down. So, first of all, if you go on one of these inhibitors and have no response, the first thing I'd do is I'd double-check the diagnostic. Was it accurate the first time or do you need to go and look with a different diagnostic? Were you misled initially?

But let's assume you initially had benefit, and then you progressed. Again, let's break it down. Did you progress in the body or the brain? If you're progressing in the brain, it may be related to drug penetration, and it's quite possible that one of the other RET inhibitors might be more effective in the brain, or you may be able to play around with the dose, depending on tolerability, to get higher CNS penetration. If none of that works, obviously the alternative is some kind of ideally focused brain radiotherapy.

If you progress in the body, there is an increasing understanding of some of the biological mechanisms of resistance. There are on-target RET mutations, which can occur, and people are developing next-generation RET inhibitors that can work on some of these. I'm sure we'll also get second driver pathways, which are challenging to identify, but essentially they're other oncogenic drivers that come in a supporting role. And there the question is, can you create some kind of combination of drugs? If it's isolated progression in the body, you can also give focused radiation for so-called oligoprogression. And if none of that works, or none of those are options, you're going to go back on the chemotherapy.

One of the things that we do know is that the RET rearranged cases of non-small cell lung cancer, like all of the other rearranged subtypes of non-small cell lung cancer – ALK, ROS1 – tend to have exaggerated sensitivity to pemetrexed-based chemotherapy. So probably carboplatin and pemetrexed is going to be the backbone of whatever you move forward to. Will immunotherapy add anything to this mix? We don't 100% know. It hasn't really been studied. Do you keep the tyrosine kinase inhibitor going and add in the chemotherapy, or do you stop the TKI and just go on to the chemotherapy? Again, we don't really know.

Dr. Sands:

That was Dr. Ross Camidge from the University of Colorado. And for ReachMD, I'm Dr. Jacob Sands. To revisit any part of this discussion and to access other episodes in this series, visit [ReachMD.com/Project Oncology](https://ReachMD.com/ProjectOncology), where you can Be Part of the Knowledge. Thanks for listening.