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Mechanistic Evolution in RAS Therapy: ON-State and Multi-Selective Targeting

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Dr. Arbour:
This is CE on ReachMD, and I'm Dr. Kathryn Arbour. And I'm pleased to be joined today by Dr. Eileen O'Reilly.

First, we're going to take a look at an animation that depicts the mechanism of action of ON-state RAS inhibitors and the key differences with OFF-state inhibitors.

Animation Voice Over:
"Inside cells, KRAS functions like a molecular switch, cycling between OFF and ON states. In the OFF state, KRAS is bound to GDP. In the ON state, it's bound to GTP, actively signaling growth pathways.

"OFF-state inhibitors target the GDP-bound form of mutant KRAS G12C. They bind to the mutant cysteine at position 12 and lock it in the OFF state, halting downstream signaling and cell growth.

"But here's the problem: Resistance develops. Tumors can bypass these inhibitors through secondary mutations or by shifting KRAS into its GTP-bound ON state where OFF-state inhibitors no longer work.

"ON-state inhibitors flip the script by targeting the active, GTP-bound RAS, even across multiple RAS mutations like G12X, G13X, and Q61X.

"RAS ON-state inhibitors use a tri-complex mechanism, reversibly binding with cyclophilin A, an abundant intracellular chaperone protein, and active RAS(ON). The tri-complex blocks RAS from binding to downstream effectors, silencing oncogenic signaling.

"Unlike OFF-state inhibitors limited to KRAS G12C, ON-state and multi-selective inhibitors address a wider range of mutations. Some are also able to inhibit wild-type variants of RAS and are able to overcome resistance linked to RAS(OFF) therapy.

"RAS targeting has evolved. From shutting off one mutation to disabling RAS at its source, the ON switch, new inhibitors are redefining what's possible in precision oncology.

"Understanding the mechanistic leap from OFF- to ON-state inhibition equips clinicians to match therapy to tumor biology, personalizing care for patients with RAS-driven cancers."

Dr. Arbour:
So, Dr. O'Reilly, what more can you tell us about these RAS(ON) inhibitors and their importance in the treatment of pancreas cancer?

Dr. O'Reilly:
Great. I love this question because these are such interesting drugs and it's fascinating, right, the chemistry changes, the drug development changes that have happened. So the OFF-state inhibitors, and you mentioned this in a prior episode, it's targeting the

GDP-bound version of RAS. The ON-state inhibitors are different. They bind cyclophilin, which is this molecule that's in the cytoplasm, and then will bind the GTP, the active version of RAS, and form this—what's called tri-complex and the ON-state inhibitors have of lots of names, multi-selective, ON-state inhibitors. And the one that's really coming to the fore in pancreas cancer is daraxonrasib, which has undergone phase 1 and now completing phase 3 testing. We'll get to specifics a little bit later, but the hope is that resistance will be a higher bar with these ON-state inhibitors, and we suspect that some of the mechanisms of resistance might be different relative to the OFF-state inhibitors. But most of all, I think where the real attraction is, is their spectrum of activity, right? They're going to be able to impact all of the common alleles that we've talked about, KRAS G12D, KRAS G12V, G12R, that's 40%, 30%, and 15% of pancreas cancer, even the 1% with the G12C, but also that smaller subset with Q61 and potential for activity in wild-type disease, so broad spectrum. Toxicity will be a discussion that we'll have, but in terms of potential opportunity, very interesting drugs.

Dr. Arbour:
So I think you bring up a crucial point here in terms of the ON-state of these drugs. There are also selective ON-state that are mutant specific, which is interesting. So they're also tri-complex inhibitors, as you pointed out, but specific for G12C. So one of these agents is called elironrasib, and again, a tri-complex inhibitor. There's another compound in development called zoldonrasib, which is a G12D ON-state inhibitor.

So we have this very interesting period of time of development where we're seeing, in parallel, drugs that are both mutant selective as well as others that are not as selective but may have other benefits for these multiple different RAS mutations.

Well, I think we nailed it. Thank you so much, and we'll see you next time.

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