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Early Approaches to RAS Targeting: Efficacy Signals and Known Limitations

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Dr. O'Reilly:
All right, this is CE on ReachMD, and my name is Dr. Eileen O'Reilly, and I'm delighted today to be joined by Dr. Kathryn Arbour.

So now let's get into RAS targeting, and we'll discuss in another episode the various mechanisms and ways that we can target RAS. But to get us going here, Dr. Arbour, can you review the approved OFF-state RAS inhibitors in lung cancer?

Dr. Arbour:
I think this is a super exciting topic, Dr. O'Reilly. RAS inhibitors were first approved in non-small cell lung cancer. And when we think about the current agents that have received accelerated FDA approval and are included in the NCCN Guidelines, there's 2 medications: sotorasib and adagrasib. Both of these drugs are what we call RAS OFF-state inhibitors or switch-II pocket inhibitors, and they typically bind the RAS protein in its inactive or OFF state and trap it and prevent it from signaling it downstream. And that's really how they function in this aspect.

There are subtle differences between the side effects of the drug as well as the efficacy, but largely similar responses have been seen in patients with non-small cell lung cancer. The landmark clinical trials really demonstrated for both drugs in the second-line setting, so those patients who'd been previously treated with immunotherapy as well as platinum doublet chemotherapy, response rates in the order of 30% to 40% in patients with advanced metastatic disease, and a median progression-free survival of 5 to 6 months.

So there's challenges and promises in both of those. These were clearly the first targeted therapies for RAS, which was once considered an undruggable target, a tremendous advance for the field, but really left us grappling with the challenges with the lack of depth of response. Response is only seen in about 30% to 40% of patients, although disease control is seen in many others, as well as notably the durability of response for these 2 particular agents.

Sometimes patients can have rapid improvement of their disease up front and then quickly develop progression of disease or resistance to these therapies. And we know that resistance is increasingly complex in this setting. We know that there can be any number of resistance mechanisms and sometimes multiple resistance mechanisms happening at the same time. And this could be because these drugs are targeting the OFF state of RAS as opposed to the active state. We'll talk about that more later. This also could be because they're only targeting G12C and patients can develop secondary RAS mutations as a mechanism of resistance.

So we are definitely in need of novel therapies to understand what targeted therapies can work in the setting of these G12C inhibitors no longer being effective, but also, can we make better agents that are more powerful to start with and really choose our best drug first, which is always our choice in non-small cell lung cancer. It's the timing and the message that we've learned again and again and again.

But I'm curious. That's our perspective in lung cancer. How have G12C inhibitors really been used in pancreas cancer, Dr. O'Reilly?

Dr. O'Reilly:
Great. Well, thanks again for a very comprehensive review of the state of the arts in non-small cell lung cancer. In pancreas cancer, G12C is one of the least common KRAS mutations that we see. So we see 90%, 95%, depending on how you look, of individuals will have a KRAS mutation. The most common alleles are D, V, and R, and G12C is about 1%, 1.5%. So it's not an everyday occurrence in this disease.

But nonetheless, this really set the scene for the fact that RAS inhibitors have a potential in pancreas cancer. And we were watching with a co-scrutiny what was happening in the lung cancer world and delighted to see that the signal held in pancreas cancer. And this really got people's attention, that in previously treated disease, mostly in a second- but actually really mostly a third-line setting, to see a single targeted agent have responses, right? Responses with chemotherapy and previously treated disease are single digit.

So this was exciting, 20%, 30% and some of the more recent 12C inhibitors having response rates even up to 70% in pancreas cancer. All small numbers, all non-randomized evaluations, but with the signal with response and progression-free survival and median survivals passing what we see in second line, that led to sotorasib and adagrasib getting NCCN Guideline endorsement.

So a real start with these OFF-state inhibitors, and we'll be circling back on this topic with the next generation of inhibitors shortly.

Dr. Arbour:
And I think one of the key things that you pointed out is how rare G12C mutations are. One of the challenges of these current KRAS inhibitors is that they are G12C specific, so they will not be effective at all in G12D or G12B or G12R, for example. And so I think that is one of the challenges as we broaden this field of who can get KRAS-targeted therapies beyond that being available. So definitely stay tuned with other exciting agents that are in clinical trial development.

So this has been a really great discussion. Our time is up. Thank you for listening.

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