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NSCLC Data Review: Efficacy and Safety Data for ON-State RAS Inhibitors

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Dr. Arbour:
This is CE on ReachMD, and I'm Dr. Kathryn Arbour. In this episode, I'll review the efficacy and safety data for ON-state RAS inhibitors in non-small cell lung cancer, and it's certainly been exciting times with multiple different clinical trials and data of novel agents that are in development. So we're going to be talking about 3 agents that are all RAS(ON) inhibitors but have different mechanisms of action and, in some instances, different patient populations looking at.

We've been talking about a drug called daraxonrasib, which is a multi-RAS inhibitor and targeting the ON state of RAS. And so this agent has been explored in patients with non-small cell lung cancer with RAS mutations such as G12. We call it G12X mutations, but that really means G12D, G12V, G12A, G12-anything, really, in the second- and third-line setting, with some, also, initial explorations in those patients with other RAS mutations outside the G12 indication.

So the phase 1 clinical trial data for daraxonrasib has been presented and is really highlighting the incredible promise of this agent in patients with non-small cell lung cancer. So we see clinical activity in patients with KRAS-mutant lung cancer with an overall response rate of 38% and a median progression-free survival of 9.8 months. The median overall survival of those patients treated with lung cancer was 17.7 months, which really is clinically encouraging beyond what we would typically see with docetaxel in a similar patient population.

And these encouraging results from the phase 1 clinical trial have really set the stage for the RASolve 301 study. This is an ongoing phase 3 clinical trial, and it's comparing daraxonrasib versus docetaxel, again, our standard second-line therapy—so can we improve upon that—in patients with previously treated metastatic or locally advanced, unresectable KRAS-mutant non-small cell lung cancer.

It is enrolling patients, I should say, not just with KRAS, but HRAS or NRAS alterations, which we rarely see as well. Those patients with G12 alterations and also more rare mutations such as Q61, G13 alterations. So it's really a broad population of patients.

And it'll be enrolling patients who've been previously treated with platinum doublet chemotherapy as well as immune checkpoint inhibitors. So focusing on a particularly unmet need patient population in that aspect.

So this study is currently ongoing globally, enrolling patients, and we really look forward to the results of this data to help guide ultimately the place in line of therapy for this agent in those patients, really those 30% of patients with non-small cell lung cancer who have a RAS mutation.

Other agents that are in development are mutant-selective inhibitors, such as elironrasib. Also known as RMC-6291. And so this is a G12C-specific inhibitor, and it's in development for patients with multiple solid tumors, including non-small cell lung cancer, where G12C mutations are common. Over 12% of patients of all non-small cell lung cancer will have a G12C mutation. It's the most common KRAS mutation that we see in non-small cell lung cancer. And it's been explored both in patients who have been previously treated with

chemotherapy and immunotherapy but not a G12C inhibitor. We call that a G12C inhibitor-naïve population. It's also being explored in those patients who have been previously treated with a G12C inhibitor before and had developed resistance to therapy.

So we've seen responses that have been presented in both groups. In a cohort of patients who were previously treated with a G12C(OFF) inhibitor and then developed resistance to the drug, the overall response rate was 42%. And we really have not seen any other targeted therapy be significantly successful in this. So this is an encouraging signal.

Ultimately, elironrasib has had breakthrough FDA designation for patients with G12C mutant non-small cell lung cancer who've been previously treated with chemotherapy and immunotherapy, but are naïve to a G12C inhibitor, and clinical trials are currently exploring further this agent specifically within the G12C population.

I'd be remiss not to bring up zoldonrasib, as well. So zoldonrasib is a G12D-specific inhibitor, a KRAS(ON) inhibitor in that setting. And this is a fairly rare mutation in non-small cell lung cancer. It is one of our less common KRAS mutations but still represents about 4% of non-small cell lung cancer patients overall. So still an unmet need. And of course, we have no targeted therapies that are currently approved for those patients with G12D alterations.

We saw encouraging data that was presented this past year in patients with non-small cell lung cancer, a small cohort, but that was presented at AACR with an overall response rate of 60% and a disease control rate of 89%.

So this is currently being explored in a larger cohort of patients with non-small cell lung cancer but substantially encouraging results in patients with G12D mutations. This is incredibly important because these patients are a little bit different than our classic KRAS-mutant lung cancer patients. Sometimes we see these in never-smokers, younger patients, and so to have targeted therapy in this setting is incredibly exciting.

I hope you found this review of RAS(ON) inhibitors in non-small cell lung cancer useful for your practice. Thank you so much for listening.

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