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KRAS G12C Biology: Why Is This Mutation Different?

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Dr. Burns:
Welcome. This is CE with GLC, and I'm Dr. Timothy F. Burns, professor of medicine at The Ohio State University Comprehensive Cancer Center. And today I'm reviewing KRAS G12C biology in non-small cell lung cancer and why this mutation is different from other alterations.

So KRAS mutations are the most common oncogenic driver that we see in non-small cell lung cancer, about 25%, and KRAS G12C is actually the most common KRAS mutation, about 50% of these, so about 13% of all non-small cell lung cancers. And so what you'll see with KRAS G12C mutations is that they're most common in lung, and that's partially because it's a smoking-associated mutation, but we see this across other solid tumor types, including colorectal, small bowel tumors, endometrial, pancreatic, and so this is something that we should be looking for and can potentially be targeted in other alterations.

Importantly, KRAS is a truncal mutation; it's an oncogenic driver. If you find a KRAS G12C, you're not going to find it in other disease types. If we look at what types of patients have these mutations, if we look across different racial subgroups, so African Americans and Caucasians have about similar percentage of mutations, slightly more common in females than males. It's less frequent in Asian populations, and actually in that case more common in men than in women.

There have been a number of studies that have looked at KRAS G12C–mutant lung cancer, and generally the prognosis for these patients, whether it be in the adjuvant setting, the metastatic setting, in first line or in later lines, is much worse, and so this is clearly an area of need.

Part of the reason that we think these mutations do so poorly is the company they keep, and so there are certain mutations that we see more frequently with KRAS-mutant disease, STK11, KEAP1, which have been associated with worse response to immunotherapy. And that probably contributes to why KRAS-mutant lung cancers can respond to immunotherapy but generally do worse than patients without KRAS mutations. And as you can see here in your slides, that patients with STK11 or KEAP1 with KRAS consistently do worse, whether it's progression-free survival or overall survival.

But there is hope. So we've thought for 3 decades that we really couldn't target KRAS, but we've now found KRAS G12C inhibitors. This started from work almost over a decade ago, showing that there are pockets that you could bind drugs to. And that led to the development of these inhibitors that bind to the cysteine residue, which subsequently led to the first KRAS G12C inhibitor called

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sotorasib, and now to a variety of KRAS G12C inhibitors, including 2 that are FDA-approved in the second-line setting.

Well, with that, our time is up. I hope that you will find these perspectives useful for your practice, and I want to thank you again for listening.

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