Targeting *KRAS*: Good, But Is It Good Enough?

Recently, the FDA granted accelerated approval to sotorasib, a drug targeting a specific *KRAS* mutation (G12C) in non–small cell lung cancer. The approval was based on a study by Skoulidis et al,[1] published in late June in *The New England Journal of Medicine*. This was a single-arm phase II trial involving 126 patients whose tumors carried this specific mutation, which occurs in about 13% of *KRAS*-driven lung cancers. In these patients, the response rate was 37.1%, median progression-free survival was 6.8 months, and median overall survival was 12.5 months. During the short follow-up period, the median duration of response was 11.1 months.

Why was this a big deal? For years, I have worked beside brilliant scientists who studied cancer signaling pathways, and it was generally held that targeting *KRAS* was the "holy grail." In fact, the NCI put millions into establishing the "RAS Initiative" for the primary purpose of promoting the successful development of these drugs. KRAS had been considered "undruggable," but after the structure was studied from every possible angle, a weak link was identified and the race to come up with a drug began. The G12C mutation is just the beginning; theoretically, every possible mutation can eventually be targeted.

I expected this drug and others like it to be blockbusters, to "knock it out of the park," and to turn *KRAS*-driven cancers into mere shadows of their former selves. I expected this to work similar to how imatinib beat down chronic myelogenous leukemia. I knew better than to think every tumor would respond—preclinical studies showed that not all cell lines died out when you shut down the KRAS pathway—but I really did think that we would see transformative and durable benefit in more patients. Please don't get me wrong. The benefit seen with sotorasib is real and it's important. I have no issue with the accelerated approval, especially given the favorable safety profile; but I honestly expected more.

Responses occurred less frequently than observed with tyrosine kinase inhibitors approved for other driver mutations in lung cancer. I didn't expect that. Clearly, we need to know more. Would the results have been different in a patient population that had received much less previous therapy? Do the resistance mechanisms have an antidote? Are there other pathways that must also be suppressed when you target *KRAS*? The possibilities, of course, are endless, and I have no doubt that our thoracic oncology colleagues will sort this out over time.

I am also puzzled why this drug doesn't seem to work as well in other diseases in which *KRAS* mutations occur, like colorectal cancer. In an earlier phase I trial, the response rate was only 7.1%.[2] This is another knowledge gap to fill.

Despite all these concerns, though, I consider this a watershed moment in the history of cancer therapy. Another victory for our patients! And I know more will come.

References

1. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with *KRAS* p.G12C mutation. N Engl J Med 2021;384:2371–2381.
2. Hong DS, Fakih MG, Strickler JH, et al. $KRAS^{G12C}$ inhibition with sotorasib in advanced solid tumors. N Engl J Med 2020;383:1207–1217.

WHAT DO YOU THINK? To submit a Letter to the Editor, email JNCCN@nccn.org or log into www.editorialmanager.com/JNCCN.

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