# Newly approved targeted therapy sotorasib prolongs survival in KRAS G12C-mutated lung cancer

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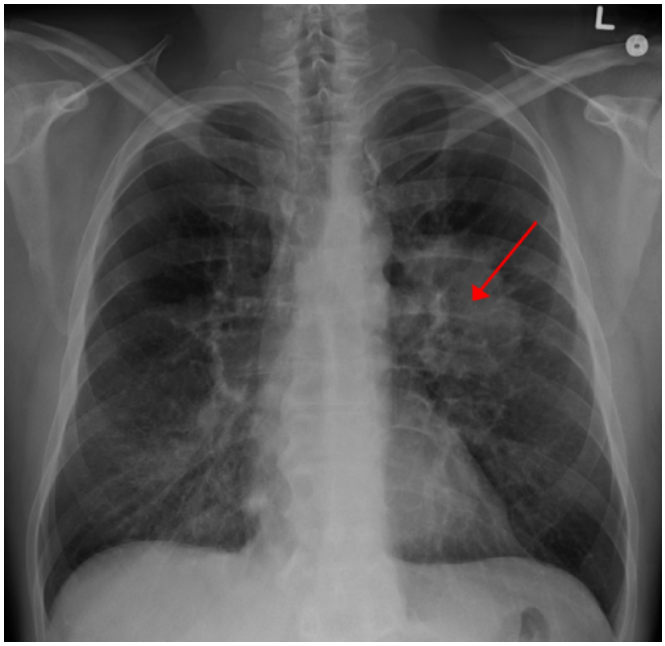

Lung CA seen on CXR. Credit: James Heilman, MD/Wikipedia

Results from the Phase II cohort of the CodeBreaK 100 study showed that treatment with the KRAS G12C inhibitor sotorasib achieved a 37.1% objective response rate and 12.5 months median overall survival in previously treated patients with KRAS G12C-mutated non-small cell lung cancer (NSCLC), according to researchers from The University of Texas MD Anderson Cancer Center. The findings were presented today at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting and published in the *New England Journal of Medicine.*

Trial results indicated the targeted therapy was safe and tolerable in a heavily pre-treated patient population. The reported findings make sotorasib the first KRAS G12C inhibitor to demonstrate overall survival benefit in a registrational Phase II clinical trial.

Sotorasib was approved by the Food and Drug Administration on May 28, 2021, based on previously reported results from the CodeBreaK 100 trial. It is the first ever direct KRAS inhibitor to earn regulatory approval.

"KRAS has been an elusive therapeutic target for more than 30 years and was deemed 'undruggable.' This trial provides convincing evidence that mutant KRAS can be successfully and selectively targeted, resulting in meaningful prolongation of survival without compromising quality of life," said lead author Ferdinandos Skoulidis, M.D., Ph.D., assistant professor of Thoracic/Head & Neck Medical Oncology. "These results, along with the regulatory approval of sotorasib, represent a major landmark for patients with KRAS G12C-mutated lung cancer, who now have an approved targeted therapy option."

KRAS is the most common oncogenic driver in NSCLC, found to be mutated in 25-30% of patients. Sotorasib (AMG 510) is an irreversible and selective small-molecule inhibitor that targets a specific type of mutant KRAS protein called KRAS G12C, which is found in approximately 13% of all lung adenocarcinomas.

**Study reveals rapid, durable clinical benefit with tolerable side effects**

The single-arm, multi-center trial enrolled 126 patients with locally advanced or metastatic KRAS G12C-mutated NSCLC that had progressed after receiving immune checkpoint inhibitors and/or platinum-based chemotherapy. Sotorasib is a once-daily oral drug. The primary endpoint was objective

response, assessed by independent central review.

The study found an objective response in 46 patients (37.1%), including four complete responses (3.2%) and 42 partial responses (33.9%). One hundred patients (80.6%) had disease control, with tumors shrinking or remaining stable. The median overall survival was 12.5 months, median duration of response was 11.1 months and median progression-free survival was 6.8 months.

Toxicities were manageable and primarily low grade, with only nine patients (7.1%) discontinuing therapy due to treatment-related adverse events. Of the 88 patients (69.8%) who had treatment-related adverse events, 25 (19.8%) were Grade 3 events and one (0.8%) was a Grade 4 event.

Study participants had a median age of 63.5 and were evenly split (50%) between men and women. The majority of patients (81.7%) were white, followed by Asian (15.1%), Black (1.6%) and other races (1.6%). Patients had received up to three previous lines of therapy and 96.8% had metastatic disease. A total of 81% of patients previously received both platinum-based chemotherapy and immune checkpoint inhibitors.

"In eight out of 10 patients, the tumor either shrank or remained stable, and these patients frequently saw improvement in their symptoms," Skoulidis said. "They're able to lead longer, active lives, because this targeted therapy is not associated with any major toxicities that would adversely affect the patient's quality of life."

**Sotorasib effective in challenging subgroup and more research is underway**

The study also analyzed responses among molecular subgroups and found particularly encouraging results among patients with STK11 co-mutations, without concurrent mutations in KEAP1. The 50% objective response rate and 11-month median progression-free survival in this group is notable because STK11-mutated tumors tend to respond poorly to standard of care therapies, including immunotherapy and chemotherapy.

Study investigators found response to sotorasib across other molecular subgroups, as well. The drug showed broad and consistent activity across patients with a wide range of baseline characteristics related to age, previous lines of therapy and other demographics.

"These study results are practice-changing, but our work isn't done," Skoulidis said. "Extensive efforts are underway to understand the determinants of response to sotorasib and to characterize the full spectrum of possible mechanisms of resistance. These results represent a foundational step in our progress against KRAS-mutant tumors and will likely be a stepping stone for even more effective combination regimens. The future looks promising."

**More information:** Ferdinandos Skoulidis et al, Sotorasib for Lung Cancers with KRAS p.G12C Mutation, *New England Journal of Medicine* (2021). DOI: 10.1056/NEJMoa2103695

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