

## KRAS Inhibitor Continues to Impress in NSCLC

— Sotorasib yielded deep and durable responses in over one-third of patients

by [Ian Ingram](#), Deputy Managing Editor, MedPage Today

February 1, 2021

More than a third of patients with pretreated non-small cell lung cancer (NSCLC) and a *KRAS* G12C mutation responded to the investigational agent sotorasib, findings from a phase II study showed.

Among 126 NSCLC patients with locally advanced or metastatic disease, most of whom had their disease progress following treatment with both chemotherapy and a checkpoint inhibitor, 37.1% had a confirmed response to the *KRAS* G12C inhibitor (95% CI 28.6-46.2), including complete responses in 2.4%, reported Bob T. Li, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York City.

An additional 43.5% achieved stable disease as their best response, for a disease control rate of 81% (95% CI 72.6-87.2%), according to findings presented at the virtual [World Conference on Lung Cancer](#) (WCLC).

Sotorasib, a first-in-class *KRAS* G12C inhibitor, "demonstrated rapid, deep, and durable responses in patients with advanced *KRAS* G12C-mutant non-small cell lung cancers," said Li during a media briefing.

The median duration of response was 10.0 months (95% CI 6.9-11.1) and the median time to response was 1.4 months. At data cutoff, 43% of responders remained on treatment without disease progression. With a follow-up of 12.2 months, the median progression-free survival reached 6.8 months (95% CI 5.1-8.2).

"These results are clinically meaningful for these patients, which represent a refractory cancer population of unmet need," Li added. "Tumor response was also seen across a range of biomarker subgroups by PD-L1 expression and *STK11* mutation."

*KRAS* G12C mutations, occurring in about 13% of NSCLC patients, are often associated with poor prognosis.

Asked about adoption in the clinic if the drug gains approval, Li said the first step will be to start testing all NSCLC patients for *KRAS* mutations.

"For 40 years we thought *KRAS* was undruggable, so there's a school of thought that there's no point testing cause you can't do anything about it. That has for the first time changed," said Li.

Sotorasib recently received [breakthrough therapy designation](#) from the FDA, and Li said the drugmaker, Amgen, has submitted the CodeBreak 100 data to the agency for regulatory review. Other *KRAS* G12C-targeted agents, [including adagrasib](#), are also in development for NSCLC.

"*KRAS* G12C inhibitors are finally here," said WCLC discussant Pasi Janne, MD, of the Dana-Farber Cancer Institute in Boston.

"*KRAS* is the largest subset of non-small cell lung cancer with an oncogenic alteration, but without an approved targeted therapy," he noted. "If we dig deeper into the *KRAS* population, about 50% harbor a *KRAS* G12C mutation, and collectively this is more patients than *ALK*, *ROS*, *RET*, and *NTRK* mutations combined."

Janne said *KRAS* G12C inhibitors have been shown to be very well tolerated due to their high selectivity and specificity, with rates of treatment discontinuation below 10% across trials.

In the current study, treatment-related adverse events (AEs) led to sotorasib dose modifications in 22.2% and discontinuation in 7.1%.

In all, 70% of patients experienced an AE, with the most common being diarrhea in 31%, nausea in 19%, increased alanine aminotransferase (ALT) in 15.1%, increased aspartate transaminase (AST) in 15.1%, and fatigue in 11.1%.

Grade 3 AEs occurred in 20%, led by diarrhea in 4%, ALT increase in 6.3%, AST increase in 5.6%, and increased blood alkaline phosphatase in 0.8%. There were no treatment-related fatalities. One patient experienced grade 4 pneumonitis and dyspnea.

Li called the treatment-related toxicities mostly treatable and reversible with supportive care or dose modification.

[CodeBreak 100](#) was a multicenter, open-label, single-arm phase II study testing oral sotorasib (960 mg daily) in 126 NSCLC patients with locally advanced or metastatic disease across 11 countries. Eligibility requirements included a *KRAS* G12C mutation, no active brain metastases, disease progression after up to three prior standard therapies, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Those with *EGFR*, *ALK*, or *ROS1* driver mutations were excluded.

Patients enrolled had a median age of 63.5 years, 92.9% were current or former smokers, 70% had an ECOG status of 1, and a majority had two or more prior lines of systemic therapy. Nearly 90% had received platinum-based chemotherapy, 91% had received a PD-1/L1 checkpoint inhibitor, and 81% had received both.

A confirmatory phase III trial -- [CodeBreak 200](#) -- is currently enrolling and will test second-line docetaxel with or without sotorasib in NSCLC.

Last Updated February 02, 2021



[Ian Ingram](#) joined MedPage Today in 2018 as Deputy Managing Editor, and covers oncology for the site.

---

## Disclosures

Li disclosed personal and/or institutional relationships with Amgen, Boehringer Ingelheim, Lilly, AstraZeneca, Daiichi Sankyo, Genentech, Guardant Health, Hengrui Therapeutics, Resolution Bioscience, MORE Health, Jiangsu Hengrui Medicine, Puma, Illumina, GRAIL, BioMed Valley Discoveries, and BOLT Biotherapeutics.

Janne reported relationships with AstraZeneca, Boehringer Ingelheim, Pfizer, Genentech/Roche, Chugai Pharmaceuticals, ACEA Biosciences, Gatekeepers Pharmaceuticals, LOXO Oncology, Ignyta, Lilly, Araxes, Mirati Therapeutics, SFJ Therapeutics, Bayer, Puma, Revolution Medicines, Daiichi-Sankyo, Biocartis, Takeda, Novartis, Silicon Therapeutics, and Eisai.

## Primary Source

World Conference on Lung Cancer

Source Reference: [Li BT, et al "CodeBreak 100: Registrational phase 2 trial of sotorasib in KRAS p.G12C mutated non-small cell lung cancer" WCLC 2020; Abstract 3037.](#)

---

## Recommended For You

**MARTY TIME**

**Op-Ed: Why I Refuse to Get the COVID Vaccine Right Now**

## Controversial Physician Joined in Storming the Capitol

## **Simone Gold Arrested for Role in Capitol Insurrection**

## **CDC Updates Contraindications to COVID-19 Vaccination**

## **J&J COVID-19 Vax Effective Against Severe Disease**

## Vaccinated but Sick With COVID-19