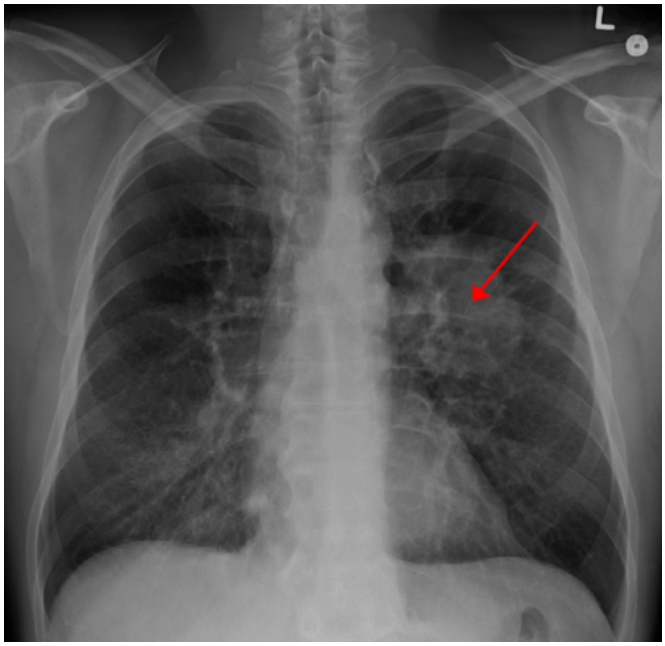
Second drug targeting KRASG12C shows benefit in mutated non-small-cell lung cancer

25 March 2021



Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

Clinical activity with a second drug inhibiting KRASG12C confirms its role as a therapeutic target in patients with advanced non-small-cell lung cancer (NSCLC) harboring this mutation, according to results from a study with the KRASG12C inhibitor adagrasib reported at the European Lung Cancer Virtual Congress 2021.

"As we strive to identify the oncogenic driver in more and more of our patients with NSCLC, it becomes critical that we develop therapies that can target these identified oncogenic drivers," said lead author Gregory Riely, from Memorial Sloan Kettering Cancer Center, New York, USA.

"KRAS mutations are the most frequent oncogenic driver that we see in patients with NSCLC and we've known about KRAS-mutant NSCLC for 30 years. We are now, finally, seeing drugs that can target this subgroup of patients," he said.

The multi-cohort phase 1/2 KRYSTAL-1 study evaluated adagrasib, a selective inhibitor of KRASG12C, in 79 patients with advanced or metastatic NSCLC harboring a KRASG12C mutation. Most (92%) of the patients had previously been treated with chemotherapy and an anti-PD-(L)1.

Results showed that nearly half (45%) of the 51 patients evaluable for clinical activity had a partial response to treatment with adagrasib, and 26 patients had stable disease.

"The 45% response rate is unprecedented activity in patients with KRASG12C mutant NSCLC," commented Myung-Ju Ahn, from Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. "A response of this magnitude could not be expected with other chemotherapy or immunotherapy in pre-treated KRAS-mutated patients, suggesting that KRASG12C is a therapeutic target." She considered the finding is potentially practice-changing although further studies are needed as long-term follow-up data are currently limited.

The results with adagrasib are comparable to those with another KRASG12C inhibitor, sotorasib, reported earlier this year at the World Conference on Lung Cancer 2021.

"Finding another promising targeted agent against KRASG12C mutant NSCLC sheds light on the treatment of these patients who currently have unmet medical need," said Ahn.

KRASG12C mutations occur in around 14% of patients with lung adenocarcinomas, the most common subtype of NSCLC, but there is currently no approved KRAS-targeting therapy.

"Having more KRASG12C inhibitors gives us additional opportunities to explore combinations of these inhibitors with other classes of agents, including immune checkpoint inhibitors as well as other small molecule MAP kinase inhibitor combinations," said Riely.

"The current data really set up future trials to establish the role for adagrasib in patients with KRASG12C mutant NSCLC. They provide a particular opportunity to explore this drug's activity in patients with KRASG12C mutant NSCLC that have been previously treated with platinum-based chemotherapies to potentially submit for regulatory approval." If approved, he suggested: "I think this would clearly set adagrasib as a preferred second-line therapy, compared with chemotherapy, for patients with KRAS mutant NSCLC."

"Given the low toxicity, adagrasib could potentially be combined with chemotherapy, immunotherapy or other molecules to increase activity in patients with KRASG12C mutant NSCLC," suggested Ahn.

Further data from KRYSTAL-1 showed an even greater response to adagrasib in the subpopulation of patients whose tumors had an STK11 mutation as well as a KRASG12C mutation. STK11 mutations have been associated with inferior responses to immune checkpoint inhibitors in patients with NSCLC. Riely noted: "Finding that the response rate was higher for patients with STK11 mutations suggests that this group of patients, who otherwise don't benefit from checkpoint inhibitors, may have even better response to adagrasib."

Provided by European Society for Medical Oncology