Sotorasib shows clinically meaningful activity in KRAS G12C-mutated advanced pancreatic cancer

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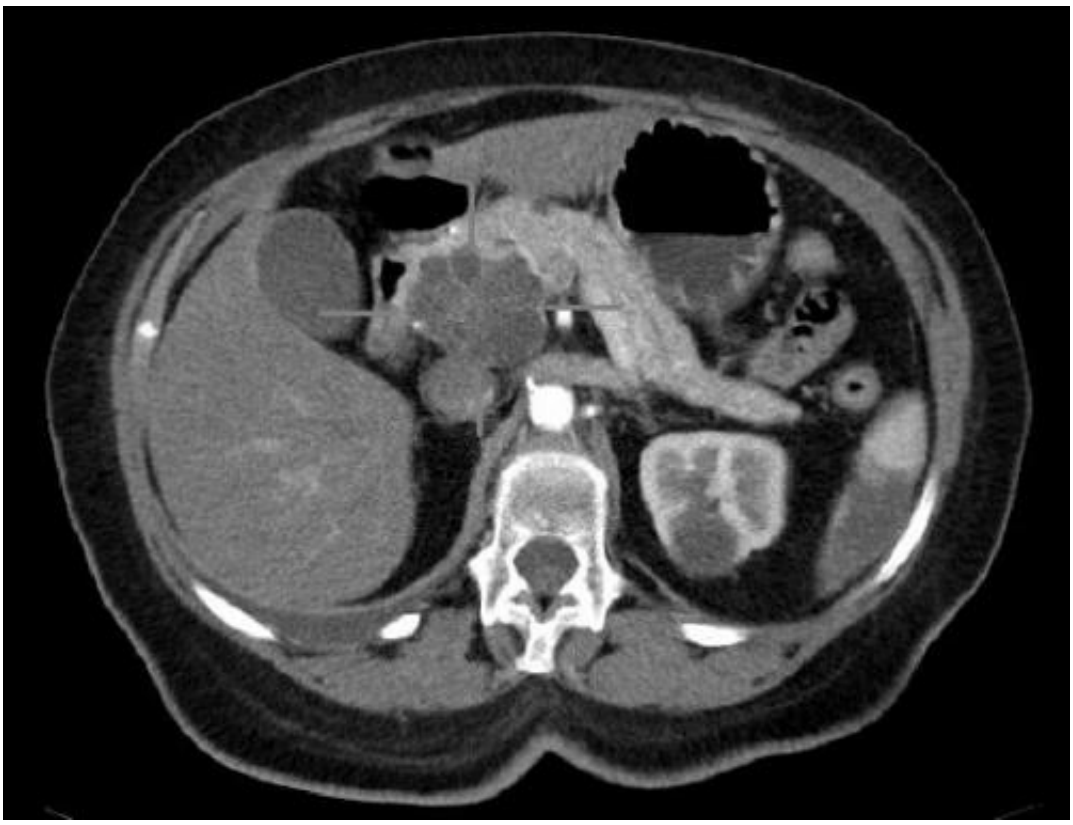

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

In the Phase I/II CodeBreaK 100 trial, the KRAS G12C inhibitor sotorasib achieved meaningful anticancer activity with an acceptable

safety profile in heavily pretreated patients with KRAS G12C-mutated metastatic pancreatic cancer, according to researchers at The University of Texas MD Anderson Cancer Center.

The results of the trial, published today in the *The New England Journal of Medicine*, indicate an objective response rate of 21.1% and a median time-to-response of 1.5 months, with 84% of patients experiencing disease control. Median progression-free survival was 4 months and overall survival was 6.9 months.

"These are encouraging early data because they point toward establishing that KRAS inhibitors can work in pancreatic cancers, which have been difficult to crack from a targeted therapy standpoint," said principal investigator David S. Hong, M.D., professor of Investigational Cancer Therapeutics. "We look forward to data from larger trials as we continue working to bring much-needed new therapies to these patients."

The KRAS protein is part of a normal signaling pathway regulating growth and proliferation of cells, but activating mutations in KRAS drives abnormal growth in cancer. KRAS mutations are especially common in pancreatic cancers, occurring in about 90% of patients, while KRAS G12C mutations are present in 1-2% of cases.

Sotorasib is a small-molecule inhibitor that irreversibly binds the mutant KRAS G12C protein to lock it in an inactive state. In 2021, this targeted therapy was approved by the Food and Drug Administration for the treatment of KRAS G12C-mutated metastatic non-small cell lung cancer, based on previous data from another cohort of this study.

The pancreatic cancer cohort enrolled 38 patients with metastatic disease and a median of two prior lines of therapy. The median age of participants was 65.5, 76.3% were men and 55.3% had stage IV disease at initial diagnosis.

All patients experienced treatment-emergent adverse events, the most common of which were abdominal pain (36.8%), diarrhea and nausea (23.7% each). Treatment-related adverse events were reported in 42.1% of patients, of which 15.8% were grade 3. The most frequently occurring grade 3 toxicities were diarrhea and fatigue (5.3% each). No adverse events resulted in discontinuation of treatment.

According to Hong, these results may be a harbinger of success for other drugs in the pipeline targeting mutant KRAS that could potentially benefit far greater numbers of patients.

"It's gratifying to see results like this, since targeting mutant KRAS seemed virtually impossible just a few years ago. Still, we must continue our research efforts to make progress against other common KRAS mutations found in pancreatic and other cancer types," Hong said. "Trials have recently begun on drugs targeting KRAS G12D, a much more common mutation in pancreatic cancer, as well as some pan-RAS therapies, which target multiple mutations."

More information: Sotorasib in KRAS p.G12C–Mutated Advanced Pancreatic Cancer, *New England Journal of Medicine* (2022). DOI: 10.1056/NEJMoa2208470.
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