Targeted Therapy Drug Shows Early Promise Against KRAS-Driven Lung and Pancreatic Cancers

Setidegrasib, designed to target KRAS G12D, shrank tumors in some patients and delayed disease progression.

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A first-in-human clinical trial led by an international team of researchers and published in the New England Journal of Medicine found that setidegrasib, an investigational targeted therapy drug designed to eliminate a key cancer-driving protein called KRAS G12D, shows encouraging early activity in patients with advanced lung and pancreatic cancers. The therapy shrank tumors in some patients and delayed disease progression, marking a potential step forward for cancers with few targeted treatment options.

Why it matters

Setidegrasib is designed to attack a mutation known as KRAS G12D, which helps cancer cells grow and survive. Unlike most targeted therapies, which work by blocking a cancer-driving protein, setidegrasib degrades and removes the abnormal KRAS protein from inside cancer cells. The KRAS G12D mutation is one of the most common genetic drivers of pancreatic ductal adenocarcinoma, occurring in about 40% of patients. It is also found in about 5% of patients with non–small-cell lung cancer. Despite its prevalence, KRAS G12D has historically been considered extremely difficult to target because the structure of the protein makes it hard for drugs to effectively bind to it. While therapies have recently been developed for a related mutation, KRAS G12C, no approved treatments currently exist for KRAS G12D, leaving a major unmet need for patients with these cancers.

What the study did

The Phase 1 clinical trial was conducted across 28 centers in five countries and included 203 patients whose cancers had already progressed after prior treatments. Researchers tested escalating doses of setidegrasib to evaluate safety and early signs of activity and identified 600 mg once weekly administered intravenously as the recommended dose for further study based on safety, drug activity, and early signs of efficacy.

What they found

The therapy demonstrated early antitumor activity in both advanced lung and pancreatic cancer. Among the 66 patients (45 with lung cancer and 21 with pancreatic cancer) who received the 600-mg dose:

- In non–small-cell lung cancer, 36% of patients experienced tumor shrinkage, and the median time before disease progression was approximately 8.3 months.
- In pancreatic ductal adenocarcinoma, 24% of patients experienced tumor shrinkage, with a median overall survival of 10.3 months in heavily pretreated patients.

The treatment was generally well tolerated. While infusion-related reactions such as rash, itching, and nausea were common, these effects were mostly mild to moderate and manageable with standard supportive care.

Laboratory analyses also showed that setidegrasib was successful at reducing levels of the KRAS G12D protein in tumors, as well as lowering the amount of tumor DNA circulating in the blood, suggesting strong biological activity against the intended target.

What this means for patients

“These are early but meaningful signals in cancers where targeted treatment options have been scarce,” said senior author of the study Dr. Jonathan Goldman, Health Sciences Clinical Professor in the department of Medicine at the David Geffen School of Medicine at UCLA and investigator in the UCLA Health Jonsson Comprehensive Cancer Center. “If confirmed in later trials, this approach could represent a broader shift in cancer therapy by moving from drugs that inhibit cancer proteins to drugs that eliminate them.”

What’s next

New clinical trials are in development to confirm setidegrasib’s benefit compared to currently available treatments for pancreatic and lung cancer. Other therapies that work by removing cancer-driving proteins from inside tumor cells are also being investigated, potentially expanding this approach to additional cancers.

About the researchers

Jonathan Goldman is also the director of clinical trials in thoracic oncology at UCLA, associate director of early drug development and recent chair of the University of California Lung Cancer Consortium. The study’s first author is Wungki Park of the Memorial Sloan Kettering Cancer Center. A full list of authors appears in the paper.

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