RAS(ON) Inhibitor Daraxonrasib Shows Promising Results in Advanced Pancreatic Cancer Phase 1/2 Study

More than 90% of pancreatic cancer patients have KRAS mutations that could be targeted by the experimental drug.

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The targeted RAS inhibitor daraxonrasib was found to be safe and showed signs of efficacy in a Phase I/II first-in-human trial in patients with previously treated, RAS-mutant, metastatic pancreatic cancer, according to a clinical trial led at Dana-Farber Cancer Institute and across the country.

The results were published in the New England Journal of Medicine and support a Phase III clinical trial currently underway, RASolute 302, that will compare the efficacy of daraxonrasib to current standard of care second-line chemotherapy for patients with metastatic pancreatic cancer.

Patients with pancreatic cancer often discover the disease after it has already spread and cannot be surgically removed. The primary treatment option for most patients is chemotherapy. Few patients survive beyond one year and second-line chemotherapy often provides modest benefit.

More than 90% of patients with pancreatic cancer have cancer-driving mutations in the KRAS oncogene. For a long time, KRAS was considered “undruggable,” but around ten years ago, advances in chemistry led to the development of the first RAS inhibitors. Today, two RAS inhibitors are approved to treat lung and colorectal cancers, but these inhibitors are active against a RAS mutation that is rarely seen in pancreatic cancer.

In contrast, daraxonrasib is a RAS(ON) multi-selective inhibitor that is active against the RAS mutations that occur commonly in pancreatic cancer. The medicine, in the trial, is given as a daily pill.

“If supported by data from future clinical trials, daraxonrasib would be a targeted therapy relevant to nearly all patients with advanced pancreatic cancer,” says first author Dr. Brian Wolpin, director of the Hale Family Center for Pancreatic Cancer Research at Dana-Farber and a lead investigator on the trial. “This trial is the first to test the drug in humans and provides the first published data showing the safety and broad activity of a RAS(ON) multi-selective inhibitor in pancreatic cancer. If

this drug proves effective in larger clinical trials, it would signify a substantial shift in how this disease is treated."

The Phase I/II trial enrolled 168 patients with advanced pancreatic cancer that harbored RAS mutations. All patients were previously treated with one or more lines of chemotherapy. Most patients experienced some side effects, with the most common adverse events of rash, inflammation in the mouth, nausea and diarrhea.

"With supportive medicines, the drug was well-tolerated by the majority of patients," says Wolpin.

The drug showed promising signs of activity against pancreatic cancer that supported further exploration in a Phase III clinical trial, RASolute 302. Primary and final analysis of that trial will be presented by Dr. Wolpin in a plenary session at the American Society for Clinical Oncology (ASCO) Annual Meeting on May 31, 2026.

At the 300 mg daily dose, which was the dose selected for further evaluation in the RASolute 302 trial, approximately 30% of patients with one prior line of treatment experienced an objective response in their cancer. Across all patients, including those who had received more than one prior line of treatment, approximately 90% experienced disease control, meaning their cancer was reduced or stabilized. Median duration of these responses was more than 8 months for patients with one prior therapy.

"The drug controlled people's cancer longer than what we have historically seen with chemotherapy as second line therapy, but we await results from the RASolute 302 trial to confirm whether daraxonrasib should be used instead of chemotherapy as a second-line treatment," says Wolpin, who serves on the steering committee for RASolute 302. "The RASolute 302 trial is designed to directly compare daraxonrasib to currently available chemotherapy and determine if it is a more effective second line treatment."

Daraxonrasib is the first RAS(ON) multi-selective inhibitor to be tested in clinical trials for pancreatic cancer. It works as a molecular glue that together with another protein, cyclophilin A, blocks the signaling of RAS proteins. Numerous other RAS inhibitors have now also begun to be tested in clinical trials for pancreatic cancer.

"Blocking mutant RAS has been an aspirational goal for treatment of pancreatic cancer for many years, due to RAS mutations being so common in this disease and serving as a main driver of pancreatic cancer growth. This aspiration is now being realized in the clinic, due to the hard work of large numbers of chemists, biologists, oncologists, patients, and many others," says Wolpin. "Although much work remains to be done, it genuinely feels like a new day is dawning for pancreatic cancer treatment, with daraxonrasib potentially serving as the first of a set of new medicines that broadly target mutant RAS and allow us to help patients with pancreatic cancers in new ways."

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