mRNA Vaccine Shows Promise for Pancreatic Cancer

People who received a personalized neoantigen vaccine had a lower rate of recurrence in an early study.

March 13, 2025 By Liz Highleyman

A custom-made messenger RNA (mRNA) vaccine plus an immune checkpoint inhibitor appears to reduce the risk of pancreatic cancer recurrence for at least three years after surgery, according to results from a small clinical trial published in Nature.

“The latest data from the Phase I trial are encouraging,” lead investigator Vinod Balachandran, MD, of Memorial Sloan Kettering Cancer Center, said in a news release. “They suggest this investigational therapeutic mRNA vaccine can mobilize antitumor T cells that may recognize pancreatic cancers as foreign, potentially years after vaccination.”

Pancreatic cancer is often diagnosed late, and it is difficult to treat. Standard treatment may include surgery, radiation, chemotherapy, targeted therapies and immunotherapy, but relapse and metastasis are common, and the five-year survival rate is only around 10%.

To create a personalized cancer vaccine, scientists genetically sequence a sample from a patient’s tumor after surgery and use algorithms to identify neoantigens—abnormal proteins unique to cancer cells—that are most likely to trigger a robust immune response. Different types of vaccines deliver bits of these proteins or their genetic code via mRNA virus vectors. Compared with some other cancers, such as melanoma, pancreatic cancer has relatively few targetable mutations to work with.

Balachandran and colleagues evaluated a vaccine called autogene cevumeran (also known as BNT122 or RO7198457) being developed by BioNTech—the German biotech company that partnered with Pfizer to develop the most widely used mRNA COVID-19 vaccine—in collaboration with Genentech.

The Phase I trial (NCT04161755) included 16 patients with pancreatic ductal adenocarcinoma at Memorial Sloan Kettering. Their tumors were sequenced after surgery, and a vaccine containing up to 20 neoantigens was custom-made for each patient. The study participants received several primer and booster doses along with Genentech’s PD-L1 checkpoint inhibitor Tecentriq (atezolizumab) and a four-drug chemotherapy regimen dubbed mFOLFIRINOX.

Some tumors can suppress natural immune responses; PD-1 and PD-L1 checkpoint inhibitors release the brakes and restore T-cell activity. Combining a vaccine that helps immune cells recognize cancer with a checkpoint inhibitor has the effect of letting up on the brakes and stepping on the accelerator at the same time.

At the 2022 American Society for Clinical Oncology annual meeting, the researchers reported that half of the participants had strong T-cell responses against one or more of the tumor neoantigens in the vaccine. Further results, reported in Nature in 2023, showed that these responders had no evidence of cancer recurrence during 18 months of follow-up.

At the 2024 American Association for Cancer Research annual meeting, and now again in Nature, Balachandran's team reported that activated T cells lasted more than three years in responders. The researchers estimated that these tumor-specific CD8 killer T-cells could have an average lifespan of 7.7 years.

What's more, patients with persistent vaccine-induced immune responses remained less likely than nonresponders to experience recurrence. Six of the eight responders remained cancer-free over a median 3.2 years of follow-up, while most of the eight nonresponders relapsed. The two responders who relapsed showed weaker vaccine-induced T cell activity. The median recurrence-free survival time was 13.4 months for the nonresponders but has not yet been reached for the responders because most are still cancer-free.

The vaccine was generally safe and well-tolerated. Adverse events were common in the trial, but these were mostly associated with the checkpoint inhibitor and chemotherapy rather than the vaccine.

The study has some limitations. Only a select subgroup of patients—those with operable pancreatic cancer for whom adequate neoantigens could be identified—were eligible for the vaccine. Around one in five pancreatic cancer patients are diagnosed with operable tumors. Only a small number of participants were included in the latest analysis. Overall survival outcomes are not yet mature. It is not clear how much the checkpoint inhibitor contributed, though prior studies have found that atezolizumab plus chemotherapy offers little or no improvement in pancreatic cancer survival.

Nonetheless, the findings were promising enough to advance the vaccine to a larger randomized Phase II trial (NCT05968326) conducted at more than 60 sites worldwide. The study is enrolling people with newly diagnosed pancreatic cancer who have not yet received systemic therapy. After surgical removal of the tumor, they will be randomly assigned to receive autogene cevumeran, Tecentriq and mFOLFIRINOX or standard treatment using mFOLFIRINOX alone.

"For patients with pancreatic cancer, our latest results continue to support the approach of using personalized mRNA vaccines to target neoantigens in each patient's tumor," Balachandran said. "If you can do this in pancreas cancer, theoretically you may be able to develop therapeutic vaccines for other cancer types."

Personalized cancer vaccines are also being developed for several other malignancies, including melanoma, colorectal cancer, kidney cancer, liver cancer and glioblastoma brain cancer. So far, these vaccines appear to work better for keeping residual cancer in check after surgery or other types of treatment, as opposed to eliminating large established tumors. These therapeutic vaccines differ from existing vaccines that prevent infections that cause cancer, such as human papillomavirus (cervical, anal and oral cancers) and hepatitis B virus (liver cancer).

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