

Promising results for chemo-immunotherapy combination against pancreatic cancer

June 4 2022



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A combination of chemotherapy with an immunotherapy meant to unleash the anticancer capacity of the immune system was effective against one of the hardest targets in cancer care, pancreatic cancer, in a national, randomized clinical trial led by researchers at the Perelman School of Medicine at the University of Pennsylvania, and sponsored by

the Parker Institute for Cancer Immunotherapy.

The results of the small but promising trial were announced today in a presentation at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, and simultaneously published in *Nature Medicine*.

The researchers found that in 34 patients with advanced [pancreatic cancer](#) randomized to receive the [immunotherapy](#) nivolumab with two [chemotherapy drugs](#), nab-paclitaxel and gemcitabine, had a one-year survival rate of 57.7 percent, significantly greater than the historical average of 35 percent with [chemotherapy](#) alone. The findings also included the identification of immune system biomarkers associated with better outcomes. A second treatment of the immunotherapy sotigalimab with chemotherapy also appeared more effective in a subgroup of patients, identified with a different set of biomarkers.

"This study suggests there is benefit of combining immunotherapy and chemotherapy in patients with advanced pancreatic cancer and there may be ways to fine tune treatment choices based on the 'immune health' of the patient," said Robert H. Vonderheide, MD, DPhil, the John H. Glick Abramson Cancer Center Professor and director of the Abramson Cancer Center at Penn. "We now hope to evaluate these potential biomarkers in further trials to see if they'll enable us reliably to identify patients who will respond best to this and other combination therapies. The most promising biomarkers were measured by a blood test of the immune system, not genetic sequencing, which opens the door for a new approach in precision oncology."

The most common form of [pancreatic cancer](#), known as pancreatic ductal adenocarcinoma (PDAC), is commonly diagnosed only after it has become advanced or metastatic, and is also notoriously aggressive and difficult to treat effectively. Historically, only about 10 percent of

patients who receive a PDAC diagnosis survive for five years, and patients newly diagnosed with metastatic PDAC usually live for less than a year even with optimal chemotherapy.

Standard chemotherapy regimens can arrest the growth of PDAC tumors, but only temporarily. Newer immune-targeted therapies, such as checkpoint blockade antibodies, have been strikingly effective against some other cancers, but almost entirely ineffective—when used on their own—against PDAC.

However, a ray of hope has come from preclinical experiments in mouse models of PDAC, and an initial small clinical trial [reported](#) by Vonderheide's team last year suggested that the addition of chemotherapy can substantially disrupt pancreatic tumors' resistance to immunotherapy—making the combination more effective than either type of treatment on its own. In the new study, they tested that approach on a larger scale.

They randomized a set of more than 100 patients with metastatic PDAC to receive a standard chemotherapy (gemcitabine/nab-paclitaxel) plus one of three immunotherapy regimens: an antibody treatment (nivolumab) targeting the immune "off switch" PD-1, a different antibody treatment (sotigalimab) that activates an immune "on switch," CD40, and a combination of the anti-PD-1 and pro-CD40 treatments. The main goal of the study was to see if any of these combinations could improve the rate of survival over one year for these patients, compared to the historical rate of just 35 percent for patients who receive chemotherapy alone.

The researchers found that all three groups had one-year survival rates higher than 35 percent: 57.7 percent for anti-PD-1 plus chemo, 48.1 percent for pro-CD40 plus chemo, and 41.3 percent for combo immunotherapy plus chemo. Only the first of these results was

statistically significant, although in a study with such small patient numbers only the most striking differences will clear the statistical significance barrier.

A key part of the clinical approach to difficult cancers such as PDAC is the discovery of factors in the patient that are linked to better outcomes for a given treatment. This enables a better understanding of the cancer, and in principle allows doctors to know which treatment to give only to patients who are likely to benefit the most. In this case, the researchers were able to identify factors, including the levels of certain immune cells in the bloodstream pre-treatment, that predicted longer survival for the anti-PD-1/chemo and pro-CD40 arms.

Patients who received chemotherapy and both types of immunotherapy did not benefit any more than chemotherapy alone. The researchers suspect that the relatively poor results for the two-immunotherapy regimen may have resulted from an excessive activation of T cells that pushed the cells into an exhausted state.

Funding and/or immunotherapy doses were provided by the Cancer Research Institute, the Parker Institute for Cancer Immunotherapy, Bristol Myers Squibb, and Apexigen. Participating clinical sites included Penn's Abramson Cancer Center, Dana-Farber Cancer Institute, MD Anderson, Memorial Sloan Kettering, Stanford University, University of California Los Angeles, and University of California San Francisco.

More information: Sotigalimab and/or nivolumab with chemotherapy in first-line metastatic pancreatic cancer: clinical and immunologic analyses from the randomized phase 2 PRINCE trial, *Nature Medicine* (2022). [DOI: 10.1038/s41591-022-01829-9](https://doi.org/10.1038/s41591-022-01829-9)

Provided by University of Pennsylvania

Citation: Promising results for chemo-immunotherapy combination against pancreatic cancer (2022, June 4) retrieved 29 June 2024 from <https://medicalxpress.com/news/2022-06-results-chemo-immunotherapy-combination-pancreatic-cancer.html>

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