CD40 Antibody Combination Looks Promising for Pancreatic Cancer

Two types of immunotherapy plus chemotherapy shrank tumors in most patients in an early study.

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An experimental antibody targeting CD40, used in combination with a checkpoint inhibitor and chemotherapy, demonstrated good antitumor activity and manageable side effects in people with advanced pancreatic cancer, according to early study findings presented at the 2019 American Association for Cancer Research (AACR) annual this week in Atlanta.

This combination approach led to tumor shrinkage in just over half of evaluable patients in a Phase Ib study, supporting further testing in a larger group, reported lead investigator Mark O'Hara, MD, of the Abramson Cancer Center at the University of Pennsylvania.

"The idea is to attack the cancer from different angles," senior study author Robert Vonderheide, MD, also from the Abramson Cancer Center, said in a press release issued by the Parker Institute for Cancer Immunotherapy, which sponsored the study. "Although the results are early, we see encouraging signs that anti-CD40 immunotherapy, checkpoint inhibition and chemotherapy in combination could be an effective new approach to treat patients with metastatic pancreatic cancer."

Pancreatic cancer is often diagnosed at a late stage, when it is difficult to treat, resulting in a high mortality rate. Nearly 46,000 people will die of pancreatic cancer this year, according to the American Cancer Society.

O'Hara's team evaluated APX005M, a monoclonal antibody directed against the CD40 receptor on antigen-presenting immune cells, which is designed to stimulate T-cell activity against tumors. The antibody was developed by a collaboration that includes the Parker Institute, the Cancer Research Institute, Bristol-Myers Squibb and the biotech company Apexigen.

Existing PD-1/PD-L1 checkpoint inhibitors—which take the breaks off T-cells—show little activity against pancreatic cancer when used alone. But a multipronged attack that combines a PD1

inhibitor, chemotherapy to release tumor antigens and a CD40 antibody to engage antigen-presenting cells holds more promise.

The PRINCE study included 30 people with previously untreated metastatic pancreatic ductal adenocarcinoma. Just over half were men, most were white and the median age was 66.

Participants were randomly assigned to receive one of two doses of APX005M plus the chemotherapy drugs gemcitabine and Abraxane (nab-paclitaxel). Half also received the PD-1 blocker Opdivo (nivolumab). The median time on treatment was about 30 months.

The primary aim of the Phase 1b portion of the study was to look at safety (in all patients) and dose-limiting toxicities, meaning participants had to stop or limit treatment because of side effects (in 24 people who received at least one dose of APX005M and two doses of chemotherapy and completed the observation period).

Thirteen of the 24 evaluable patients, or 54 percent, had a partial response, meaning some tumor shrinkage; 11 of these were confirmed responses, O'Hara reported. In some cases, these responses lasted nearly a year. No one had a complete response.

In addition, nine people (38 percent) had stable disease, one experienced disease progression and one could not be evaluated. The partial response rate was higher, at 67 percent, for those who included Opdivo in their regimen.

"Given that most patients with metastatic pancreatic cancer have evidence of progression of their cancer within about five months of starting first line chemotherapy, seeing several patients stay on treatment on this trial for more than one year is exciting," O'Hara said in an Apexigen press release.

Treatment was generally safe. There were two dose-limiting toxicities (both febrile neutropenia, or white blood cell deficiency) and one death (due to sepsis) associated with the chemotherapy, but none attributed to APX005M or Opdivo. Severe (grade 3 or 4) treatment-related adverse events were common, but again these were mostly blood cell deficiencies related to chemotherapy. No one developed cytokine release syndrome, a potential side effect of immune-based therapies.

Based on these findings, the researchers concluded that the immunotherapy combination "demonstrated encouraging clinical activity" with a "manageable" safety profile.

The three-pronged approach for pancreatic cancer is now being further evaluated in the Phase II portion of the PRINCE study, currently ongoing at all seven Parker Institute member institutions.

Researchers also presented early data from a trial of APX005M plus Opdivo in people with metastatic melanoma. Here too, treatment was well tolerated in patients who progressed on checkpoint inhibitor monotherapy. One of the five participants had a partial response and two had prolonged stable disease, according to Apexigen.

“What we learn in this trial can inform the work being done on other solid tumor types, so that we can make immunotherapy beneficial for more patients,” said Parker Institute chief medical officer Ramy Ibrahim, MD.

Click here to read the AACR study abstract.

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