Genetic biomarker may predict cancer patients' response to immunotherapy drug

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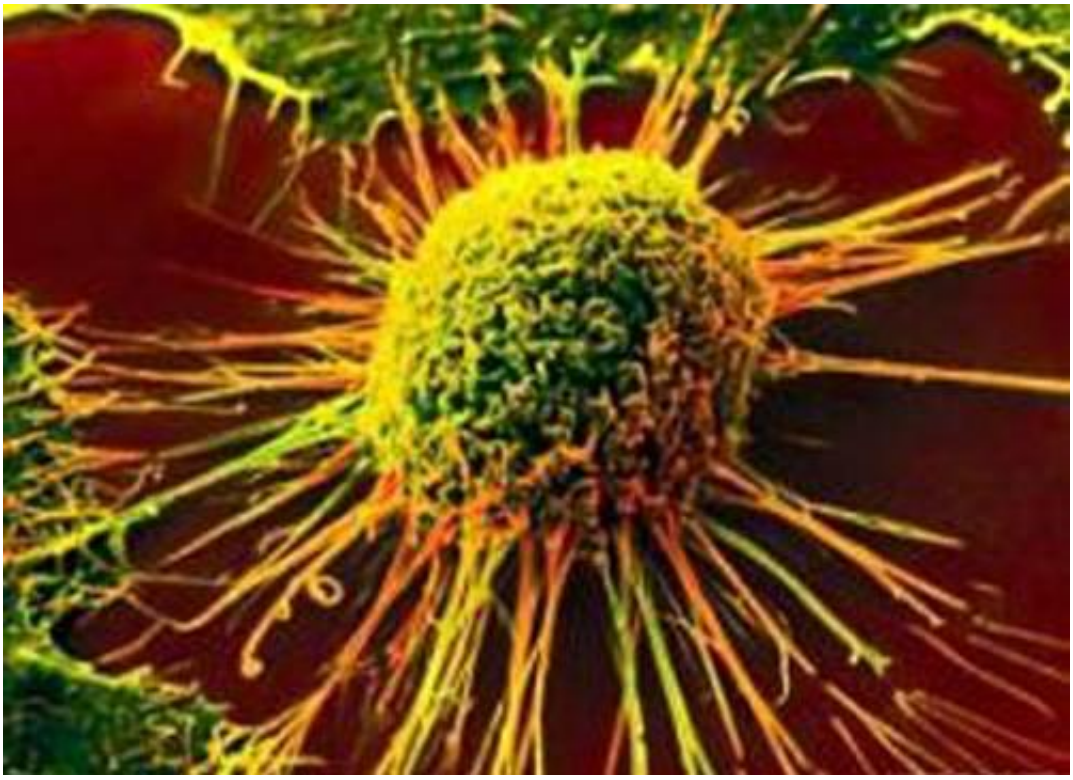

In a report of a proof-of-principle study of patients with colon and other cancers for whom standard therapies failed, researchers at the Johns Hopkins Kimmel Cancer Center say that mistakes in so-called mismatch repair genes, first identified by Johns Hopkins and other scientists two decades ago, may accurately predict who will respond to certain

immunotherapy drugs known as PD-1 inhibitors. Such drugs aim to disarm systems developed by cancer cells to evade detection and destruction by immune system cells.

Results of the trial with pembrolizumab, marketed as Keytruda, will be presented at the American Society of Clinical Oncology 2015 Annual Meeting and published online May 30 in the *New England Journal of Medicine*.

"This study gives us a solid clue about how immunotherapy may work in cancer and how to guide immunotherapy treatment decisions based on the genetic signatures of a cancer rather than class of cells or organ of origin," says Luis Diaz Jr., M.D., an oncologist at the Johns Hopkins Kimmel Cancer Center, a member of the Ludwig Center at Johns Hopkins and the director of the Swim Across America Laboratory at Johns Hopkins.

"Defects in mismatch repair genes are found in a small percentage of many cancer types, and this type of biomarker for immunotherapy response could apply to tumors containing errors in other DNA repair genes, as well," says Dung Le, M.D., an oncologist at the Johns Hopkins Kimmel Cancer Center. "Using a predictive biomarker can help us direct the use of immunotherapy drugs to patients who are more likely to respond, avoiding giving people expensive and time-consuming treatments that are not likely to work or delaying the use of other treatments."

For the Johns Hopkins-led study, scientists enrolled and treated 48 patients with cancer, primarily at The Johns Hopkins Hospital, and divided them into three groups. Other patients enrolled were from Providence Cancer Center in Oregon, the University of Pittsburgh Cancer Institute, Stanford University and The Ohio State University Comprehensive Cancer Center.

In one group of 13 patients with advanced colon and rectal cancers and mismatch repair gene defects, eight had partial responses to pembrolizumab, meaning their cancers shrunk by at least 30 percent in diameter. Four patients had prolonged disease stability, and one patient experienced disease progression. In another group of patients with colon and rectal cancer who had no defects in mismatch repair genes, all 25 failed to respond. In a third group of 10 patients with a variety of other cancers that tested positive for mismatch repair gene defects (four with pancreatic/bile duct cancers, two with uterine cancers, two with small bowel cancers, one with stomach cancer and one with prostate cancer), one patient with uterine cancer had a complete response, meaning there was no radiographic evidence of their cancer, five had partial responses, one had stable disease and three patients' cancers progressed.

All patients had received and were no longer responding to previous therapies.

"It's rare for patients with colon cancer who have failed all standard therapies to respond and most of them only have a few months to live," says Kenneth W. Kinzler, Ph.D., co-director of the Ludwig Center at Johns Hopkins. "While it's promising to see that patients with mistakes in mismatch repair genes responded more often to immunotherapy than those who did not have these mistakes, we need to test this idea in more patients and potentially earlier on in the sequence of therapies for these advanced cancers."

Median overall and disease progression-free survival in the colon cancer group with mismatch repair-defect group have not been reached yet, since several patients in this group have continued to respond to the immunotherapy drug for more than 12 months. Median follow-up for this group is 36 weeks (ranging from five to 55 weeks). In the group of patients with colon cancer who lack the mismatch repair errors, median overall survival was 7.6 months, and median disease progression was 2.3

months. These patients were followed for up to 42 weeks. In the third group of patients with mistakes in mismatch repair genes, median overall survival has not been reached, and their median disease progression-free survival was 5.4 months after being followed for up to 42 weeks.

For the study, overall response rates and some disease progression-free survival rates were classified and assessed as "immune-related," because patients often experience some tumor growth before shrinkage begins in those who respond. Typically, such initial tumor growth, also known as pseudo-progression, would prompt researchers to remove patients from a clinical trial, but scientists have recognized the temporary growth trend in immunotherapy trials and created new definitions of response to account for it, say the Johns Hopkins scientists.

The research team also accounted for differences in how long each patient had metastatic disease and his or her length of response to previous therapies.

Tests for mistakes in mismatch repair genes are commercially available and used routinely for newly diagnosed colon and endometrial cancer patients, according to Le. Pembrolizumab, sold by Merck, is approved by the Food and Drug Administration for certain patients with melanoma. The drug blocks a protein on immune cells called PD-1 and takes the brakes off of these immune cells so they can attack cancer cells .

Its cost can reach more than $100,000 per year per patient, a cost that gives urgency to sorting out which patients stand to benefit and which do not.

Mistakes in mismatch repair genes, which occur in sporadic and hereditary forms of colorectal, endometrial, stomach, biliary tract, pancreas, ovarian and small intestine cancer, disable cells' ability to

repair errors in the DNA replication process, which triggers unchecked cellular growth, a hallmark of cancer. The mutations were first identified in 1993 by co-authors of the current study, including Bert Vogelstein, M.D., of the Ludwig Center at Johns Hopkins and an investigator for the Howard Hughes Medical Institute; Nickolas Papadopoulos, Ph.D., and Kenneth Kinzler, Ph.D., also of Johns Hopkins' Ludwig Center; and Albert de la Chapelle at Ohio State University.

Two decades later, an idea for the current study took root when Diaz and his Ludwig Center colleagues met with other Johns Hopkins scientists who led one of the first large clinical trials of a type of immunotherapy similar to the one used in the current study. In it, a single patient with colon cancer in the trial responded to the drug when other patients with colon cancer did not. The search began, Diaz says, for why that one patient responded.

Diaz and his colleagues previously proposed that immunotherapy may work best in patients with more mutations in their cancer cells, because multiple mutations trigger production of more abnormal proteins in cancer cells and, in turn, may cause the immune system to mount a bigger response against cancer cells with more "foreign" proteins. Knowing that a small percentage of patients with colon cancer have errors in mismatch repair genes, which produce thousands more mutations in tumors than patients without the defects, they guessed that the lone colon cancer responder in the earlier study had such error-prone mismatch repair genes, a guess that was subsequently verified when the team sequenced the genome of the patient's tumor.

Provided by Johns Hopkins University School of Medicine

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