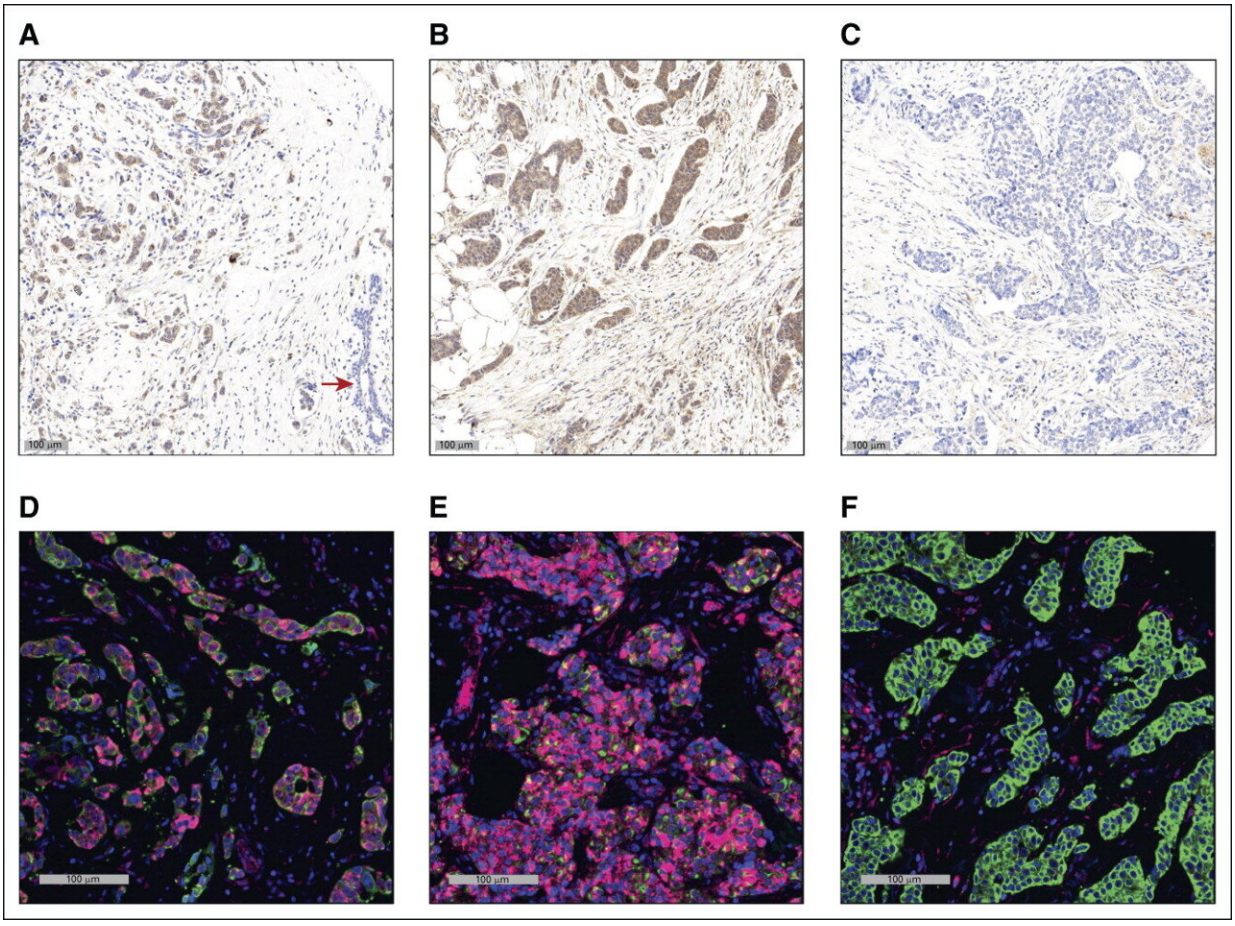
Scientists find new marker that predicts early recurrence of breast cancer

January 25 2023



PD-L2 immunostaining in ER+ breast cancer. (A-C; brown signal) Immunohistochemistry of PD-L2 using diaminobenzidine chromogen and (D-F; red signal) immunofluorescence. A, B, D, and E are different examples of ER+ tumors with high cancer cell expression of PD-L2, whereas C and F are examples with low cancer cell PD-L2 expression. Note the absence of PD-L2 in nearby normal duct epithelium (A; arrow). Tumors stained for PD-L2 (D-F; red

signal) by the immunofluorescent protocol used for quantification were counterstained for pan-cytokeratin (green signal) to help identify cancer cells and DAPI (blue signal) to identify cell nuclei. Scale bar represents 100 µm. DAPI, 4′,6-diamidino-2-phenylindole; ER+, estrogen receptor–positive; PD-L2, programmed cell death-1 ligand-2. Credit: *JCO Precision Oncology* (2023). DOI: 10.1200/PO.21.00498

A multi-institutional team led by scientists from the Medical College of Wisconsin (MCW) Cancer Center has discovered PD-L2 as a therapy-relevant marker to identify patients with estrogen receptor-positive breast cancer who may benefit from new immunotherapies.

The study is published in the journal *JCO Precision Oncology*.

Hallgeir Rui, MD, Ph.D., Wisconsin Breast Cancer Showhouse Endowed Professor of Breast Cancer Research at MCW, led a team of clinical investigators to study the immune checkpoint protein PD-L2 in breast cancer. While most efforts have focused on the immune checkpoint protein PD-L1, the alternative PD-1 ligand known as PD-L2 has been largely overlooked.

In the study, high PD-L2 protein levels in cancer cells were detected in one-third of therapy-naïve estrogen receptor-positive breast tumors and were validated as an independent predictor of early breast cancer recurrence after adjustment for common clinicopathological variables. PD-L2 is a therapy-relevant marker and may help identify patients with estrogen receptor-positive breast cancer who are at elevated risk of progression and who may benefit from promising new immunotherapies, so-called PD-1 inhibitors.

"We recently discovered that a protein called PD-L2 is often expressed

on breast cancer cells and that patients with such PD-L2-positive breast tumors have much less favorable prognosis than others. This is because PD-L2 blocks the tumor-killing activity of T-lymphocytes and allows cancer cells to fend off the body's immune cells," said Dr. Rui.

Prior to this work, attention was focused on a similar protein called PD-L1. However, "measuring PD-L1 alone in breast cancer has failed to effectively identify patients who are likely to benefit from PD-1 inhibitors. It's our hypothesis that measuring PD-L2 in addition to PD-L1 will improve our ability to predict which breast cancer patients will benefit from immune checkpoint inhibitors."

These observations have motivated the group to activate a Phase II clinical trial, led by MCW Cancer Center's Lubna Chaudhary, MD, which is actively accruing patients at MCW and Froedtert Hospital, to provide insight into whether a combined analysis of both PD-L1 and PD-L2 in breast cancer will improve prediction of response to immune checkpoint inhibitors.

Key aspects of the study were presented by Dr. Chaudhary at the 2023 San Antonio Breast Cancer Symposium.

In addition to MCW Cancer Center, major contributors to this work included investigators at the Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA; John P. Murtha Cancer Center, Uniformed Services University, Bethesda, MD; and the Chan Soon-Shiong Institute of Molecular Medicine at Windber, Windber, PA.

More information: Inna Chervoneva et al, High PD-L2 Predicts Early Recurrence of ER-Positive Breast Cancer, *JCO Precision Oncology* (2023). DOI: 10.1200/PO.21.00498

Provided by Medical College of Wisconsin