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Study confirms new prognostic markers for triple negative breast cancer

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Physicians who treat patients with triple negative breast cancer have two new ways to predict which patients may benefit most from the well-established post-surgery treatment known as AC chemotherapy, short for adjuvant doxorubicin and cyclophosphamide.

Investigators from the SWOG Cancer Research Network, a cancer clinical trials network funded by the National Cancer Institute, part of the National Institutes of Health, confirm in research findings published in the *Journal of Clinical Oncology* that two biomarkers—a 44-gene DNA Damage Response (DDIR) signature and stromal tumor-infiltrating lymphocytes (sTILs) - can serve as prognostic markers in people diagnosed with triple negative breast cancer. These new tests could be used to guide cancer treatment in the same way that cancer stage or tumor size are currently used to personalize care.

"This moves us a little closer to basing triple negative breast cancer treatment on the biology of individual patients," said Priyanka Sharma, M.D., a SWOG investigator and a physician and researcher at University of Kansas Cancer Center. "If you knew, up front, which women would respond well to AC chemotherapy, we could preferentially pick this treatment—and spare them other treatment. With other patients, we would want to investigate different strategies such as immunotherapies or targeted drugs."

Triple negative breast cancers get their name for the common cancer growth factors they lack—estrogen receptors, progesterone receptors, and the HER2 gene. Triple negative breast cancers tend to grow faster and spread more frequently than other types of breast cancer, and many current drugs aren't effective in slowing or stopping their growth. Sharma has spent more than 10 years investigating these cancers, trying to better understand how they work in the body and how they can be treated more effectively. Triple negative breast cancers account for about 15 to 20 percent of all breast cancers diagnosed in the United States each year.

Preliminary research had shown that two biomarkers, the DDIR signature and sTILs, could be used to predict good outcomes after AC chemotherapy in patients with hormone receptor-negative and HER2

negative breast cancers. Sharma and her team wanted to see if they could confirm these findings in patients with triple negative breast cancer. To do so, they dipped into SWOG's vast specimen bank—which contains over 800,000 tissue, blood, and other biological samples. Sharma used tumor samples from patients enrolled in S9313, a SWOG breast cancer trial assessing the effectiveness of AC chemotherapy in patients with high- and moderate-risk breast cancers. S9313 stopped enrolling patients in 1997, but breast tumor tissue from those patients remains, preserved in paraffin wax.

Analyzing these samples, Sharma and her team confirmed 425 cases of triple negative breast cancer. They then conducted two analyses. One was creating a DDIR signature, an RNA-based tumor profile that shows whether a patient's immune system is activated based on the working of 44 different genes. In the other analysis, breast cancer histopathologists counted stromal tumor-infiltrating lymphocytes (sTILs), white blood cells that migrate into tumors.

Here's why these tests matter. Both DDIR status and sTIL density can be gauges of the bodies' ability to repair DNA damage and mount immune response against cancer; AC chemotherapy works best in tumors with DNA repair deficiency. So a positive DDIR status, and a high sTILs density, could be used to predict better outcomes with AC chemo.

That's just what the SWOG team confirmed.

Researchers were able to complete DDIR assessments on tissue from 381 patients. Of those, 62 percent were DDIR positive—and had better outcomes from AC chemotherapy based on the S9313 results. Researchers were able to get sTIL density results from 423 patient samples—and the higher the density, the better the outcomes from AC chemo, their analysis showed. In both cases, AC chemo treated patients with a positive DDIR signature and a higher sTIL density were cancer-

free longer and also lived longer.

The results have implications for cancer care and research. DDIR scores could be used to guide treatment for triple negative breast cancer patients. Those with DDIR positivity could be treated with AC chemotherapy alone, while those with DDIR negativity could get alternative therapies alone or in conjunction with AC chemotherapy. In addition, the research showed that the most significant biological process in DDIR-positive tumors was immune system activation, suggesting these tumors may be a good target for immune checkpoint inhibitors—a possible line of investigation for future clinical trials.

More information: Priyanka Sharma et al, Validation of the DNA Damage Immune Response Signature in Patients With Triple-Negative Breast Cancer From the SWOG 9313c Trial, *Journal of Clinical Oncology* (2019). DOI: 10.1200/JCO.19.00693

Provided by SWOG