Trial results show PARP inhibitor benefit in 'BRCA-like' breast cancer

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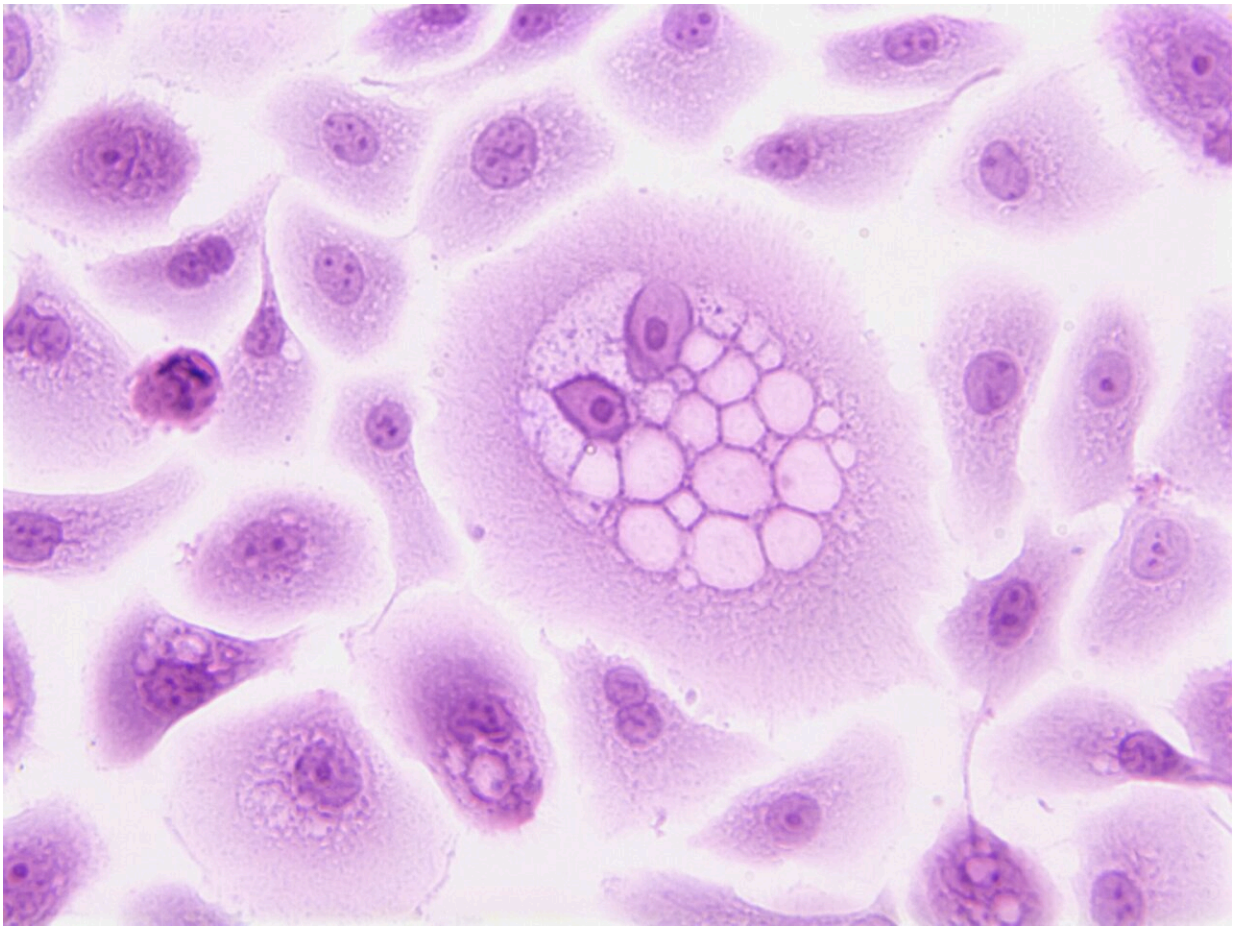

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Results from the SWOG S1416 clinical trial show that adding veliparib

to chemotherapy can significantly extend progression-free survival (PFS) times in patients with triple-negative breast cancer (TNBC) that has a "BRCA-like" phenotype.

Veliparib belongs to a class of drugs known as PARP inhibitors. PARP inhibitors have been shown to be effective in treating breast cancer with germline mutations in the BRCA1 or BRCA2 gene. But this is the first trial to demonstrate a PARP inhibitor benefit in breast cancer that is not BRCA1/2-mutated but is BRCA-like based on the presence of other changes that similarly affect cells' DNA repair abilities.

Results from the trial, which was led by researchers from SWOG Cancer Research Network, are published in *The Lancet Oncology*.

Priyanka Sharma, MD, a SWOG investigator who is professor of medicine at the University of Kansas Medical Center was co-lead author on the paper with Eve Rodler, MD, associate professor of medicine at University of California, Davis.

"SWOG 1416 is the first trial to report benefit of a PARP inhibitor in metastatic TNBC with a BRCA-like phenotype in absence of germline mutations in BRCA1 or BRCA2 genes," Sharma said. "BRCA-like phenotype is noted in 40 to 50 percent of triple negative breast cancers, making these findings and BRCA-like classification relevant for a substantial proportion of patients with TNBC."

Germline mutations in the BRCA1 or BRCA2 gene increase the number of errors made in the DNA repair process in cells. Poly (ADP-ribose) polymerase—or PARP—is an enzyme in cells that helps repair damaged DNA, and drugs that inhibit PARP activity have been shown to be effective in treating breast cancer occurring in the setting of germline BRCA1 or BRCA2 mutations.

Many triple negative tumors, however, have no germline mutations in these genes but do have other alterations that negatively affect the DNA repair process in ways similar to the effects of germline BRCA1/2 mutations. The S1416 team asked whether these BRCA-like cancers could also be treated effectively with PARP inhibitors.

They randomized 320 patients with metastatic breast cancer to either cisplatin chemotherapy plus the PARP inhibitor veliparib or cisplatin chemotherapy plus a placebo. Patients had breast cancer that was either triple-negative (without estrogen or progesterone receptors or HER2 overexpression) or was HER2 negative and suspected to be associated to germline mutations in BRCA1 or BRCA2.

After patients were randomized, researchers tested their blood and tumor tissue for biomarkers and, based on the results, assigned patients to one of three distinct groups describing their type of breast cancer: BRCA-mutated, BRCA-like, or non-BRCA-like.

The S1416 team found that among patients who had BRCA-like breast cancer, those treated on the veliparib arm had statistically significantly longer median PFS than those on the placebo arm: 5.9 months versus 4.2 months (HR=0.57; 95 percent CI 0.37-0.88; p=0.011). These patients also had a numerically better median overall survival (OS) time and objective response rate than patients on the placebo arm, however, these differences did not achieve statistical significance.

The researchers further reported higher overall rates of Grade 3/4 treatment-related adverse events (side effects) on the veliparib arm than on the placebo arm (74 percent versus 52 percent), including higher rates of Grade 3/4 neutropenia, anemia, and thrombocytopenia.

"While these results are not immediately practice changing, since veliparib is not FDA approved," Sharma said, "S1416 findings open new

clinical trial directions by extending the patient population that could benefit from PARPi therapy. With demonstration of efficacy in BRCA-like phenotype TNBC, S1416 results provide a basis for expanding the therapeutic role of PARP inhibitors (e.g., veliparib) beyond germline BRCA mutation in breast cancer."

More information: Eve Rodler et al, Cisplatin with veliparib or placebo in metastatic triple-negative breast cancer and BRCA mutation-associated breast cancer (S1416): a randomised, double-blind, placebo-controlled, phase 2 trial, *The Lancet Oncology* (2023). DOI: 10.1016/S1470-2045(22)00739-2

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