PARP inhibitor improves progression-free survival in patients with advanced breast cancers

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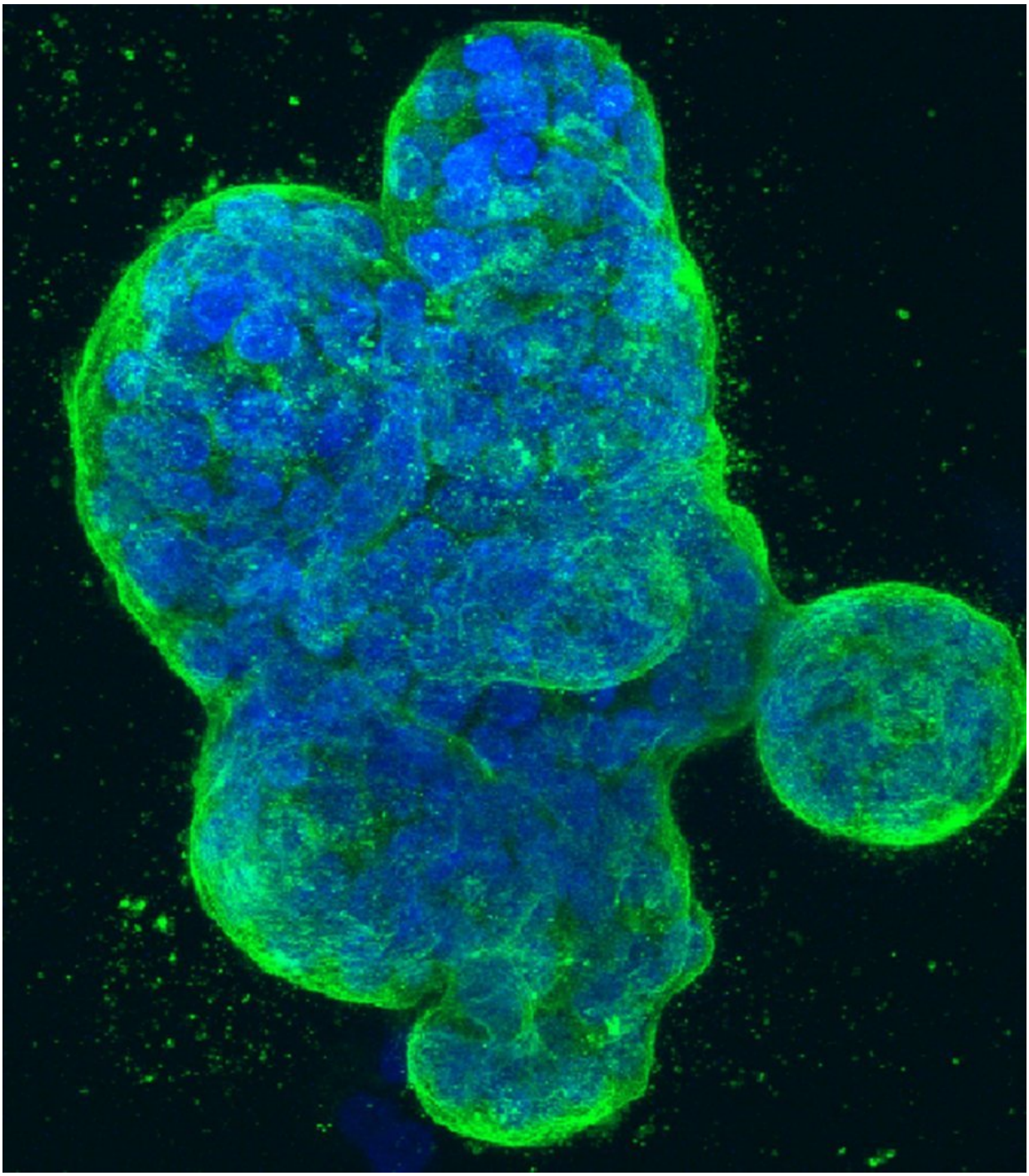

Three-dimensional culture of human breast cancer cells, with DNA stained blue and a protein in the cell surface membrane stained green. Image created in 2014 by Tom Misteli, Ph.D., and Karen Meaburn, Ph.D. at the NIH IRP.

In a randomized, Phase III trial led by researchers at The University of Texas MD Anderson Cancer Center, the PARP inhibitor talazoparib extended progression-free survival (PFS) and improved quality-of-life measures over available chemotherapies for patients with metastatic HER2-negative breast cancer and mutations in the BRCA1/2 genes.

The results of the EMBRACA trial were published today in the *New England Journal of Medicine*. The findings were first presented at the 2017 San Antonio Breast Cancer Symposium by Jennifer Litton, M.D., associate professor of Breast Medical Oncology, also corresponding author of the study.

"The trial found that talazoparib provides a significant clinical benefit to all patient subgroups, including those with hormone receptor-positive and triple-negative disease," said Litton. "The results of this trial are quite exciting and indicate talazoparib is a novel treatment option for patients with metastatic breast cancer and BRCA mutations."

Mutations in the BRCA1/2 genes, which account for 5 to 10 percent of all breast cancers, cause defects in normal DNA damage repair. PARP inhibitors block an additional DNA repair pathway, and the anti-tumor effects of PARP inhibitors can be intensified in patients with BRCA mutations. Talazoparib works by not only inhibiting the PARP enzyme, but by trapping the enzyme on DNA to further prevent DNA repair.

The international Phase III clinical trial, EMBRACA, enrolled 431 patients with locally advanced or metastatic and hereditary BRCA1/2 gene mutations. Patients with HER2-positive disease were excluded as there are approved targeted therapies for those cancers. Patients could have had up to three previous chemotherapies, including platinum-based therapies.

Participants were randomized 2:1 to receive either talazoparib (287) or

physician's choice of treatment (PCT) of single-agent therapy (144), either capecitabine, eribulin, gemcitabine or vinorelbine. Fifty-four percent of participants had HR+ disease and 46 percent had TN breast cancer; BRCA1 and BRCA2 mutations were split at 45 and 55 percent, respectively.

"Importantly, the trial met its primary endpoint of progression-free survival. Patients were nearly 46 percent less likely to have progressed on talazoparib compared to physician's choice," said Litton. "Secondary endpoints also were promising, including a dramatic improvement in time to clinical deterioration among patients receiving talazoparib."

The median PFS, assessed by blinded independent review, was 8.6 months in the talazoparib arm, compared with 5.6 months in the PCT arm, a statistically significant improvement. The overall response rate, or percentage of patients with tumor shrinkage, was 62.6 percent and 27.2 percent in the talazoparib and PCT arms, respectively. Twelve participants had complete responses, all in the talazoparib arm.

Patient-reported quality-of-life measures revealed a prolonged time to deterioration of overall health, 24.3 months in the talazoparib arm compared to 6.3 months for the PCT arm.

Grade 3-4 hematological adverse events occurred in 55 percent of patients receiving talazoparib and 39 percent of those on chemotherapy, but talazoparib was associated with fewer high-grade non-hematological events, including gastrointestinal and skin/subcutaneous tissue disorders. Grade 3-4 serious events occurred in 26 and 25 percent of patients receiving talazoparib and PCT, respectively. Adverse events resulting in death occurred in 2.1 percent of patients on talazoparib and 3.2 percent on PCT.

Final overall survival will be reported at a later date when the data fully

matures, said Litton.

"It is encouraging to see this oral PARP inhibitor was well-tolerated and superior to chemotherapy alone. We look forward to seeing how overall survival is affected, but I think talazoparib will be an excellent option for patients with metastatic disease and BRCA mutations," said Litton.

Litton hopes to continue investigating the utility of PARP inhibitors in additional breast cancer patients with BRCA mutations, including those with early-stage disease, as well as possibilities for enhancing the activity of PARP inhibitors in patients without inherited BRCA mutations.

Provided by University of Texas M. D. Anderson Cancer Center