# New PARP Inhibitor Improves Survival in Women With Advanced Breast Cancer

Talazoparib may offer an additional option for women with BRCA gene mutations.

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Women with advanced breast cancer who used an experimental therapy that prevents cancer cells from repairing damaged DNA, leading to their death, had prolonged progression-free survival compared with those treated with standard chemotherapy, researchers reported this month at the San Antonio Breast Cancer Symposium.

Women treated with talazoparib were 46 percent less likely to experience disease progression, and their overall response rate—meaning complete or partial tumor shrinkage—was more than double that of patients treated with chemotherapy.

Jennifer Litton, MD, of the University of Texas MD Anderson Cancer Center presented findings from Pfizer's EMBRACA study, an international Phase III trial comparing talazoparib versus chemotherapy for women with BRCA1 or BRCA2 gene mutations, inherited genetic changes that confer a high risk of breast and ovarian cancer. Up to 70 percent of women with these BRCA mutations will develop breast cancer in their lifetime, and this occurs about 20 years earlier on average than non-BRCA-related cancer.

Talazoparib, being developed by Pfizer, is a poly (ADP-ribose) polymerase, or PARP, inhibitor. It appears to have a dual mechanism of action, both blocking PARP enzyme activity and trapping PARP on broken DNA and preventing its repair. People with BRCA1 or BRCA2 mutations lack proteins needed to fix damaged DNA, so BRCA-related cancers are especially vulnerable to PARP inhibitors.

Three PARP inhibitors, AstraZeneca's Lynparza (olaparib), Clovis Oncology's Rubraca (rucaparib) and Tesaro's Zejula (niraparib), are currently approved for advanced or recurrent ovarian cancer.

EMBRACA—described as the largest randomized clinical trial of its kind—enrolled 431 participants with locally advanced or metastatic breast cancer. Almost all were women, and the median age was 46. About one in six had central nervous system metastases, or cancer that had spread to their brain or spinal cord.

All participants had HER2-negative breast cancer, meaning their tumors were not susceptible to HER2 blockers like Herceptin (trastuzumab). About half had tumors with estrogen or progesterone receptors (known as HR-positive), meaning they could be treated with hormone therapy. The other half had triple-negative breast cancer, which doesn't express any of these receptors and is hardest to treat. About 40 percent had not been treated with chemotherapy for advanced breast cancer, while the rest had received up to three prior chemotherapy regimens.

Participants in this open-label study were randomly assigned to receive once-daily talazoparib pills or single-agent chemotherapy using the treating physician's choice of capecitabine, eribulin, gemcitabine or vinorelbine; capecitabine is a tablet, but the other drugs require IV infusion. Participants were treated until they experienced disease progression or unacceptable toxicity.

After nearly a year of follow-up, the median duration of progression-free survival (PFS)—meaning patients were still alive with no worsening of disease—was 8.6 months in the talazoparib group compared with 5.6 months in the chemotherapy group, representing a 46 percent lower likelihood of disease progression. The difference was statistically significant, meaning it was probably not attributable to chance.

"The [PFS] curves separate early, and the separation continues," Litton reported.

Overall survival could not yet be determined because a majority of patients are still alive, and follow-up is continuing. However, an interim analysis appeared to favor talazoparib.

The overall response rate was 63 percent in the talazoparib group compared with 27 percent in the chemotherapy group. All 12 complete responses occurred in the talazoparib group (6 percent versus 0 percent). Stable disease was more common in the chemotherapy group (21 percent versus 32 percent).

The median duration of response was longer with talazoparib (5.4 months versus 3.1 months), exceeding two years in some cases. Clinical benefits were seen for all subsets of patients, including those with HR-positive cancer and those with brain metastases.

The researchers also looked at patient-reported quality-of-life measures and found that women treated with talazoparib reported a substantially longer time until deterioration of their health status.

"Most notable for this study was not only the improvement to date of PFS but the time to clinical deterioration, which was 24.3 months for patients on talazoparib versus 6.3 months for those on standard-of-care chemotherapy," Litton said in a SABCS press release.

Side effects were common, and about 30 percent of women in both treatment groups developed serious adverse events; 8 percent of talazoparib recipients and 10 percent of chemotherapy recipients stopped treatment because of adverse events. The most common severe adverse events were blood cell deficiencies, seen in 55 percent of talazoparib recipients (mainly anemia) and 39 percent of chemotherapy recipients (mainly neutropenia, or low white blood cells). People

taking talazoparib had fewer gastrointestinal symptoms and skin problems.

“EMBRACA supports the potential of talazoparib to give these patients additional time without disease progression, compared to chemotherapy,” Litton concluded.

However, as with other targeted therapies and immunotherapies for cancer, some people respond very well to PARP inhibitors while others do not respond so well, and researchers are working to figure out who is likely to benefit.

[Editor’s note: Talazoparib (brand name Talzenna) was approved by the Food and Drug Administration on October 16, 2018.]

Click here to read the study abstract.

Click here to read a SABCS press release about the study.

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