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Phase III EMBRACA Trial Meets Primary Endpoint

Talazoparib prolonged progression-free survival in patients with advanced, BRCA-mutated breast cancer

SAN ANTONIO — Patients with advanced HER2-negative breast cancer with germline BRCA mutations had significantly prolonged progression-free survival (PFS) when treated with the PARP inhibitor talazoparib compared with those who received chemotherapy of physician's choice, according to data from the phase III trial, EMBRACA, presented at the 2017 San Antonio Breast Cancer Symposium, held Dec. 5–9.

"We are very pleased that the phase III EMBRACA trial—the largest randomized clinical trial conducted in this group of patients with hereditary breast cancer—met its primary efficacy endpoint of progression-free survival," said Jennifer Litton, MD, associate professor in the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center.

Talazoparib is a dual mechanism PARP inhibitor that inhibits the PARP enzyme and also traps PARP on DNA, thus preventing DNA damage repair, leading to death in BRCA1/2-mutated cells, Litton explained. Prior studies had shown that talazoparib's unique structural properties make it more effective in trapping PARP-DNA complexes. This therapeutic had yielded promising results in preclinical studies and previous phase I and II clinical trials.

"In EMBRACA, talazoparib demonstrated superior clinical benefit in all subsets of patients, regardless of receptor subtype (HR-positive or triple-negative breast cancer), number of prior lines of chemotherapy, BRCA mutation type and central nervous system metastasis," noted Litton.

The U.S. Food and Drug Administration has approved three PARP inhibitors so far—olaparib (Lynparza), rucaparib (Rubraca), and niraparib (Zejula)—to treat certain ovarian cancers, including those with BRCA gene mutations.

EMBRACA is an open-label, randomized, phase III trial to compare the efficacy and safety of 1 mg/day talazoparib with standard single-agent physician's choice of therapy (PCT) (capecitabine, eribulin, gemcitabine, or vinorelbine) in patients with advanced breast cancer and a germline BRCA1/2 mutation. Patients were randomly assigned (2:1) to talazoparib (287) or PCT (144).

The primary objective was PFS, assessed by blinded independent central review, and secondary objectives were overall survival (OS), overall response rate (ORR) and clinical benefit rate at 24 weeks (CBR24), and safety. Patient-reported outcomes were also measured.

The median PFS was 8.6 months for patients in the talazoparib arm, versus 5.6 months for those in the PCT arm, and this difference was statistically significant. Patients in the talazoparib arm were 45.8 percent less likely to have disease progression, compared with those in the PCT arm.

ORR and CBR24 showed a statistically significant improvement for those in the talazoparib arm compared with those in the PCT arm: The ORR was 62.6 percent for patients in the talazoparib arm, versus 27.2 percent for those in the PCT arm. Twelve complete responses were observed in the study, all in the talazoparib arm. The CBR24 was 68.6 percent for patients in the talazoparib arm, versus 36.1 percent for those in the PCT arm.

An interim analysis of overall survival was also conducted; although data are not yet mature, a positive trend favoring talazoparib was observed, with a 24 percent reduction in the risk of death. Survival data will continue to be monitored and final OS estimates reported once the data matures, Litton said.

Quality-of-life measurements revealed that in the talazoparib arm, patents had a significant delay in the time to deterioration in health compared with patients in the PCT arm, using the EORTC QLQ-C30 questionnaire.

“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 noted.

Fifty-five percent of patients in the talazoparib arm experienced grade 3-4 hematologic adverse events, versus 39 percent of those in the PCT arm. Talazoparib was associated with fewer grade 3-4 gastrointestinal disorders and skin/subcutaneous tissue disorders than PCT. Grade 3-4 serious adverse events were observed in 26 percent and 25 percent of patients in talazoparib and PCT arms, respectively. Adverse events resulting in death occurred in 2.1 percent and 3.2 percent of patients in talazoparib and PCT arms, respectively.

“Overall, once-daily oral talazoparib was well tolerated in comparison to chemotherapy, with improvements in progression-free survival and clinical responses, providing a significant option for patients with BRCA mutations and metastatic breast cancer. We look forward to following the OS results as those data mature,” said Litton.

This study was funded by Pfizer. Litton has research funding with EMD Serono, AstraZeneca, Pfizer, Genentech, and GlaxoSmithKline, and serves on advisory boards for Pfizer and AstraZeneca, all uncompensated.

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