ZEST Trial Offers Insights for Using ctDNA to Predict Breast Cancer Recurrence

Half of patients with detectable circulating tumor DNA had already relapsed, according to imaging scans.

December 16, 2024 By American Association for Cancer Research

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The ZEST clinical trial, designed to evaluate niraparib (Zejula) for the prevention of breast cancer recurrence in patients with circulating tumor DNA (ctDNA), failed to accrue enough patients positive for ctDNA, according to results presented at the San Antonio Breast Cancer Symposium (SABCS), held December 10-13, 2024.

As some of the lessons learned from this trial, investigators suggest beginning ctDNA testing during treatment rather than waiting for treatment completion as done in ZEST, and including patients with high-risk disease, which may lead to more patients with a positive ctDNA test who would therefore be eligible for intervention with a therapeutic.

Identifying patients with minimal residual disease (MRD) after treatment and intervening with appropriate therapies is critical to delaying or preventing disease recurrence, explained study presenter Nicholas Turner, MD, PhD, the director of clinical research and development at The Royal Marsden Hospital and Institute of Cancer Research in London.

Turner and colleagues initiated the ZEST Phase III clinical trial to evaluate the potential of the PARP inhibitor niraparib to prevent breast cancer recurrence in patients with MRD, defined in this study as the presence of ctDNA after the completion of their recommended treatment course.

“The aim was to develop a new treatment strategy for patients with Stage I to III breast cancer who have detectable ctDNA and therefore are at higher risk of recurrence,” said Turner.

To be eligible for the trial, patients were required to have Stage I to III triple-negative or BRCA-mutated, hormone receptor (HR)-positive breast cancer; to have completed their recommended treatment (patients with HR-positive breast cancer were permitted to continue a stable regimen of endocrine therapy); and to have detectable ctDNA, as measured by a personalized test that examined blood samples for 16 mutations specific to each patient’s tumor.

Of the 1,901 patients who underwent ctDNA testing to determine their eligibility for the trial, 147 (7.7%) had detectable ctDNA and were therefore eligible. Of these patients, 55% had detectable ctDNA within six months of completing treatment. Ninety-eight of the 147 patients had detectable ctDNA on their first test, at which point 51 (55%) of them already had disease recurrence that was detectable by imaging. For

the 48 patients who had detectable ctDNA on subsequent tests, 21 (44%) had recurrence that was detectable by imaging at the time of their first ctDNA-positive test.

Compared with patients without detectable ctDNA, those who were ctDNA-positive were more likely to have positive lymph nodes, larger tumors, Stage 3 disease, residual disease after neoadjuvant therapy, and to have received both neoadjuvant and adjuvant therapy.

Prior to trial termination, 40 patients were enrolled and randomly assigned to receive either niraparib or placebo. This was an insufficient number of patients to allow for meaningful assessment of niraparib efficacy; however, median recurrence-free interval was 11.4 months for patients in the niraparib arm and 5.4 for those in the placebo arm. Six patients in the niraparib arm and four patients in the placebo arm remained recurrence-free at the time of data cutoff.

“While the low enrollment and early termination of the study precludes any conclusions about the efficacy of niraparib, the challenges the study faced have implications for future clinical trial design,” said Turner.

“First, given our observation that half of patients with detectable ctDNA already had relapsed disease, future studies should begin ctDNA testing prior to the end of neoadjuvant therapy instead of waiting for completion of treatment,” he recommended, noting that periodic ctDNA testing throughout neoadjuvant therapy would help identify patients who are still ctDNA-positive after neoadjuvant therapy. He added that this is particularly relevant for triple-negative breast cancers, which can relapse rapidly if neoadjuvant treatment fails to clear the cancer.

“Further, future studies should also focus on patients at higher risk of relapse who are more likely to have ctDNA-positive disease, such as patients with Stage IIB or III cancers that do not have a pathologic complete response after neoadjuvant therapy. We may also want to focus on different subtypes where ctDNA is potentially more impactful with longer lead times over relapse,” he said.

The study was supported by GSK. Turner has received advisory board honoraria from AstraZeneca, Lilly, Pfizer, Roche/Genentech, Novartis, GSK, Repare Therapeutics, Relay Therapeutics, Gilead, Inivata, Guardant Health, Exact Sciences. Turner has received research funding from AstraZeneca, Pfizer, Roche/Genentech, MSD, Guardant Health, Invitae, Inivata, Personalis, and Natera.

This news release was published by the American Association for Cancer Research on December 13, 2024.

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