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To interview Ruth O'Regan, please contact Julia Gunther at julia.gunther@aacr.org or 770-403-7690. For a photo of O'Regan, click here.

A Genomic Assay May Predict Long-term Prognosis in Premenopausal Patients With Hormone Receptor-positive Early-stage Breast Cancer

Assay can also help identify patients who may benefit from ovarian suppression therapy

SAN ANTONIO – Among premenopausal women with hormone receptor (HR)-positive, early-stage breast cancer enrolled in the SOFT trial, those with a high score on a genomic assay called Breast Cancer Index (BCI) had increased risk of distant recurrence, and those with low BCI benefited more from the addition of ovarian suppression therapy to endocrine therapy after 12 years of follow-up, according to data presented at the San Antonio Breast Cancer Symposium, held December 6-10, 2022.

"The SOFT trial showed that adding ovarian function suppression (OFS) to endocrine therapy benefited a subset of premenopausal women with HR-positive, early-stage breast cancer. However, OFS increases short and long-term toxicity and is not tolerated by all patients," said presenter Ruth O'Regan, MD, professor and chair of the Department of Medicine at the University of Rochester. "Therefore, determining which patients truly need OFS is crucial to avoid added toxicities in patients who are unlikely to benefit."

BCI is a genomic assay incorporating a gene expression signature called molecular grade index and the expression ratio of the *HOX13* gene to the *IL17BR* gene (H/I ratio). BCI assesses the risk of late distant recurrence (5-10 years after diagnosis) of HR-positive, early-stage breast cancer. The H/I ratio determines which patients benefit from extended durations of endocrine therapy in this patient population. O'Regan and colleagues evaluated BCI in a subset of 1,687 patients enrolled in the SOFT trial to determine whether BCI can predict prognosis and benefit from OFS in premenopausal women with HR-positive, early-stage breast cancer who received endocrine therapy with or without chemotherapy. The analysis showed that, after 12 years of follow-up, BCI was prognostic of distant recurrence: Among patients without lymph node involvement, those with high BCI had a 98 percent increased risk of distant recurrence than those with low BCI. A similar increase was observed in patients whose cancer had spread to one to three lymph nodes.

Furthermore, among patients with low H/I ratio, adding OFS to exemestane or tamoxifen resulted in reduced risk of recurrence after 12 years compared to treatment with tamoxifen alone (11.6 percent and 7.3 percent, respectively).

The predictive benefit of the H/I ratio was observed regardless of age, lymph node involvement, and receipt of chemotherapy.

"Previously, high H/I ratio has been shown to predict which patients benefit from longer durations of endocrine therapy, which could indicate sensitivity to such therapy. However, benefiting from OFS may

not be related to endocrine sensitivity," O'Regan said. "It is possible that patients with endocrine-resistant cancers may benefit more from OFS, which could explain our findings."

"If validated, the H/I ratio may be useful to determine which premenopausal patients require OFS, thereby avoiding additional toxicity in those who are unlikely to benefit," O'Regan added.

A limitation of this study is the small sample size. "Larger numbers are needed to validate our findings," O'Regan said.

This study was funded by Biotheranostics. O'Regan served as an advisor for Biotheranostics, Novartis, AstraZeneca, and Pfizer.

Abstract

GS1-06

Evaluation of the Breast Cancer Index in premenopausal women with early-stage HR+ breast cancer in the SOFT trial

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Background: The landmark Suppression of Ovarian Function Trial (SOFT) in premenopausal breast cancer patients revealed that the addition of ovarian function suppression (OFS) to adjuvant endocrine therapy with either tamoxifen (T+OFS) or exemestane (E+OFS) reduces the risk of recurrence compared with adjuvant tamoxifen alone. The benefit from the addition of OFS was most clinically meaningful for patients at higher clinico-pathologic risk of recurrence. There are no biomarkers to aid decision-making about intensification of endocrine therapy with OFS and its resultant toxicities. The Breast Cancer Index (BCI) is a gene expression–based signature that stratifies patients based on the risk of overall (0-10 years) and late (post-5 years) distant recurrence (DR) and predicts the likelihood of benefit from extended endocrine therapy in early stage HR+ breast cancer. The purpose of this study is to assess BCI's prognostic and predictive ability in premenopausal women randomly assigned to 5-years treatment with E+OFS or T+OFS vs T alone in the SOFT trial. **Methods:** All available FFPE tumor samples from the SOFT trial (n=1718 of 3047) were included in the study. BCI testing was performed blinded to clinical characteristics, treatment and outcome. Median follow-up was 13 years. Primary endpoint was breast cancer-free interval (BCFI). Secondary endpoints were distant recurrence-free interval (DRFI) and disease-free survival (DFS). Kaplan-Meier analysis and Cox proportional hazards regression models, stratified by prior chemotherapy and lymph node status, were used to evaluate the predictive performance of BCI (H/I) status (High vs Low), and secondarily H/I as a continuous score. Hypothesis testing for interaction was performed by stratified log-rank tests. **Results:** Tumor samples from 1687 (98%) patients (30.4% < 40 years, 64.1% T1, 50.1% G2, 65.8% N0, 85.5%% HER2-, 53.3% received prior chemotherapy) were successful in BCI testing and included in the final analysis. Patient characteristics in the translational cohort are representative of the parent SOFT trial. 42.4% of patients' tumors had H/I-High status. Prognostic and predictive analyses are ongoing and will be presented at the meeting.

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