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Abstract OT3-09-02: A large-scale multicenter phase II study evaluating the protective effect of a tissue selective estrogen complex (TSEC) in women with newly diagnosed ductal carcinoma in situ (DCIS)

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Abstract

Background: TSECs were developed to treat menopausal symptoms after progesterone containing hormone replacement therapy was found to significantly increase the risk of invasive breast cancer (IBC). The first of this class of agents combines conjugated estrogens (CE), a collection of steroidal estrogens that collectively have both estrogen receptor (ERα) agonistic and antagonistic activity, and bazedoxifene (BZA), a third generation selective estrogen receptor modulator that does not stimulate the mammary gland or endometrium. The FDA approved CE/BZA for treatment of menopausal symptoms and osteoporosis after five randomized placebo controlled trials demonstrated the safety, efficacy and tolerability of CE/BZA in healthy postmenopausal women. Since then, a substantial body of evidence has emerged suggesting that CE/BZA may have additional therapeutic benefits in women. It is widely accepted that progression to IBC occurs through both epithelial and stromal mechanisms. Recent *in vitro* and in *vivo* data provide support that CE/BZA prevents progression to IBC through its effects on both epithelium and stroma. In epithelial cells, CE/BZA antagonizes estrogen-induced proliferation and expression of markers of ERα activity and also degrades ERα protein. In the stroma, CE/BZA increases expression of the scavenger receptor CD36 and consequently, reduces expression of extracellular matrix proteins (ECM) and pro-inflammatory cytokines that have been shown to contribute to the development of pro-tumorigenic microenvironment. Based on these preliminary data, we hypothesized that CE/BZA will have an anti-tumorigenic effect in the breast. Our ultimate objective is to provide postmenopausal women diagnosed with DCIS a novel and safe therapeutic option to prevent progression to IBC. Specific Aims: Aim 1: To assess epithelial contributions by determining if a short intervention of CE/BZA will have antagonistic activity in breast epithelium of postmenopausal women with ER + DCIS. Aim 2: To assess stromal contributions by determining if a short intervention of CE/BZA will alter expression of stromal markers of progression in breast tissue of postmenopausal women with ER + DCIS. Aim 3: To determine if a short intervention of CE/BZA is well tolerated and safe in postmenopausal women with ER + DCIS. Trial Design: We are currently conducting a multicenter randomized placebo controlled window of opportunity trial with CE/BZA in post-menopausal women with DCIS, a non-obligate precursor to IBC. The duration of intervention is 28 ± 7 days prior to surgical resection to enable comparison of CE/BZA on the breast using the diagnostic core biopsy and surgical sample. To date 33/166 women have enrolled in the trial. Eligibility Criteria: Post-menopausal women between 18-79 years of age diagnosed with ER (+) DCIS (≥1cm on imaging) undergoing surgery are eligible. Women must not be on current hormonal therapy, have a current or past diagnosis of IBC, other ER sensitive tumors or have recurrent DCIS. Statistics: Results will be compared between diagnostic biopsy and surgical resection specimens and contrasted between the CE/BZA intervention group and placebo group using Fisher's exact test for categorical variables and independent sample t-tests, or rank sum tests for continuous data. For RNAseq data, transcripts that have >1.5-fold expression change (at 20% FDR) between control and experimental samples will be used for downstream analysis, such as to plot heat maps, pathway and gene ontology analysis. Summary: At the conclusion of this study, we will have the first direct evidence of the potential benefits of CE/BZA therapy on DCIS lesions in the human breast, along with an initial assessment of symptoms and pharmacogenomics that will inform the design of future studies.

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