Title

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)

Journal

ANNALS OF SURGICAL ONCOLOGY, 27(SUPPL 2)

ISSN

1068-9265

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Publication Date

2020

#787943

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 (The PROMISE Study)

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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 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.

In order to test this hypothesis, we are conducting a multicenter randomized clinical trial of 160 postmenopausal women with newly diagnosed ER-positive DCIS. To date we have enrolled 45 patients.

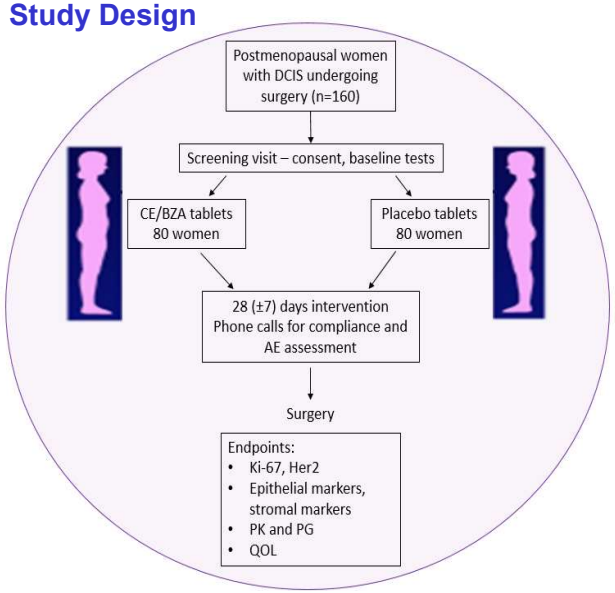
Specific Aims

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.

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.

3)To determine if a short intervention with CE/BZA is safe and well tolerated in postmenopausal women with DCIS by assessment of metrics of Quality of Life (QOL), Breast Cancer Prevention Trial Eight Symptom Scale (BESS) and by coagulation variables.

Study Design



Eligibility Criteria

Inclusion Criteria
- Postmenopausal women ≤ 79 y/o
- Newly diagnosed ER+ DCIS undergoing surgical treatment greater than 1cm on imaging
- No concurrent malignancy

Exclusion Criteria
- History of Ipsilateral DCIS or IDC
- Current use of Tamoxifen, Raloxifene, aromatase inhibitors
- Current use of oral hormone replacement therapy

Funding: This study is funded by NCI 1R01CA218436-01-GRANT12261263 (PI S. Kulkarni), the Robert H. Lurie Comprehensive Cancer Center, the California Breast Cancer Research Program, and Dancing with Chicago Celebrities.

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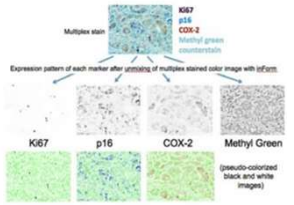
Methods

- **Sample Collection**: Tissue will be processed per standard protocol with formalin fixation and paraffin embedding. Twenty slides from the diagnostic biopsy and twenty sides from the surgical specimen will be used for the tissue analysis.
- **Immunohistochemistry:** Ki-67, HER-2. Slides will be scanned at low-power magnification to select DCIS foci with highest mitotic activity. If possible, at least 500 cells will be counted by Dr. Blanco in mitotically active areas with the aid of a grid graticule and cell counter (Ki-67 staining and analysis will be performed after each patient completes the study).
- **Multiplex staining:** Module 1: "ER-alpha / PR / HER2 / AGR2 signature Module 2: "p16 / Ki-67 / COX-2 (ARCS) / activin A signature" Module 3: "CD36 / FN1 / IL-6 / VIM pro-tumorigenic stromal signature" Module 4: "CD4 / CD8 / FOXP3 / PD-L1: Immunosuppressive T cell signature" Module 5: "CD36 / CD68 / CD206, pro-tumorigenic macrophage signature".
- **RNAseq for transcriptional profiling of the epithelium and stroma:** Exome capture RNA-seq libraries will be prepared in Dr. Greene's laboratory from laser capture microdissected and stromal tissue (U of C). Sequencing will be performed either at the CGL or at the U of C Functional Genomics Facility.
- **UGT1A1*28polymorphisms:** Given the ethnic distribution of patients at participating centers, we anticipate enrolling 10-12 subjects homozygous for *UGTIA1**28. Genotyping will be performed using established TaqMan allelic discrimination assays with validation by Sanger sequencing of PCR generated amplicons across the variant region.
- **Pharmacokinetics:** Plasma concentrations of BZA and common metabolites will be measured by LC/MS high-performance liquid chromatography with fluorescence detection.

Figure 1. Workflow of analysis of multiplex stained breast tissue section



Significance

If Successful-
- This would be first study to test the hypothesis in a human population that a mixture of steroidal and nonsteroidal molecules with different estrogenic/antiestrogenic effects on ERα action will have a net beneficial effect on multiple tissues and cells that make up the breast, reproductive tract, the brain and bone.
- We would achieve simultaneous monitoring of changes in expression of epithelial and stromal markers after short-term intervention with CE/BZA using multiplex staining
- We would confirm the anti-proliferative effect of CE/BZA in the ductal epithelium of women with DCIS.
- We would validate that CE/BZA can modulate stromal signals and flip a pro-tumorigenic stromal signature to an anti-tumorigenic signature.
- We would Identify novel modes of action for drugs targeting ER signaling via complex signaling networks, leading to an improved mechanistic understanding of these networks and how to better target ER and its co-regulators in diverse contexts.