Northwestern Cancer Prevention Consortium, Robert H. Lurie Comprehensive Cancer Center

A Phase IIB pre-surgical trial of oral tamoxifen (TAM) versus transdermal 4-hydroxytamoxifen (4-OHT) in women with DCIS of the breast

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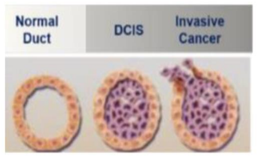
Background

Study Disease: Ductal carcinoma in situ (DCIS) is diagnosed in 60,000 women annually in the US.



Tamoxifen: TAM is proven to reduce risk of local recurrence and new primary breast cancer in women with estrogen receptor (ER) positive DCIS. However, acceptance of TAM has been low, primarily because of toxicity related to systemic exposure.

Transdermal 4-hydroxytamoxifen: Local delivery to the breast is an attractive alternative as low systemic levels could minimize toxicity. 4-OHT is an active metabolite of TAM. When formulated as a gel and applied to the breast, it is well tolerated, and results in 4-OHT breast tissue drug levels comparable to oral TAM.

Rationale: In small pilot studies, 4-OHT's anti-proliferative effects on invasive breast tumors and DCIS are also similar to oral TAM [Lee O, et al. PMID 25028506]. The goal of our study is to validate these results in preparation for a Phase III trial of 4-OHT gel compared to oral TAM.

Methods

Study Plan: We are conducting a randomized, double-blinded, placebo-controlled, Phase IIB pre-surgical trial to demonstrate that daily application of 4-OHT gel will result in a reduction in the Ki-67 labeling index of DCIS lesions that is not inferior to that seen in women receiving daily oral TAM. Ki-67 of the base-line diagnostic core needle biopsy will be compared to that of the therapeutic surgical excision sample after intervention.

Sample Size: 100 women (assuming 20% non-evaluable samples or non-compliance) with DCIS (10% ER positive) will be enrolled across 6 institutions.

Intervention: For 8 ± 2 weeks oral TAM 20mg daily and placebo gel or 4-OHT gel 4mg daily (2mg/breast) and placebo capsule.

4-OHT gel pump

Evaluation of Toxicity: All participants will be evaluable for toxicity from their first dose.

Evaluation of Response: All samples from all subjects who receive drug will be evaluated and included in the primary analysis, which will be based on intent to treat principle.

Objectives

Primary Objective: To demonstrate that daily, topical application of a gel formulation of 4-OHT to the breasts results in a **reduction in the Ki-67 labeling index** of **DCIS** lesions that is **not inferior** to that seen with oral TAM 20 mg daily.

Secondary Objectives: To evaluate effects of therapy on

- Oncotype DCIS Score
- Drug concentrations in breast tissue and plasma
- Fraction of women with no residual DCIS in surgical sample
- IHC markers (CD68, COX2, p16)
- Plasma levels of proteins related to estrogenic effects and coagulation

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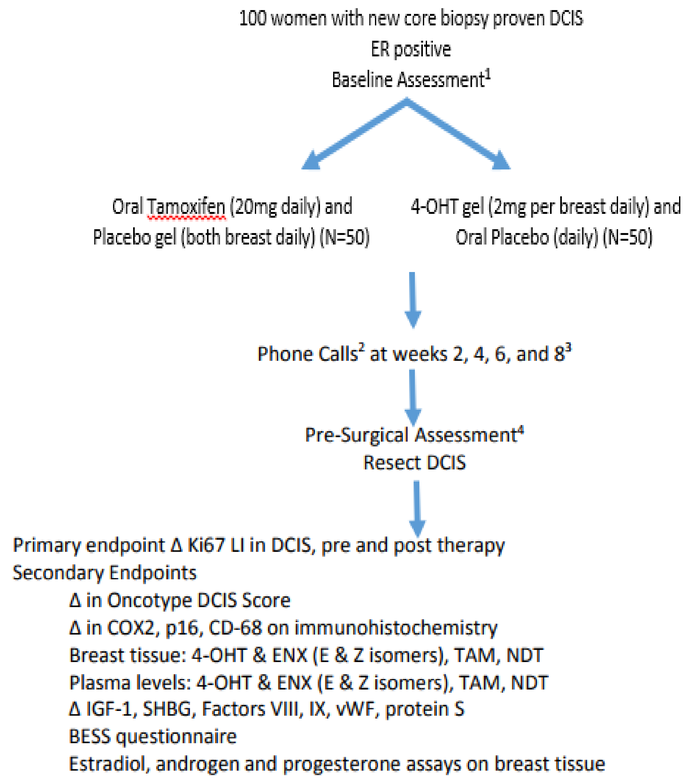
Schema



Eligibility

Key Inclusion Criteria

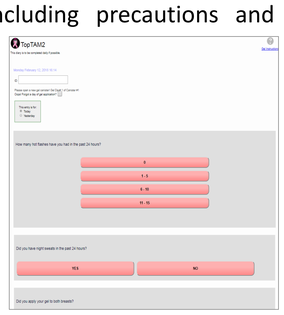
- Screen-detected, ER positive DCIS of the breast diagnosed on core needle, defined as ≥10% ER positive cells
- There must be 5mm total area of DCIS on core

Key Exclusion Criteria

- DCIS presenting as palpable lump
- Exogenous sex steroid hormone use <4 weeks prior to CNB
- Prior ipsilateral breast cancer therapy
- Skin diseases affecting the breast (eczema, psoriasis)
- Current smoker
- Current use of tamoxifen inhibitors
- Prior use of SERMS or AIs including tamoxifen within 5 years
- Pregnancy or breastfeeding

Agent Compliance

Gel Application Instructions: Participants are given instruction sheets for daily gel administration including precautions and contraindications.



Demonstration Pumps: The study team uses a demonstration pump to show participants how to use the study gel.

Paper or Electronic Diary: Participants record their daily use of study agent (capsule and gel), adverse events, and changes in concomitant medications using a paper diary or electronic website.

Gel Canister Weights and Capsule Counts: Gel Canisters are weighed by study pharmacist at dispensing and re-weighed upon return. Capsule counts are also performed.

Recruitment

Target Enrollment: 100 participants enrolled across 6 institutions over 24 months.

- 20 – Northwestern University (Chicago, IL)
- 16 – St. Elizabeth HealthCare (Edgewood, KY)
- 16 – Cleveland Clinic (Cleveland, OH)
- 16 – Mayo Clinic (Rochester, MN)
- 16 – Duke University (Durham, NC)
- 16 – Memorial Sloan Kettering Cancer Center (New York, NY)

Materials and Methods: All patient-facing materials are National Cancer Institute Division of Cancer Prevention (NCI DCP) and NCI Central Institutional Review Board (NCI CIRB) approved.

- DCIS Fact Sheet
- Study Brochure
- Dear Patient Letter
- Dear Colleagues Letter (for physicians)
- Google Ads – geographically targeted
- Dr. Susan Love Foundation, Army of Women

Enrollment

Study Open: The study opened at Northwestern University on May 31st, 2017 and is currently open to accrual at 5 institutions.

Number of Potential Participants Approached since Study Open n = 59	
Not Consented for Screening	45 (76%)
Consented for Screening	14 (24%)
Screen Failure	2 (4%)
Started Study Intervention	12 (20%)

Reasons Potential Participants Chose Not to Consent:

- Patient chose to schedule surgery sooner
- Prohibited concomitant medications
- Attitudes toward medical research

Current Enrollment: 12 of 100 target participants enrolled as of May 2018.

References

Lee O, Page K, Ivancic D, Helenowski I, Parini V, Sullivan ME, Margenthaler JA, Chatterton ,RT, Jr., Jovanovic B, Dunn BK *et al*: A randomized phase II presurgical trial of transdermal 4-hydroxytamoxifen gel versus oral tamoxifen in women with ductal carcinoma in situ of the breast. *Clin Cancer Res* 2014, 20(14):3672-3682. PMID 25028506.

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