I-SPY2 Trial

(Trial in Progress) A phase 2, open-label, randomized multicenter trial to evaluate neoadjuvant lasofoxifene in molecularly-selected HR+/HER2- Clinical Stage 2/3 breast cancer

J. Chien[1], L. Esserman[1], A. Elias[2], M. Wei[3], P. Plourde[4], D. Portman[4]

[1]University of California, San Francisco, San Francisco, United States, [2]University of Colorado Medical Center, Anschutz, Aurora, United States, [3]University of Utah, Salt Lake City, United States, [4]Sermonix Pharmaceuticals, Columbus, United States

BACKGROUND

- Chemotherapy offers limited benefit for early-stage breast cancer (BC) patients with molecular low risk, clinical high risk, hormone receptor positive (HR+), HER2-negative tumors.[1]
- Neoadjuvant endocrine therapy (NET) can downstage breast tumors and facilitates breast conservation similar to neoadjuvant chemotherapy in women with locally advanced HR+, HER2- BC, but with lower toxicity.[2]
- Aromatase inhibition (AI) (+/- ovarian function suppression (OFS)) is the standard NET for locally advanced, HR+, HER2- BC. However, the toxicity profile of AI/OFS causes poor tolerance thus more tolerable and effective endocrine-based treatments are needed.[3]
- Lasofoxifene is a next-generation selective estrogen receptor modulator (SERM) that has shown efficacy and a favorable toxicity profile in women with HR+, HER2- metastatic BC.[4]
- This Endocrine Optimization Protocol (EOP) is a phase 2, open-label, randomized multicenter sub-study within the **I**nvestigation of **S**erial Studies to **P**redict **Y**our **T**herapeutic **R**esponse with **I**maging **A**nd mo**L**ecular analysis 2 (I-SPY 2 TRIAL) to determine the feasibility, safety, and efficacy of lasofoxifene versus AI as NET among women with molecular low risk, clinical high risk, HR+, HER2 -, locally advanced BC with 6 months of NET.

STUDY OBJECTIVES

Primary Objectives

- To determine the feasibility of enrolling and treating molecularly-selected patients with early-stage HR+ BC in a randomized neoadjuvant trial using novel endocrine therapy. Feasibility is defined as ≥80% of enrolled patients completing 6 months of protocol-defined study therapy.

Secondary Objectives

- Safety and tolerability of 5 mg daily lasofoxifene (AEs, SAEs, laboratory abnormalities)
- Assess efficacy: Ki-67, PEPI score, residual cancer burden at time of surgery, rate of pCR, change in tumor volume by DCE-MRI, rates of breast conservation, and 3/5/10-year relapse-free survival and overall survival.
- Patient reported outcomes (adherence, QoL questionnaire)

Exploratory

- Correlates between exploratory biomarkers and clinical/pathological/radiological response

KEY INCLUSION CRITERIA

- Breast tumors ≥ 2.5cm, T2 or greater, any N, M0
- No prior cytotoxic treatment
- HR+/HER2-
- MammaPrint Low, any SET OR MammaPrint High 1, SET High
- Adequate bone-marrow, renal and liver function
- ECOG performance status of 0 or 1

KEY EXCLUSION CRITERIA

- Use of any investigational agents within 30d of starting study treatment
- History of allergic reactions to study agents or similar compounds
- Uncontrolled intercurrent illness
- A second malignancy other than adequately treated non-melanoma skin cancers, in situ melanoma or in situ cervical cancer. If other non-mammary malignancies, must be disease-free for ≥ 5 years
- Sentinel lymph node dissection/biopsy on the nodes draining from the study index tumor site
- Impairment of gastrointestinal absorption
- Pregnant or breastfeeding

STATISTICAL ANALYSIS

- Statistical analysis will be descriptive. The number and percentage of patients completing 6 months of protocol-defined study therapy will be reported for each arm.
- Duration of treatment, treatment holds, dose-reductions and delays, and reasons and timing of early discontinuation will be reported.

Design of EOP sub-study of I-SPY 2 TRIAL

About I-SPY 2

- The I-SPY 2 Main Protocol was launched in 2010 as a neoadjuvant chemotherapy trial designed to identify effective combinations of investigational agents with standard chemotherapy in patients with high-risk early-stage BC. The goal is to identify/graduate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial, defined by hormone-receptor (HR) & HER2 status & MammaPrint (MP).
- Patients with molecularly low risk (MammaPrint low risk signature), clinically high risk, hormone receptor positive (HR+), and HER2-negative breast cancers were originally excluded from the Main I-SPY 2 chemotherapy study since chemotherapy was predicted to have little benefit for this group.
- The EOP sub-study within the main I-SPY 2 clinical trial opened in 2020 for patients with tumors that are predicted to be sensitive to endocrine therapy and having less benefit from chemotherapy.
- Based on pre-specified clinical and molecular inclusion criteria, patients will be eligible for the I-SPY 2 chemotherapy Main protocol, the EOP, or both. If the patient is eligible for both protocols, the patient and the treating provider can choose which protocol to participate in (**Figure 1**).

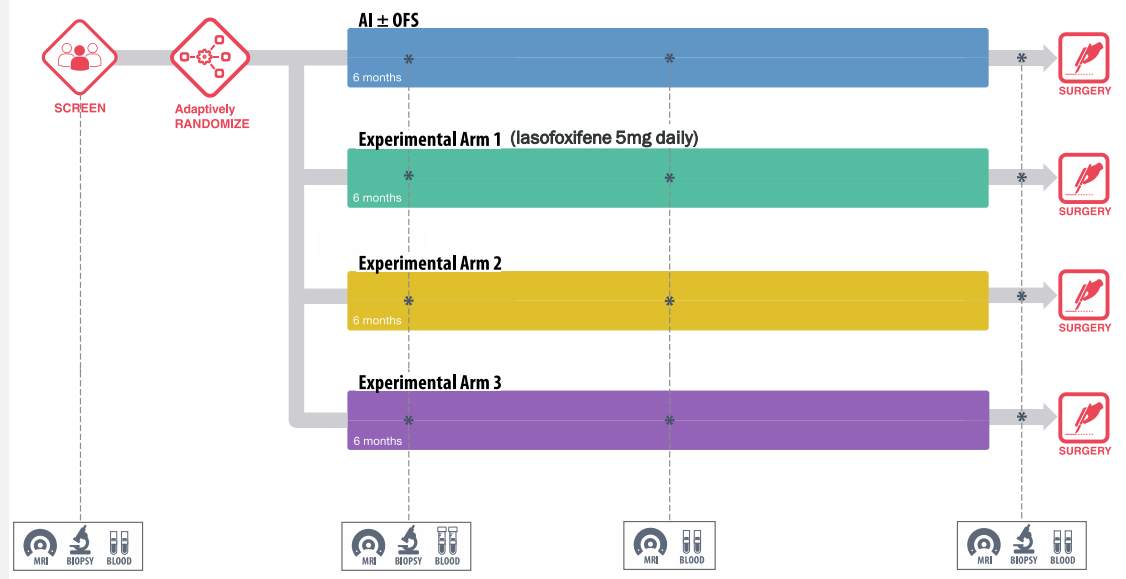

Figure 2: EOP sub-study schema within Master I-SPY2 TRIAL. Experimental Arm 1 will test lasofoxifene 5mg daily.

About the EOP sub-study

- Subjects will be randomized (1:1:1) to one of three types of arms: 1) lasofoxifene 5 mg orally daily; 2) AI+/- OFS, or 3) other concurrent experimental arms (if applicable) (**Figure 2**).
- All pre- or peri-menopausal patients will have OFS added to their treatment regimen at the 3-week timepoint, following first MRI and biopsy.
- Subjects will receive neoadjuvant treatment for six consecutive 28-day cycles.
- Enrolled patients will undergo biopsy at screening, 3 weeks, and surgical tissue collected at 6 months; MRI at screening, 3 weeks, 12 weeks and 6 months; and blood draw at screening, 3 weeks, 12 weeks, and 6 months.
- Subjects will be followed yearly for 10 years post-surgery for relapse free survival and overall survival. Surveys will assess quality of life and patient reported outcomes.
- Sample size: 20 patients on the lasofoxifene arm.
- **Clinical trial information**: NCT01042379.

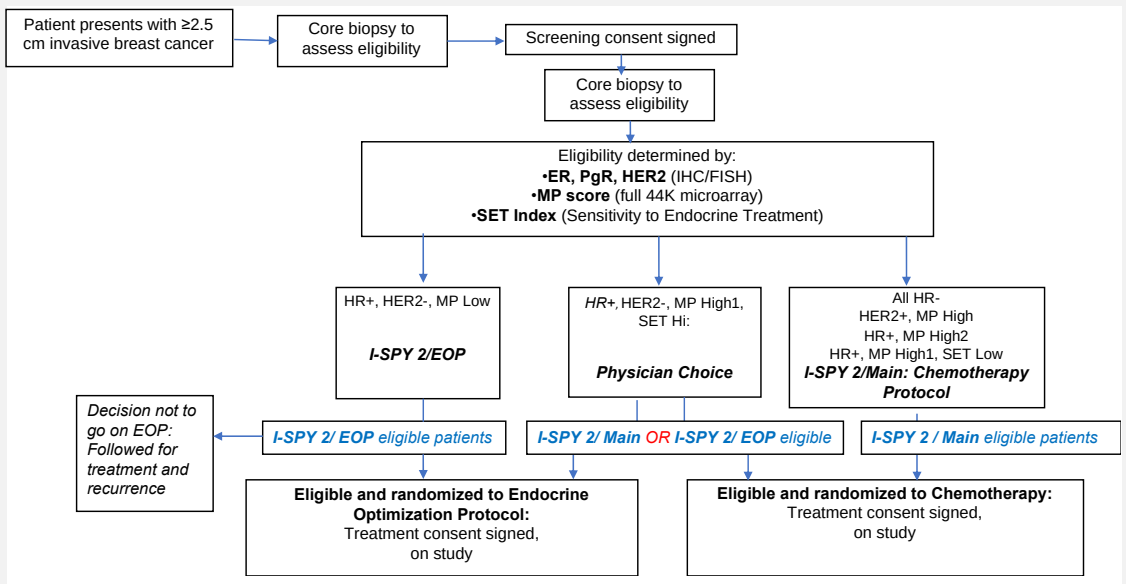

Figure 1: Master I-SPY2 Trial Patient Triage for EOP Eligibility.

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CONTACT

Correspondence: David Portman, dportman@sermonixpharma.com

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DECLARATIONS

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