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S1207: Phase III randomized, placebo-controlled clinical trial evaluating the use of adjuvant endocrine therapy +/- one year of everolimus in patients with high-risk, hormone receptor-positive and HER2-neu negative breast cancer (NCT01674140).

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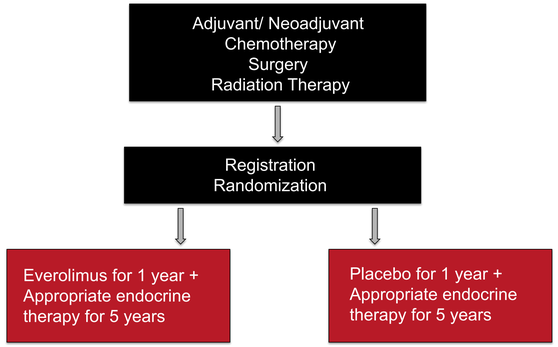
SWOG Leading cancer research. Together. NSABP National Surgical Adjuvant Breast and Bowel Project

Background

- Abnormalities of the PI3kinase/AKT/mTOR signaling network are some of the most common molecular anomalies in breast cancer.
- This pathway has been associated with resistance to endocrine therapies among HR-positive breast tumors.
- Everolimus, an mTOR-inhibitor, has been shown to increase the biological activity of aromatase inhibitors.
- In the metastatic setting, everolimus in combination with tamoxifen or exemestane increased the progression-free survival in patients previously treated with endocrine therapy.
- **S1207 proposes to evaluate the role of everolimus used in combination with endocrine therapy in the adjuvant setting.**

Clinical Trial Design

- S1207 is a SWOG/NSABP randomized phase III double-blind, placebo-controlled clinical trial.
- Parallel randomization design with equal allocation to the two treatment groups (everolimus vs. placebo).
- Patients will be stratified according to risk group.



Objectives

- **Primary Objective**
  Determine if the addition of one year of everolimus to standard adjuvant endocrine therapy improves IDFS in high risk patients with HR+, HER2 negative breast cancer.
- **Secondary Objectives**
  Overall Survival
  Distant Recurrence-Free Survival
  Evaluate safety and toxicities
  Evaluate adherence
  QOL (patient-reported fatigue and symptoms, fatigue-related biomarkers)
  To collect specimens in order to evaluate biomarkers of therapeutic efficacy

Key Eligibility Criteria

- Histologically confirmed HR+, HER2 negative breast cancer .
- All patients must complete chemotherapy before registration (within 21 weeks).
- When indicated, all patients must complete radiation therapy before registration (no sooner than 21 days and must be recovered ≤ grade 1 from effects of XRT).
- Patients may have started endocrine therapy before registration.

4 high risk groups:

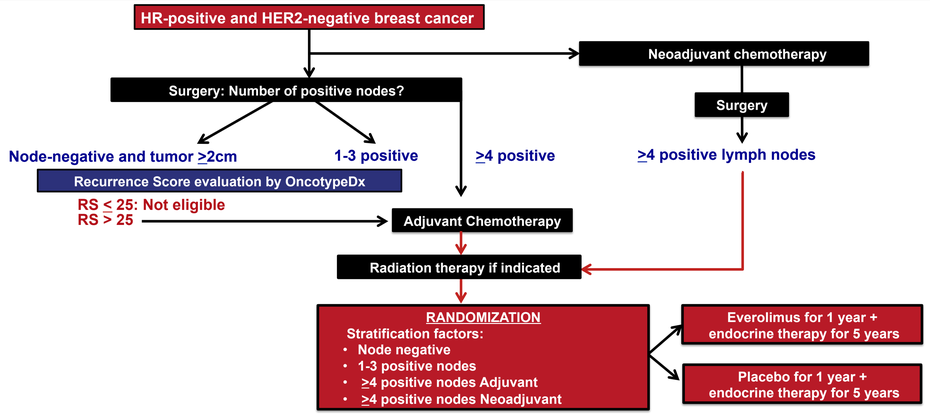
- Node-negative and primary tumor ≥ 2cm and RS >25 and completed adjuvant chemotherapy.
- 1-3 + LN and RS>25 (screened via S1007 or otherwise) and completed adjuvant chemotherapy.
- ≥ 4 positive lymph nodes and completed adjuvant chemotherapy.
- Completion of NST and ≥ 4 positive lymph nodes.

Treatment Plan

Patients will be randomized to receive one of the following:

- Everolimus 10mg/PO daily for one year + adjuvant endocrine therapy (selected by treating physician).
- Matched placebo daily for one year + adjuvant endocrine therapy (selected by treating physician)

Schema and Statistical Considerations



- The study plans to randomize 3,500 patients over a 3.5-year accrual period.
- The study has 90% power (with 2-sided α=0.05) to detect an effective hazard ratio of 0.75 for everolimus vs placebo, corresponding to a gain in IDFS of approximately 4.3% at 5 years. All patients will be followed for 10 years to assess OS and late adverse events. The expected trial duration from activation to reporting of IDFS is about 7 years.

Behavioral and Health Outcomes Study (BAHO) and Translational Studies

BAHO

- At CCOP institutions patients will have the opportunity to participate in the BAHO study.
- Patients who have already started endocrine therapy are not eligible.
- The objectives are to determine the severity of symptoms (fatigue, stomatitis, MSK complaints), QOL according to treatment arm and to determine if fatigue and the development of anemia are associated with proinflammatory cytokines and biomarkers of inflammation.
- N=492 to have 90% power to detect a difference of 1/3 standard deviation between treatment groups for any primary endpoint with and α level at 0.05

TRANSLATIONAL STUDIES

- Blood is mandatory
- Tissue is mandatory if available (one paraffin block of the primary tumor, + LN and negative LN)
- Tissue from biopsies at the time of recurrence will be collected.

STATUS: ACTIVE, NOT YET RECRUITING. Expected start accrual date: January 2013.