**BACKGROUND**

- Endocrine therapies are effective in the treatment of hormone receptor (HR)-positive breast cancer, however, de novo or acquired resistance is a significant clinical problem.
- A potential mechanism of resistance involves changes in gene expression secondary to epigenetic modifications, which might be modulated with the use of histone deacetylase (HDAC) inhibitors such as entinostat.
- The ENCORE 301 phase II randomized, placebo-controlled study demonstrated a significant improvement in progression-free survival (PFS) and overall survival (OS) with the addition of entinostat to exemestane in patients with HR-positive advanced breast cancer with disease progression after prior non-steroidal aromatase inhibitor (AI).

**METHODS**

**Study Schema and Treatment Plan**

**Eligibility**

- Disease progression after non-steroidal AI in metastatic setting OR relapse while on or within ≤ 12 months of end of adjuvant non-steroidal AI therapy
- Prior CDK inhibitor or everolimus permitted, but not fulvestrant or exemestane (other than <4 weeks in advanced setting prior to study entry)
- One prior chemotherapy permitted in metastatic setting
- ECOG 0-1 and adequate organ function
- No CNS metastases

**Statistical Plan**

- Randomized double blind placebo-controlled phase 3 design (1:1 randomization)
- Primary Endpoint: PFS and/or OS
- One-sided type 1 error 0.025 split between two hypotheses tests: 0.001 for PFS test and 0.024 for OS
- PFS is tested in the first 360 pts; 88.5% power to detect 42% reduction in the hazard of PFS failure (median PFS 4.1 to 7.1 months)
- OS is tested in all 600 pts; 80% power to detect 25% reduction in the hazard of death (median OS 22 to 29.3 months)

**Enrollment**

- Screening and patient enrollment initiated March 2014
- 398 sites open to accrual nationally via the National Cancer Institute’s (NCI) National Clinical Trials Network (NCTN)
- Accrual anticipated over 40 months (2014-2017)

**Figure 2. Proposed Treatment Flow For Patients with Advanced HR-Positive Breast Cancer**

**SUMMARY**

- The phase III E2112 trial aims to validate the preclinical and clinical findings supporting the role of HDAC inhibitors in overcoming resistance to endocrine therapy in breast cancer.
- The OS advantage observed in the phase II ENCORE 301 trial has led the FDA to designate entinostat a Breakthrough Therapy when used in combination with exemestane in hormone receptor-positive advanced breast cancer.
- It is hoped that the results of E2112 will confirm this benefit, leading to FDA approval of this agent for use in the advanced breast cancer setting.
- E2112 is open to accrual nationally via the NCTN.

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**Figure 1. ENCORE 301: Overall Survival (Yardley DA. JCO 2013)**

- Entinostat has been designated a Breakthrough Therapy by the FDA in combination with exemestane in HR-positive advanced breast cancer.
- E2112 is a phase III registration trial that will evaluate the addition of entinostat/placebo to exemestane in patients with disease progression after prior non-steroidal AI (NCT02115282)

**Hypothesis**

The addition of the HDAC inhibitor entinostat to endocrine therapy will improve PFS and/or OS in patients with HR-positive, HER2-negative advanced breast cancer with disease progression after prior non-steroidal AI.