E2112: A randomized phase III trial of endocrine therapy plus entinostat or placebo in patients with hormone receptor-positive advanced breast cancer

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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).

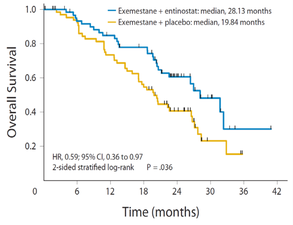


Figure 1.
ENCORE 301: Overall Survival
(Yardley DA. JCO 2013)

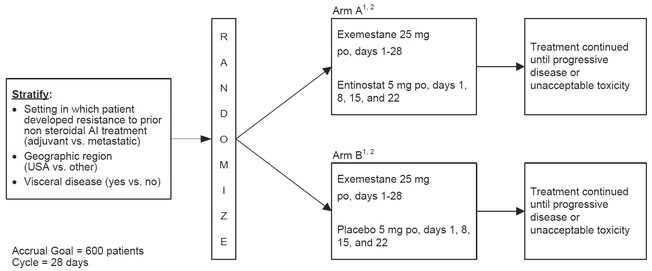
- Entinostat has been designated a Breakthrough Therapy by the FDA in combination with exemestane in HR-positive advanced breast cancer.
- E2112 is a phase III registration trial that will evaluate the addition of entinostat/placebo to exemestane in patients with disease progression after prior non-steroidal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

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.

METHODS

Study Schema and Treatment Plan



Accrual Goal = 600 patients
Cycle = 28 days

1. Treatment is blinded. Confirmation of randomization will indicate that patient is on Arm X.
2. Male participants will receive Goserelin 3.6 mg SubQ injection on day 1.

Objectives

Primary

- To determine whether the addition of entinostat to exemestane improves PFS (independent central review) and/or OS in men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer with disease progression after prior non-steroidal AI

Secondary

- Safety and tolerability
- Objective response rate
- To evaluate whether the efficacy of exemestane + entinostat varies with change in acetylation status (PBMCs)
- To evaluate the time to treatment deterioration of exemestane + entinostat vs exemestane + placebo
- To evaluate the differences in overall health-related quality of life (HRQL) between the arms
- To evaluate the difference with respect to specific symptoms that are associated with entinostat, between the arms
- To measure adherence to protocol therapy

Eligibility

- Men and postmenopausal women (≥ 18 yrs)
- Advanced invasive breast adenocarcinoma
- ER/PR-positive (≥1% staining), HER2-neg
- Measurable or evaluable (cap 20%) disease
- 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
- 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)
- Interim futility analysis for PFS
- Interim efficacy/futility analysis for OS
- Interim toxicity analysis

ENROLLMENT

- Screening and patient enrollment initiated March 2014
- 281 sites open to accrual nationally via the National Cancer Institute's (NCI) National Clinical Trials Network (NCTN)
- 30 patients have been enrolled at 22 sites (Table)
- Accrual anticipated over 40 months (2014-2017)

Characteristics	Arm X (n=30)
Age, years	
Median	61
Range	35 – 88
Sex	
Male	2
Female	28
Race	
White	24
African-American	4
Unknown/Unreported	2
Disease location	
Visceral	18
Non-visceral	12

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.

ACKNOWLEDGMENTS

- The patients who have and will generously volunteer to participate in this study
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