A Randomized Phase III Trial of Endocrine Therapy Plus Entinostat or Placebo in Patients With Hormone Receptor–Positive Advanced Breast Cancer

Overall E2112 Study Objective

Determine whether the addition of entinostat to exemestane improves and extends the benefits of hormone therapy in patients with hormone receptor (HR)–positive breast cancer who have progressed on a nonsteroidal aromatase inhibitor (AI)

Study Objectives

Primary
- Evaluate whether the addition of entinostat to endocrine therapy (exemestane) improves progression-free survival and/or overall survival in patients with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer who have previously progressed on a nonsteroidal AI
- Evaluate the objective response rate
- Evaluate whether the efficacy of exemestane with entinostat varies with changes in acetylation status in peripheral blood mononuclear cells
- Evaluate time to treatment deterioration (defined by decrease in health-related quality of life [HRQL], progression, death)
- Evaluate differences in overall HRQL between arms
- Evaluate the differences with respect to specific symptoms that are associated with entinostat, ie, fatigue, nausea, anorexia, and diarrhea, between arms
- Measure adherence to protocol therapy
- Evaluate entinostat pharmacokinetics
- Evaluate if any patient variables alter the entinostat pharmacokinetic profile

Secondary
- Collect archival tumor samples and germline DNA to explore other potential biomarkers of therapeutic efficacy
- Collect patient ratings of adverse events using select items from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to evaluate their psychometric properties and explore their incorporation into a phase III double-blind placebo-controlled trial

Study Schema

Table 1. Regimens for Treatment Arms

<table>
<thead>
<tr>
<th>Arm X*</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment and administration schedule</td>
<td>Exemestane 25 mg PO, d 1-28</td>
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<tr>
<td></td>
<td>Entinostat 5 mg PO, d 1, 8, 15, and 22</td>
<td>Placebo 5 mg PO, d 1, 8, 15, and 22</td>
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</tbody>
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Assessment schedule
- Imaging\(^1\): Patients undergo imaging within 4 weeks of randomization, at the end of 12 weeks from randomization and every 12 weeks thereafter, at the end of treatment (within 4 weeks of end of treatment), and post-treatment.
- Blood monitoring: Patients will undergo periodic CBC and chemistry monitoring beginning ≤ 72 hours prior to cycle 2 and continuing every cycle or every third cycle (for chemistries) thereafter.

Long-term monitoring
- All patients will be followed for a response until progression even if nonprotocol therapy is initiated. Patients are monitored every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, and every 12 months if patient is > 5 years from study entry for up to 10 years, including patients removed from study for unacceptable adverse events.

*Patients will be randomized to Arm A (entinostat) or Arm B (placebo), but as this is a double-blind trial, all patients will be identified as on Arm X

\(^1\)Response and progression are measured using the international RECIST guidelines (version 1.1; Eur J Cancer. 2009;45:228-247)

\(^1\)Imaging studies include CT, MRI, PET, or any combination. Bone scans are required within 4 weeks of randomization

AI = aromatase inhibitor; CBC = complete blood count; PO = orally
Eligibility Criteria*

**Main Inclusion Criteria**

- Estrogen receptor- and/or progesterone receptor-positive histologically confirmed adenocarcinoma of the breast with staining of ≥ 1% cells will be considered positive. Receptor status may be based on any time during treatment prior to study randomization, and from any site (ie, primary, recurrent, or metastatic).
- Measurable or nonmeasurable stage III/locally advanced or metastatic carcinoma of the breast, where local therapy with curative intent is not possible. Lesions must be evaluated ≤ 4 weeks prior to study randomization.
- Pre-, peri-, and postmenopausal women and all men; postmenopausal is defined as:
  - Age ≥ 55 years and 1 year or more of amenorrhea
  - Age < 55 years and 1 year or more of amenorrhea, with estradiol < 20 pg/mL
  - Age < 55 with prior hysterectomy but intact ovaries, with estradiol < 20 pg/mL
  - Prior bilateral oophorectomy

*Note: Women who do not fit the criteria for being postmenopausal are deemed pre- or perimenopausal. Pre- or perimenopausal women and all men can enroll provided they agree to receive a concomitant luteinizing hormone–releasing hormone (LHRH) agonist. Pre- and perimenopausal women must have started LHRH agonist treatment ≥ 4 weeks prior to randomization. Patients receiving alternative LHRH agonist prior to study entry must switch to goserelin for the trial duration.*

- At least 1 of the following:
  - Disease progression any time after nonsteroidal AI use in the advanced disease setting
  - Relapse while on or within ≤ 12 months of the end of adjuvant nonsteroidal AI therapy with or without prior endocrine therapy for advanced disease

*Note: In either setting, any prior endocrine therapy must be completed ≥ 2 weeks before C1D1 of study. The exception is exemestane, permitted in the advanced disease setting within ≤ 4 weeks immediately prior to C1D1. Prior adjuvant exemestane is allowed if the disease-free interval is > 12 months from stopping exemestane. Prior faslodex, everolimus, palbociclib, or other cyclin-dependent kinase (CDK) inhibitor (eg, ribociclib, abemaciclib) is allowed and must have been completed ≥ 2 weeks prior to C1D1. Failure to adhere to this washout guideline results in protocol violation.

- Disease-free of prior invasive malignancies for > 5 years with the exception of curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix; if there is a history of prior malignancy, not receiving other specific treatments for that cancer

- May have received only 1 prior chemotherapy regimen for metastatic disease, provided that treatment was completed ≥ 3 weeks prior to randomization
- Prior radiation therapy must have been completed ≥ 2 weeks prior to randomization and patients must have recovered from the radiation toxicity. Patients may receive concurrent radiation therapy to painful sites of bony disease or areas of impending fracture as long as sites of measurable or nonmeasurable disease outside the radiation therapy port are available to follow.
- Treatment with bone-modifying agents such as bisphosphonates or receptor activator of nuclear factor κ-B (RANK)–ligand agents (eg, denosumab) is permitted
- Recovery from all clinically relevant adverse events to grade 1 or baseline due to previous agents administered (except alopecia)
- For known HIV-positive patients, a CD4 count > 250/mm³
- ECOG performance status 0-1
- ≥ 18 years of age with a life expectancy of ≥ 12 weeks
- Adequate hematologic, hepatic, and renal function
- Use of effective contraception

**Main Exclusion Criteria**

- Tumors that have HER2 immunohistochemistry 3+, in situ hybridization ≥ 2.0, or average HER2 copy number ≥ 6.0 signals per cell. Receptor status may be based on any time during treatment prior to study randomization, and from any site (ie, primary, recurrent, or metastatic).
- Known central nervous system (CNS) metastasis, history of CNS metastases, or leptomeningeal disease
- Prior use of exemestane (other than ≤ 4 weeks before study entry)
- Concurrent anticancer therapy or investigational agent unless specified in protocol
- Receiving valproic acid or a histone deacetylase (HDAC) inhibitor, or previously received any HDAC inhibitor prior to enrollment (eg, valproic acid, entinostat, vorinostat), unless discussed with the study chair
- Known allergies to exemestane, entinostat, or medications that have a benzamide structure (eg, tiapride, remoxipride, clebopride)
- Medical or psychiatric conditions that would interfere with protocol compliance, ability to provide informed consent, or assessment of response to anticipated toxicities
- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection
- Pregnancy or breast-feeding

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria*

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**For Further Study Information**

- For more information about the E2112 study, please visit the following:
  - Cancer.gov; search E2112
  - Clinicaltrials.gov; search NCT02115282
- For more information about ECOG-ACRIN, visit ecog-acrin.org