May 22, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #7 to E2112, *A Randomized Phase III Trial of Endocrine Therapy plus Entinostat/Placebo in Patients with Hormone Receptor-Positive Advanced Breast Cancer.*

Please note that this study is under the Special Protocol Assessment which will require FDA review.

There are revised case report forms as a result of this amendment. Case Report Forms in Medidata Rave will be amended to reflect changes in data collection related to this amendment.

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

An expedited review by the IRB can be considered for this amendment. However, please consult your local IRB's standard operating procedures, since their requirements may differ and require a full board review.

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. If your local IRB has different SOPs, they must be available at future E-A audit.

The following revisions to E2112 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated version date Inserted study champions
2.	5.2.3	Updated NCI fax number
3.	5.6.1	Renamed Medication Adherence Scale
4.	5.6.3.3	Renamed Medication Adherence Scale
5.	5.6.3.5	Renamed Medication Adherence Scale
6.	6.2.4	Renamed Medication Adherence Scale

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	Section	Change
7.	7	Renamed Medication Adherence Scale in footnote 7
8.	8.2.10	Removed note regarding site participation from Korea and Peru
9.	8.3.10	Removed note regarding site participation from Korea and Peru
10.	9.6	Renamed Medication Adherence Scale
11.	9.7	Renamed Medication Adherence Scale
12.	9.7.2	Renamed Medication Adherence Scale
13.	Appendix VIII	Updated CTEP fax number
14.	Appendix X	Included Sarcopenia imaging substudy

The following revisions to E2112 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date

If you have any questions regarding this addendum, please contact csamuel@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to E2112 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Enclosure

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

E2112

This is an FDA Registration Trial

A Randomized Phase III Trial of Endocrine Therapy plus Entinostat/Placebo in Patients with Hormone Receptor-Positive Advanced Breast Cancer

STUDY CHAIR: Roisin Connolly, MB, BCh
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BREAST CANCER COMMITTEE CHAIR: Joseph Sparano, M.D.

Version Date: May 22, 2019
NCI Update Date: October 4, 2017

Rev.7/14, 4/15

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG

Rev. Add7

Study Champions
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ACTIVATION DATE

March 19, 2014

Update #1 – Incorporated Prior to Activation
Addendum #1 – 7/14
Addendum #2 – 4/15
Addendum #3 – 10/15
Addendum #4 – 10/16
Update #2 – 9/17
Update #3 – 10/17
Addendum #5
Addendum #6
Addendum #7

Rev.10/15

Agents	IND#	NSC#	Supply
Exemestane		NSC 713563	NCI-Supplied (for U.S. sites only)
Goserelin Acetate		NSC 606864	Commercially Available
Entinostat/Placebo	[redacted] IND Sponsor: DCTD, NCI	NSC 706995	Syndax Pharmaceuticals (NCI-Supplied)

Table of Contents

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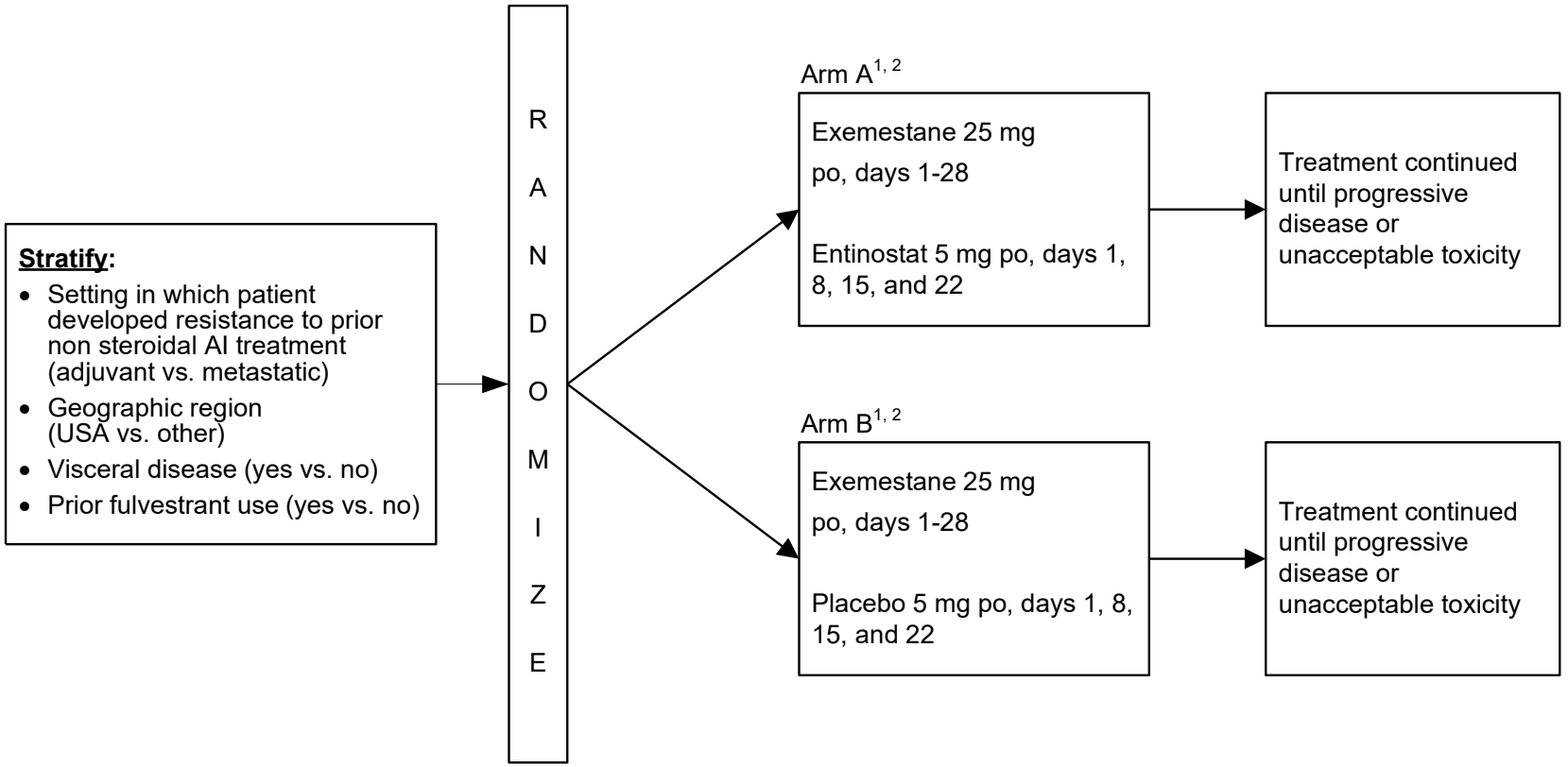
Rev.7/14
Rev. Add5

CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation can be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
Rev.10/16 **For clinical questions (i.e., patient eligibility or treatment-related)** Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Rev.10/15

Schema



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 and pre/perimenopausal women will receive Goserelin 3.6 mg SubQ injection on day 1.

1. Introduction

1.1 Metastatic Breast Cancer

Breast cancer is the most common malignancy in women in Western societies. It is estimated that more than 200,000 women will be diagnosed with breast cancer in the US in 2012.[1] Advances in the early detection and optimal adjuvant treatment of breast cancer have led to a significant reduction in disease relapse and death. Nevertheless, approximately 40,000 women per year continue to die from this disease. New therapeutic agents, or combinations of agents, are therefore urgently required in an effort to improve both the efficacy of adjuvant therapy and management of metastatic disease.

1.2 Targeting the ER Pathway

Hormone therapy is an important component of the treatment paradigm for the majority of women with hormone receptor-positive breast cancers. Estrogen signaling is a key driver of breast cancer cell growth and targeting this pathway is an effective method of treating this subtype of breast cancer. There are two isoforms of the estrogen receptor (ER), ERα and ERβ, with ERα mediating the growth properties of breast cancer cells. Several therapeutic options exist for blocking estrogen signaling including selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs) and selective estrogen receptor down-regulators (SERDs) such as faslodex. SERMs such as tamoxifen bind to the ER and selectively inhibit transcriptional activity in breast cancer cells, while functioning to activate the receptor in other tissues.

For patients with metastatic disease, the response rate to first-line hormonal therapy with anti-estrogens or AIs ranges from 21% to 33%.[2-4] The objective response rates of second-line hormonal therapies, such as exemestane or fulvestrant, measured by Response Evaluation Criteria in Solid Tumours (RECIST) criteria were approximately 7%.[4] A study of low dose estradiol as second- or third-line therapy documented stable disease, but no objective responses.[5] Thus, novel approaches to improve the efficacy of currently available strategies for hormone receptor-positive breast cancer are urgently needed.

1.2.1 Aromatase Inhibitors

Anti-estrogen or endocrine therapy remains the mainstay of treatment for patients with hormone-sensitive metastatic breast cancer. Due to both the clinical activity and the benign side effect profile of endocrine agents, the standard of care typically involves sequencing of these agents until either the development of resistance and/or visceral crises necessitates switching to chemotherapy. For patients with metastatic disease, the response rate to first-line endocrine therapy with anti-estrogens such as tamoxifen, or AIs ranges from 21% to 33%.[2-4] The AIs function by inhibiting the aromatase (CYP19A1) enzyme, a protein that plays a critical role in estrogen biosynthesis and is encoded by the aromatase gene. Aromatase catalyzes conversion of androgens to aromatic estrogens in the adrenal gland and adipose tissue, which results in profound estrogen deprivation in post-menopausal women whose ovaries no longer produce estrogen. Anastrozole and letrozole are non-steroidal AIs that bind reversibly to

aromatase while exemestane is a steroidal AI that functions through irreversible binding and inactivation of the enzyme.

The AIs have been studied extensively in a variety of breast cancer settings. In terms of breast cancer prevention, the only published data we have related to use of the AIs is with the steroidal AI, exemestane. Exemestane was found to significantly reduce invasive breast cancers in postmenopausal women who were at moderately increased risk for breast cancer when compared to placebo.[6] During a median follow-up period of 3 years, exemestane was associated with no serious toxic effects and only minimal changes in health-related quality of life. The AIs are the agent of choice in treating postmenopausal women with hormone receptor-positive early breast cancer, with over a dozen large randomized trials comparing adjuvant AIs with tamoxifen in several sequences demonstrating significant improvement in disease-free survival and reduction in breast cancer events.[7] These trials have investigated the use of both nonsteroidal and steroidal AIs. In addition, a meta-analysis of randomized trials of AIs compared with tamoxifen in the adjuvant setting revealed that AIs produce significantly lower recurrence rates compared with tamoxifen, either as initial monotherapy or after 2 to 3 years of tamoxifen.[8] It is generally believed that the efficacy of the non-steroidal and steroidal AIs is equivalent, although no head to head comparisons in the adjuvant setting have been published to date. The MA.27 trial randomly assigned postmenopausal women with hormone receptor-positive breast cancer in the adjuvant setting to receive exemestane 25 mg/daily or anastrozole 1 mg/daily for 5 years. The aim of the trial was to determine which of the nonsteroidal AI anastrozole and the steroidal AI exemestane was superior in terms of preventing recurrence and/or death from breast cancer, and whether either had a superior toxicity profile. Data reported to date found no differences in efficacy or toxicity between the agents[9].

In addition to the benefits observed with the AIs in the breast cancer prevention and early breast cancer settings, the AIs are generally the agent of choice in treating post-menopausal patients with advanced breast cancer. A Cochrane review was performed to evaluate the available randomized controlled trials in postmenopausal women comparing the effects of any AI versus another endocrine therapy, no endocrine therapy or another AI in advanced breast cancer. This review demonstrated a survival benefit of 10% with the use of AIs for the treatment of advanced breast cancer. Notably, the greatest benefit (a survival benefit of 12%) was associated with use of the 3rd generation AIs in current clinical use, namely anastrozole, exemestane and letrozole. No significant differences were observed between the different 3rd generation AIs.[10] As in the adjuvant setting, it is generally believed that the efficacy of the non-steroidal and steroidal AIs is equivalent and these may be used essentially interchangeably based on physician preference. Depending on the agent used for first line therapy, an AI from a different class may be used as second line therapy or other endocrine therapies such as tamoxifen or faslodex. However, the objective response rates of

second-line hormonal therapies, such as exemestane or fulvestrant, measured by RECIST criteria has been shown to be approximately 7%.[4] Thus, novel approaches to improve the efficacy of currently available strategies for hormone receptor-positive breast cancer are urgently needed.

1.2.2 Exemestane

Exemestane is an irreversible, steroidal AI, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation, an effect also known as “suicide inhibition”. Exemestane significantly lowers circulating estrogen concentrations in postmenopausal women, but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone. Exemestane has no effect on other enzymes involved in the steroidogenic pathway up to a concentration at least 600 times higher than that inhibiting the aromatase enzyme.[11] We propose to use exemestane as a backbone for this proposal in order to parallel the ENCORE phase 2 trial described in Section 1.3.4.[12] As discussed in Section 1.2.1, data from trials in the metastatic and adjuvant setting suggest that the efficacy of the non-steroidal and steroidal AIs is equivalent.

1.3 Resistance to Hormonal Therapy

Although pharmacologic therapies that reduce or block estrogen signaling are effective in the treatment of ER-positive breast cancer, acquired resistance to individual drugs can develop. Furthermore, these therapies may be ineffective as initial therapy for a subgroup of receptor-positive patients (de novo resistance). The mechanisms of drug resistance are not completely understood, but the presence of alternative signaling pathways for activating ER response appears to play a significant role. Cross-talk between signaling pathways can activate ERs when conventional ER pathways are blocked or inactivated. For example, signaling via epidermal growth factor or HER-2 receptors, mitogen-activated protein kinases, phosphatidylinositol 3' kinase (PI3K)/protein kinase B, and vascular endothelial growth factor receptor can lead to estrogen-independent stimulation of ERs and tumor growth. The discovery that alternative pathways are involved in estrogen signaling has prompted development of newer endocrine therapies, such as AIs and pure estrogen antagonists, with distinct mechanisms for interrupting signal transduction. The existence of multiple pathways may explain the effectiveness of follow-up therapy with a different class of endocrine agents after failure of prior endocrine treatment. Although optimal sequencing of these agents has not been determined and is continuing to evolve, current evidence allows rational recommendations to be made. The multiple pathways involved in activating ERs also provide a rationale for combining endocrine and non-endocrine therapies that block different signaling pathways, which may have synergistic and overlapping interactions.[13]

Whether strategies combining endocrine therapies with novel agents are more efficacious than endocrine therapy alone has been investigated recently. An emerging mechanism of endocrine resistance is aberrant signaling via the PI3K/Akt/mTOR intracellular signaling pathway. mTOR has been identified as a

rational target to enhance the efficacy of hormonal therapy. The BOLERO-2 trial was a randomized Phase III study evaluating exemestane in combination with everolimus (mTOR inhibitor)/placebo in post-menopausal women with ER-positive refractory metastatic breast cancer (with recurrence or progression following prior therapy with letrozole or anastrozole).[14] Patients could have received any prior number of endocrine treatments and a single prior chemotherapy. The trial met its primary endpoint of improvement in progression-free survival (PFS) by local review with the combination therapy (7.8 months) vs the placebo arm (3.2 months). These results were confirmed with the use of an independent, blinded radiologic assessment (10.6 months vs 4.1 months). Overall survival (OS) data remains immature at this time. The most common grade 1-4 adverse reactions (incidence greater than or equal to 30%) in patients receiving everolimus plus exemestane were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common grade 3-4 adverse reactions (greater than or equal to 2%) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. Fatal adverse reactions occurred in 2% of patients on the everolimus arm compared to 0.4% of patients on the placebo arm. Adverse reactions resulting in permanent discontinuation occurred in 24% and 5% of patients in the everolimus and placebo arms, respectively. Dose interruptions or reductions were necessary in 63% of patients on the everolimus arm compared to 14% on the placebo arm. Based on the PFS benefit observed, this regimen has been approved for use in patients with metastatic breast cancer who have experienced disease progression on anastrozole or letrozole. Everolimus is, therefore, the first agent to be approved for use in addition to endocrine therapy in patients with HER2-negative disease. However, other strategies to improve outcomes with endocrine therapy in patients with hormone receptor-positive metastatic breast cancer are needed. Ideally, agents that prolong OS and are associated with less toxicity than that observed with everolimus would be welcome. A promising potential mechanism of overcoming resistance and which we anticipate will lead to improved clinical outcomes for patients with a manageable toxicity profile may lie in the use of epigenetic modifiers such as the histone deacetylase (HDAC) inhibitors.

1.3.1 Targeting Epigenetic Changes

The development and progression of cancer is now recognized as being not only secondary to inherited or sporadic genetic mutations, but also epigenetic changes in the genome.[15] Epigenetics is a term which refers to changes in gene expression that are not secondary to alterations in the primary nucleotide sequence of a gene, such as is the case with a genetic mutation. Epigenetic changes include both histone hypoacetylation and abnormal methylation of DNA in the promoter region of important genes. These changes may result in alterations in chromatin structure leading to a repressive chromatin state and silencing of both gene expression and transcription of DNA into RNA. Importantly, epigenetic changes contribute to drug resistance, are generally considered to be reversible and thus represent an active and attractive area of new drug investigation.

Histone acetylation is controlled by a balance in activity between histone acetyltransferase (HAT) and HDAC. The HDACs exert their

targeted action during post-translational acetylation of core nucleosomal histones, which affects chromatin structure, thereby regulating gene expression. DNA that is wrapped around condensed, non-acetylated histones is transcriptionally inactive, whereas acetylation of N-terminal histone lysine residues exposes DNA to important transcription factors that promote transcriptional activity.[16,17] The dynamic equilibrium between histone acetylation and deacetylation is regulated by HATs and HDACs. The action of HDACs on nucleosomal histones leads to tight coiling of chromatin and silencing of expression of various genes, including those implicated in the regulation of cell survival, proliferation, differentiation, and apoptosis.[18] The effects of HDACs are not limited to histone deacetylation. HDACs also act as members of a protein complex to recruit transcription factors to the promoter region of genes, including those of tumor suppressors, and they affect the acetylation status of specific cell cycle regulatory proteins.[17] Because aberrant HDAC activity has been implicated in a variety of cancers, development of HDAC inhibitors is a rational approach to the design of targeted anticancer therapeutics.

1.3.2 HDAC Inhibitors

Because of the frequency of detection of epigenetic alterations in breast cancers, agents that target these changes are of great interest. Several strategies have been initiated to relieve transcriptional repression and include the use of HDAC inhibitors. Examples of HDAC inhibitors include entinostat (SNDX-275, previously MS-275), trichostatin (TSA), vorinostat (SAHA), LAQ824 and LBH589. Vorinostat was found to induce differentiation or arrest growth of a wide variety of human carcinoma cells including breast cancer.[19-21] The antitumor activity of vorinostat was also demonstrated in several in vivo models of cancer, including in the carcinogen-induced mammary tumor model. It reduced tumor incidence in NMU-induced rat mammary tumorigenesis by 40%.[22] In vitro studies demonstrated that vorinostat inhibits clonogenic growth of the breast cancer cell lines MCF-7, MDA-231, and MDA-435 by inducing G1 and G2/M cell cycle arrest and subsequent apoptosis.[19] Further analysis demonstrated that exposure to low concentrations of vorinostat was associated with accumulation of cells mainly in G1, while higher vorinostat concentrations caused cell cycle arrest predominantly in G2/M.[20] This agent also induced a dose-dependent increase in H3 acetylation in MCF-7 cells and its' effects are reversible upon drug discontinuation.

The ability of the HDAC inhibitors to relieve transcriptional repression in preclinical breast cancer models has also been investigated. The accumulation of acetylated H3 and H4 histone tails in conjunction with re-expression of a functional ER in ER-negative breast cancer cell lines has been observed with a novel HDAC inhibitor, scriptaid.[23] Treatment of ER-negative breast cancer cell lines with vorinostat was also found to result in reactivation of silenced ER, as well as downregulation of DNMT1 and EGFR protein expression.[24] The

significance of an epigenetically reactivated ER was demonstrated when the formerly unresponsive ER-negative MDA-MB-231 breast cancer cells became responsive to tamoxifen after treatment with both HDAC (trichostatin A) and DNA methyltransferase inhibitors.[25] Entinostat has been shown to induce not only re-expression of ERα but also the androgen receptor, and the aromatase enzyme (CYP19) in both in vitro and triple-negative breast cancer xenografts.[26] In addition, the combination of entinostat and letrozole resulted in a significant and durable reduction in the xenograft tumor volume when compared to treatment with either agent alone. These experiments have provided the strong rationale for combining epigenetic modifiers with hormonal therapy in breast cancer clinical trials.

1.3.3 Entinostat

Several HDAC inhibitors have been studied in phase I and II trials in hematological malignancies and solid tumors.[27-30] Entinostat belongs to the class of HDAC inhibitors which are critically important in the regulation of gene expression and in the field of target-specific anticancer drug development.[31] It is a synthetic benzamide derivative that appears to be a potent inhibitor of histone deacetylases that has shown anti-tumor activity against multiple human tumors.[28] Vorinostat has been approved by the Food and Drug Administration (FDA) for those with heavily pretreated T-cell lymphoma.[32] In a phase II trial in the advanced breast cancer setting, administration of single agent oral vorinostat resulted in stable disease in four out of fourteen patients.[33] Accumulating evidence has demonstrated the effectiveness of HDAC inhibitors in combination with several other agents in vitro including hypomethylating agents, [34,35] anti-metabolites,[36,37] retinoids,[38] and many novel agents. Combination strategies with hormonal treatments for breast cancer will now be described.

1.3.4 Combination Strategies: HDAC Inhibitors and Hormonal Therapy

Whether the addition of a HDAC inhibitor to hormonal strategies for breast cancer can reverse resistance to hormonal therapy and therefore improve breast cancer outcomes has been investigated. Preclinical models which suggested that the efficacy of tamoxifen can be enhanced by vorinostat[39] prompted the development of a phase II trial in advanced breast cancer patients. Oral vorinostat 400mg daily (21 days of a 28 day cycle) and tamoxifen 20 mg daily administered to women with hormone-resistant breast cancer yielded an objective response rate of 19% and a clinical benefit rate of 40% (n=43).[40] The combination of agents was well tolerated with no unexpected adverse events. Prior tamoxifen had been received in the adjuvant setting in approximately 60% of patients and 54% had received two prior lines of therapy with AIs. Histone hyperacetylation and higher baseline HDAC2 levels were found to correlate with response. These findings suggest that vorinostat may indeed restore responsiveness to tamoxifen in patients with hormone-resistant disease, and support the development of a randomized trial for further delineation of the clinical relevance of the combination.

The ENCORE 301 randomized phase 2 study evaluated the role of entinostat, a class 1 selective HDAC inhibitor, in combination with exemestane (steroidal AI) in the advanced breast cancer setting. Postmenopausal women who had received ≤ 1 prior chemotherapy and were progressing on a non-steroidal AI were randomized to exemestane 25 mg daily plus entinostat 5 mg weekly versus exemestane plus placebo weekly.[12] A significant improvement in PFS was noted in the entinostat arm versus placebo (median 4.3 versus 2.3 months, respectively). In an exploratory analysis of patients who were deemed resistant to prior AI, patients randomized to the entinostat arm had a greater PFS than those in the placebo arm. OS, an exploratory endpoint, was also significantly longer in the entinostat arm versus the placebo arm (28.1 versus 19.8 months, respectively). Interestingly, in a subset analysis examining protein acetylation in entinostat patients (n=27), the median PFS increased to 8.5 months in those exhibiting protein lysine hyperacetylation, and this was apparent after just 2 weeks of therapy.[41] The addition of entinostat to AI therapy may delay the initiation of subsequent therapies such as chemotherapy by prolonging PFS on exemestane. We propose to evaluate the addition of entinostat or placebo to exemestane in patients who have progressed on a non-steroidal AI. In addition, we will explore whether benefit varies with changes in lysine acetylation.

Rev.10/15 **Table 1.1: Select Clinical Trials of Novel Combinations with Endocrine Therapy in Metastatic Breast Cancer**

Clinical Trial	Treatment Arms	Patient Population	Results
ENCORE Phase 2 Trial[12]	Exemestane + Entinostat/Placebo 5mg po weekly	Postmenopausal women Prior progression on a non-steroidal AI and ≤ 1 prior chemotherapy	Median PFS 4.3 (entinostat) versus 2.3 months (placebo); HR 0.73 Median OS 28.1 (entinostat) versus 19.8 months (placebo); HR 0.59
Rev. 4/15 **ECOG-ACRIN Phase 3 Trial (Connolly)**	Exemestane + Entinostat/Placebo 5 mg po weekly	Pre/perimenopausal and post-menopausal women and men HR-positive advanced breast cancer Prior progression on a non-steroidal AI (adjuvant/metastatic) and ≤ 1 prior chemotherapy for metastatic disease	Pending
BOLERO-2 Phase 3 Trial[14]	Exemestane + Everolimus/Placebo	Postmenopausal women Prior progression on a non-steroidal AI and ≤ 1 prior chemotherapy	Median PFS 7.8 (everolimus) vs 3.2 (placebo) months

1.4 Study Rationale

Despite advances in the treatment of patients with ER-positive breast cancer, many women fail to respond to an AI or suffer recurrence of disease notwithstanding optimal adjuvant therapy. Patients with advanced stage ER-positive breast cancer have a median survival of approximately 18-24 months and in this setting hormonal therapy provided a 20-30% response rate and a 9-11 month PFS. Tumors may be intrinsically (de novo) resistant to hormonal therapy and will therefore never respond to an AI, or they may acquire resistance at a

later time-point through various host or tumor-mediated mechanisms.[42] Women with hormone receptor-positive metastatic breast cancer receiving hormonal therapy are also subject to drug resistance. Clearly strategies to overcome resistance to hormonal agents are urgently required in an effort to improve outcomes for breast cancer patients and delay the time to chemotherapy use.

A variety of resistance mechanisms have been shown to occur in tumor cells resistant to AIs, including loss of ER expression, activated growth factor signaling pathways, estrogen independent tumor growth, hypersensitivity of tumor cells to low estrogen concentrations and cyclin D1 over-expression. Targeting these mechanisms would be expected to restore sensitivity to AIs and increase both the number of patients that respond as well as prevent or delay the time to progression on AI therapy. HDAC inhibitors are one class of compounds that have been shown to inhibit many of the AI resistance pathways pre-clinically.

Pre-clinically, entinostat has been shown to induce protein lysine acetylation, resulting in down-regulation of estrogen-independent growth factor signaling pathways and normalization of ER levels. In addition, there is a suggestion that entinostat may have longer term effects on cancer phenotypes, cancer stem cell or progenitor cell pool and potentially sensitization to subsequent post-study treatments.[43] In a recently reported randomized phase II trial, the addition of entinostat to exemestane improved PFS and OS in patients with previously treated hormone-sensitive metastatic breast cancer. Pharmacodynamic analysis in a subset of patients links HDAC inhibitor activity to breast cancer clinical outcome. A phase II biomarker validation study is being planned to further delineate the role of entinostat and the potential biomarker of lysine acetylation in this setting (refractory to non-steroidal AI).

We propose to simultaneously evaluate the addition of entinostat to exemestane in patients who have experienced disease progression on a non-steroidal AI. Observing a positive treatment effect for entinostat in this ECOG-ACRIN trial would be practice changing and if successful would lead to FDA approval of this agent for use in the metastatic setting. This clinical trial will, therefore, serve to validate the preclinical and clinical findings supporting the role of HDAC inhibitors in overcoming resistance to hormonal therapy in breast cancer patients. We anticipate that it will provide a novel treatment approach which will both improve and extend the benefits of hormone therapy in breast cancer patients. Finally, if successful this trial may provide impetus to study entinostat in the 1st line metastatic and adjuvant settings.

1.5 Patient Reported Outcomes

Patient-reported outcomes (PROs) capture unique data on treatment toxicities and disease symptoms that complements clinician-rated toxicities. In addition, it is important to understand from the patient perspective how the addition of this novel agent, entinostat, will impact overall health-related quality of life (HRQL). Collecting PROs to document treatment toxicities from the patient's perspective will provide invaluable data to inform patient-centered counseling regarding the risks and benefits of endocrine therapy plus entinostat if the combination should prove to prolong PFS or OS. This lesson has been re-capitulated in the experience with exemestane and everolimus, where concerns over increased toxicity limit the use of everolimus in the hormone-refractory setting.

Prior studies have generally indicated entinostat is well tolerated, so we expect that overall HRQL will be comparable between treatment arms. However, we

recognize the use of this novel agent in a novel treatment regimen may be associated with unanticipated side effects. We have designed the PRO endpoints for this trial to detect the most common treatment side effects and to also detect decrements to HRQL related to unanticipated side effects. We anticipate the most common side effect associated with entinostat combination will be fatigue,[12,44,45] which is common in metastatic breast cancer due to disease. However, entinostat has also been associated with nausea, anorexia and diarrhea[12,44,45] and these symptoms may also be more common in the exemestane and entinostat arm. Therefore, we propose to administer PRO measures to assess overall HRQL as well as specific treatment-related symptoms to detect differences between the two treatment arms.

Given that PFS is a primary endpoint for this trial, we will also evaluate whether improvement in PFS is associated with improved HRQL. To answer this question, we will assess whether the addition of entinostat to exemestane improves time to treatment deterioration (TTD) compared to exemestane + placebo. TTD is a composite endpoint consisting of time to death, disease progression, or worsening of symptoms. TTD has been used as an endpoint in a phase III study of renal cell cancer comparing two similar oral agents (axitinib vs sorafenib)[62,63]. As the primary endpoint, Rini et al were able to demonstrate that axitinib extended PFS compared with sorafenib (6.7 mos vs 4.7 mos, $p<0.0001$). Because of the valuable addition of TTD as an endpoint, they were also able to demonstrate that axitinib accomplished this without negatively affecting HRQL, and in fact was associated with less deterioration in HRQL (axitinib was associated with a 17% reduction in risk for TTD, HR 0.83,$p=0.01$). This is invaluable data for clinicians and patients when making treatment decisions that balance PFS benefit with possible treatment toxicities.

Because we believe that the benefits from improving PFS (and thus symptoms from disease) will outweigh any increase in toxicity from the addition of entinostat to exemestane, we hypothesize that the combination arm (EE) will have a significantly longer TTD than the EP arm.

The National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a library of 78 items developed to obtain patient reporting of Adverse Events (AEs) in clinical trials. The NCI is seeking partnerships with clinical trials investigators by embedding PRO-CTCAE into therapeutic trials. The PRO-CTCAE data collected will be used to provide descriptive and parallel information about using this new measurement system to gather information directly from patients about the symptomatic adverse effects of their treatment. Content validity of PRO-CTCAE items has been established through cognitive interviews with 127 adults with different cancer types and undergoing chemotherapy or radiation therapy. Interviews and review of PRO-CTCAE items established the content validity of PRO-CTCAE items for patient-reporting of AEs[71]. Interviews demonstrated that most AE terms were comprehended, and the attribute terms and response options required no modifications. The next step in establishing the validity of PRO-CTCAE items includes administering select items in the context of a cancer clinical trial. Given the phase III, double-blind placebo-controlled randomized design of this trial, E2112 offers the opportunity to validate PRO-CTCAE items to measure six symptoms: decreased appetite, diarrhea, nausea, vomiting, joint aches, and muscle aches. These toxicities were selected because we anticipate these to be the most common toxicities associated with entinostat or

exemestane. In addition, we anticipate that PRO-CTCAE items may identify toxicities earlier than would be identified using the clinician-rated CTCAE system. This will provide the opportunity to intervene earlier to manage symptoms that may interfere with treatment adherence.

2. Objectives

2.1 Primary Objective

2.1.1 To evaluate whether the addition of entinostat to endocrine therapy (exemestane) improves progression-free survival (PFS) and/or overall survival (OS) in patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have previously progressed on a non-steroidal aromatase inhibitor (AI).

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2.2 Secondary Objectives

2.2.1 To evaluate the safety and tolerability of entinostat in combination with exemestane, and to compare the safety profile to that of endocrine therapy with placebo.

2.2.2 To evaluate the objective response rate of exemestane in combination with entinostat or placebo.

2.2.3 To evaluate whether the efficacy of exemestane with entinostat varies with changes in acetylation status in peripheral blood mononuclear cells (PBMCs).

2.2.4 To evaluate the time to treatment deterioration (as defined by decrease in HRQL, progression, death) of exemestane + entinostat versus exemestane + placebo arms.

2.2.5 To evaluate the differences in overall health-related quality of life (HRQL) between the exemestane + entinostat versus exemestane + placebo arms.

2.2.6 To evaluate the difference with respect to specific symptoms that are associated with entinostat, i.e., fatigue, nausea, anorexia and diarrhea, between the exemestane + entinostat versus exemestane + placebo arms.

2.2.7 To measure adherence to protocol therapy.

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2.2.8 To evaluate the pharmacokinetics of entinostat in patients with advanced breast cancer.

2.2.9 To evaluate what, if any, patient variables alter the pharmacokinetic profile of entinostat in patients with advanced breast cancer.

2.3 Exploratory Objectives

2.3.1 To collect archival tumor samples and germline DNA to explore other potential biomarkers of therapeutic efficacy.

2.3.2 To collect patient ratings of AEs using select PRO-CTCAE items to evaluate the psychometric properties of PRO-CTCAE items and explore the incorporation of PRO-CTCAE items into a phase III double-blind placebo-controlled trial.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Estrogen receptor (ER) and/or progesterone receptor (PR) 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 (i.e. primary, recurrent, or metastatic).

_____ 3.1.2 Patients whose tumors have HER2 IHC 3+, ISH ≥ 2.0, or average HER2 copy number ≥ 6.0 signals per cell are not eligible.[74] Receptor status may be based on any time during treatment prior to study randomization, and from any site (i.e. primary, recurrent, or metastatic).

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_____ 3.1.3 Patients must have measurable or non-measurable Stage III/locally advanced or metastatic carcinoma of the breast, as defined in Section 6.1.2, where local therapy with curative intent is not possible. Lesions must be evaluated ≤ 4 weeks prior to study randomization. Diagnostic-quality CT scans with both oral and IV contrast are the expected radiologic method, unless an alternative is approved per Section 6.1.3.

NOTE: Where baseline imaging has already been performed ≤ 6 weeks prior to study randomization, repeat imaging may not be required. Please refer to footnotes 5 and 6 of Study Calendar (Section 7).

NOTE: As of October 16, 2016, accrual of new patients having non-measureable disease has stopped. Per Section 9.2, the planned accrual for this target population has been reached.

Rev.10/15 _____ 3.1.4 Pre/peri- and postmenopausal women and all men are eligible for this trial. Postmenopausal is defined as:

- Age ≥ 55 years and one year or more of amenorrhea.
- Age < 55 years and one 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 as above are deemed pre-or peri-menopausal. Pre/perimenopausal women and all men can enroll provided they agree to receive concomitant LHRH agonist. Pre/perimenopausal women must have commenced treatment with LHRH agonist at least 4 weeks prior to randomization. If patients have received alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial.

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_____ 3.1.5 Sexually active males and pre/perimenopausal women must agree to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study and for 3 months after discontinuation of therapy.

Rev.10/15 _____ 3.1.6 Women must not be pregnant or breast-feeding.

All females of childbearing potential must have a blood test or urine study ≤ 2 weeks prior to randomization.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.7 Patients must not have known central nervous system metastasis or a history of CNS metastases. Patients with leptomeningeal disease are not eligible.

_____ 3.1.8 Patients must be 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.

NOTE: If there is a history of prior malignancy, patients must not be receiving other specific treatment for that cancer.

Rev. 4/15 _____ 3.1.9 Patients must meet at least one of the following criteria:

_____ 3.1.9.1 Disease progression any time after non-steroidal AI use in the advanced disease setting.

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3.1.9.2 Relapse while on or within ≤ 12 months of end of adjuvant non-steroidal AI therapy with or without prior endocrine therapy for advanced disease.

NOTE: In either setting, treatment with any prior endocrine therapy must be completed ≥ 2 weeks prior to C1D1 of study treatment with the exception of exemestane which is 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 the discontinuation of exemestane. Prior faslodex, everolimus, palbociclib or other CDK inhibitor (e.g. ribociclib,

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abemaciclib) use are allowed and must have been completed ≥2 weeks prior to C1D1. Failure to adhere to this washout guideline will result in a protocol violation.

_____ 3.1.10 Patients may have received only one prior chemotherapy regimen for metastatic disease provided treatment was completed ≥ 3 weeks prior to randomization.

_____ 3.1.11 Patients may be treated with bone modifying agents such as bisphosphonates or RANK-ligand agents (e.g. denosumab) per ASCO guidelines. Whenever possible, patients requiring bone modifying agents should start treatment ≥ 7 days prior to study therapy and should continue the same agent throughout study unless clinically compelled to change.

_____ 3.1.12 Prior radiotherapy must in general have been completed ≥ 2 weeks prior to randomization and patients must have recovered from the toxicity of the radiation.

NOTE: Patients may receive concurrent radiation therapy to painful sites of bony disease or areas of impending fracture as long as sites of measurable or non-measurable disease outside the radiation therapy port are available to follow.

_____ 3.1.13 Patients must NOT receive concurrent anti-cancer therapy or investigational agent unless specified in protocol.

Rev. 10/16 _____ 3.1.14 Patients must NOT be receiving valproic acid, an HDAC inhibitor, and may not have previously received any HDAC inhibitor prior to enrollment (e.g valproic acid, entinostat, vorinostat) unless discussed with the study chair. Patients must not have received prior HDAC therapy for the treatment of their malignancy.

Rev. 10/16 _____ 3.1.15 Patients must have no known allergies to exemestane, entinostat, or medications that have a benzamide structure (e.g., tiapride, remoxipride, clebropride).

_____ 3.1.16 Patients must NOT suffer from medical or psychiatric conditions that would interfere with protocol compliance, the ability to provide informed consent, or assessment of response or anticipated toxicities. This includes uncontrolled intercurrent illness including, but not limited to ongoing or active infection.

_____ 3.1.17 Patients must have recovered from all clinically relevant adverse events to grade 1 or baseline due to previous agents administered (except alopecia) and the criteria outlined in Section 3.1.18.

_____ 3.1.18 Patients must have adequate hematologic, liver and renal function as defined below ≤ 28 days prior to randomization:

_____ 3.1.18.1 Hemoglobin (HgB) ≥ 9.0 g/dL

Hemoglobin: _____

Date of Test: _____

_____ 3.1.18.2 Platelet count ≥ 100,000/ mcL

Platelets: _____

Date of Test: _____

_____ 3.1.18.3 Absolute neutrophil count ≥ 1,500/mcL

Neutrophil count:_____

Date of Test:_____

_____ 3.1.18.4 Creatinine ≤ 2.0 mg/dL

Creatinine: _____

Date of Test: _____

_____ 3.1.18.5 Total bilirubin < 1.5 x institutional upper limit of normal (≤ 3 mg/dL in case of Gilbert's syndrome)

Total bilirubin: _____ ULN:_____

Date of Test: _____

_____ 3.1.18.6 Transaminases (ALT, AST) ≤ 2.5 x institutional upper limit normal

ALT: _____ ULN:_____

Date of Test: _____

AST: _____ ULN:_____

Date of Test: _____

NOTE: It is preferred that laboratory values for eligibility be assessed after the last dose of prior treatment, especially in cases where most-recent treatment prior to study entry is chemotherapy.

_____ 3.1.19 Known HIV-positive patients should have a CD4 count > 250/mm^3.

_____ 3.1.20 Patients must have ECOG Performance Status 0-1. See Appendix V.

_____ 3.1.21 Patients must have a life expectancy ≥ 12 weeks.

_____ 3.1.22 Patients must be ≥ 18 years of age.

_____ 3.1.23 Patients must be able to swallow tablets.

Physician Signature	Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Randomization Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>.

For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E2112** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen

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- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol E2112
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for E2112 site registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents

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Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

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Treatment must start within ten working days of randomization.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-

ctep.nci.nih.gov/iam/index.jsp>) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of randomization and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Randomization

Please note that no blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be shipped from the Pharmaceutical Management Branch (PMB) of the NCI to the registering investigator at the time of patient randomization and should arrive within five working days (see Section 8.0).

For sites within the United States, the Pharmaceutical Management Branch will ship patient-specific open label exemestane with the initial blinded, patient specific supplies of entinostat or placebo.

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Please note that when a patient has been successfully randomized, the confirmation of randomization will indicate that the patient is on arm X. The patient will actually be randomized to arm A or B, but as this is a double-blind trial, that information cannot be displayed.

At time of randomization, the following information will be requested:

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race

- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.3 Stratification Factors

- Setting in which patient developed resistance to prior non steroidal AI treatment (adjuvant vs. metastatic)
- Geographic region (USA vs. other)
- Visceral disease (yes vs. no)

  NOTE: Visceral disease for this protocol refers to liver and/or lung involvement.

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- Prior fulvestrant use (yes vs. no)

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4.4 Additional Requirements

4.4.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

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4.4.2 Clinical data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

ECOG-ACRIN has contracted with Alpha Oncology, a contract research organization (CRO) to conduct on-site and remote monitoring activities. The goal of these monitoring activities is to provide source document verification (SDV). Alpha Oncology will be in contact with sites as patients reach the pre-defined milestones for initiation of monitoring activities.

Alpha Oncology will also be conducting data sweeps. The goal of these data sweeps is to assist institutions with timely data entry and query resolution. Alpha Oncology will utilize phone requests and email notifications to request entry of outstanding data and/or completion of open queries. The objective of these sweeps is to collect data; they are not designed as an audit, nor are they intended to generate corrections to previously submitted data.

4.4.3 Pathological materials are to be submitted for future undefined research as indicated in Section 11.

4.4.4 Blood samples are to be submitted for laboratory research studies and future undefined research as outlined in Section 11.

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4.4.5 Plasma samples are to be submitted for population pharmacokinetic studies as outlined in Section 11 per patient consent.

NOTE: To obtain starter kits and the Site Laboratory Instruction Manual please Email or Fax Appendix IX E2112 Covance Site Information/Initial Kit Order Form to Syndax. Please note Covance requires ten (10) days to process the form and ship the initial kits.

4.5 Additional Registration Training Requirement

Mandatory Participating Site Training Course

ECOG-ACRIN has developed a training course to provide an overview of the E2112 trial to site research staff and investigators. This training includes information regarding the general protocol overview, data collection and data management, and the imaging component of the trial which will require submission of scans for routine tumor assessments. ECOG-ACRIN recommends all research staff (CRAs, Data Managers, Imaging Staff, Investigators, Pharmacy Staff, etc) involved in E2112 complete the training.

Prior to the first patient enrollment at a participating site, one person from the research staff (i.e. a research coordinator or an investigator) must review and

complete the training course. The course is available 24/7 via the following URL: http://coccg.mindflash.com/PublicCoursePage.aspx?c=832897692

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Upon completion of training, please complete the form titled E2112 Mandatory Participating Site Training Form, available in Appendix VII, and submit directly to the CTSU Regulatory Office via Fax: 215-569-0206 or email: CTSURegulatory@ctsu.coccg.org. Patient enrollments will be blocked via the OPEN system until one individual at your site completes the required protocol training.

4.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the E2112 Forms Completion Guidelines.

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4.7 Emergency Unblinding

The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an emergency or adverse event that may result in the need to unblind the patient.

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. Roisin Connolly, at (410) 614-9217, or email: rconnol2@jhmi.edu first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operations Office – Boston drug team at (857) 504-2900, Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., "E2112"), the patient ID number (e.g., "44444"), and the patient initials (e.g., "FL") to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment.

NCI CTEP should also be notified of a request for unblinding.

5. Treatment Plan

5.1 Administration Schedule

Cycle = 4 weeks (28 days)

Rev.4/15 A complete cycle of treatment is defined as 28 days (± 3 days) of once daily continuous treatment of exemestane in combination with entinostat/placebo. A new cycle start is defined as the first planned date of entinostat/placebo for the cycle.

Rev. 10/16 Entinostat/placebo should be taken on an empty stomach, at least 1 hour before and 2 hours after a meal/snack. Missed doses should not be made up later.

5.1.1 Arm X (Arms A and B)

Exemestane 25mg po (single dose), days 1-28

Entinostat/placebo 5mg po (single dose), days 1, 8, 15, and 22

Rev. 10/15 Goserelin (Pre/perimenopausal female and all male participants only): 3.6 mg SubQ injection day 1

Repeat cycles every 28 days until development of disease progression per Section 6 or unacceptable toxicity.

NOTE: The patient 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.

Rev. 10/16 The schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.) with the guidance of the protocol chair/designee, as appropriate, and will not be reportable as a deviation unless the endpoints of the study are affected.

Rev. Add5 5.2 Adverse Event Reporting Requirements

NOTE: Effective April 1, 2018 expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines on this study will continue to be based on CTCAE version 4.0 terminology and grading.

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The

following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they

may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

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5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use the CTEP Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the NCI (301-897-7497)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

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Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301-897-7404) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event

- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E2112 and outline the specific expedited adverse event reporting requirements for study E2112.

5.2.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arm X (Arms A and B)

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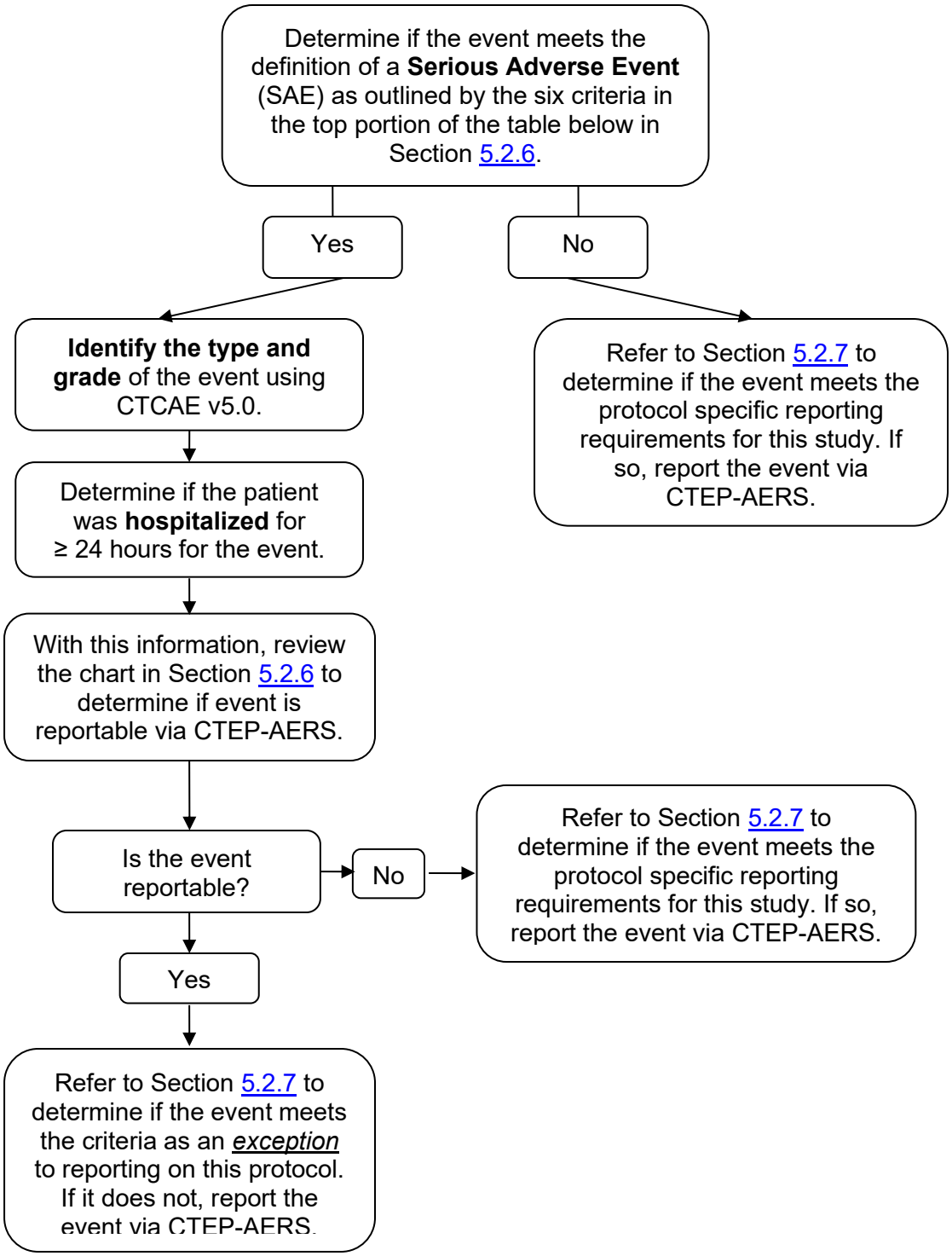
5.2.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.6, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.6 Expedited Reporting Requirements for Arm X (Arms A and B) on protocol E2112

Investigational Agents: Entinostat/Placebo

Commercial Agents: Exemestane

When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events follows the guidelines for investigational agents.

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Effective Date: May 5, 2011

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5.2.7 Additional instructions, requirements and exceptions for protocol E2112

Additional Instructions:

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study**: A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "Disease progression" under the System Organ Class (SOC) "General disorder and administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

E2112 specific expedited reporting requirements:

- **Thrombocytopenia**

  Any ≥ grade 4 platelet count must be reported via CTEP-AERS within 24 hours of learning of the event followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

  Any grade 3 platelet count with significant bleeding, regardless of whether or not the patient was hospitalized, must be reported via CTEP-AERS within 10 calendar days of learning of the event.

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- **Pregnancy**

  Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring with a female patient while the subject is on Entinostat/Placebo, or within 3 months of the subject's last dose of Entinostat/Placebo, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.** Please refer to Appendix VIII for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

E2112 specific expedited reporting exceptions:

The adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event. The only exception is that platelet count decrease (thrombocytopenia) must be reported via CTEP-AERS as outlined above.

5.2.8 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave.

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol).** Second malignancies require ONLY routine reporting as follows:
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol).** Secondary malignancies require both routine and expedited reporting as follows:
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     - *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy*

3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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[redacted]

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

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5.2.7

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PIO@CTEP.NCI.NIH.GOV

[redacted]

[redacted]

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5.4 Dose Modifications

Although entinostat and exemestane have distinct toxicity profiles, they do share some adverse events such as fatigue, nausea, and diarrhea. There is the theoretical possibility that one agent may potentiate the other and hence drug causality will not always be clear. In the event of uncertainty, dose reductions and/or delays will follow the most conservative approach.

Treatment will be modified based on treatment-related toxicity as described below for all patients receiving entinostat/placebo. Dose omits due to toxicity will not be made-up; patients may resume treatment once toxicity resolves as per the regular schedule. Dose reductions due to toxicity are permanent. Dose escalation is not allowed.

If more than two doses of entinostat/placebo are omitted in a single cycle due to entinostat/placebo-related toxicity, the patient will be permanently discontinued from protocol therapy, followed until event resolution, and managed at the investigator's discretion. Exemestane may continue in this case.

Regular dosing and compliance with medication is strongly encouraged. If ≥ 2 doses of entinostat/placebo per cycle are omitted for reasons other than toxicity in > 2 cycles, the patient will discontinue protocol therapy. However, if the treating investigator believes the subject is benefitting from treatment and feels it is in the best interest of the participant to continue on study, exceptions may be considered after discussion with the Study Chair.

Prior to administration of first dose of entinostat/placebo in each cycle, patient's organ function must have recovered to the following values:

Minimum Values for Dose Administration	
Absolute Neutrophil Count	≥ 1 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine	≤ 2 x institutional upper limit of normal (ULN)

NOTE: The dose modifications noted below refer to administration of entinostat/placebo. Exemestane dose reductions are not allowed. If exemestane administration is held for any reason, patient can remain on study for up to 7 days. If exemestane administration is held for > 7 days, patient will be considered off protocol treatment.

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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5.4.1 Entinostat/Placebo Dose Modifications

5.4.1.1 Special Considerations

For any grade 4 toxicity that recurs despite prophylaxis or dose reduction, protocol treatment should be permanently discontinued.

Any consideration of changes to these dose modification guidelines must be discussed with the Study Chair for approval in advance.

NOTE: If a patient experiences a grade 3 or 4 event that requires a dose modification after dose has previously been reduced, entinostat/placebo should be omitted for 2 weeks and continued at the reduced dose of 3mg.

Table 5.4.1: Dose Reductions for Entinostat/Placebo-Related Toxicity[1,2,]

Hematologic Toxicity			
CTCAE System Organ Class (SOC)	**Adverse Event**	**Grade**	**Entinostat/Placebo Dose Change**
Investigations	Neutrophil count decreased	Grade 1 or 2	No change
		Grade 3 or 4	Omit for 2 weeks and reduce to 3mg
	Platelet count decreased	Grade 1 or 2	No change
		Grade 3 or 4	Omit for 2 weeks and reduce to 3mg
	White blood cell decreased	Grade 1 or 2	No change
		Grade 3 or 4	Omit for 2 weeks and reduce to 3mg
Non-Hematologic Toxicity			
CTCAE System Organ Class (SOC)	**Adverse Event**	**Grade**	**Entinostat/Placebo Dose Change**
Gastrointestinal disorders	Diarrhea (Reduce dose only after optimal use of loperamide)	Grade 1 or 2	No change
		Grade 3 or 4	Omit for 2 weeks and reduce to 3mg
	Nausea / Vomiting (Reduce dose only after optimal use of anti-emetics)	Grade 1 or 2	No change
		Grade 3 or 4	Omit for 2 weeks and reduce to 3mg
Metabolism and nutrition disorders	-Hyperglycemia -Hypoglycemia -Hypophosphatemia -Hypernatremia -Hyponatremia -Hypercalcemia -Hypocalcemia	Grade 1 or 2	No change
		Grade 3 or 4	Omit for 2 weeks and reduce to 3mg
Other non-hematologic adverse events not mentioned above		Grade 1 or 2	No change
		Grade 3 or 4	Omit treatment until toxicity resolves to Grade 1 then dose reduce to 3mg

[1]Unless otherwise specified, grade 3 or 4 toxicity should improve to grade 2 or better prior to resuming treatment

[2]If more than two doses of entinostat/placebo are omitted in a single cycle due to entinostat/placebo-related toxicity, the patient will be permanently discontinued from protocol therapy

5.5 Supportive Care

5.5.1
All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.2 Bone-modifying agents

Patients may be treated with bone modifying agents such as bisphosphonates or RANK-ligand agents (e.g. denosumab) per ASCO guidelines. Whenever possible, patients requiring bone modifying agents should start treatment 7 days prior to study therapy and should continue the same agent throughout study unless clinically compelled to change.

5.5.3 Hypersensitivity Reactions

Hypersensitivity reactions to exemestane or entinostat/placebo should be managed as per standard of care at the treating institution. Severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Subjects who experience a severe hypersensitivity reaction to treatment should not be re-challenged.

5.5.4 GI Medications

Drugs used to reduce the acidity (increase pH) of the stomach, i.e. H2 antagonists, proton-pump inhibitors, antacids, etc., could potentially interfere with entinostat absorption. **Delay administration of H2-antagonists, antacids, or proton pump inhibitors, or other drugs that lower acidity for at least 2 hours after dosing entinostat/placebo.**

5.5.5 Nausea and Vomiting

Nausea and vomiting after entinostat/placebo administration are expected. Prophylactic 5-HT3 serotonin receptor antagonist will be administered prior to ingestion of entinostat/placebo as well as on an as needed basis. Other anti-emetic medications (prochloroperazine, lorazepam, etc.) may also be taken for delayed nausea as needed.

5.5.6 Diarrhea

If diarrhea occurs during dosing, an antidiarrheal agent(s) may be used. Loperamide may be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every two hours (4 mg every 4 hours while asleep) around the clock until diarrhea-free for at least 12 hours. Additional or institutional standard antidiarrheal measures may be used at the discretion of the treating physician.

5.5.7 Neutropenia without fever

The clinical situation should be closely followed for fever, focal signs of infection, and neutrophil nadir. Growth factor support should be administered in accordance with ASCO guidelines.

5.5.8 Neutropenia with fever

Hospitalization and urgent broad-spectrum antibiotics are required for this potentially life-threatening complication. The occurrence of a temperature higher than 38.3°C (100.9°F) demands prompt evaluation of blood counts and examination for source of infection. Growth factor support should be administered in accordance with ASCO guidelines.

5.5.9 Anemia

Red blood cell support should be given for any patient with symptomatic anemia and is recommended for patients with asymptomatic anemia when hemoglobin is below 8 g/dL.

5.5.10 Platelet Count Decrease

Platelet transfusion should be given for a platelet count below 10,000/mm^3 in the absence of bleeding. If bleeding develops or invasive procedures are planned, platelet transfusion should be administered in accordance with standard practice.

5.6 Patient-Reported Outcomes Administration

A detailed description of the PRO measures to be administered has been included in Section 6.2.

5.6.1 PRO Instruments to be administered:

1) The Functional Assessment of Cancer Therapy–General (FACT-G); 27 items
2) The PROMIS Fatigue 7-item Short Form
3) The Functional Assessment of Anorexia/Cachexia Treatment (FAACT; 12 items)
4) Functional Assessment of Chronic Illness Therapy-Diarrhea (FACIT-D; 11 items)
5) FACT-Breast Symptom Index (FBSI; 8 items) – taken from 8-item FBSI outlined by Yost et al that has event-based anchor points

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6) Medication Adherence Scale

5.6.2 PRO-CTCAE items to be administered:

Select PRO-CTCAE items (16 items) will be administered to measure patient reporting of AEs.

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5.6.3 Patient-Reported Outcomes Assessment Schedule

5.6.3.1 Brief symptom index to evaluate TTD: we plan to use 6 items from the FBSI -- FACT Breast Symptom Index to detect symptom deterioration. These 6 items have been selected to focus on proximal change in symptoms. However, we will collect all 8 of the items from the FBSI 8 outlined by Yost et al.[73] These items will be administered at the following times:

1) Baseline (before Cycle 1 Day 1)

2) End of Every Cycle for Cycles 1-6
3) End of Cycles 8, 10, and 12
4) Then administered on the same schedule as tumor assessments until disease progression (Note, for FBSI there are not assessments planned at or post progression).

5.6.3.2 PRO measures of treatment toxicities (PROMIS Fatigue, FAACT, FACIT-D) will be administered at the following time points:

1) Baseline (before Cycle 1 Day 1)
2) End of Cycle 3
3) End of Cycle 6
4) End of Cycle 12
5) At end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy)
6) 4-weeks after end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy).

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5.6.3.3 The ECOG-ACRIN Medication Adherence Scale Modified from the Morisky Index will be administered:

1) End of Cycle 3
2) End of Cycle 6
3) End of Cycle 12
4) At end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy)

5.6.3.4 Patient-reported HRQL will be assessed using the FACT-G and will be administered:

1) Baseline (before Cycle 1 Day 1)
2) End of Cycle 3
3) End of Cycle 6
4) End of Cycle 12
5) At end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy)

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5.6.3.5 PRO-CTCAE: PRO-CTCAE items will be administered

1) Baseline and prior to every cycle, following the same schedule as trial symptom/toxicity assessments.
2) End of each Cycle during treatment

3) At end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy)

NOTE: The PRO-CTCAE should be completed each time a Symptom/Toxicity Assessments is completed.

The total length of this assessment is dependent on the assessment time point. One of the lengthiest assessments will occur at Baseline (FACT-G, PROMIS-fatigue, FAACT-subscale, FACIT-diarrhea subscale, FBSI, PRO-CTCAE) is 80 multiple choice items. The anticipated time to complete all items is roughly 15-20 minutes. Assessments prior to cycles 4, 7 and 13 will also include the ECOG-ACRIN Medication Adherence Scale Modified from the Morisky Index that will include 8 multiple choice or yes/no items and will take roughly 2-3 minutes. This assessment schedule corresponds to the first, second, and fourth disease assessments. We have scheduled PRO assessments with standard clinic office visits to minimize participant and site burden, thus minimizing the risk of missing PRO data. Assessments to be administered at every cycle (FBSI, PRO-CTCAE) will include 21 multiple choice items and will take 4-5 minutes to complete.

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PRO assessments at treatment discontinuation and 4 weeks post-treatment discontinuation for all participants regardless of the reason for treatment discontinuation (toxicity, progression) will provide valuable information on HRQL and symptom burden. As noted by Rini et al.[72] HRQL can appear to improve overall as the trial progresses due to participant selection bias. Participants with poorer performance status, more aggressive disease, and greater treatment toxicities come off treatment earlier. We may observe a high rate of attrition due to progression of illness. Patients on EE are expected to remain on treatment longer than patients on EP due to anticipated benefit in PFS. To obtain an unbiased assessment of HRQL and treatment toxicities, PRO assessment at the end of treatment and a short period of time following end of treatment (4 weeks) for all participants is needed. Otherwise, PRO assessments only capture data on participants who remain on treatment and are likely to be healthier, therefore, presenting a biased source of data that will likely indicate that HRQL improves over time. In addition, the assessment 4 weeks post-end of treatment will evaluate whether entinostat-related symptoms resolve within 4 weeks. This design (retaining participants who discontinue treatment) has been employed with other PROs studies such as the side effect sub-study of MA.27.

A PRO measure of breast cancer-specific symptoms will be administered at baseline, and every 28-day cycle for the first six months after randomization, and then every two cycles between 6 months and 1 year. After 1 year, the FBSI will be administered on the same schedule as tumor assessments until disease progression. The FBSI will be administered more frequently to allow for an assessment of time to treatment deterioration (TTD), a critical secondary endpoint.

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The PRO measure of adherence to therapy, the Medication Adherence Scale - , will be administered as outlined in Section 5.6.3 (before Cycle 4, 7, 13, and end of protocol therapy). With the exception of baseline, these assessment time points correspond with other study PRO.

The FBSI and Medication Adherence Scale include 8 and 8 items each and the anticipated time to complete the 16 items is roughly 5-6 minutes. Please note there will be one Medication Adherence Scale form completed for each agent (entinostat/placebo and exemestane).

5.6.4 PRO Administration Instructions

All PRO questionnaires will be administered as a paper survey. Ideally, participants will complete questionnaires at the time of scheduled study visits. For the first assessment (Cycle 1), PRO should be administered prior to the administration of study drug. With the exception of the 8-item FBSI, PRO time points overlap with protocol-specified clinic visits. If the 8-item FBSI does not overlap with protocol-specified clinic visits and/or if PRO assessments are not administered in clinic, the study questionnaires will be mailed to participants who will be asked to complete questionnaires and return by mail to clinic. After 7 days, clinic or research staff may contact participants by telephone and ask participants to complete the questionnaire on paper and then read their answers over the telephone to the staff person.

In the event that the 8-item FBSI for TTD endpoint is being assessed at a protocol-specified clinic visit that includes an evaluation for progression, questionnaires will be completed before participants discuss disease status with health-care professionals. This will minimize potential bias, and is modeled after the study by Rini et al.[72]

For the post-end of treatment PRO, we propose to administer to participants who return to clinic via paper. In the event that a participant does not return to clinic for a visit after end of treatment, we will collect the PROs via telephone. This will compensate for potential responder bias, wherein healthier patients are more likely to return to clinic and thus, to complete the post-treatment surveys. In collecting PRO data via phone, the survey will be mailed to the participant, who will complete it and then read their responses to the interviewer. This procedure will minimize mode effect, whereby participants report less symptoms burden during phone or in-person

interviews than with written surveys. This approach will approximate the completion of PROs in clinic as closely as possible.

PRO-CTCAE items will be administered on paper along with study PRO measures following procedures for PRO administration as described above. PRO-CTCAE items will be administered prior to clinic visits, or prior to participant's discussion of disease status and treatment side effects with health-care professionals. This is modeled after NCI PRO-CTCAE study procedures employed in other clinical trial validation studies. Clinicians will be instructed to complete clinician-rated treatment toxicities (CTCAE) prior to reviewing PRO-CTCAE ratings. This will minimize the extent to which PRO-CTCAE responses introduce a bias to clinician CTCAE ratings. PRO-CTCAE are currently undergoing validation and thus exploratory in nature, therefore, at this point should not be used to inform clinician CTCAE ratings. Clinicians will be instructed to review PRO-CTCAE items after clinician toxicity ratings have been completed to identify any patient-reported symptoms and toxicities that warrant clinical attention. Supportive care measures to manage treatment toxicities are described in Section 5.5.

5.7 Duration of Therapy

Patients will receive protocol therapy unless:

- Progressive disease by RECIST criteria. See Section 6.1.
- Severe toxicity at discretion of treating physician or unresolved Grade 3 or 4 toxicity.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event, submit forms according to the instructions in the E2112 Forms Packet.
- Patient withdraws consent.
- Exemestane or entinostat/placebo is held for longer than permitted per Section 5.4.
- Patient receives non-protocol therapy, including chemotherapeutic or investigational anti-neoplastic drugs or radiation therapy to only lesion available to monitor response.

5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression even if non-protocol therapy is initiated. Upon discontinuation of treatment, patients will be followed for survival per the standard ECOG-ACRIN follow-up schedule: 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.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for response according to the schedule in Section 7.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[46] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST 1.1.

For purposes of comparability to the phase 3 study of exemestane in advanced breast cancer patients by Chia et al,[4] enrollment in this study will attempt to achieve a target patient population that consists of approximately 80% of patients having measurable disease (with at least 1 measurable lesion at study entry) and approximately 20% of patients having non-measurable disease only.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before randomization.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area may only be considered measurable if there is evidence of post-radiation progression.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before randomization.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI

This RECIST 1.1 guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Diagnostic quality CT is preferred (with oral and IV contrast); any deviations from this must be approved by the Study Chair in advance. See note below regarding contrast allergy.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

NOTE: If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the anatomic location(s) of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist and Protocol Chair/designee to determine if substitution of these other approaches is possible and, if not, the patient may be considered not evaluable from that point forward.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by

ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression. See Section 6.1.4.3.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or

more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Non-CR/Non-PD

Persistence of one or more non-target lesions.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel.

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node

at baseline should only be reported as a new lesion (and therefore progressive disease) if it: a) increases in size to ≥ 15 mm in the short axis, or b) there is new pathological confirmation that it is disease (regardless of size).

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 12 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 guidelines for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks.

6.2 Patient-Reported Outcomes Endpoints

The patient-reported outcomes assessment for this protocol will measure overall HRQL, treatment-related toxicities, breast cancer-specific symptoms, and adherence to protocol therapy.

6.2.1 Overall HRQL

Overall HRQL will be measured using the Functional Assessment of Cancer Therapy – General (FACT-G).[57] The FACT-G includes 27 items that assess physical, functional, social and emotional well-being. We will select individual items *a priori* from the FACT-G to assess nausea, diarrhea, other side effects and overall bother by treatment side effects based on differences in the side effects noted with arm A vs. arm B. This *a priori* approach has also been employed for ATAC[59] and E1Z03[60] data analysis. Use of the FACT-G will allow us to assess for overall HRQL, while performing a relatively broad screen for other, potentially unanticipated symptoms related to the Exemestane + Entinostat combination. All items are rated on a 5-point Likert scale, from 0 to 4.

6.2.2 Treatment-related toxicities

PROs to assess fatigue and GI distress will be administered to measure treatment-related side effects.

6.2.2.1

PROMIS Fatigue: The PROMIS Fatigue is a 7-item short-form. Minimally important difference (MIDs) scores have been empirically derived for the PROMIS Fatigue short form[56] and use of the PROMIS fatigue short form will also allow us to compare this metastatic breast cancer sample to other cancers, non-cancer chronic illnesses, and general population norms. All items are rated on a 6-point Likert scale, from 0 to 5.

6.2.2.2

FAACT: The Functional Assessment of Anorexia/Cachexia Treatment (FAACT) subscale consists of 12 items focused on appetite and nausea[61]. We will use the 12-item FAACT-additional concerns subscale to assess differences in nausea and anorexia. All items are rated on a 5-point Likert scale, from 0 to 4.

6.2.2.3

FACIT-Diarrhea: The 11-item Functional Assessment of Chronic Illness Therapy (FACIT)-Diarrhea subscale will be used to assess diarrhea. All items are rated on a 5-point Likert scale, from 0 to 4.

6.2.2.4 PRO-CTCAE: The NCI PRO-CTCAE library includes 78 items to quantify patient reports of AEs. We have selected 6 common treatment-related symptoms which will be measured using 13 PRO-CTCAE items: decreased appetite, diarrhea, nausea, vomiting, joint aches, and muscle aches. We have selected 2 additional symptoms (bruising, hiccups) that we anticipate to be similar between treatment arms for validation purposes. Hiccups will be measured using 2 PRO-CTCAE items.

6.2.3 Breast cancer-specific symptoms

8-items of the FACT-Breast Symptom Index were assessed by Yost et al among patients with metastatic breast cancer being treated on E1193.[73] The 8-items includes items assessing fatigue, pain (general and pain in specific bodily areas), nausea, shortness of breath, worry about condition worsening, trouble meeting needs of family and content with QOL. We will use six of the eight items that we believe will focus on the most proximal changes to assess TTD (an important secondary endpoint). We will NOT use the following questions: "I worry that my condition will get worse" and "Because of my physical condition, I have trouble meeting the needs of my family" in assessing TTD but will collect these items for additional exploratory work. All items are rated on a 5-point Likert scale, from 0 to 4.

According to Yost et al, using distribution-based criteria, the minimally important differences for the 8-items above ranged from 1.5 to 2.5 points with a median of 2.2 points.[73] Cross-sectional anchor-based criteria yielded similar estimates, with score differences between adjacent categories of performance status ratings of 2.8 and 3.2 points.

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6.2.4 Adherence

The ECOG-ACRIN Medication Adherence Scale Modified from the Morisky Index will be administered to understand the reasons for non-adherence to protocol therapy. There will be one Medication Adherence Scaleform completed for each agent (entinostat /placebo and exemestane). The Medication Adherence Scale measures the likelihood that a patient will take prescribed medications. The Medication Adherence Scale has been validated against medication pill count methods of assessing compliance and used in a variety of settings. It is an 8-item measure with a Likert response scale[69]. The minimal detectable change has been defined as 1.98 points (Muntner).

Patient's adherence to protocol therapy will be quantified using the pill count (entinostat/placebo) and diary (exemestane) methods. Patients will be instructed to bring their medication bottles and diaries to clinic visits. Clinic or pharmacy staff will count the number of remaining entinostat/placebo pills or note the number of exemestane pills as taken on the pill diary, and will calculate the number of pills taken using a treatment form.[69,70]

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7. Study Parameters

1. Baseline evaluations within 4 weeks prior to randomization unless specified.
2. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done ≤ 4 weeks prior to randomization.
3. Prestudy CBC (with differential and platelet count) and all required prestudy chemistries must be done ≤ 4 weeks before randomization, as outlined in Section 3.

	Baseline	Cycle 1 Day 15	End of Cycles 1 and 2	End of Cycle 3	End of each cycle (cycle 3-forward) [10]	Every 3 cycles (cycle 3, 6 etc)	At discontinuation of treatment[10]	Post treatment[11]
History, Physical Exam, ECOG PS, Vital signs, Height, Weight	X[1]		X	X	X		X	X
Symptom/Toxicity assessments	X[1]		X	X	X		X	
CBC[2]	X	X	X	X	X		X	
Chemistries[3]	X	X	X	X		X	X	
Serum estradiol[4]	X							
ECG	X							
Bone scan[5]	X			X		X		X[12]
Tumor assessment by CT or MRI[6]	X			X		X	X	X[12]
Serum or Urine Pregnancy Test[20]	X							
PRO Assessments[7]	X			X		X	X	X
PRO Assessment: FBSI[8]	X		X	X	X			
PRO-CTCAE[16]	X		X	X	X		X	
Exemestane[18]		X (daily)						
Entinostat/placebo[18]		X (weekly)						
LHRH agonist (pre/perimenopausal female and all male participants only)[19]		X (monthly)						
Pill Count/Diary[9]			X	X	X	X	X	
Concomitant Medications	X		X	X	X		X	X[17]
Biological Sample Submissions [See Sections 11 and 12]								
Whole blood, one (1) 8mL CPT citrate tube[13,14,15]	X	X						

	Baseline	Cycle 1 Day 15	End of Cycles 1 and 2	End of Cycle 3	End of each cycle (cycle 3-forward) [10]	Every 3 cycles (cycle 3, 6 etc)	At discontinuation of treatment[10]	Post treatment[11]
FFPE tumor tissue (primary & metastatic)[13,14]	X							
Whole blood, one (1) 8mL ACD yellow top[13,14,15]	X							

	Cycle 1, Day 1 [2 samples drawn at least 2 hours apart, 2-5 hours after dosing]	Cycle 1, Day 15 [1 sample drawn 1 hour after dosing]	Within 72 hours prior to the start of Cycle 2
Population Pharmacokinetics [OPTIONAL PER PATIENT CONSENT]: Plasma, one (1) 6mL K2EDTA lavender top tube per time point [14, 21]	X	X	X

1. Physical exam, ECOG PS, vital signs, and symptom/toxicity assessment must be performed ≤ 2 weeks before randomization.
   NOTE: Height measurements may have been taken > 4 weeks from baseline.
2. CBCs, which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done ≤ 72 hours prior to Cycle 2 and every cycle thereafter. Baseline CBCs do not need to be repeated prior to Cycle 1 Day 1.
3. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, magnesium, phosphorus, potassium, total protein, SGOT (AST), SGPT (ALT), sodium must be done ≤ 72 hours prior to Cycles 2-4 and every 3 cycles thereafter. Baseline chemistries do not need to be repeated prior to Cycle 1 Day 1.
4. Only required for women age < 55 years and with intact ovaries as described in Section 3.1.
5. Baseline bone scan required in all patients.
   NOTE: If bone scan done ≤ 6 weeks prior to registration showed no evidence suggesting bone metastases and no clinical indication of skeletal pain or other evidence suggesting bone metastases, a repeat baseline bone scan is not required.
6. CT of the chest and CT or MRI of abdomen/pelvis are required at baseline. Subsequent imaging for the subject should be conducted on the same scanner using the same acquisition and reconstruction parameters. Those tests required to follow known site(s) of disease must be repeated at the end of 12 weeks from randomization and then every 12 weeks (3 cycles) during treatment and according to the follow up schedule if off treatment, until first progression of disease. NOTE: All tumor assessment should be scheduled based on calendar time (every 12 weeks) and not cycle length. Image thickness (reconstructed) should be 5 mm or less for CT and MRI, and contiguous slices are preferred to those with intervening gaps. Consistent use of contrast agent, dose, and injection parameters (including time of image collection after contrast) are recommended. See Section 10 for additional details and submission instructions.
   NOTE: If the CT of the chest and CT or MRI of abdomen/pelvis done ≤ 6 weeks prior to randomization showed no evidence of disease in the area(s) and no clinical indication suggesting new metastases, full re-staging including all areas is not required; however, ensure that disease is evaluable per RECIST 1.1 requirements (Section 6).
7. Patient-Reported Outcomes to be assessed at the following time (see Section 5.6 for detailed instructions):

PROMIS Fatigue, FAACT, FACIT-D: Baseline (before Cycle 1 Day 1), end of Cycle 3, end of Cycle 6, end of Cycle 12, at end of protocol treatment, including treatment discontinuation for any reason (i.e., toxicity, progression, completion of protocol therapy) and 4 weeks after end of protocol treatment, including treatment discontinuation for any reason (i.e., toxicity, progression, completion of protocol therapy).

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The ECOG-ACRIN Medication Adherence Scale Modified from the Morisky Index: end of Cycle 3, end of Cycle 6, end of Cycle 12, and at end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy). Please note there will be one Medication Adherence Scale form completed for each agent (entinostat/placebo and exemestane).

FACT-G: Baseline (before Cycle 1 Day 1), end of Cycle 3, end of Cycle 6, end of Cycle 12, and at end of protocol treatment, including treatment discontinuation for any reason (i.e. toxicity, progression, completion of protocol therapy).

8. The FBSI will be administered at baseline, end of each cycle for the first six months after randomization, and then at the end of Cycles 8, 10, and 12. After Cycle 12, the FBSI will be administered on the same schedule as Tumor assessments until disease progression.
9. Pill counts for entinostat/placebo and diaries for exemestane should be collected at the end of each cycle until discontinuation of study treatment.
10. Repeat any test not done ≤ the prior 28 days.
11. Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, and annually if patient is >5 years from study entry. No specific requirements if patient is more than 10 years from study entry.
12. Tumor assessments are to be done up to (and including) the assessment which shows first progression of disease. If patient discontinues treatment due to reasons other than disease progression, concomitant medication and tumor assessments should be performed until disease progression on the following schedule: Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, and annually if patient is >5 years from study entry. No specific requirements if patient is more than 10 years from study entry.
13. Submit blood samples to the Trepel Laboratory from patients who answer “Yes” to “I agree to participate in the laboratory research studies that are being done as part of this clinical trial.” Baseline blood samples should be collected after randomization, prior to start of treatment on Day 1 (preferably within 2 days of Day 1). Day 15 blood samples should be collected prior to entinostat/placebo dose on that day.

    NOTE: Do not start treatment on Fridays as the baseline and day 15 blood collections cannot be shipped on Fridays.

    Submit optional blood and tissue samples for future research to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) from patients who answer “Yes” to “I agree to provide additional specimens for research.”

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14. All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). The exact date and time of entinostat/placebo administration and of PK plasma sample collection must be entered into the STS.

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15. Kits are available for blood collection and shipment. Kit order instructions are provided in Appendix VI. Kit orders will, on average, be delivered within 3 business days from time of order placement.
16. PRO-CTCAE items will be administered at Baseline, end of each Cycle, and at end of protocol treatment, including treatment discontinuation following the same schedule as trial Symptom/Toxicity assessments.
17. Concomitant Medications will be collected up to 90 days from the end of study treatment.
18. A complete cycle of treatment is defined as 28 days (± 3 days) of once daily continuous treatment of exemestane in combination with entinostat/placebo. A new cycle start is defined as the first planned date of entinostat/placebo for the cycle.

19. Pre/perimenopausal females must have commenced treatment with LHRH agonist at least 4 weeks prior to randomization. If patients have received alternative LHRHR agonist prior to study entry, they must switch to goserelin for the duration of the trial.
20. For all women of child bearing potential, must be done ≤ 2 weeks prior to randomization.

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21. Kits are being provided for the collection and shipment of the plasma samples for the population pharmacokinetic studies. Process and submit the plasma samples to Covance Central Laboratory Services. See Section 11.4 for instructions. To obtain starter kits and the Site Laboratory Instruction Manual please Email or Fax Appendix IX E2112 Covance Site Information/Initial Kit Order Form to Syndax. Please note Covance requires ten (10) days to process the form and ship the initial kits.

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8. Drug Formulation and Procurement

Agent Accountability and Availability

Entinostat and matching Placebo (IND# [redacted]) will be provided free of charge by Syndax Pharmaceuticals and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

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Entinostat is supplied by the Syndax Pharmaceuticals, Inc. and distributed by DCTD, NCI as 1 mg (pink to light red, in bottles of 15 tablets), or 5 mg (yellow, in bottles of 5 tablet) film-coated tablets (round-biconvex). Each tablet also contains mannitol, sodium starch glycolate, hydroxypropyl cellulose, potassium bicarbonate, and magnesium stearate. The film coating consists of hypromellose, talc, titanium dioxide, and ferric oxide pigments (red and yellow) as colorants.

Matching placebo for entinostat has the same appearance as the corresponding active tablets and contains the same inactive ingredients and film coating.

NOTE: Under no circumstances can commercially supplied Entinostat be used or substituted for the NCI-supplied Entinostat/Placebo.

Commercial exemestane will be provided free of charge by Syndax Pharmaceuticals. In the United States it will be distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). Outside of the United States, distribution will be arranged by Syndax Pharmaceuticals.

Each tablet is round, biconvex, and off-white to slightly gray. Exemestane is packaged in HDPE bottles with a child-resistant screw cap, 30 tablets per bottle. Exemestane tablets contains the following inactive ingredients: mannitol, crospovidone, polysorbate 80, hypromellose, colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, simethicone, polyethylene glycol 6000, sucrose, magnesium carbonate, titanium dioxide, methylparaben, and polyvinyl alcohol. [Pfizer, Package Insert]

NCI Supplied Agents – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time. You may also contact PMB via e-mail at PMBAfterHours@mail.nih.gov.

Drug Orders, Transfers, Returns, Accountability and Emergency Unblinding

No blinded starter supplies will be available for this study.

Once a patient has been randomized, blinded, patient specific supplies will be sent automatically to the registering investigator and should arrive within 10 days. Study drug requests are transmitted by the ECOG-ACRIN Operations Office – Boston the day the patient is randomized and will be processed by PMB the next business day and shipped the following business day. Shipments within the United States are sent by FedEx ground (generally three to five day delivery) and shipments to Canada are sent by FedEx (generally one to two day delivery) Thus, if a patient is registered on Monday, ECOG-ACRIN would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States

sites could expect to receive their order approximately Wednesday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the ECOG-ACRIN Operations Office – Boston at the time the patient is randomized.

The initial request will be for 3 bottles of Entinostat or matching placebo. Ten (10) weeks after the initial electronic request [i.e., two (2) weeks before needed], sites may reorder an additional 3 bottles of Entinostat or matching placebo by using the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an “active” account status and a “current” password. The assigned patient ID number (e.g., "999999") and the patient initials (e.g., "L,FM") must be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g., "999999") being ordered. All drug orders will be shipped directly to the physician responsible for treating the patient.

Each blinded, patient -specific bottle will be labeled with:

- The protocol number (i.e., “E2112”)
- The bottle number (i.e., “Bottle 1 of 3, 2 of 3, 3 of 3”)
- The number of tablets (i.e., “5 tablets” or “15 tablets”)
- The patient ID number (e.g.,"44444", where “44444” represents a unique patient identifier assigned at randomization)
- The patient initials (i.e., first initial, last initial [e.g., "FL"])
- The agent identification (i.e., “Entinostat 5 mg or placebo”)
- A blank line for the pharmacist to enter the patient’s name
- Administration instructions
- Storage instructions (i.e., Store at 25°C (77°F), excursions permitted from 15°C to 30° C (59-86 °F))
- Emergency contact instructions
- A Julian date

The Julian date indicates the day the bottles were labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2013 = 13, 2014 = 14) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2013 would have a Julian date of ‘13001’ and a bottle labeled and shipped on December 31, 2013 would have a Julian date of ‘13365’. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles shipped on or before that date thus eliminating any chance of breaking the blind.

Sites within the United States

No exemestane starter supplies will be available for this study.

Once a patient has been randomized, patient specific supplies will be sent automatically to the registering investigator and should arrive within 10 days. Exemestane requests are transmitted by the ECOG-ACRIN Operations Office – Boston the day the patient is randomized and will be processed by PMB the next business day and shipped the following business day. Shipments within the United States are sent by FedEx ground (generally three to five day delivery). Thus, if a patient is registered on Monday, ECOG-

ACRIN would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States sites could expect to receive their order approximately Wednesday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the ECOG-ACRIN Operations Office – Boston at the time the patient is randomized.

The initial request will be for 3 bottles of Exemestane. Ten (10) weeks after the initial electronic request [i.e., two (2) weeks before needed], sites may reorder an additional 3 bottles of Exemestane by using the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. The assigned patient ID number (e.g., "999999") and the patient initials (e.g., "L,FM") must be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g., "999999") being ordered. All drug orders will be shipped directly to the physician responsible for treating the patient.

Each open label, patient-specific bottle will be labeled with:

- The protocol number (i.e., "E2112")
- The bottle number (i.e., "Bottle 1 of 3, 2 of 3, 3 of 3")
- The number of tablets (i.e., "30 tablets")
- The patient ID number (e.g.,"44444", where "44444" represents a unique patient identifier assigned at randomization)
- The patient initials (i.e., first initial, last initial [e.g., "FL"])
- The agent identification (i.e., "Exemestane 25 mg")
- A blank line for the pharmacist to enter the patient's name
- Administration instructions
- Storage instructions (i.e., Store at 25°C (77°F), excursions permitted from 15°C to 30° C (59-86 °F))
- Emergency contact instructions
- A Julian date

The Julian date indicates the day the bottles were labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2016 = 16, 2017 = 17) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2016 would have a Julian date of '16001' and a bottle labeled and shipped on December 31, 2016 would have a Julian date of '16365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles shipped on or before that date.

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Special Ordering Procedures for Patients Requiring a Dose Reduction: If the patient is **dose reduced** from entinostat/placebo **5 mg** once a week TO entinostat/placebo **3 mg** once a week (see Section 5.4.1), a request must be placed by using the PMB Online Agent Order Processing (OAOP) application to obtain the entinostat 1 mg and matched placebo tablets.

Drug Transfers: Patient specific study drug supplies MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical

site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "44444"') and the patient initials (e.g., "FL") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "E2112").

Drug Returns: Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "44444") and the patient initials (e.g., "FL") should be entered in the "Lot Number" field. A separate line item is required for each patient ID number (e.g., "44444") that is being returned. Bottles with remaining tablets should be documented in the patient-specific NCI Investigational Agent Accountability Record (i.e., logged is as "returned by patient" and logged out as "destroyed on site") and destroyed on site in accordance with institutional policy.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record for Oral Agents available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "44444") on this protocol.

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Emergency Unblinding

The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an emergency or adverse event that may result in the need to unblind the patient.

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. Roisin Connolly, at (410) 614-9217, or email: rconnol2@jhmi.edu first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operations Office – Boston drug team at (857) 504-2900 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. Remember, AnswerConnect should only be contacted outside of normal business hours and only in the event of an emergency. The ECOG-ACRIN Operations Office – Boston or AnswerConnect will require the protocol number (i.e., "E2112"), the patient ID number (e.g., "44444"), and the patient initials (e.g., "FL") to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment.

NCI CTEP should also be notified of a request for unblinding

8.1 Entinostat/Placebo (NSC 706995) (IND# [redacted])

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8.1.1 Other Names

MS-27-275, MS-275, SNDX-275

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8.1.2 Chemical Name

3-Pyridylmethyl N-{4-[(2-aminophenyl)carbamoyl]benzyl}carbamate

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8.1.3 Classification

Histone deacetylase inhibitor (HDACi)

8.1.4 Molecular Formula

$C_{21}H_{20}N_4O_3$ M.W.: 376.41

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8.1.5 Mode of Action

Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones. Entinostat inhibits histone deacetylases, changes chromatin configuration, and induces differentiation and apoptosis of cancer cells through an epigenetic mechanism.

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8.1.6 Storage and Stability

Store the bottles at controlled room temperature (15-25oC), and protect from light. Entinostat is not to be exposed to extremes of temperature (greater than 30ºC or less than 5ºC). Shelf life stability studies of the intact bottles are on-going.

8.1.7 Dose Specifics

Entinostat/Placebo 5mg once every week (days 1, 8, 15, and 22) of a 28 day cycle. See Section 5.4 for information regarding dose reductions. Entinostat/Placebo 1mg tablets are also available in case of dose reduction.

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8.1.8 Route of Administration

Oral, on an empty stomach, at least 1 hour before and 2 hours after a meal. Entinostat tablets should not be split, crushed, or chewed.

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8.1.9 Incompatibilities

Metabolism: Data from in vitro metabolism experiments in human tissues demonstrated that entinostat is not metabolized by CYP enzymes (Acharya 2006), but UGT 1A4 did metabolize entinostat to its M2 glucuronide metabolite. No metabolites could be detected after incubation of entinostat in human liver microsomes (Acharya 2006). While inhibition of CYP enzymes 2B6 and 3A4 was seen, the data show that the degree of the inhibition makes it unlikely that any in vivo systemic interactions would occur. Intestinal CYP 3A4 may be inhibited by entinostat. However, entinostat did not inhibit any UGT enzymes tested. Entinostat was found to induce CYP 1A2, CYP 2C6, and CYP 2B8 as well as UGT 1A4. Finally, entinostat was found to be a substrate for P-gp and BCRP transporters, but did not inhibit either of these transport proteins.

8.1.10 Availability

See Section 8.0 above for complete details.

8.1.11 Side Effects

See Section 5.3 for CAEPR.

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8.1.12 Nursing/Patient Implications

Entinostat should be taken on an empty stomach, at least 1 hour before and 2 hours after a meal/snack. If the patient's dose requires more than one tablet, the tablets should be taken one at a time. Delay administration of H2-antagonists, antacids, or proton pump inhibitors, or other drugs that lower acidity for at least 2 hours after dosing entinostat.

Entinostat may cause fatigue or malaise; advise patient to exercise caution while driving a vehicle or operating machinery.

Administration of entinostat is contraindicated in patients with a history of allergy to entinostat or other medications that have a benzamide structure (eg, tiapride, remoxipride, clebropride).

Careful monitoring of patients for signs of infection or reactivation of past infections is recommended, as reactivation of infection has been reported in patients treated with entinostat, in some cases without evidence of neutropenia. The clinical significance of this finding and the potential association with entinostat is unknown.

Entinostat must not be used during pregnancy or while breast-feeding. Women and men participating in entinostat clinical studies must agree to use acceptable contraceptive methods, as indicated in the clinical study protocol, during treatment and for 3 months thereafter.

8.2 Exemestane

NOTE: Please refer to package insert for complete prescribing and toxicity information.

8.2.1 Other names

Aromasin

8.2.2 Chemical name

6-methylenandrosta-1,4-diene-3,17-dione

8.2.3 Classification

Exemestane is a steroidal aromatase inhibitor (inhibitor of estrogen synthesis).

8.2.4 Molecular Formula

$C_{20}H_{24}O_2$

8.2.5 Mode of Action

Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme, and is processed to an intermediate that binds irreversibly to the active site of the enzyme causing its inactivation, an effect also known as "suicide inhibition". Exemestane significantly lowers circulating estrogen concentrations in

postmenopausal women, but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone. Exemestane has no effect on other enzymes involved in the steroidogenic pathway up to a concentration at least 600 times higher than that inhibiting the aromatase enzyme. [Pfizer, Package Insert].

8.2.6 Storage and Stability

Store at 25°C (77ºF); excursions permitted to 15°–30°C (59°–86°F). Exemestane tablets should remain in their original container.

8.2.7 Dose Specifics

Exemestane 25 mg once daily after a meal, days 1-28 of each cycle.

8.2.8 Route of Administration

Oral

8.2.9 Incompatibilities

CYP3A4 inducers: Caution, may significantly decrease exposure to exemestane. CYP 3A4 inhibitors: Significant pharmacokinetic interactions appear unlikely. [Pfizer, Package Insert]

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8.2.10 Availability

Sites within the United States should refer to Section 8.0 above for complete details. Information for sites outside of the United States will be included once available.

8.2.11 Nursing/Patient Care Implications

Exemestane should be taken with food.

8.2.12 Adverse Effects

Advanced breast cancer: Most common adverse events were mild to moderate and included hot flushes (13% vs. 5%), nausea (9% vs. 5%),fatigue (8% vs. 10%), increased sweating (4% vs. 8%), and increased appetite (3% vs. 6%) for exemestane and megestrol acetate,respectively. [Pfizer, Package Insert] Please see the Exemestane Package Insert for more details on the known precautions, warnings, and adverse reactions.

8.2.13 References

Pfizer Package Insert

(http://labeling.pfizer.com/showlabeling.aspx?id=523)

8.3 Goserelin

NOTE: Please refer to package insert for complete prescribing and toxicity information. This will be used in pre/perimenopausal female and all male participants only in this clinical trial.

8.3.1 Other names

Zoladex

8.3.2 Chemical name

Pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu^t)-Leu-Arg-Pro-Azgly-NH_2 acetate

8.3.3 Classification

Goserelin is a GnRH agonist.

8.3.4 Molecular Formula

$C_{59}H_{84}N_{18}O_{14}$

8.3.5 Mode of Action

Goserelin is a synthetic decapeptide analogue of GnRH. It acts as an inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation. In animal and *in vitro* studies, administration of goserelin resulted in the regression or inhibition of growth of the hormonally sensitive dimethylbenzanthracene (DMBA)-induced rat mammary tumor and Dunning R3327 prostate tumor. [AstraZeneca, Package Insert].

8.3.6 Storage and Stability

Goserelin will be handled per routine pharmaceutical standards.

8.3.7 Dose Specifics

Goserelin is available commercially as 3.6 mg doses in disposable syringe devices.

8.3.8 Preparation

Not applicable, dose is ready for administration.

8.3.9 Route of Administration

Subcutaneous injection

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Rev. Add7

8.3.10 Availability

Goserelin is commercially available and will be prescribed by the treating physician and covered by the patients insurance.

8.3.11 Adverse Effects

Most common adverse events occurring in >10% of men: hot flashes, sexual dysfunction, decreased erections and lower urinary tract symptoms.

8.3.12 References

AstraZeneca Package Insert

(http://www1.astrazeneca-us.com/pi/zoladex3_6.pdf)

9. Statistical Considerations

9.1 Study Objectives

The primary objective of this randomized, placebo-controlled, double-blinded, phase III study is to determine whether Exemestane + Entinostat (Arm A) improves progression-free survival (PFS) and/or overall survival (OS) compared to the Exemestane + Placebo (Arm B) in patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer (MBC) who have experienced disease progression after non-steroidal AI use in the adjuvant setting (within 12 months prior to enrollment) or in the metastatic setting.

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Both PFS and OS are primary endpoints, and the study is designed to show an improvement in either PFS or OS. PFS is defined to be time from randomization to the earliest of documented disease progression as defined by the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria, new primary breast cancer, or death without progression. Disease assessment will continue until disease progression, even after non-protocol anti-cancer therapy is started. Cases with incomplete follow up or without adequate disease evaluations will be censored at the date last documented to be free of progression, regardless of whether non-protocol anti-cancer therapy is started or not. Tumor response and progression will be defined by central review, including time point-by-time point radiologist reader review at the ACR Imaging Core Lab for patients with radiographically measurable/evaluable disease, and/or an independent review committee for patients with measurable/non-measurable disease that is not radiographically evident (i.e., skin lesions). OS is defined to be time from randomization to death from any cause, censoring cases who had not died at the date last known alive.

This study is aimed to give adequate power for both PFS and OS comparisons. The one-sided type I error of 0.025 is split between two hypotheses tests to control the overall type I error rate for the whole trial. Specifically, type I error rate is 0.001 for PFS test and 0.024 for OS test.

9.2 Study Design

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Patients with histologic confirmation of invasive adenocarcinoma of the breast will be randomized according to the permuted block algorithm with a 1:1 randomization ratio to arms A and B. Stratification factors include:

- Setting in which patient developed resistance to prior non steroidal AI treatment (adjuvant vs. metastatic)
- Geographic region (USA vs. other)
- Visceral disease (yes vs. no)
- Prior fulvestrant use (yes vs. no)

NOTE: Visceral disease is defined as lung and/or liver involvement.

Taking into consideration the accrual rates of the BOLERO-2 study (40 patients/month, 700 patients over 18 months with 24 international sites), the ENCORE 301 study (5 patients/month, 130 patients over 2 years at 38 sites US and international) and the CONFIRM study (24 patients/month at 128 sites), all of which have been conducted in the AI refractory setting, and the 1st line SWOG

S0226 study (10 patients/month,700 patients over 6 years), we anticipate an accrual rate of approximately 15 patients per month in our study.

Enrollment of 600 patients will be required to provide adequate power for the OS endpoint (see Section 9.2.2). The first 360 patients will be used for the primary evaluation of PFS (see Section 9.2.1), objective response rate (ORR), toxicity, time to treatment deterioration and patient-reported outcomes. If the PFS analysis is positive, the data for first 360 patients would be used for a submission to the FDA. At the time of final analysis for the OS endpoint, secondary analyses of PFS, objective response and toxicity will be conducted in all 600 patients, along with the primary analyses for the pharmacodynamic acetylation marker data and adherence to protocol therapy data. Imaging studies for all 600 participants will be collected and archived at the ACR Imaging Core Laboratory.

For purposes of comparability to the phase 3 study of exemestane in advanced breast cancer patients by Chia et al.,[4] enrollment in this study will attempt to achieve a target patient population that consists of approximately 80% of patients having measurable disease (with at least 1 measurable lesion at baseline assessment and identification of up to 5 total target lesions [maximum of 2 lesions per organ] and 5 total non-target lesions) and approximately 20% of patients having non-measurable disease only.

No early stopping for efficacy based on PFS will be considered in the study so that there will be sufficient death events for OS comparison in the final analysis. Hence, for PFS, the study will only be monitored for early stopping for futility. Interim analyses of OS will start at about 30 months (24 months of accrual + 6 months of data collection and cleaning) after study activation. Details about interim analysis for PFS and OS are described in Section 9.2.3.

9.2.1 Sample size and accrual for PFS

For patients with HR-positive, HER2-negative MBC, the median PFS on the Exemestane + Placebo arm will be about 4.1 months in AI refractory setting based on BOLERO-2 central assessment results[14]. The null hypothesis is hazard ratio (HR)=1 for comparison of PFS in the two treatment arms, and the alternative hypothesis is HR=0.58 for arms A/B. The primary analysis of PFS will be performed using a stratified log-rank test, with one-sided type I error of 0.1%, stratifying on randomization stratification factors. The primary comparisons will be intention-to-treat analysis (defining groups by assigned treatment regardless of treatment received) among all refractory patients regardless of eligibility status. A total accrual of 360 patients and total information of 247 PFS failures is planned, to give 88.5% power to detect a 42% reduction in the PFS failure hazard rate with no interim efficacy analysis. This difference corresponds to an improvement in median PFS from 4.1 to 7.1 months (i.e., 3.0 months of benefit), under the assumption of exponential distribution of PFS. Assuming an accrual rate of 15 patients per month, about 24 months of accrual will be needed without additional follow up to reach the expected number of PFS events.

The data for the primary analysis for the PFS comparison is expected to be available at about 30 months (24 months of accrual + 6 months of data collection and cleaning) after study activation, when the first

interim analysis for OS will be conducted. When to release the PFS data, however, depends on the result for the first interim analysis of OS. If the OS interim analysis is positive (ie, crossing the efficacy boundary listed in Table 9.2, see Section 9.2.3) at the final PFS analysis time, the whole study will be stopped early for efficacy and the results for both PFS and OS will be released to Syndax and the public. If OS does not cross the efficacy boundary, in order to minimize the potential effect of releasing PFS result on the OS endpoint, the results of primary analysis for PFS will be held by the ECOG-ACRIN study statistician and the ECOG-ACRIN Data Safety Monitoring Committee (DSMC) members and not released to Syndax, CTEP, the principal investigators, anyone at ECOG-ACRIN involved in the day-to-day running of the trial or publically until all 600 patients required for the OS endpoint have been accrued for the whole trial (expected to occur at about 40 months after study activation, see Section 9.2.2). In this case, the primary analysis of PFS will use follow-up through the calendar time of the 247th PFS event among the first 360 patients enrolled, even though more follow-up is expected to be available at that time (ie, completion of accrual). After completion of overall study accrual, the PFS results will be released to Syndax and may be released publically if allowed by the ECOG-ACRIN DSMC.

9.2.2 Sample size and accrual for OS

Taking into consideration the median OS in the ENCORE 301 trial (20 months in the Exemestane + Placebo arm and 28 months in the entinostat arm) and the CONFIRM 2 trial (25.1 months in the high dose fulvestrant arm and 22.8 months in the low dose arm), it is expected that the median OS for patients on the Exemestane + Placebo arm will be about 22 months in the AI refractory patients. The null hypothesis for the OS comparison is HR=1, and the alternative hypothesis is HR=0.75 for arms A/B. The primary analysis of OS will be performed using a stratified log-rank test, with one-sided type I error of 2.4%, stratifying on randomization stratification factors. The primary comparisons will be intention-to-treat analysis among all refractory patients regardless of eligibility status. A total accrual of 600 patients and total information of 410 OS failures is planned to give 80% power to detect a 25% reduction in the OS failure hazard rate with interim analysis plan described in Section 9.2.3 (Table 9.2).This difference corresponds to an improvement in median OS from 22 to 29.3 months (i.e., 7.3 months of benefit), under the assumption of exponential distribution of OS. Assuming an accrual rate of 15 patients per month, about 40 months of accrual will be needed with additional 24 months of follow up to reach the expected number of OS events. The final analysis for the OS comparison is expected to occur at about 70 months (40 months of accrual + 24 months of follow up + 6 months of data collection and cleaning) after study activation.

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9.2.3 Interim analysis

Interim futility analysis for PFS tests

As mentioned above, in order to ensure sufficient sample size for OS comparison, no early stopping for efficacy based on PFS is considered in the study, and the study will only be monitored for early stopping in favor of the null hypothesis for PFS tests (i.e., futility) by the ECOG-ACRIN DSMC via its semi-annual DSMC meetings.

We adopt the general inefficacy interim monitoring method (described in the paper by Freidlin, Korn and Gray, Clinical Trials, 2010, which is called Linear 20% Inefficacy Boundary method)[49] for futility monitoring in the study. This method generally results in less than 1% loss of power, there will be no sample size increase to account for the futility monitoring in the study.

Before interim analysis using the Linear 20% Inefficacy Boundary method, we will first perform a “harm” look at 25% information (about 9.5 months after study activation), using the rule that stops the trial for harm if the one-sided lower 95% unadjusted confidence bound for the observed hazard ratio (HR) is above 1 (i.e., HR > 1.52). This is the same as one-sided 0.05 level test of the null hypothesis in the direction of harm. If the trial does not stop at the “harm” look, the study will be monitored by formal interim analysis via Linear 20% Inefficacy Boundary method as described below. If the study stops at the “harm” look, the whole trial stops for lack of efficacy.

The one-sided type I error is 0.1% and the power is 88.5% for the PFS test, the first interim analysis could take place at as early as 21% information time per the Linear 20% Inefficacy Boundary method, at which the observed hazard ratio > 1 would imply that the two-sided 95% confidence interval for log hazard ratio would not contain the log(0.58). Since the “harm” look will take place at 25% information time, and a 10% increment in information time is suggested for interim futility analysis by the method, the first interim analysis will be performed at the first DSMC meeting when at least 35% of the total information has been reported. Since 247 PFS events are required as the total information under the alternative hypothesis, the first interim analysis for futility is estimated to take place after 87 PFS events have occurred, which corresponds to 11.5 months after activation of the study in calendar time, under the accrual and failure rate assumptions mentioned above. Interim analysis will be performed for each subsequent DSMC meeting until either the criteria for early stopping (described below) are met or the total planned number of PFS events has been reported. In total, this design is expected to incorporate 2 interim analyses and one final analysis for PFS comparisons. The cut-off values for HRs and lower two-sided 95% confidence interval bound (unadjusted) are given in Table 9.1. If at any time point, the observed hazard ratio (arms A/B) is larger than the cut off values, the trial will stop in refractory setting for lack of efficacy.

In each interim analysis, the observed hazard ratio will be calculated using stratified Cox proportional-hazards model, stratified on randomization stratification factors, without any other covariates.

Because interim analyses are timed to coincide with the semi-annual ECOG-ACRIN DSMC meetings, the boundaries for HRs may change depending on the number of observed PFS events at that time. Also, because of delays in data submission and processing, it is likely that actual analysis times will be 6-12 months later.

Table 9.1: Inefficacy stopping boundaries for PFS endpoint (Alternative HR=0.58, Full information=247 PFS events, Type I error=0.1%, Power=88.5%)

Repeated interim futility analysis	1	2
Information time	35%	65%
Calendar time (months after study activation)	11.5	17.5
Hazard ratio (stopping boundaries)	0.981	0.941
Lower two-sided 95% confidence bound (unadjusted, Z=1.96 at all interim looks)	0.643	0.691

Interim analysis for OS tests

Regardless of PFS results, the first interim analysis of OS will be performed at the final PFS analysis time (expected to be 24 months after study activation-see Section 9.2.1). Interim analysis for OS will then be performed biannually until either the criteria for early stopping (described below) are met or the total planned number of OS events has been reported. Of note, interim analyses will be skipped if the change in the information since the previous interim analysis is less than 10%. In addition, when the information time reaches 90% or more, interim analysis will not be conducted, and the final analysis of OS will be performed when full information is reached. These interim analyses will be monitored by ECOG-ACRIN DSMC. Table 9.2 shows the operating characteristics for OS endpoint.

At each interim analysis, the stratified log rank test statistic will be computed. To preserve the overall one-sided type I error rate at 2.4% for the OS endpoint, critical values for rejecting null hypothesis at the interim analyses will be determined using a truncated version of the Lan-DeMets spending function[50] corresponding to the O'Brien-Fleming boundary (1979)[51]. If the boundary is crossed at an interim analysis or at the final analysis, then the null hypothesis will be rejected, and the Exemestane + Entinostat therapy is superior to the exemestane monotherapy in terms of OS. If the criteria for rejecting the null hypothesis are not met, then it will be concluded that this trial fails to show superiority of Exemestane + Entinostat therapy over the exemestane monotherapy on OS.

Because interim analyses are timed to coincide with the ECOG-ACRIN DSMC meetings, these boundaries may change depending on the number of observed OS events at that time. Also, because of

delays in data submission and processing, it is likely that actual analysis times will be 6-12 months later.

Table 9.2: Operating Characteristics for OS Endpoint

Repeated Analysis	Real time (months)	Information time	Failures under alternative hypothesis	Nominal significance (one-sided)	Upper boundary
1	24	0.24	101	0.00048	3.3020
2	30	0.36	149	0.00048	3.3020
3	36	0.49	203	0.00068	3.2036
4	42	0.64	261	0.00400	2.6518
5	48	0.76	313	0.00805	2.4065
6	54	0.87	355	0.01193	2.2593
Final	64	1.00	410	0.01872	2.0808

If PFS test is negative in the primary analysis, this study will also be monitored for early stopping in favor of the null hypothesis (i.e., futility) for the OS test using the Jennison-Turnbull repeated confidence interval (RCI) method. At each interim OS analysis, the RCI on the observed hazard ratio will be computed using the critical values from the above error spending rate function. If the RCI does not include the alternative hazard ratio of 1.33 (arms B/A), then the OS comparison would be stopped early for lack of benefit. The observed hazard ratio will be calculated using stratified Cox proportional-hazards model, stratified on randomization stratification factors, without any other covariates. If the PFS test is positive in the primary analysis, no interim futility analysis for OS will be conducted.

As mentioned in Section 9.2.1, if the first interim analysis of OS is positive, the interim OS data will be released to Syndax and the public and the study will be stopped early for efficacy. If the first interim analysis of OS does not cross the efficacy boundary, then at the time study accrual is completed, if (1) the primary PFS test is positive at the 0.001 level, and (2) the estimated PFS hazard ratio for Exemestane + Entinostat vs. Exemestane + Placebo is < 0.675, the interim OS data will also be confidentially released to Syndax. The DSMC will also be asked to allow use of interim OS data from the first 360 patients enrolled in an application to the FDA, with the understanding that the data not be made public unless required as part of the FDA review process.

Interim analysis for toxicity

For safety considerations, an interim analysis for toxicity data will be conducted when 30 patients have been assigned to arm A and have received at least one dose (expected to occur at about 4 months after study activation). If more than 6 Grade 4 non-hematologic toxicity

events (at a rate of 20%) are observed in the first 30 patients in this arm, the study will be terminated. Table 9.3 shows the probability that the trial will be terminated early due to excessive toxicity. This probability is provided under different assumptions about the true proportion of Grade 4 non-hematologic toxicity in this arm.

Table 9.3: Probability that the trial will be terminated early due to excessive toxicity on arm A

True proportion of the toxicity	0.10	0.15	0.20	0.25	0.30	0.35
Probability of early termination	0.026	0.15	0.39	0.65	0.84	0.94

9.3 Statistical Consideration for Objective Response, Toxicity and Time to Treatment Deterioration

9.3.1 Objective response

Objective response in the two arms will be evaluated by comparing objective response rate (ORR, PR+CR) using a Fisher's exact test on the intention-to-treat patients with one-sided type I error of 2.5%. The primary analysis of ORR will be evaluated on the first 360 patients enrolled for the PFS analysis, a secondary analysis of ORR will be conducted on all patients. Patients who are unevaluable for response and patients never starting protocol therapy will be included as non-responders in this analysis. Based on the BOLERO-2 results, the ORR will be about 0.4% on arm B. For the primary analysis of objective response, with 180 refractory patients on each arm, the study will have 86% power to detect an increase to a 6% objective response rate on arm A.

9.3.2 Toxicity

Another secondary endpoint of the study is to evaluate toxicities. Toxicity will be evaluated on the first 360 patients for the PFS analysis and on all patients for the OS analysis. All patients who start protocol therapy (i.e., receive at least one dose of protocol treatment) will be included in toxicity analysis. For the 360 patients for the PFS analysis, assuming 9 patients (9/180=5%) will not start protocol therapy in each arm, with 171 evaluable patients per arm, there is 92% power to detect a difference in grades 3-4 toxicity rate of 24% vs. 10% between arms A and B, assuming an one-sided type I error rate of 2.5%, based on the Fisher’s exact test. For each arm, with 171 patients, the binomial exact 95% confidence interval for toxicity rate would be no wider than 0.16.

9.3.3 Time to Treatment Deterioration (TTD)

Another secondary endpoint of the study is to evaluate time to treatment deterioration (TTD) of arm A vs. B. TTD is a composite endpoint and it captures toxicity (measured by symptom worsening), symptom worsening due to disease progression between radiological tumor assessments (provided symptoms are being assessed more frequently than the radiological disease assessments), radiological confirmed disease progression and death. TTD is defined as time

from randomization to radiological confirmed disease progression or death or worsening of symptoms, whichever occurs first. Disease progression is assessed per RECIST v1.1. Symptoms deterioration will be measured by 6 items from the 8-item FACT-Breast Symptom Index (FBSI). The 6 items (GP1, GP2, GP4, GF7, B1, P2, scored 0-24) were selected as being most clinically relative and most responsive to "proximal" change based from clinical deterioration. In addition, the other two items (GP3 or GE6) in the 8-item FBSI will be collected as well for explanatory analysis.

The selected 6 items capture both symptoms related to progressive breast cancer (fatigue, malaise, pain, shortness of breath, overall change in QOL) as well as symptoms related to entinostat (fatigue, nausea, overall change in QOL). According to Yost et al, the minimally important difference (median 2.2, range 1.5-2.5) and anchor-based criteria overlapped (PSR 2.8 and 3.2), [73] and based on these criteria, 2-3 point changes in this 8-item FBSI survey can be interpreted as a MID. To be conservative, symptom deterioration is defined as two consecutive available decreases of at least 3 points from baseline using the 6-item FBSI[57] in this trial, and the second visit time will be used as the time of symptom deterioration in this case, unless it is the final score, for which one decrease is sufficient.

In order to fully capture the impact of toxicity and disease progression before radiological assessment on patient's QOL, symptoms will be assessed every cycle for the first six months after randomization, every two cycles between 6 months and 1 year. It then will be assessed based on the same schedule for tumor assessments until disease progression. Since symptom change cannot be associated with protocol therapy if the patient never receives any treatment on protocol, the primary population for the TTD analysis will be the enrolled 360 patients for the PFS analysis who receive at least one dose of protocol therapy (i.e., all treated patients in the first 360 enrolled patients). TTD will not be evaluated on the additional 240 patients primarily enrolled for the OS endpoint.

Because we expect that the benefits from improving PFS (and thus less symptoms from disease) on arm A will outweigh any increase in toxicity from the addition of entinostat to exemestane (more symptoms from the treatment), we hypothesize that the combination arm (A) will have a significantly longer TTD than arm B. It is expected that symptom deterioration will occur before radiological confirmed disease progression or death for some patients. Hence, the median TTD should be shorter than the median PFS for the same patient population. To be conservative, we assume that the median TTD is 4 months for patients on arm B, similar with our estimate for PFS in these patients. Assuming 9 patients (9/180=5%) will not start protocol therapy in each arm, with 171 evaluable patients per arm, there is 88% power to detect a HR of 0.67 for arms A/B based on the log-rank test when the analysis is conducted 30 months after study activation (same time as the primary analysis of PFS), assuming a median TTD

of 6 months on arm A (i.e., 50% improvement in median TTD), with a 2.5% one-sided type I error rate.

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9.4 Analysis Plan for Primary Endpoints, Objective Response, Toxicity and Time to Treatment Deterioration

The primary endpoints are progression-free survival (PFS) and overall survival (OS). Both of the two endpoints will be used for potential entinostat registration with FDA. ORR, toxicity and TTD are secondary endpoints. The primary analysis of PFS will include follow-up through the 247th PFS event within the first 360 patients enrolled. For the primary analysis, progression will be defined by central review. A sensitivity analysis for PFS will be performed using the first 360 patients based on progression defined by local investigators. The TTD analysis will include similar follow-up. The primary analyses of ORR and toxicity will include the first 360 patients enrolled. Final analysis for OS is expected to be conducted at about 70 months after study activation (40 months of accrual + 24 months of follow up + 6 months of data collection and cleaning). At the time of the final OS analysis, secondary analyses of the other endpoints (PFS, ORR and toxicity) including all cases enrolled will be conducted. The secondary analysis of PFS will be conducted in all 600 patients based on progression defined by the local investigators since central review is anticipated for the first 360 patients only.

Tumor response will be assessed per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 following the standard ECOG-ACRIN review procedures.[46] PFS is defined to be time from randomization to the earliest documented disease progression as defined by the RECIST criteria, new primary breast cancer, or death without progression. Disease assessment will continue until disease progression, even after non-protocol anti-cancer therapy is started. Cases with incomplete follow up or without adequate disease evaluations will be censored at the date last documented to be free of progression, regardless of whether non-protocol anti-cancer therapy is started or not. As a sensitivity analysis, PFS will also be defined in the following ways: 1) Considering the start of a new non-protocol anti-cancer therapy as a PFS event, in addition to disease progression, new primary breast cancer and death without progression. 2) Censoring PFS observation at the last assessment before a new non-protocol anti-cancer therapy is started for the patients who start new anti-cancer therapy without a documented PFS event. OS is defined to be time from randomization to death from any cause. Cases who are still alive will be censored at the date last known alive. ORR is defined as the proportion of patients with complete response (CR) or partial response (PR) among all patients (including patients with unevaluable tumor response).

All primary analyses regarding PFS, OS and ORR will be based on intention-to-treat population regardless of eligibility status. A secondary analysis for PFS, OS and ORR will be conducted in eligible patients. The distributions of PFS and OS will be estimated using the Kaplan- Meier method (1958)[52], with 95% confidence intervals calculated using Greenwood's formula. In the primary analyses of PFS and OS, differences in treatment effect will be tested using stratified log rank tests, stratifying on the randomization stratification factors. Stratified univariate and multivariable Cox proportional-hazard models (1972)[53] will be built to estimate the hazard ratios (HRs) for treatment effect for PFS and OS as a supportive analysis. In the multivariable Cox models, known prognostic factors will be included as covariates when appropriate, such as age at diagnosis, race/ethnicity, body mass index (BMI), ECOG performance status, disease stage

at diagnosis, prior adjuvant chemotherapy, prior hormonal therapy, et al. The assumption of proportionality in the Cox models will be assessed by investigating the weighted Shoenfeld residuals for each predictor. Patients with missing values for covariates will be excluded from modeling when the proportion of missingness is less than 5% and will be imputed appropriately if the proportion of missingness ≥5%. ORR will be summarized along with the exact binomial 95% confidence interval and compared between the two arms using Fisher's exact tests.[54]

TTD is defined as time from randomization to disease progression or death or worsening of symptoms, whichever occurs first. All primary analysis for TTD will be based on all cases receiving at least one dose of protocol treatment (i.e., all treated population). The distribution of TTD will be estimated using Kaplan-Meier method, and TTD comparisons between treatment arms will be tested primarily using log-rank test. Cox proportional-hazards models will be conducted to estimate the HR for treatment effect for TTD as a supportive analysis. Same factors included in the multivariable Cox model for PFS and baseline symptom level will be included as predictors for TTD.

Analyses pertaining to toxicity will be based on all treated cases. Adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). All treatment-emergent and baseline adverse events and hematological/biochemical toxicities based on laboratory measurements, as well as drug related AE's, will be summarized by treatment group and NCI CTCAE worst grade. The incidence of deaths and treatment-emergent serious adverse events (defined as number of patients experiencing the AE divided by all treated patients) will be summarized and compared between treatment arms using Fisher's exact test. Also, the incidence of adverse events leading to discontinuation of investigational product and/or withdrawal from the study will be summarized and listed.

In all analyses, P-values will be two-sided. A level of 0.2% will be considered statistically significant for stratified log rank test for the primary PFS analysis. For OS comparison, the significance level for stratified log rank test will be 4.8%. For all other tests, a level of 5% will be considered statistically significant.

9.5 Integrated Pharmacodynamic Biomarker Study of Acute Change in Protein Lysine Acetylation

HDAC inhibition leads to elevated protein lysine acetylation in tumor and peripheral-blood cells, which could serve as a surrogate early pharmacodynamic biomarker of entinostat activity. ENCORE 301 collected peripheral blood samples (PBMCs) for assessment of lysine acetylation, both prior to therapy and post-therapy on Days 8 and 15, using an assay developed by the Trepel Laboratory, NCI/NIH. Protein lysine acetylation in the combined therapy subgroup (i.e., arm A) was associated with a striking improvement in PFS across all cell types (B cells, T cells and monocytes). In Exemestane +Entinostat-treated hyperacetylators (i.e., acetylatoin above the median) versus those with acetylation below the median, median PFS was 8.5 versus 2.7 months (HR=0.32, 95% CI 0.13, 0.79) (B cells); 6.6 versus 3.6 months (HR=0.44, 95% CI 0.18, 1.08) (T cells); and 6.2 versus 3.6 months (HR=0.50, 95% CI 0.21, 1.20) (monocytes).

We will use the identical methodology, central laboratory (Trepel Laboratory, NCI/NIH), and timing (Day 15) for the integrated acetylation pharmacodynamic

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biomarker studies planned in E2112. PBMCs will be collected at baseline and 15 days after initiating therapy consisting of drawing 8cc of blood into one blue/black CPT citrate tube at each time point.

Since exemestane is not expected to induce significant increase in protein lysine acetylation, we expect no significant increase in protein lysine acetylation after two weeks of arm B treatment on E2112. The primary test of association between increased protein lysine acetylation (as an early pharmacodynamic biomarker of entinostat activity) and PFS will be examined in arm A in E2112. However, since the study is blinded, the PBMCs will be collected on all patients (including both arm A and arm B). The prognostic value of increase of lysine acetylation will be conducted in arm B as well as an exploratory analysis. All 600 patients enrolled in the main trial will be included in the integrated acetylation pharmacodynamic biomarker study. The analysis will be performed at about 70 months after study activation (same time as that for final OS analysis).

9.5.1 Statistical consideration for integrated acetylation pharmacodynamic biomarker study

The objective of this pharmacodynamic biomarker study is to examine the prognostic value of acute acetylation change for PFS in patients receiving Exemestane + Entinostat combination therapy. We hypothesize that patients with percentage change in protein lysine acetylation above median will have a prolonged PFS compared to those with changes in protein lysine acetylation below or equal to median in arm A. For this integrated pharcodynamic biomarker study, the endpoint is PFS. The group variable is change in protein lysine acetylation between baseline and 2 weeks after initiating therapy.

Of the 300 refractory patients on arm A, 270 (90%) of them will be expected to have measures for protein lysine acetylation at both baseline and 2 weeks after initiating therapy. The percentage change in lysine acetylation will be calculated for all patients on arm A and the median percentage change will be determined and used as the threshold to dichotomize all patients into two groups on the arm: > median and ≤ median. There will be about 266 PFS events on arm A at the time of the analysis (70 months after study activation) under the alternative hypothesis. With a total of 266 PFS events and 270 patients, there will be adequate power (80%) to detect a hazard ratio of 0.71 and excellent power (90%) to detect a hazard ratio of 0.67 using log rank test with one-sided type I error equal to 2.5%.

9.5.2 Analysis plan for integrated acetylation pharmacodynamic biomarker study

The primary analyses for this integrated acetylation pharmacodynamic biomarker study will be conducted in all patients on arm A who have data about the protein lysine acetylation at both baseline and 2 weeks after initiating therapy. The analysis time for this acetylation biomarker study is at about 70 months after study activation (same time as final analysis for OS).

The distributions of PFS and OS will be estimated using the Kaplan-Meier method, with 95% confidence intervals calculated using

Greenwood's formula. Differences between patients with above or below median of percentage change in protein lysine acetylation will be tested using log rank test. Univariate and multivariable Cox models will be built to estimate the HRs for the effect of increased protein lysine acetylation for PFS and OS, respectively. The adjusting variables in the multivariable Cox model include patient demographics and disease characteristics, such as age at diagnosis, ECOG PS, disease stage, prior therapy, et al.

Similar analysis will be conducted in patients on arm B to explore whether increase of protein lysine acetylation is prognostic for PFS and OS in patients with the exemestane monotherapy.

In all the above survival analyses, landmark method[55] will be used, with landmark set at 2 weeks. OS is defined to be week 2 to death from any cause, censoring cases who are alive at the date last known alive. PFS is defined to be week 2 to the earliest of documented disease progression as defined by the RECIST criteria, new primary breast cancer, or death without progression. Cases with incomplete follow up or without adequate disease evaluations will be censored at the date last documented to be free of progression. Patients who have events for OS or PFS within 2 weeks are excluded from the landmark analysis.

The distribution of the percentage change in protein lysine acetylation will be plotted for the two treatment groups and difference will be compared using the Wilcoxon ranks sum test. Tumor response rate will be compared between the patients with percentage change in acetylation being above or below median using Fisher's exact tests in each treatment arm.[54]

All above analyses for protein lysine acetylation change will be repeated for all three types of peripheral blood mononuclear cells (CD3+ T cells, CD19+ B cells and CD14+ monocytes). In all analyses, P-values will be two-sided and a level of 5% will be considered statistically significant. No adjustment will be made for multiple comparisons.

If PFS endpoint is positive in the primary analysis within the first 360 patients, the acetylation data will be analyzed for a subgroup analysis for PFS (all 360 patients will be dichotomized into one of two groups based on the whole sample median: > median and ≤ median) at the PFS primary analysis time.

9.6 Patient-Reported Outcomes Assessment

There are two objectives in the patient-reported outcomes (PROs) assessment study. The first objective is to compare overall HRQL between treatment arms. The second objective is to compare symptoms associated with entinostat between arms. The type I error rate is equally split between the two objectives to control the overall one-sided type I error at 2.5% for the PROs analysis. In order to provide sufficient power for the two objectives, all 360 patients included for the PFS endpoint on the main study and receive at least one dose of protocol therapy (i.e., all treated patients) will be eligible for the PROs study. PROs will

not be evaluated on the additional 240 patients primarily enrolled for the OS endpoint.

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With the exception of the FBSI and the Medication Adherence Scale, the PROs assessment will be administered at the following time points: baseline, 3, 6, and 12 months (the timing of these assessments coincides with the first, second and fourth disease assessments), at the end of protocol treatment/time of protocol treatment discontinuation and 4 weeks after protocol treatment is discontinued. Given that anticipated median survival is about 2 years and median PFS is about 4-7 months, the 3-month assessment is expected to provide the best assessment of treatment-emergent symptoms. Hence the primary comparison of PROs between treatment arms is based on the month 3 assessment.

9.6.1 Statistical consideration for PROs

The primary objective of the PROs study is to test whether the overall HRQL is significantly worse in the Exemestane + Entinostat arm (arm A) compared to the Exemestane + Placebo arm (arm B) at month 3. The null hypothesis is that patients on the two arms have same overall HRQL. The alternative hypothesis is that patients on arm A have worse HRQL than patients on arm B. The endpoint for the objective is the overall HRQL score measured by the Trial Outcome Index (TOI), an aggregate score of the 5 items from the FACT-G-Physical subscale (GP2, GP3, GP4, GP6, and GP7), and 6 items from the FACT-G-Functional subscale (GF1, GF2, GF3, GF4, GF6, and GF7). Higher score represents better HRQL (score range 0-44).

Assuming an overall attrition rate of approximately 10% by month 3 for the PROs assessment in both arms, it is expected that about 324 refractory patients will be included for the primary analysis for HRQL. At month 3, a difference of 5 points in the overall HRQL score between the treatment arms would be considered clinically meaningful. The common standard deviation is expected to be 12 points. With 162 analyzable patients on each arm for the month 3 assessment, there will be about 93% power to test the difference using a two independent samples t test, assuming a two-sided type I error of 0.025.

The second objective of the PROs study is to assess differences between the two arms in symptoms associated with entinostat at month 3 (i.e., fatigue, nausea, anorexia and diarrhea, measured by PROMIS Fatigue short form, FAACT-additional concerns and FACIT-Diarrhea, respectively). The null hypothesis is that there is no difference between two arms regarding fatigue, nausea, anorexia and diarrhea at 3-month assessment. The alternative hypothesis is that patients on the Exemestane + Entinostat arm have more severe symptoms than patients on the Exemestane + Placebo arm. For each of the four symptoms, with 162 analyzable patients on each arm in the study, there will be an adequate power (80%) to detect an effect size of 0.40 and an excellent power (90%) to detect an effect size of 0.45, using two independent samples t test, assuming a two-sided type I error of 0.00625 (=0.025/4). The effect size is the difference in the survey score between two arms divided by the population standard deviation for each symptom.

For the fatigue assessment, the clinically minimally important differences (MIDs) have been estimated for the PROMIS Fatigue short form in advanced-stage cancer patients, which is 3.0-5.0 points and corresponds to effect sizes between 0.4 and 0.63[56].For the nausea/anorexia assessment, the clinically minimally important differences is estimated to be 6 points using the FAACT-additional concerns subscale, corresponding to an effect size of 0.53. For the diarrhea assessment, we are planning to use the FACIT-Diarrhea subscale, which does not yet have published MIDs[57]. We propose using 1/2 of the standard deviation of the FACIT-D scores (this is comparable to an effect size of 0.5) along with a general estimate of 0.36 points per item. Since the FACIT-D has 11 items, the estimated MID would be 4 points. Overall, this study should have an at least adequate power to detect a clinically important difference in each of the four symptoms, controlling the overall type I error rate at 2.5% for the second objective.

9.6.2 Analysis plan for PROs

The analysis time for PROs endpoints is at about 40 months (24 months of accrual + 12 months of treatment + 1 month follow up after treatment + 3 months of data collection and cleaning) after study activation. Subscale scores for all endpoints will be prorated by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered: Prorated subscale score= (sum of items cores) * (number of items in subscale) /(number of items answered). When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items are answered in each subscale. For overall QOL, the FACT-G scale is considered to be an acceptable indicator of patient quality of life as long as overall item response rate is greater than 80%. For the four symptoms, the measurement scales (i.e., PROMIS-Fatigue, FAACT-Additional Concerns subscale, FACIT-Diarrhea) must be completed over 50% of the items (e.g., 4 of 7 items, 6 of 11 items and 7 of 12 items) in order to consider each subscale score valid.

Standard descriptive and graphical analyses will be used initially to examine missing data patterns, and to understand the relationship between variables. The assessment scores for the four symptoms and HRQL will be compared between the two treatment arms at baseline, month 3, month 6, month 12, at the end of protocol treatment and 4-week post-treatment (regardless of the reasons for off treatment), using two independent samples t test (or Wilcoxon rank sum test[58] if the distribution of the score is not symmetric). Change in the four symptoms and HRQL between month 3 visit and the baseline visit will be compared between the two arms using two independent sample t tests. Similar analyses will be conducted for each FACT-G subscales as well. The mean score and proportion of moderate/severe symptoms will be compared between treatment arms for each individual FACT-G item at month 3 using Wilcoxon rank sum test and Fisher exact test, respectively, as an exploratory analysis.

Mixed effect models will be constructed as another exploratory analysis to estimate the time profile of HRQL in the two treatment arms and to evaluate treatment-by-time interactions. Time will be included as a continuous variable if there is a linear trend in HRQL over time or a set of dummy variables if non-linear trend exits for HRQL. Likelihood ratio test will be used for model selection. Adjusted covariates included in the mixed effect models will include patient demographic and disease characteristics, such as age, ECOG PS, disease stage, prior therapy, et al.

As an exploratory analysis, patient-reported outcomes will be correlated with PFS (prognostic value of PROs) in the study patients. Patients will be dichotomized (e.g., by median) and/or categorized into groups (e.g, quantiles) based on their HRQL at baseline and 3-month assessment. Kaplan-Meier method, log rank test and Cox models will be used to compare PFS between patients with good QOL and those with poor QOL in the overall patient population. The predictive value of QOL for benefit from entinostat therapy will be examined via the QOL-by-treatment interaction test in a Cox model for PFS. Landmark method will be used when we correlate QOL at month 3 with PFS, and PFS will be defined as time from landmark time point to disease progression or death for these analyses.

In all analyses, P-values will be two-sided. A level of 2.5% will be considered statistically significant for QOL comparison between two arms. For the four symptoms, a level of 0.625% will be considered statistically significant for comparison between treatment arms. For all other analysis, a level of 5% will be considered statistically significant. No adjustment will be made for multiple comparisons for individual FACT-G items.

9.7 Adherence to Protocol Therapy

Another secondary objective of the study is to measure adherence to protocol therapy. Patient's adherence to protocol therapy will be quantified using pill count (entinostat/placebo) and diary methods (exemestane). The number of pills a patient has taken will be recorded for every cycle (4 weeks). Patients will be instructed to bring their medication bottles (entinostat/placebo) and diaries (exemestane) with them for clinic visits. Clinic or pharmacy staff will count the number of remaining pills (entinostat/placebo) or pill diary doses taken (exemestane), and will calculate the number of pills taken using a treatment form. As administration of entinostat/placebo is weekly, it will be 0-4 doses per cycle.

Dose reduction (from 5mg to 3mg) is allowed for entinostat/placebo due to toxicity in the trial. If more than two consecutive doses of entinostat/placebo, or > two doses of entinostat/placebo per cycle are omitted due to toxicity, the patient will be permanently discontinued from protocol therapy. For exemestane, it will be administered once daily in each cycle, it will be 0-28 pills per cycle. Exemestane dose reductions are not allowed. If exemestane administration is held for > 7 days due to any reason, patient will be considered permanently off protocol treatment.

The adherence score will be calculated as the proportion of the total number of pills a patient actually took over the whole treatment period divided by the total

number of pills a patient should have taken. The strength of doses will be taken into account and the reduced dose of 3mg will be counted as 0.6 full dose (5mg) in adherence score calculation. The timing of doses will not be considered in the study. Data about adherence to protocol therapy will be collected for exemestane and entinostat /placebo separately for each arm. The adherence score will be calculated for each patient for each agent (exemestane and entinostat /placebo) separately. For the evaluation of each agent, patients will be categorized into 3 groups based on the adherence score. An adherence score of > 85% will be considered as high adherence, and an adherence score of < 65% will be considered as low adherence, and patients with an adherence score of 65%-85% will be considered as medium adherence.

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The ECOG-ACRIN Medication Adherence Scale Modified from the Morisky Index will be administered to understand the reasons for non-adherence to protocol therapy. There will be one Medication Adherence Scale form for each agent (entinostat /placebo and exemestane) in the study and the Medication Adherence Scale form will be administered at 3, 6, 12 months and at the end of treatment (same time with PROs assessment).

9.7.1 Statistical consideration for adherence

The primary analyses for this adherence study will be conducted in patients on arm A who have data about adherence to entinostat. All 300 patients on arm A will be eligible for the analysis. It is expected that about 80% (240) of the 300 patients on arm A will have sufficient data for evaluation of adherence to entinostat therapy and will be included in the analysis. With 240 analyzable patients on the arm A, the binomial exact 95% confidence interval for high adherence rate (defined by adherence score > 85%) to entinostat would be no wider than 0.13. Comparing adherence to entinostat and placebo, there is 84% power to detect a difference in high adherence rate of 75% vs. 86% between arms A and B, assuming a one-sided type I error rate of 2.5%, based on the Fisher's exact test.

9.7.2 Analysis plan for adherence

The analysis time for adherence endpoint is at about 70 months after study activation (same time as final OS analysis). All patients who receive at least one dose of protocol therapy and have sufficient adherence data will be included in the analysis.

The distribution of the adherence score for each agent will be displayed via box-and-whisker plot. The proportion of high, medium and low adherence to each agent will be calculated along with the binomial exact 95% confidence interval. The proportion of high adherence to entinostat and placebo will be compared between arms A and B using Fisher exact test. The proportion of adherence to exemestane will be compared between treatment arms using Fisher exact test as well. In addition, the adherence score for each cycle will be calculated for each agent and plot by treatment cycle to examine how adherence changes over time. The reasons for non-adherence will be summarized for each agent on each arm. The agreement on adherence level during a treatment period will be examined between the pill counts method and the Medication Adherence Scale method.

As an exploratory analysis, the association between baseline HRQL (categorized as good, fair, poor) and adherence to protocol therapy (categorized as high, medium and low adherence or dichotomized as good or poor) during the whole treatment period will be examined in each treatment arm using Fisher exact test. Multivariable logistic regression analysis will be conducted to identify the baseline factors which can predict high adherence. The covariates will include HRQL and other patient demographics and disease characteristics, such as age at diagnosis, ECOG PS, disease stage, prior therapy, et al.

The association between adherence to protocol therapy during the whole treatment period (categorized as high, medium or low) and HRQL (continuous score) at one-month after treatment discontinuation will be examined using ANOVA test and linear regression analysis, adjusting for HRQL at baseline and other demographic and disease characteristics.

Another exploratory analysis is to examine the association between the occurrence of toxicity in the first two cycles and adherence to entinostat after cycle 2 in patients on arm A.

In all analyses, P-values will be two-sided. A level of 5% will be considered statistically significant. No adjustment will be made for multiple comparisons.

9.8 Gender and Ethnicity

Male breast cancer accounts for approximately 1% of all breast cancers. Meanwhile, some elderly male patients may not be eligible or consider trials. We could anticipate that about 5 male patients with HR-positive, HER2-negative metastatic breast cancer could enroll out of a sample size of 600, and all of them are expected to be non-Hispanic White patients. For the 600 patients, based on previous data from SWOG S0226 and ECOG E2100 studies, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	44	0	44
Not Hispanic or Latino	551	5	556
Ethnic Category: Total of all subjects	**595**	**5**	**600**

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	11	0	11
Black or African American	51	0	51
Native Hawaiian or other Pacific Islander	0	0	0
White	533	5	538
Racial Category: Total of all subjects	**595**	**5**	**600**

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.9 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Center.

10. Imaging Study

ECOG-ACRIN plans to bank standard practice and protocol-defined imaging studies at the central ACR Imaging Core Laboratory for all 600 enrolled participants. An independent imaging review conducted by the ACR's Image Metrix will centrally evaluate imaging (only for the first-360-enrolled subjects) in relation to therapeutic response, PFS, OS, differences among therapeutic arms, and histologic biology. The independent review will be performed after quality assurance and according to standard operating procedures of the ACR Imaging Core Laboratory. For the ECOG-ACRIN E2112 trial, we plan to evaluate specific clinical data elements to associate images with treatment milestones. In the future, the de-identified image bank may be used for additional research, such as retrospective reviews of disease or software validation. Patient identifiers will never be included in future research and no patients will be named in publications related to future research.

10.1 Imaging Recommended Parameters and Time Points

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10.1.1 Images provided for the independent review will consist of CT scans of the chest, CT or MRI scans of the abdomen and pelvis, and bone scans. CT of the chest and CT or MRI of the abdomen and pelvis is required at baseline and for follow-up assessment of known sites of disease or as clinically indicated. Contrast-enhanced CT (intravenous [IV] and oral contrast appropriate to anatomic area of coverage) is the preferred imaging modality for this study. If IV contrast is medically contraindicated for CT examination, then IV-contrast-enhanced MRI is the secondary imaging modality preference for abdomen/pelvis imaging, and non-contrast CT is the secondary imaging modality preference for chest imaging.

10.1.2 Bone scans are required at Baseline for all subjects. On-study bone scan submission is expected in different circumstances and frequencies. Bone scanning is most commonly performed utilizing a Technetium-99m (Tc-99m)-diphosphonate radiotracer with a standard gamma camera; however, ^{18}F-Sodium Fluoride (NaF) PET/CT bone imaging may be performed for this requirement. Adverse reactions to both tracers are rare, and with the exception of a previous hypersensitivity reaction, there are no contraindications.

10.1.3 Baseline CT or MRI and bone scan will be used to define target and non-target lesions to define future treatment response according to RECIST 1.1 criteria.

10.1.4 If additional anatomic sites of disease are known or suspected, these should be imaged with the appropriate exams at each time point.

10.1.5 For a given subject, the modality (or combination of modality-body region [e.g., CT Chest, MRI Abdomen] exams) used at Baseline should be used consistently for all follow-up time points throughout the trial.

10.1.6 The same scanner and same acquisition and reconstruction parameters should be used for a given participant throughout the trial (both on- and off-treatment imaging).

10.1.7 Image slice thickness (reconstructed) should be 5 mm or less for CT and MRI, and contiguous slices are preferred to those with intervening gaps.

10.1.8 The specific contrast agent utilized, dose and injection parameters (including time of image collection after contrast) should be consistent across all time points for a subject.

10.1.9 Subject Preparation and Subject Positioning

For subject preparation prior to imaging, the technologist/study coordinator should follow the local imaging facility's standard procedures taking into account guidance from the Imaging Manual. For image acquisition, subject positioning and comfort should follow the same paradigm. Refer to the study's Imaging Manual for more information.

10.1.10 Baseline Time Point

According to the Schedule of Assessments, CT chest, CT (or) MRI abdomen and pelvis and a bone scan must be acquired as close as possible to randomization (within 28 days prior to randomization). Repeat baseline imaging is not required if the CT chest, CT (or MRI) abdomen and pelvis and the bone scan were performed ≤ 6 weeks prior to study randomization. Additional sites of known or suspected disease should be imaged at the Baseline visit as clinically indicated. Baseline time point images will be assessed for image quality by Image Metrix within five (5) business days of receipt, barring any exam date identification or subject verification issues preventing processing.

- **CT**

The CT exam should be performed with a slice thickness of 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of comparable diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- **MRI**

In subjects where contrast-enhanced CT is contraindicated, an MRI may be performed to image the abdomen and pelvis.

- **Bone Scans**

Bone scans should include imaging of the entire axial skeleton as well as at least the proximal appendicular skeleton. For Tc-99m scans, this could be performed as planar whole body (WB) acquisitions (anterior

and posterior) or as a complete set of spot scintigrams. For NaF scanning, both the non-attenuation corrected (NAC) and attenuation corrected (AC) image sets as well as the corresponding low-dose CT should be submitted.

10.1.11 On-Treatment Imaging

Following randomization into the trial, subjects will be imaged at the end of 12 weeks from randomization and then every 12 weeks thereafter until disease progression. Additionally, subjects will be imaged within 28 days of treatment discontinuation.

10.1.12 Follow-Up Imaging

If a subject discontinues treatment due to reasons other than disease progression, off-treatment imaging should be performed until disease progression is identified by the local site on the following schedule: every three (3) months if the subject is < 2 years from study entry, every six (6) months if patient is 2-5 years from study entry, and annually if patient is >5 years from study entry. No specific requirements if patient is more than 10 years from study entry. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted.

For some subjects, it is expected that there will be discordance in the determination of progressive disease between the local site and independent review. Consequently, there will most likely be cases where follow-up imaging is expected based on the independent reviewer's assessment (since PD is not identified), but no imaging was performed given an assessment of PD at the local site.

10.1.13 Unscheduled and Off-Protocol Imaging

Exams performed outside the protocol-defined visit window (unscheduled exams) and off-protocol imaging (e.g., FDG PET and radiographs) also will be submitted to the ACR Imaging Core Laboratory/Image Metrix.

Table 1 illustrates when scans are required for the duration of subject follow-up as well as instances where scans do not need to be performed nor submitted to the ACR Imaging Core Laboratory/Image Metrix.

Table 1: Schedule of Assessments

Image	Baseline (within 4 weeks of randomization)[1]	End of 12 weeks of randomization and every 12 weeks thereafter	End of Treatment[2] (within 4 weeks of end of treatment)	Post-Treatment[3]
CT Chest, CT or MRI Abdomen/ Pelvis	Required	As Clinically Indicated	As Clinically Indicated	As Clinically Indicated
Bone Scan	Required	As Clinically Indicated	As Clinically Indicated	As Clinically Indicated
CT/MRI Other Body[3]	As Clinically Indicated	As Clinically Indicated	As Clinically Indicated	As Clinically Indicated
Off-Protocol[4, 5]	As Clinically Indicated	As Clinically Indicated	As Clinically Indicated	As Clinically Indicated

[1] Repeat baseline imaging is not required if already performed ≤ 6 weeks prior to study randomization.

[2.] Repeat any imaging not performed in ≤ the prior 28 days.

[3] If subject discontinues treatment for reasons other than disease progression, imaging is to be repeated until progression every three months if patient is < 2 years from study entry, every six months if patient is 2-5 years from study entry, and annually if patient is >5 years from study entry. No specific requirements if patient is more than 10 years from study entry.

[3] Imaging of anatomic regions not covered by above mentioned scans must be obtained when there is clinical suspicion of metastasis. Such additional scans must be consistently repeated at all time points if a metastatic lesion is documented.

[4] FDG-PET scans, radiographs - as clinically indicated, based on local standards of care.

[5] Ultrasound, Other - as clinically indicated, based on local standards of care.

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10.1.14 In general, all imaging studies (including CT, MRI, PET, or any combination), including all phases completed, conducted for the subject while participating in a study will be submitted to ACR per instructions in Section 10.3.

10.1.15 In addition to the images themselves, sites must provide:

a. De-identified imaging reports for all required scans at each protocol-specified time point, and

b. Copies of any other relevant de-identified source documents showing evidence of measurable and/or non-measurable disease not captured by the imaging reports (e.g., photographs of skin lesions).

10.2 Independent Imaging Review

The independent imaging review will be conducted only on the first 360-participants-enrolled cohort identified for the primary endpoint analysis. Radiologist readers will review each case's series of imaging studies to identify progression using RECIST 1.1 criteria. Independent readers will be blinded to

local radiologist findings. Local reads will be used to define progression for study-related treatment decisions.

Subject scans will be considered ready for independent image review once the following occurs:

- Applicable Baseline clinical data available; and
- Baseline and one on-study time point available and acceptable; and
- Subject has completed all imaging visits; or
- Subject is off-treatment; or
- Sponsor (or designee)-defined cutoff, if applicable.

For each subject, the time point-by-time point imaging response evaluation will be performed by two (2) independent, qualified, and approved radiologist reviewers in a sequential locked-read paradigm. Neither primary reviewer will have access to the other reviewer's annotations or tumor response data. Baseline clinical data, if applicable, will be provided.

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10.3 Images Submission

Imaging exams required for each time point for the first 360 enrollees are to be submitted to the ACR Imaging Core Laboratory/Image Metrix. Baseline images should be submitted within five (5) business days of registration and follow-up images within five (5) business days after image acquisition. This is a request of sites. It is the investigational site's responsibility to ensure complete and timely collection of imaging and non-imaging data for submission to the core lab/Image Metrix. Imaging exams for all 600 subjects will be submitted to the ACR Imaging Core Laboratory, but rigid submission timeline may be looser than five (5) days after the first-360 subject cohort.

For each individual time point, the investigational site (or imaging facility) personnel will submit images in standard DICOM format along with a completed Image Transmittal WebForm/Worksheet (ITW). All images must be submitted in DICOM format.

There are two (2) methods for subject image submission:

- TRIAD™: Electronic submission utilizing software provided by Image Metrix
- Media (DVD/CD), using a trackable courier (not recommended)

There are two (2) methods for ITW completion and submission:

- Electronically, utilizing ACR Image Metrix's Clinical Conductor Enterprise (CCE);
- Using a paper ITW form and submitting via courier or email.

Clinical sites/imaging facilities will submit subject images to Image Metrix via electronic submission through TRIAD or on hard-copy media (CD) via a trackable courier. Clinical sites/imaging facilities will submit ITWs for subject images via electronic submission through CCE or as hard-copy (paper) via a trackable courier or via fax/email.

Regardless of the submission method employed by the site, all subject images are routed through TRIAD and all ITW information maintained in CCE.

TRIAD® is ACR's proprietary image exchange application that will be used as the sole method of data transfer to the ACR Clinical Research Center Core

Laboratory for this trial. ACRIN will provide installation on one or several computers of choice within the institutional "firewall" and on the institutional network; internet access is required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software de-identifies, encrypts, and performs a lossless compression of the images before they are transferred to the ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software.

For more information, contact:

TRIAD-support@phila.acr.org or call 703-390-9858.

If images are submitted to the ACR Imaging Core Laboratory on media, subject personal identifiers must be removed by the investigational site prior to submission. To promote the de-identification of all personal identifier information, the sites are instructed to make specific DICOM-tag replacements, which will be inserted into the DICOM header wherever personal information exists. The DICOM tag replacement guidelines are included in the Imaging Manual. If the site/imaging facility submits a CD with personal identifiers intact, the CD will be returned to the site with a query requesting resubmission with prior de-identification, as per the Informed Consent Form for this study.

De-identified media will be submitted to:

American College of Radiology Independent Review Facility
Attn: ECOG-ACRIN 2112
Rev. 10/16 1818 Market Street 17th floor Suite 1720
Philadelphia, PA 19103
Phone: 215-574-3150
Fax: 215-717-2764

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11. Biological Sample Submissions

Whole blood is to be submitted from consenting patients for laboratory research studies and/or future undefined research. These studies are defined in Section 12. Tumor tissue (primary and metastatic) is to be submitted from consenting patients for future undefined research. Plasma samples are to be submitted for population pharmacokinetic studies as defined in Section 11.4.

The IRB approved consent must allow patients the option to provide samples for use in the optional laboratory research studies and/or for undefined future research studies.

Logging and tracking of sample submissions: It is required that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 11.5). An STS shipping manifest form is to be included with every submission.

Labeling of samples: All samples must be labeled clearly with the ECOG-ACRIN protocol number (E2112), ECOG-ACRIN patient sequence number, patient's initials, date and time of collection, time point, and sample type (e.g. primary tumor, PB citrate CPT).

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11.1 Sample Collection and Submission Schedule

Samples are to be submitted as follows:

- Pathology samples are to be submitted to the ECOG-ACRIN CBPF within one (1) month following randomization. See Section 11.3.
- Whole blood samples (for future undefined research) are to be submitted to the ECOG-ACRIN CBPF as outlined in Section 11.3 on the day of collection. Samples are to be collected at the following time point:
  - Baseline [after randomization, prior to start of treatment]
- Whole blood samples (for laboratory research studies) are to be submitted to the Trepel Laboratory as outlined in Section 12.2 on the day of collection. Samples are to be collected at the following time points:
  - Baseline [within two (2) days prior to start of treatment]
  - Cycle 1, Day 15 [two (2) weeks after initiating therapy, prior to entinostat/placebo]

    NOTE: Do not start treatment on Fridays as the baseline and day 15 blood collections cannot be shipped on Fridays.

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- Plasma samples are to be submitted for population pharmacokinetic studies to Covance Central Laboratory Services as outlined in Section 11.4 per patient consent. Samples are to be collected at the following time points:
  - Cycle 1, Day 1 [**two samples** drawn at least 2 hours apart, 2-5 hours after dosing]
  - Cycle 1, Day 15 [one sample drawn 1 hour after dosing]
  - Within 72 hours prior to the start of Cycle 2

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11.2 Submissions to Trepel Laboratory

Kits for the collection and shipment of the blood samples are ordered online from Cenetron Central Laboratories. Instructions are provided in Appendix VI.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials group at (512) 439-2000. Kits must be ordered after the patient has been registered to the trial and will generally arrive within three (3) business days from when the order was placed. A single kit will contain three "sub-kits" with all supplies for the collection and shipment of the three blood samples to be collected.

Whole blood samples should be shipped the day they are drawn. If you have any questions concerning blood sample collection and shipment, please contact Min-Jung Lee at leemin@mail.nih.gov or Jane Trepel at trepelj@mail.nih.gov or by phone at (240) 760-6330.

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Submit from patients who answer "Yes" to "I agree to participate in the laboratory research studies that are being done as part of this clinical trial."

11.2.1 Sample Preparation Guidelines

Whole blood samples are to be collected prior to start of treatment and on cycle 1, day 15 and are to be shipped at ambient temperature the day they are drawn (do not freeze) with cool packs during hot season.

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Draw 8mL of whole blood into one (1) blue/black CPT citrate tube (provided in kit) at each time point. Mix gently by inverting tube several times. Ship day of collection.

Please completely fill CPT citrate tube as full as possible.

NOTE: Do not start treatment on Fridays as the baseline and day 15 blood collections cannot be shipped on Fridays.

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11.2.2 Shipping Procedures

Blood samples should be mailed the day they are obtained and shipped FedEx overnight priority to arrive during normal working hours.

Ship using the CBPF's FedEx account using the FedEx on-line Ship Manager.

Access to the shipping account can only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

The laboratory is open to receive shipments Monday through Friday.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

The link to the holiday closures for the laboratory:

http://www.opm.gov/policy-data-oversight/snow-dismissal-procedures/federal-holidays/

NOTE: International institutions should contact the laboratory to discuss processing and shipping guidelines.

Ship to:

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Trepel Laboratory
Preclinical Development Research Core, NCI, NIH
Building 10, Room 12C208
10 Center Drive
Bethesda, MD 20892
Phone: (240) 760-6330

Please e-mail Min-Jung Lee at leemin@mail.nih.gov and Jane Trepel at trepelj@mail.nih.gov to notify the laboratory when the patient is scheduled and when the blood is shipped. Indicate the ECOG-ACRIN protocol number, FedEx tracking number, and site contact information.

An STS shipping manifest form must be generated and shipped with all sample submissions.

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11.3 Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

Submit blood and tissue samples for future undefined research to the CBPF from patients who answer "Yes" to *"I agree to provide additional specimens for research*".

If you have any questions concerning sample collection and shipment, please contact the CBPF at 1-844-744-2420 or eacbpf@mdanderson.org.

11.3.1 Tissue Submissions

Submitting pathologist and clinical research associate may refer to Appendix I, which outlines the Pathology Submission Guidelines.

The tissue samples are to be labeled with the Pathology ID as well as the information above.

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11.3.1.1 Required Materials

Forms: Must be submitted with all tissue submissions.

- STS generated shipping manifest form
- Copy of the surgical pathology report

Pathology Submissions:

- Representative **primary tumor** diagnostic formalin fixed paraffin embedded [FFPE] tumor tissue block
- Representative **metastatic tumor** diagnostic formalin fixed paraffin embedded [FFPE] tumor tissue block

  NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

  - One (1) H&E slide, and
  - Twenty (20) 4 µm unstained air-dried plus slides, and

- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF at 1-844-744-2420. Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

11.3.2 Blood Submissions

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Kits for the collection and shipment of the blood samples are ordered online from Cenetron Central Laboratories. Instructions are provided in Appendix VI. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials group at (512) 439-2000. Kits must be ordered after the patient has been randomized to the trial and will generally arrive within three (3) business days from when the order was placed. A single kit will contain three "sub-kits" with all supplies for the collection and shipment of the three blood samples to be collected.

Whole blood samples are to be collected at baseline, after randomization, prior to start of treatment.

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Draw 8mL of whole blood into one (1) ACD yellow top tube (provided in the kit). Mix gently by inverting tube several times.

11.3.3 Shipping Procedures

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Pathology materials are to be shipped at ambient temperature within one (1) month following patient randomization.

Blood samples are to be shipped the day of collection via overnight delivery at ambient temperature (do not freeze) with cool packs during hot season.

Friday shipments are ill advised, similarly shipping before a long holiday is often problematic. The laboratory is closed Saturday, Sunday and holidays.

Ship using the CBPF's FedEx account using the FedEx on-line Ship Manager.

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085

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Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Boulevard
Houston, TX 77030
Toll Free Phone: 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

Access to the shipping account for shipments to the CBPF can only be obtained by logging into fedex.com with an account issued by the CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the CBPF by email at eacbpf@mdanderson.org.

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11.4 Submissions to Covance Central Laboratory Services for Population Pharmacokinetics [OPTIONAL]

Plasma samples are to be collected at the following time points per patient consent:

- Cycle 1, Day 1 [**two samples** drawn at least 2 hours apart, 2-5 hours after dosing]
- Cycle 1, Day 15 [one sample drawn 1 hour after dosing]
- Within 72 hours of the start of Cycle 2

Collection and shipping kits are available and will contain the materials necessary for the preparation and shipment of the plasma samples, including tubes, labels, shippers, preprinted air bills, and bar-coded requisition forms.

To obtain starter kits and the Site Laboratory Instruction Manual please Email or Fax Appendix IX E2112 Covance Site Information/Initial Kit Order Form to Syndax. Please note Covance requires ten (10) days to process the form and ship out the initial kits.

Covance will ship out three (3) initial kits upon receipt of the above form. Once Covance receives two (2) of the kits, they will send out an auto-resupply of one (1) kit. If you require more kits than provided through the auto-resupply, please contact Covance directly at the number provided in the Site Laboratory Instruction Manual. Shipment usually takes about five (5) to seven (7) business days. Please refer to the Site Laboratory Instruction Manual provided in the initial kits for details on Specimen Collection, Processing, Packaging, and Shipping Guidelines.

If you have any questions concerning plasma sample collection and shipment please refer to the contact information provided in the Site Laboratory Instruction Manual for the Covance Site Support Group.

The exact date and time of entinostat/placebo administration and of PK plasma sample collection must be entered into the ECOG-ACRIN Sample Tracking System, and provided with the documentation submitted with the plasma samples.

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11.5 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Any case reimbursements associated with specimen submissions will not be credited if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html.

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

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Study Specific Notes

The exact date and time of entinostat/placebo administration and of PK plasma sample collection must be entered into the ECOG-ACRIN Sample Tracking System, and provided with the documentation submitted with the plasma samples.

Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory. Indicate the appropriate Lab ID# on the submission form:

- ECOG-ACRIN CBPF
- Trepel Laboratory
- Covance Central Laboratory Services

NOTE: Covance Central Laboratory Services will not be utilizing the STS to confirm receipt.

Retroactively enter all specimen collection and shipping information when STS is available.

11.6 Reimbursements for Population Pharmacokinetic Plasma Sample Submissions

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11.6.1 Institutional Reimbursements

To offset research-related costs associated with the collection and submission of the plasma samples at the four time points outlined above in Section 11.4, institutions are eligible to receive reimbursements. Please see the Funding Sheet for further details. Plasma samples must be collected and submitted to trigger payment. Receipt of the plasma samples will be verified prior to the release of funds.

NOTE: Neither patients nor their insurance companies are to be billed for the collection or submission of the pharmacokinetic plasma samples.

Distribution of the reimbursements requires:

- Submission of the required pharmacokinetic plasma samples using the ECOG-ACRIN Sample Tracking System (STS) [Refer to Section 11.5 for STS requirements]
- Receipt and verification of the plasma samples by Covance Central Laboratory Services

11.6.2 Patient Vouchers

Vouchers will be distributed to institutions for use by the patients to off-set expenses incurred during the 2-5 hour time period of the cycle 1, day 1 pharmacokinetic plasma sample collections. Vouchers will be sent to the contact person and institutional shipping address provided in OPEN.

Vouchers are being provided by Syndax.

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11.7 Use of Specimens in Research

Blood will be distributed to investigators for the laboratory research studies defined in Section 12.

Specimens from patients who consented to allow their specimens to be used for future ECOG-ACRIN approved research studies will be retained in an ECOG-ACRIN designated central repository.

For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs). DNA and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

Any residual blocks will be available for purposes of individual patient management on specific written request.

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Residuals/derivatives from the plasma samples submitted for the population pharmacokinetic studies will not be retained for future research studies.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

11.8 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of samples forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office – Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office – Boston.

12. Correlative Studies

The results of these studies are for the purposes of the trial only and will not be returned to the site or reported to the patient.

12.1 Acute Change in Protein Lysine Acetylation as a Predictor of Benefit from Entinostat

This analysis will be performed in the laboratory of Dr. Jane Trepel at NCI/NIH (See Section 12.2). Protein lysine acetylation will be measured by multiparameter flow cytometry in peripheral blood mononuclear cells (PBMCs; CD19+ B cells, CD3+ T cells, and CD14+ monocytes). Dr. Trepel and her team have developed and published the method to be utilized to perform this correlative analysis, which includes determination of the stability of acetylation in PBMC samples[64]. In addition the team has been coauthors on four clinical trials, including ENCORE 301, in which the flow cytometric pharmacodynamic assay has been performed[65,66,67,68].

Peripheral blood mononuclear cells (PBMCs) offer an opportunity to assess pharmacodynamic effects of entinostat and to correlate the observed effects with breast cancer outcome. In PBMCs, the effects of entinostat will be measured by global protein acetylation using multi-parameter flow cytometry.

We hypothesize that patients with increased protein lysine acetylation in the two weeks after initiating therapy will have a prolonged PFS compared to those without changes in protein lysine acetylation.

To briefly review, ENCORE 301 collected PBMCs for assessment of lysine acetylation prior to therapy, and post-therapy on Days 8 and 15 using an assay developed by the Trepel Laboratory, NCI/NIH. Protein lysine acetylation in the combined therapy subgroup was associated with a striking improvement in PFS across all cell types. In EE-treated hyperacetylators versus those with acetylation below the median, median PFS was 8.5 versus 2.7 months (HR=0.32, 95% CI 0.13, 0.79) (B cells); 6.6 versus 3.6 months (HR=0.44, 95% CI 0.18, 1.08) (T cells); and 6.2 versus 3.6 months (HR=0.50, 95% CI 0.21, 1.20) (monocytes).

We will use the identical methodology, central laboratory (Trepel Laboratory, NCI/NIH), and timing (Day 15) for the acetylation studies planned in E2112. While our data will not independently contribute to the validation effort, it will further expand the pharmacodynamic data and add measurably to our interpretation of the clinical data.

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12.2 Population Pharmacokinetics

The population pharmacokinetic analysis for entinostat will be used to describe the pharmacokinetics of entinostat in patients and to assess the effects of patient factors on the entinostat pharmacokinetics. Specific details for this analysis will be provided in a separate population pharmacokinetic analysis plan.

12.3 Future Research Studies

The following correlative studies are proposed as outlined below. Final analysis of the proposed studies requires the results of the parent study. When sufficient information is available from the parent study a full correlative science proposal or amended protocol document detailing the scientific hypothesis, research plan,

assay methods for use of the biospecimens, and a formal statistical analysis plan with adequate power justification will be submitted to and reviewed by CTEP.

12.3.1 Pharmacogenomics

Genomic DNA isolated from whole blood at baseline can be used to genotype candidate genes that may affect pharmacodynamic effects of response and toxicity. We will store the sample obtained at baseline for potential future analyses in the event that further information becomes available from the literature about promising candidate genes that may predict response to exemestane and/or entinostat.

12.4 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secure data transfer to the ECOG-ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator.

13. Electronic Data Capture

Please refer to the E2112 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

13.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

14. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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A Randomized Phase III Trial of Endocrine Therapy plus Entinostat/Placebo in Patients with Hormone Receptor-Positive Advanced Breast Cancer

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

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Guidelines for Submission of Pathology Materials

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E2112 A Randomized Phase III Trial of Endocrine Therapy plus Entinostat/Placebo in Patients with Hormone Receptor-Positive Advanced Breast Cancer

Instructions:

1. Pathology submissions:
   - Representative primary tumor FFPE block
   - Representative metastatic tumor FFPE block

   NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:
   - One (1) H&E slide, and
   - Twenty (20) 4 µm unstained air-dried plus slides, and
   - One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (1-844-744-2420). Adequately label every slide and core submitted.

   If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.
2. The following items are to be included with the pathology materials.
   - Copy of the surgical pathology report and surgical procedure report.
   - STS generated shipping manifest form

   NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, for interactions between the ECOG-ACRIN CBPF, the central testing laboratory and the site, and will help to expedite any required communications with the institution (including site pathologists).
3. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Rev. 10/16 Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Boulevard
   Houston, TX 77030

If you have any questions concerning the above instructions or if you anticipate any problems in submitting the required pathology material, contact the Pathology Coordinator at the ECOG-ACRIN CBPF by telephone 1-844-744-2420, by fax (713) 563-6506, or by email eacbpf@mdanderson.org.

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MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for E2112: A Randomized Phase III Trial of Endocrine Therapy plus Entinostat/Placebo in Patients with Hormone Receptor-Positive Advanced Breast Cancer.

A patient has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for banking for future undefined research.

Return the surgical pathology report(s), the slides and/or blocks and any other required material to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN CBPF for undefined future research studies. Paraffin blocks will be returned upon written request for purposes of patient management. If you have any questions regarding this request, please contact the ECOG-ACRIN CBPF at 1-844-744-2420, or by fax (713) 563-6506.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

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A Randomized Phase III Trial of Endocrine Therapy plus Entinostat/Placebo in Patients with Hormone Receptor-Positive Advanced Breast Cancer

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Randomized Phase III Trial of Endocrine Therapy plus Entinostat/Placebo in Patients with Hormone Receptor-Positive Advanced Breast Cancer

Appendix III

Patient Pill Calendar

NOTE TO SITES: Local study teams may use a different calendar format as long as all drug dates/doses are recorded for study reporting/data completion. These should be shared with the Protocol Chair/Study Liaison, and approved by local IRBs per local guidelines, prior to use.

Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. If you forget, the missed pills will not be taken later.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.

Patient Pill Calendar-Exemestane and Entinostat/Placebo

This is a calendar on which you are to record the time and number of pills you take each day for the study. You should take your scheduled dose of each pill. If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided.

Instructions:

Exemestane: Take by mouth once every day with food.

Dose of each pill: 25 mg

Number of pills to take at each dose: 1

Total dose to take each day: 25 mg

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Entinostat/Placebo: Take by mouth once each week on an empty stomach (either 1 hour before and 2 hours after meals).

Dose of each pill: _____

Number of pills to take at each dose: _____

Total dose to take each week: _____

Please bring this study diary/calendar and your bottle of entinostat/placebo to each study visit.

CYCLE DAY	Date			Exemestane		Entinostat/ Placebo		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	(Month / Day / Year)			# pills	Time	# pills	Time	
1				1				
2				1				
3				1				
4				1				
5				1				
6				1				
7				1				
8				1				
9				1				
10				1				
11				1				
12				1				
13				1				
14				1				
15				1				
16				1				
17				1				
18				1				
19				1				

CYCLE DAY	Date			Exemestane		Entinostat/ Placebo		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	(Month / Day / Year)			# pills	Time	# pills	Time	
20				1				
21				1				
22				1				
23				1				
24				1				
25				1				
26				1				
27				1				
28				1				

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Appendix IV

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

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Appendix V

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix VI

E2112 Collection and Shipping Kit Order Instructions

As of February 12, 2016 Specimen Collection/Shipping Kits are provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Starter kits are not available. Kit requests are to be made AFTER patient randomization.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at 512-439-2000.

Ordering process:

- At time of patient randomization, provide the contact for kit ordering in OPEN
- Following randomization of the patient to the trial, Go to the website www.cenetron.com and Click on the “Order Kits” button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The Order Form is not study specific and can be used for any study. Complete the online form as follows
  - **Sponsor (REQUIRED):** ECOG-ACRIN
  - **Contact Name (REQUIRED):** Name of the site’s kit contact. Should match the name of the individual provided in OPEN as the kit contact
  - **Protocol Number (REQUIRED):** E2112
  - **Phone Number (REQUIRED):** Phone number of the kit contact. Please insure that this is a number that can be reached from an external caller.
  - **FAX Number:** Fax number of the kit contact
  - **Investigator:** Last name of the kit contact is adequate
  - **Email (REQUIRED):** The email of the site’s kit contact. Must be entered twice to confirm
  - **Date Supplies Needed (REQUIRED):** Add 3 business days or more to order date. E.g. if ordering on 2/5/2016, indicate 2/10/2016 to accommodate the weekend. Reminder that holidays must also be considered in this timeline.
  - **KIT NAME (required):** E2112 Collection Kit
  - **Quantity:** 1
  - **Comments:** Provide E2112 Case ID and full shipping address
    - “Patient case ID =” #####
    - Ship kit to Name of the individual to whom the kit is shipped. May be different than the kit contact provided above.
    - Full street address, town, state and zip code
  - Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN case number and complete shipping address. If information is missing kit processing will be delayed.

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Appendix VII

E2112 Mandatory Participating Site Training Form

Protocol Number	**E2112**
Protocol Name	**A Randomized Phase III Trial of Endocrine Therapy Plus Entinostat/Placebo in Patients with Hormone Receptor-Positive Advanced Breast Cancer**

Instructions for Mandatory Participating Site Training Course:

- Each site participating in E2112 is required to have at least ***one person*** (i.e. research coordinator or investigator, etc) from the research staff complete ECOG-ACRIN's E2112 mandatory participating site training course.
- This course must be completed ***PRIOR to the first patient enrollment*** for the site.
- ***An ENROLLMENT BLOCK*** is in place within the OPEN system which will prevent the site from enrolling patients until this training requirement is complete.
- Please note that ECOG-ACRIN recommends ***all research staff*** (CRAs, Data Managers, Imaging Staff, Investigators, Pharmacy Staff, etc) involved in E2112 complete the training course.

The training course is available 24/7 via the following URL:
http://coccg.mindflash.com/PublicCoursePage.aspx?c=832897692

Please complete the bottom of this form and submit it directly to the CTSU Regulatory Office via Fax: 215-569-0206 or Email: CTSURegulatory@ctsu.coccg.org.

Section A: Please provide the name of one of the individuals who completed the E2112 mandatory participating site training course.

Name	**CTEP ID (Associate or Investigator)**

Section B: Please provide **ALL Site Name(s)** and **Site CTEP IDs** where the research staff that completed this course may enroll a patient to E2112:

Site Name	**Site CTEP ID (example: AL000)**

Section C: Please complete.

_____
Name

_____
Signature

_____
Date

Thank you for your participation.

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Appendix VIII

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Entinostat/Placebo, or within 3 months of the patient's last dose of Entinostat/Placebo must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

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How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERs)

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERs.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- *It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERs report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

It must be reported via CTEP-AERs as Grade 4 "*Pregnancy loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A disorder characterized by cessation of life occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERs AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to Entinostat/Placebo must also be reported via CTEP-AERs.

It must be reported via CTEP-AERs as Grade 4 "Death neonatal" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Additional Required Forms:

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When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix IX

E2112 Covance Site Information/Initial Kit Order Form

******If your site is not participating in the optional population PK study, this form is not required******

Please complete this form for the initial shipment of three (3) kits and the Site Laboratory Instruction Manual. Covance requires ten (10) days to process this form and ship out the initial kits. Please complete and Email this form to Syndax (E2112@Syndax.com) or Fax to (781-419-1420, Attn: MaryAnn Ashley) as soon as possible.

Once two of the three initial kits are received by Covance an auto-resupply of one kit will be sent out by Covance. If more kits are needed than provided by the auto-resupply, please contact Covance directly at the number provided in the Site Laboratory Instruction Manual. Shipment usually takes about five (5) to seven (7) business days.

Attn: Clinical Trials Manager

Date:

NCI CTEP ID#:

Please write using block letters

STUDY COORDINATOR WHERE KITS SENT TO

LAST NAME	
FIRST NAME	
STUDY ROLE	
INSTITUTION	
DEPARTMENT	
BUILDING/FLOOR/ ROOM*	
STREET	
CITY/POSTAL CODE/COUNTRY	
TELEPHONE	
FAX	
EMAIL	
INVESTIGATOR LAST NAME	
INVESTIGATOR FIRST NAME	

***Mandatory information for hospital, clinic or large sites.**

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Appendix X

Sarcopenia Imaging Substudy

Impact of muscle quality and quantity on outcome in patients receiving endocrine based therapy for metastatic breast cancer in ECOG- 2112

Investigator: Tarah Ballinger, M.D., Indiana University

Statistician: Constantine Gatsonis, PhD, Brown University

Background

Observational data investigating the relationship between body habitus and outcome or toxicity in breast cancer has been largely centered on weight-based metrics such as BMI, with variable and inconsistent results. Body weight alone does not tell a full story, as body composition is highly variable with respect to muscle and adipose tissue. Muscle is a large, active endocrine organ affecting physical function, quality of life, metabolism, and inflammation, and may impact outcome or toxicity in metastatic breast cancer (MBC) patients receiving endocrine based therapies.

Rev. Add7

Low muscle mass (LMM) has been associated with poorer outcome and increased toxicity in advanced cancer[1]. Low muscle attenuation (LMA), reflecting muscle "quality" and intramuscular fat infiltration, is also associated with poor outcome. In comparison to muscle mass, muscle attenuation correlates better with muscle strength and function[2]. The few studies that have investigated these parameters in patients with MBC have been small and focused on patients receiving cytotoxic chemotherapy[3-5]. The largest of these was a retrospective study of patients receiving first line chemotherapy, finding no significant difference in overall survival based on LMM (40 versus 30 months, p=0.07), but a significantly reduced survival for those patients with LMA (23 versus 15 months, p = 0.005)[5].

To date, there has been no evaluation of how muscle characteristics affect outcome or toxicity in patients receiving endocrine therapy for MBC. The ongoing study E2112, a randomized, double-blinded phase III study of exemestane with or without the HDAC inhibitor entinostat with co-primary objectives of progression free survival (PFS) and/or overall survival (OS), offers a homogeneous population with centrally collected imaging and outcome follow-up to investigate this question.

Specific hypotheses:

1. Primary: Low muscle attenuation (LMA) is prognostic of poor overall survival in patients receiving endocrine based therapy for metastatic breast cancer (MBC)
2. Secondary: Low muscle mass (LMM) is prognostic of poor overall survival in patients receiving endocrine based therapy for MBC.

Objectives:

1. Primary: To determine the prognostic value of baseline LMA by CT imaging on overall survival in patients receiving endocrine based therapy for MBC.
2. Secondary:
   - To determine the prognostic value of baseline LMM by CT imaging on overall survival in patients receiving endocrine based therapy for MBC.

- To determine the prognostic value of LMA and LMM on overall survival in the subset of patients receiving endocrine based therapy for metastatic breast cancer who have sarcopenic obesity at study entry.
- To assess the correlation between LMA, LMM, and sarcopenic obesity with PRO_CTCAE of muscle ache and joint pain at 3 months.
- To assess the correlation between LMA, LMM, and sarcopenic obesity with patient reported health related quality of life score at 3 months.
- To determine the optimal stratification for LMA and LMM to predict overall survival.

Study Design:

In this proposed imaging correlative study, evaluation of muscle attenuation and mass will be determined using baseline CT scans collected for central review. A transverse cut at the L3 level will be extracted, as muscle area at this level is linearly related to whole body muscle mass[6]. SliceOmatic software (version 5, Tomovision) will be used to process images, providing a highly accurate estimation of cross-sectional skeletal muscle area and muscle attenuation with high inter-observer reliability[7]. The software is semi-automated and will be run by two independent investigators, with a subset of images read by both investigators to determine a coefficient of variation. LMM is defined as skeletal muscle index (SMI, lean muscle area/height, cm^2/m^2) less than 41 and LMA will be defined as average muscle density less than 25 HU, or less than 33 HU if the patient is overweight/obese by BMI. These cut-points are based on previously determined thresholds associated with reduced survival in patients with metastatic solid tumors[1]. An additional exploratory objective will be to determine whether there are alternate cut-points predictive of survival in this particular population based on optimal stratification.

This evaluation will allow us to establish prevalence of LMM and LMA in this population, and to investigate the importance of muscle mass and quality, rather than body weight alone, on outcomes and toxicity in patients receiving AI-based therapy for MBC. This may lead to further refinement of prognostic/stratification criteria, support development of targeted exercise interventions, and investigation of AI drug resistance or alternate dosing strategies. In addition, the use of CT software to quickly calculate body composition measures may have important clinical applications across many treatments and disease types within ECOG-ACRN trials.

Statistical Design and Analysis:

Primary Endpoint:

- Overall Survival (OS) defined as time from start of on-study therapy to death from any cause.

Sample size and power justification:

We will plan initially to evaluate the study population as a whole (n=600), and later analyze the treatment and placebo groups separately (n=300 per group) once primary data are available. For the primary objective, assuming 60% of participants have LMA, we will have a 95% power to detect a difference in median survival time between 20 and 28 months (HR 1.4) for those with LMA versus those without LMA, based on a two- sided log rank test with type I error rate of 0.05. Reducing the sample size to 300 participants, we will achieve a 73% power to detect the same difference in median survival time.

Study population	% LMA	Median survival for LMA (month)	Median survival for non-LMA (month)	Hazard ratio	Study power(%)
600	60%	20	28	1.4	95
300	60%	20	28	1.4	73

Statistical analysis plan:

1. Primary aim:
   - To determine the prognostic value of LMA on overall survival in patients receiving endocrine based therapy for metastatic breast cancer.
     - Kaplan Meier survival curve and log-rank test are used to test the difference in OS between the LMA participants and the non-LMA participants. Multivariable Cox proportional hazard model will be used to model the association between LMA and OS while adjusting for age, race, prior chemotherapy, ECOG PS and BMI.
2. Secondary aims:
   - To determine the prognostic value of LMM on overall survival in patients receiving endocrine based therapy for metastatic breast cancer.
     - Kaplan Meier survival curve and log-rank test are used to test the difference in OS between the LMM participants and the non-LMM participants.
   - To determine the prognostic value of LMA and LMM on overall survival in the subset of patients receiving endocrine based therapy for metastatic breast cancer who have sarcopenic obesity at study entry.
     - Kaplan Meier survival curve and log-rank test are used to test the difference in OS between the sarcopenic obese participants who had LMA or LMM and those without LMA or LMM.
   - To assess correlation between LMA, LMM, and sarcopenic obesity with PRO_CTCAE of muscle ache and joint pain at 3 months

     We will use two sample t-test to compare the muscle ache score or joint pain score between participants who had LMA (or LMM, or sarcopenic obesity) with those who didn't.
   - To assess the correlation between LMA, LMM, and sarcopenic obesity with patient reported health related quality of life score at 3 months.

     We will use two sample t-test to compare the quality of life score between participants who had LMA (or LMM, or sarcopenic obesity) with those who didn't.
   - To determine the optimal stratification for LMA and LMM to predict overall survival.
     - We will use a search algorithm, together with the method of the time-dependent ROC curve to determine the optimal cut-off point for the determination of LMA and LMM to identify groups with differential overall survival.

References

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7. van Vugt JL, Levolger S, Gharbharan A, et al: A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. J Cachexia Sarcopenia Muscle 8:285-297, 2017