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Press Release

ECOG-ACRIN Opens Phase III Trial of Syndax's Entinostat in Advanced Breast Cancer

Entinostat is being investigated in patients with advanced hormone receptor-positive breast cancer by the ECOG-ACRIN Cancer Research Group in its latest trial, E2112.

PHILADELPHIA, Pa., and WALTHAM, Mass., March 20, 2014/PRWeb – The ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) and Syndax Pharmaceuticals, Inc., announced today that patient recruitment has begun for E2112, a randomized phase III clinical trial of Syndax's entinostat in treatment of patients with advanced breast cancer. The trial will evaluate whether the addition of entinostat to endocrine therapy (exemestane) improves progression-free survival and/or overall survival in men and postmenopausal women with hormone receptor-positive, human epidermal growth factor 2-negative advanced breast cancer who have previously progressed on a nonsteroidal aromatase inhibitor.

E2112 was designed and is being conducted by ECOG-ACRIN under the sponsorship of the National Cancer Institute (NCI). Syndax Pharmaceuticals, the developer of entinostat, is supporting E2112 under a Cooperative Research and Development Agreement with the NCI and a separate agreement with ECOG-ACRIN.

"This trial is designed to determine whether the addition of entinostat to endocrine therapy improves progression-free survival or overall survival in patients with advanced breast cancer," said study lead investigator Roisin M. Connolly, MB, BCh, Assistant Professor of Oncology, Johns Hopkins University, Baltimore, Md. "Furthermore, E2112 is a registration trial, which if successful, could lead to FDA approval of entinostat in combination with exemestane in patients with advanced HR-positive breast cancer."

Entinostat, an oral synthetic benzamide derivative that acts by binding to and inhibiting class one histone deacetylase (HDAC), has been designated a Breakthrough Therapy by the Food and Drug Administration (FDA) when used in combination with exemestane in hormone receptor-positive (HR+) advanced (locally advanced or metastatic) breast cancer. Entinostat has also been investigated as part of combination therapy in patients with non-small cell lung cancer, acute myeloid leukemia and acute lymphoblastic leukemia. Exemestane (brand name Aromasin) is a steroidal aromatase inhibitor that acts through irreversible binding and inactivation of the aromatase enzyme, resulting in a reduction in circulating estrogen levels.

"ECOG-ACRIN's opening of this phase III study is an important milestone for Syndax and the development of entinostat," said Arlene M. Morris, chief executive officer of Syndax. "Together with ECOG-ACRIN and the NCI, we've designed a rigorous clinical trial capable of examining entinostat's ability to improve clinical outcomes in patients with hormone receptor-positive advanced breast cancer. Because the study is being conducted under a Special Protocol Assessment, Syndax expects that positive data from either of the two primary endpoints, progression-free survival or overall survival, will enable it to submit a New Drug Application to the FDA."

E2112 has an accrual goal of 600 patients and recruitment to the trial will involve participation from the three other network groups of the NCI National Clinical Trials Network that, like ECOG-ACRIN, conduct cancer research in adults.

Aromatase inhibitors, including exemestane, are one of the most commonly prescribed initial treatments in postmenopausal patients with advanced breast cancer. Median progression-free survival in patients with HR+ advanced breast cancer who have previously progressed on a nonsteroidal aromatase inhibitor is approximately three to seven months, thus new approaches are urgently required. Therapeutic strategies that combine endocrine therapies with novel agents aim to improve outcomes for patients by overcoming drug resistance.

A potential mechanism of resistance to endocrine therapy involves changes in gene expression secondary to epigenetic modifications, which might be modulated with the use of HDAC inhibitors such as entinostat. Because of the frequency of detection of epigenetic alterations in breast cancers, agents that target these changes are of great interest.

“Targeting epigenetic changes, which contribute to drug resistance and are generally thought to be reversible, represents an active area of new drug investigation,” said Dr. Connolly. “A potentially promising mechanism to overcome resistance to standard therapies may lie in the use of epigenetic modifiers, such as HDAC inhibitors.”

A previous phase II study, ENCORE 301, has shown that the addition of entinostat to exemestane, when compared to placebo plus exemestane, resulted in an improvement in both progression-free survival and overall survival, with an acceptable toxicity profile ([Yardley J Clin Oncol 2013](#)). “We hope that the results of E2112 will confirm this benefit, offering a new treatment option for this patient population,” said Dr. Connolly.

“The E2112 trial continues the focus of the ECOG-ACRIN Breast Committee to join with our partners at the NCI and in industry to bring new therapies to our patients,” said committee chair Kathy D. Miller, MD, Ballve Lantero Scholar in Oncology and Associate Professor, Indiana University, Bloomington, Ind. “E2112 study findings showing a positive treatment effect for entinostat would provide the rationale to evaluate it in the first-line advanced and adjuvant breast cancer settings.”

The E2112 trial contains secondary patient-reported outcomes (PRO) endpoints to evaluate differences between arms in treatment toxicities, reduced symptom burden as an indicator of treatment response, and overall health-related quality of life. PRO measures are common in ECOG-ACRIN therapeutic trials due to the scientific aims of its [Cancer Control and Outcomes Program](#), which seeks to increase understanding, from the patient perspective, about how novel therapies impact quality of life. E2112 investigators are also collaborating with the NCI to validate a new system that ascertains in real time the presence, severity, and interference of symptoms experienced by patients in the trial. The measure is called the [Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, or PRO-CTCAE](#).

About the ECOG-ACRIN Cancer Research Group

The ECOG-ACRIN Cancer Research Group is a multidisciplinary, membership-based scientific organization that designs and conducts biomarker-driven cancer research involving adults who have or are at risk of developing cancer. The Group was formed in May 2012 by a merger that combined the complementary strengths of the Eastern Cooperative Oncology Group (ECOG) in cancer therapy and the American College of Radiology Imaging Network (ACRIN) in cancer imaging. ECOG and ACRIN were two highly respected National Cancer Institute (NCI)-sponsored cancer cooperative groups. ECOG-ACRIN comprises nearly 650 member institutions in the United

States and around the world. Approximately 6,000 physicians, translational scientists and associated research professionals from the member institutions are involved in Group research, which is organized into three scientific programs: Cancer Control and Outcomes, Therapeutic Studies, and Biomarker Sciences. ECOG-ACRIN is supported primarily through NCI research grant funding, but also receives funding from private sector organizations through philanthropy and collaborations. It is headquartered in Philadelphia, Pa., as is PrECOG, LLC, a not-for-profit company that partners with ECOG-ACRIN and industry to develop and conduct clinical trials in all areas of oncology. For more information, visit www.ecog-acrin.org or call 215.789.3631.

About Syndax Pharmaceuticals

Syndax is developing entinostat for the treatment of patients with therapy-resistant cancers. Entinostat is designed to prolong the effectiveness of current cancer treatments through an epigenetic mechanism and has been designated a Breakthrough Therapy by the FDA when used in combination with exemestane in HR+ advanced breast cancer. The company holds worldwide rights to entinostat, an oral, selective HDAC inhibitor that is being evaluated in combination with exemestane in E2112, a pivotal phase III clinical study for the treatment of HR+ advanced breast cancer.

Cautionary Note on Forward-Looking Statements

This press release contains forward-looking statements. Forward-looking statements contained in this press release include statements about the timing and results of the phase III trial, whether the E2112 trial will serve as a basis for regulatory approval, potential changes in clinical practice, and the timing and results of the FDA approval process generally. Words such as "may," "will," "expect," "plan," "anticipate," "estimate," "intend" and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. These forward-looking statements are not guarantees of future performance and involve a number of unknown risks, assumptions, uncertainties and factors that are beyond Syndax's control. All forward-looking statements are based on Syndax's expectations and assumptions as of the date of this press release. Actual results may differ materially from these forward-looking statements. Except as required by law, Syndax expressly disclaims any responsibility to update any forward-looking statement contained herein, whether as a result of new information, future events or otherwise.

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