



**SYNDAX ANNOUNCES START OF NCI SPONSORED PHASE 2 STUDY OF ENTINOSTAT IN COMBINATION IN TRIPLE NEGATIVE BREAST CANCER**

***--Trial based on data appearing in Cancer Research showing entinostat elicits hormone sensitivity in animal models--***

**Waltham, Mass. – March 1, 2011** – Syndax Pharmaceuticals, a clinical-stage epigenetics oncology company, announced the National Cancer Institute (NCI) will sponsor a multi-center phase 2 study of Syndax's lead product entinostat, a novel inhibitor of histone deacetylases (HDAC), and anastrozole, an aromatase inhibitor, in postmenopausal women with operable triple negative breast cancer to evaluate biomarkers and surrogates for response. The trial, to be conducted under a Cooperative Research and Development Agreement (CRADA) executed between the NCI and Syndax, will investigate whether patient tumors can be reprogrammed to express estrogen receptor and render them to be sensitive to hormonal agents. This trial is based on animal data being published in the March 1, 2011, issue of *Cancer Research*.

Laboratory studies by Dr. Angela Brodie, professor of pharmacology and experimental therapeutics, and Gauri J. Sabnis, Ph.D., assistant professor of pharmacology and experimental therapeutics at the University of Maryland School of Medicine, in collaboration with Saraswati Sukumar, M.S., Ph.D., professor of oncology and pathology at the Johns Hopkins University School of Medicine, provided the basis for the phase 2 clinical trial. Their work demonstrates that entinostat induces hormone sensitivity in an animal model of triple negative breast cancer and that the combination with aromatase inhibitors prevents tumor growth as well as tumor metastasis.

"In the pre-clinical study that is being published in *Cancer Research* we demonstrated that entinostat can induce re-expression of estrogen receptor and aromatase in triple negative breast cancer cell lines and render them sensitive to an aromatase inhibitor," said Saranya Chumsri, M.D., assistant professor of medicine at the University of Maryland School of Medicine and a medical oncologist at the University of Maryland Marlene and Stewart Greenebaum Cancer Center, principal investigator of the trial. "Moreover the combination of entinostat with an aromatase inhibitor suppressed the growth of tumors in an animal model of triple negative breast cancer. Given this promising data, we are evaluating entinostat with anastrozole in a neoadjuvant setting to see if we can extend the benefit of hormone therapy seen in patients with estrogen receptor positive breast cancer to those with triple negative disease - where cytotoxic therapy is the only treatment option."



While the mortality rate in breast cancer has decreased in the past few decades, some subsets still have poor outlooks. With the advent of targeted therapy, particularly endocrine and anti-human epidermal growth factor receptor 2 (HER2) therapies, the outcome of breast cancer has changed dramatically. Nevertheless, approximately 15 to 20 percent of breast cancers lack expression of all three constructive cell surface receptors, namely estrogen receptor (ER), progesterone receptor (PR) and HER2, hence the term “triple negative” breast cancer (TNBC). Due to an absence of ER and/or PR, these tumors typically do not respond to endocrine therapy like tamoxifen and aromatase inhibitors, which have minimal toxicities and are generally well tolerated. For that reason, the treatment option for these tumors is solely chemotherapy.

It has been demonstrated in multiple studies that the loss of ER protein expression is a result of epigenetic changes such as aberrant DNA methylation and recruitment of histone modifying enzymes to the ER promoter in the tumors. Targeting such changes with epigenetic treatments has been validated as a successful strategy in other cancer indications and the data being published suggest that it may be effective as a therapeutic intervention in the treatment of ER-negative breast cancers.

“Triple negative breast cancer is a particularly challenging form of breast cancer that is normally unresponsive to hormone therapy as well as many forms of chemotherapy,” said Joanna Horobin, M.D., president and chief executive officer of Syndax. “The pre-clinical research provides us with a provocative question. Can we turn some of these tumors into estrogen receptor positive breast cancer and extend the benefit of well tolerated hormone therapy to this otherwise underserved patient population? The clinical study is designed to address this issue.”

This multi-center trial sponsored by NCI is being coordinated through the University of Chicago Consortium.

### **About Triple Negative Breast Cancer**

Approximately 15-20% of all breast cancers do not express functional cell surface receptors like ER, PR, and HER2. Patients with triple negative breast cancer (TNBC) often have poorer prognosis compared to other breast cancer subtypes. It is commonly misconceived that TNBC is more sensitive to chemotherapy. Although higher pathologic complete response rate (pCR) was observed in TNBC (25–45%) compared to luminal breast cancers (6–7%), patients with TNBC had worse four-year distant disease-free and overall survival<sup>1</sup>.



## **About Entinostat**

Entinostat is an orally bioavailable, highly selective, class I histone deacetylase (HDAC) inhibitor with a long half-life that allows for weekly or every-other-week dosing. Entinostat is currently being investigated at Syndax in multiple phase 2 clinical studies: in advanced breast cancer in combination with aromatase inhibitors; in combination with erlotinib in metastatic lung cancer and as a single agent in Hodgkin's lymphoma. Entinostat also is being studied in various cancers including advanced non-small-cell lung cancer and in advanced colorectal cancer in combination with azacitidine under the CRADA with the NCI.

Research has shown that HDACs are involved in the expression of various genes, such as the estrogen receptor, that regulate cell growth, differentiation and apoptosis. Such genes are frequently silenced in cancer cells through the over-expression of enzymes including HDACs. HDACs are therefore recognized as promising targets for cancer treatment. Further, studies have demonstrated that HDAC inhibition can significantly enhance anti-cancer activity when used in combination with a broad range of anti-cancer agents. The potential therefore exists to overcome tumor resistance to targeted agents.

## **About Anastrozole**

Anastrozole will be provided by AstraZeneca Pharmaceuticals LP under a Clinical Supply Agreement between NCI and AstraZeneca for the phase 2 combination trial.

## **About Syndax**

Syndax Pharmaceuticals, Inc. is a Waltham, MA-based, oncology-focused pharmaceutical company. Syndax is building a portfolio of new oncology products to extend and improve the lives of patients by developing and commercializing novel cancer therapies in optimized, mechanistically driven combination regimens. Formed in 2005, the company's intellectual property is based on work from scientific founder Ronald Evans, Ph.D., recipient of the 2004 Albert Lasker Prize for Basic Medical Research, a member of the National Academy of Sciences, a professor at the Salk Institute for Biological Studies and a Howard Hughes Medical Institute Investigator. Syndax has worldwide rights to develop and commercialize entinostat and is backed by top-tier Venture Capital firms: Domain Associates, MPM Capital, Avalon, Pappas and Forward Ventures. For more information please visit [www.syndax.com](http://www.syndax.com).

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<sup>1</sup> WJ I, LA C: What is triple-negative breast cancer? Eur J Cancer:doi:10.1016/j.ejca.2008.09.034, 2008