Syndax Pharmaceuticals Presents Data Linking Pharmacodynamic Marker to Clinical Benefit in Advanced Breast Cancer Patients

-- Study associates changes in entinostat-dependent protein modification with prolonged progression free survival --

-- Data selected for oral presentation at AACR Molecular Targets and Cancer Therapeutics Conference --

San Francisco, CA and Waltham, Mass. – Nov. 13, 2011 – Syndax Pharmaceuticals, Inc., a clinical-stage epigenetics oncology company, announced today that pharmacodynamic analysis in a subset of patients from ENCORE 301, a placebo-controlled, randomized phase 2 study of exemestane with and without entinostat in postmenopausal estrogen-receptor positive breast cancer patients demonstrates the association of the pharmacodynamic marker lysine hyperacetylation with clinical outcome. The pharmacodynamic results will be presented as an oral presentation at the **American Association for Cancer Research (AACR) Molecular Targets and Cancer Therapeutics Conference** in San Francisco, CA today. The study was previously announced to have hit the primary endpoint of improving progression-free-survival, showing that patients who received entinostat, a novel, oral small molecule inhibitor of class I histone deacetylases, with the aromatase inhibitor exemestane, lived longer without their disease getting worse than people who received exemestane alone. Moreover, in those patients receiving entinostat where acetylation of protein lysine was demonstrated in peripheral blood cells, the progression free survival was markedly extended.

"Consistent with entinostat's mechanism of action, the prolonged progression-free survival in exemestane and entinostat-treated patients with increased acetylation is to our knowledge the first time that this surrogate marker of HDACi activity has been linked with clinical outcomes in a randomized study" said Peter Ordentlich, Ph.D., Executive Director, Translational Science and Founder. "Such data may allow physicians to identify which patients are most likely to benefit from entinostat in breast cancer, as well as potentially other tumor types."

In ENCORE 301 blood samples were obtained in a planned subset of patients before treatment and again within the first 2 weeks of starting treatment (N=49: exemestane and entinostat = 27, exemestane and placebo = 22). Baseline characteristics among these 49 patients with metastatic breast cancer were consistent with the overall study population. Acetylation in entinostat-treated patients was associated with prolonged progression-free survival across all peripheral mononuclear cell types analyzed. In exemestane and entinostat-treated hyperacetylators versus non-acetylators, 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=0.45, 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).

"As a clinician treating breast cancer patients for 20 years, I am always interested in improving outcomes and ideally finding new ways to determine whether a treatment is right for my patient," said Joyce A. O'Shaughnessy, M.D., Co-Chair, Breast Cancer Research, Baylor Sammons Cancer Center, Texas Oncology and US Oncology "For years researchers have been interested in the association with HDACi-induced hyperacetylation and outcomes, but up until now no one has been able to demonstrate it. These data demonstrate that there is promise and we can potentially improve how we identify the right patient to benefit from entinostat."

The pharmacodynamics data from ENCORE 301 will be presented in an oral session called the Proffered Paper Session 1 today, Sunday, November 13 from 4:30 to 6:00 PM PT in San Francisco, CA during the AACR Molecular Targets and Cancer Therapeutics Conference.

ENCORE 301

ENCORE 301 (ENtinostat Combinations Overcoming REsistance) was a multicenter, randomized, double-blind, placebo-controlled, phase 2 study of exemestane with and without entinostat in 130 postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer, progressing on treatment with the non-steroidal aromatase inhibitors anastrozole or letrozole. The primary endpoint of the study was progression-free survival. Other endpoints included objective response rate (ORR), clinical benefit rate (CBR), overall survival (OS) and safety and tolerability. All patients had received prior hormonal therapy (1 prior line 42%; >1 prior line 58%), and 33% had received prior chemotherapy in the advanced breast cancer setting. The results of this study with well-balanced arms included the following:

- In the intent-to-treat population progression-free survival was significantly longer (defined prospectively as 1-sided p <0.10) with exemestane plus entinostat than with exemestane plus placebo (4.28 versus 2.27 months, respectively; hazard ratio (HR) = 0.73; p=0.06);
- In the intent-to-treat population, with a median follow-up of 18 months, overall survival was significantly longer with exemestane plus entinostat than with exemestane plus placebo (26.94 versus 20.33 months, respectively; hazard ratio (HR) = 0.56; p=0.027);
- In the subset of entinostat patients with protein acetylation data (n=27), median PFS increased to over six months in the patients exhibiting protein lysine hyperacetylation;
- Entinostat combined with exemestane was well tolerated with the most frequent adverse events (AE) consisting of fatigue, gastrointestinal disturbances and hematologic abnormalities; and
- Serious AE rate was similar for exemestane plus entinostat (13%) and exemestane plus placebo (12%).

Breast Cancer and Hormone Therapy

Approximately 230,000 new cases of invasive breast cancer are diagnosed in women annually in the United States and there are approximately 150,000 women living with metastatic breast cancer (MBC). Over 70 percent of women with breast cancer have estrogen receptor-positive (ER+) breast cancer. The most effective cancer treatments target the underlying biology and in breast cancer the most common oncogenic driver is estrogen receptor signaling. Blocking estrogen activity with aromatase inhibitors represents an effective treatment for most ER+ MBC patients, however acquired drug resistance to aromatase inhibitors leads to disease progression, ultimately requiring less effective, more toxic chemotherapies.[1] Delaying resistance and disease progression represents a significant unmet need that could prolong survival while decreasing health care costs associated with chemotherapy and hospitalization.

About Entinostat
Syndax's lead product entinostat is a novel, oral small molecule inhibitor of class I histone deacetylases, key enzymes that alter the structure of chromatin to control gene expression. Entinostat is differentiated from other members of the class through its unique selectivity profile, pharmacokinetic properties and safety profile. Entinostat has been studied in more than 600 cancer patients where objective tumor responses have been observed in both solid and hematologic malignancies.
Breast cancer animal models demonstrated that resistance to aromatase inhibitors occurs through up-regulation of growth factor signaling pathways and down-regulation of estrogen receptor alpha. Entinostat effectively down-regulates growth factor signaling in breast cancer cells where these pathways are active. Entinostat also up-regulates the expression of ER in breast cancer cells which have negligible or undetectable levels of estrogen receptor. The ability to target multiple mechanisms of resistance establishes entinostat as a promising candidate for preventing and overcoming aromatase inhibitor resistance through epigenetic modulation. In pre-clinical testing entinostat induced tumor regression when combined with aromatase inhibitors after the development of aromatase inhibitor resistance.

Additional phase 2 studies with entinostat have demonstrated promising results in combination with the EGFR-TKI erlotinb (ENCORE 401) in non-small cell lung cancer and as a single agent in Hodgkin's lymphoma (ENGAGE 501). Results from the ENCORE clinical program provide the basis for moving entinostat into pivotal, phase 3 testing in metastatic breast and lung cancer settings.

About Syndax
Syndax Pharmaceuticals, Inc. is a Waltham, MA-based, late-stage, oncology-focused pharmaceutical company. The company 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. Syndax has worldwide rights to develop and commercialize entinostat which has shown promise in randomized clinical trials in solid tumors. Syndax is backed by top-tier Venture Capital firms: Domain Associates, MPM Capital, Avalon, Pappas and Forward Ventures. Formed in 2005, Syndax'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. For more information please visit www.syndax.com.

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