Synta Announces Results Demonstrating Potent Ganetespib Activity across Broad Range of Crizotinib-Resistant ALK+ NSCLC models at the European Lung Cancer Conference

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-Broader range of activity seen against resistant mutations than seen with direct ALK inhibitors-
-Complementary mechanism and positive results in xenograft models suggest promise for combination approach with ganetespib plus direct ALK inhibitors-

LEXINGTON, Mass., Apr 18, 2012 (BUSINESS WIRE) --Synta Pharmaceuticals Corp. (NASDAQ: SNTA) presented preclinical results today at the 3rd European Lung Cancer Conference in Geneva, Switzerland that show ganetespib, a potent inhibitor of heat shock protein 90 (Hsp90), equally inhibits growth of both crizotinib-sensitive and -resistant cancer cells driven by the EML4-ALK fusion protein regardless of ALK mutation status. Additional results from mouse ALK+ NSCLC xenograft models demonstrated anticancer activity with combined administration of ganetespib and crizotinib that was significantly higher than when either drug was administered alone.

Direct ALK inhibitors such as crizotinib act by targeting a particular site on the ALK protein and reducing its ability to drive cancer cell growth and proliferation. Secondary mutations in the ALK protein generate resistance to these ALK inhibitors. Both crizotinib and second-generation ALK inhibitors have shown mixed results against acquired resistance in ALK+ NSCLC, including reduced potency against certain secondary ALK mutations and near complete lack of activity against other ALK mutations. In contrast, ganetespib, which acts by inhibiting Hsp90, a necessary chaperone for ALK activity, is equally potent against crizotinib-sensitive cells as well as all crizotinib-resistant cells with secondary ALK mutations.

"While targeted ALK inhibitors such as crizotinib have shown clinical efficacy in non-small cell lung cancer, the majority of tumors develop resistance to these inhibitors highlighting the need for new therapies," said Vojo Vukovic, M.D., Ph.D, Chief Medical Officer, Synta. "These results show that NSCLC cells that have become crizotinib-resistant remain extremely sensitive to ganetespib, while the xenograft model work supports the rationale for combining ganetespib with ALK inhibitors in clinical trials going forward."

Ganetespib: An effective strategy to overcome crizotinib resistance in ALK-driven cancers

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In this study, ganetespib displayed greater potency than other targeted agents and chemotherapeutics utilized in ALK+ NSCLC, including ALK inhibitors and pemetrexed. While both ganetespib and crizotinib were effective in deactivating ALK in NSCLC cells harboring the EML4-ALK translocation, only ganetespib was effective in eliminating the ALK fusion kinase from

the cell. Given the distinct actions of ganetespib and crizotinib on targeting ALK, combinations of the two drugs resulted in enhanced antitumor activity *in vitro* and *in vivo*. ALK inhibitors have shown tremendous activity in the clinic; however, resistance is inevitable. To recapitulate ALK-resistant lung cancer, ALK+ cancer cells were exposed to crizotinib or ganetespib over the course of several weeks. The cancer cells treated with ganetespib did not survive; however, cells chronically exposed to crizotinib eventually grew out. These crizotinib-resistant cells retained sensitivity to ganetespib. Further, cell lines engineered to express mutations in ALK clinically observed to induce crizotinib resistance were as sensitive to ganetespib as cells driven by non-mutated ALK.

"The mechanism of action for ganetespib and ALK inhibitors is quite distinct," said David Proia, Ph.D., Director, Cancer Biology, Synta. "Kinase inhibitors like crizotinib specifically target one or a few kinases. Over time these kinases evolve to bypass the inhibitory actions of the drug. Targeting Hsp90 with ganetespib represents an entirely new way to battle ALK+ lung cancer. Ganetespib is not directly affecting ALK; rather it is blocking the chaperone protein that ALK requires to function. As a result, the ALK kinase is eliminated from the cell, even when ALK is mutated due to prolonged exposure to ALK inhibitors. We can take advantage of the unique mechanism of actions of ganetespib and ALK inhibitors by combining the two drugs together to obtain greater anticancer activity than when either drug is used individually."

About Ganetespib

Ganetespib is a potent, small-molecule inhibitor of heat shock protein 90 (Hsp90). Hsp90 is a molecular chaperone required for the proper folding and activation of many cancer-promoting proteins, and is recognized as a key facilitator of cancer cell growth and survival. In preclinical experiments, ganetespib has shown activity in multiple tumor models both as a single agent and in combination with certain widely used cancer agents. Ganetespib is currently being evaluated in a broad range of cancer clinical trials. In these trials, ganetespib has shown clinical activity in heavily pretreated patients and has been well tolerated to date with no evidence of severe liver or common ocular toxicities seen with other Hsp90 inhibitors. The most common adverse event seen to date has been transient, mild or moderate diarrhea, which has been manageable with standard supportive care. Information on clinical trials with ganetespib can be found at www.clinicaltrials.gov.

About Non-small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related mortality in the United States, with over 226,000 new cases and 160,000 deaths estimated in 2012 according to the American Cancer Society. The five year survival rate for advanced-staged lung cancer is approximately 4%. Approximately 85% of all lung cancers are classified as non-small cell. Estimates for the global incidence of ALK+ NSCLC range from 40,000 to 70,000 new cases per year.

About Synta Pharmaceuticals

Synta Pharmaceuticals Corp. is a biopharmaceutical company focused on discovering, developing, and commercializing small molecule drugs to extend and enhance the lives of patients with severe medical conditions, including cancer and chronic inflammatory diseases. Synta has a unique chemical compound library, an integrated discovery engine, and a diverse pipeline of clinical- and preclinical-stage drug candidates with distinct mechanisms of action and novel chemical structures. All Synta drug candidates were invented by Synta scientists using our compound library and discovery capabilities. For more information, please visit www.syntapharma.com.

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Synta Pharmaceuticals Corp.
George Farmer, Ph.D., 781-541-7125