



Synta Announces Ganetespib Results at AACR - Inhibition of Multiple Oncogenes and Resistance Mechanisms Leads to Potent Activity in NSCLC and Strong Enhancement of Radiation Therapy

April 4, 2011

- Simultaneous inhibition of multiple oncogenes present in NSCLC including EML4-ALK, EGFR, MET, AKT, MEK, ERK, STAT3, and HER2 leads to potent activity in a broad range of NSCLC models-*
- Inhibition of DNA repair and cell cycle checkpoint resistance mechanisms enhances activity of radiation therapy-*
- Clinical trial as radiosensitizer to start later in 2011-*

LEXINGTON, Mass., Apr 04, 2011 (BUSINESS WIRE) -- Synta Pharmaceuticals Corp. (NASDAQ: SNTA) today presented five posters at the American Association for Cancer Research (AACR) 102nd Annual Meeting. Three posters reported results from studies of ganetespib (STA-9090), and two posters reported results from studies of elesclomol, a small-molecule mitochondria metabolism inhibitor.

Ganetespib is a potent inhibitor of heat shock protein 90 (Hsp90) currently being studied in a broad range of clinical trials, with over 350 patients treated to date and a Phase 2b/3 trial in non-small cell lung cancer (NSCLC) expected to start this quarter. Ganetespib is structurally unrelated to earlier Hsp90 inhibitors such as 17-AAG and has shown superior activity to these agents in preclinical studies. In clinical trials, ganetespib has shown single-agent activity in multiple tumor types and an absence of the serious liver and ocular toxicities seen with other Hsp90 inhibitors.

"The results presented today shed further light on the strong activity seen with ganetespib both in preclinical models and in patients," said Vojo Vukovic, M.D., Ph.D., Senior Vice President and Chief Medical Officer, Synta Pharmaceuticals. "The simultaneous inhibition of multiple critical oncogenes, and the potent anti-cancer activity seen in lung cancer models with distinct genetic profiles, suggests broad potential application for ganetespib in NSCLC. These results provide insight into our ongoing Phase 2 trial in NSCLC, in which a number of patients who have failed prior therapies such as carboplatin, Taxol, Avastin, Tarceva, and Alimta achieved durable objective responses or tumor shrinkage with single-agent ganetespib."

"The findings that ganetespib can inhibit critical components of repair mechanisms to the double-strand DNA breaks induced by irradiation are very encouraging and suggest important potential application as a radiosensitizer," continued Dr. Vukovic. "There is a high unmet need for improving the outcome of radiotherapy in human cancers: 50-60 percent of all cancer patients receive radiotherapy as part of their treatment. The favorable safety profile observed with ganetespib in the clinic is a critical advantage for this application. We have established a strong collaboration with a leading radiotherapy group, which will be initiating a clinical trial of ganetespib as a radiosensitizer later this year."

"Our ganetespib clinical program has benefited not only from thorough *in vitro* and *in vivo* studies, but also from a Phase 1 clinical trial in dogs with spontaneous cancers," continued Dr. Vukovic. "The results from our collaborators at Ohio State University have been instrumental in helping us think through clinical trial choices for ganetespib on dose, schedule, and biomarker evaluation. The single-agent activity seen in dogs with cancer has been encouraging, and consistent with single-agent activity that has been seen in human clinical trials."

Synta is currently conducting a Phase 2 clinical trial of ganetespib as a single agent in NSCLC. A Phase 2b/3 trial of ganetespib in combination with docetaxel in 2nd-line advanced NSCLC patients is expected to initiate in Q2 of 2011 with preliminary results from the Phase 2b portion of the trial expected either late this year or in Q1 2012. Additional details regarding upcoming trials will be announced as those trials initiate.

In January of this year, the Multiple Myeloma Research Foundation announced funding of up to \$1 million to support a study of ganetespib in combination with bortezomib (VELCADE[®]) in multiple myeloma.

Ganetespib posters and publications are available at www.syntapharma.com or by contacting Synta directly.

Ganetespib (STA-9090) Posters

Title: Potent anticancer actions of the Hsp90 inhibitor STA-9090 in wild-type EGFR models of lung cancer

Poster Presentation April 4, 8:00 a.m. ET

Abstract Number: 1638

Abstract:

Non-small cell lung cancer (NSCLC) is a heterogeneous disease that can be sub-classified based on the specific alterations in oncogenes that drive it. While EGFR and KRAS are most often implicated in the molecular epidemiology of NSCLC, aberrations in several other genes have been shown to contribute to oncogenesis. These include mutation and/or amplification of MET, mutation in BRAF or chromosomal rearrangements involving ALK. Targeted therapy against these kinases has shown signs of therapeutic success; however, acquired drug resistance universally develops.

Heat Shock Protein 90 (Hsp90) is a molecular chaperone that mediates the post-translational stability of its protein substrates, many of which are validated oncogenes. Hsp90 is emerging as an important target in cancer therapy because its inactivation results in the abrogation of multiple signaling pathways simultaneously, irrespective of the mutational status of its substrate. STA-9090 is a second-generation, synthetic, small-molecule Hsp90 inhibitor that has shown potent and selective activity preclinically and is currently in Phase 2 trials in a number of indications. We show here that in the presence of STA-9090, upregulation of the MET pathway, either through transient stimulation by its ligand, HGF, or through amplification of MET itself, is incapable of maintaining survival in EGFR-inhibitor-resistant NSCLC. To identify additional genetic lesions sensitive to Hsp90 inhibition, we screened a panel of wild-type EGFR NSCLC cell lines for viability in the presence of STA-9090. All the cell lines assayed, driven by mutations in genes such as PDGFRA, BRAF, PI3K and EML4-ALK or amplification of wild-type EGFR, were sensitive to STA-9090, with IC₅₀ values

between 10 and 150 nM.

Further analysis demonstrated that STA-9090 potently destabilized the oncogenic driver for each cell line. *In vivo*, STA-9090 showed strong single-agent activity in xenograft models of human NSCLC carrying either a BRAF mutation or EML4-ALK fusion, in accordance with the sensitivity of these client proteins to the effects of STA-9090 action. Inhibition of Hsp90 activity therefore presents a promising approach for combating NSCLC induced by mutations in genes other than EGFR, as well as by compensatory pathways upregulated in the context of EGFR-inhibitor resistance.

Title: Novel Hsp90 inhibitor, STA-9090, for combination with radiotherapy

Poster Presentation April 4, 1:00 p.m. ET

Abstract Number: 2677

Abstract:

Introduction: Radiation is accepted as an important standard therapy for locally unresectable cancers, and as such is given to approximately 60% of cancer patients. However, radio-resistance and repair of sublethal radiation damage can limit its efficacy.

Recent studies have shown that Heat Shock Protein 90 (Hsp90), a molecular chaperone that mediates maturation and activation of client proteins, plays a critical role in establishing resistance to radiation therapy. Inhibiting Hsp90 has been reported to sensitize tumors to radiation, resulting in tumor growth suppression and augmenting therapeutic cell death induction. Unfortunately, many of the Hsp90 inhibitors currently in clinical trials exhibit hepatotoxicity as well as ocular toxicity, hindering their clinical use. Taken together, development of clinically acceptable Hsp90 inhibitors for combination with radiation could serve as an important strategy for improving radiotherapy success.

Ganetespib is a second generation Hsp90 inhibitor that has shown potent preclinical activity and is currently in twelve Phase II trials across a broad range of indications. Ganetespib has demonstrated encouraging activity in a Phase II trial in patients with stage IIIB and IV non-small cell lung cancer. Importantly, ganetespib has displayed a favorable safety profile with substantially lower incidence of hepatic or ocular toxicity than that reported for other Hsp90 inhibitors.

Results: We evaluated the radiosensitizing potential of ganetespib *in vivo*. Monotherapy treatment with either ganetespib or 2 Gray (Gy) ionizing irradiation resulted in moderate reductions in human tumor growth rates in a mouse xenograft model. Combination of ganetespib with 2 Gy irradiation resulted in substantial tumor regression. Increasing the dose of radiation in the combination arm to 4 Gy further enhanced tumor regression, resulting in a 50% reduction in tumor volume. In summary, ganetespib offers an effective strategy for improving the outcome of radiotherapy in human cancers.

Title: Phase I evaluation of STA-1474, a pro-drug of the novel HSP90 inhibitor STA-9090, in dogs with spontaneous cancer

Poster Presentation April 4, 8:00 a.m. ET

Abstract Number: 1282

Abstract:

Purpose: The novel water soluble compound STA-1474 is metabolized to ganetespib (formerly

STA-9090), a potent HSP90 inhibitor previously shown to kill canine tumor cell lines *in vitro* and inhibit tumor growth in the setting of murine xenografts. The purpose of the following study was to extend these observations and investigate the safety and efficacy of STA-1474 in dogs with spontaneous tumors.

Experimental Design: This was a Phase 1 trial in which dogs with spontaneous tumors received STA-1474 under one of three different dosing schemes. Pharmacokinetics, toxicities, biomarker changes, and tumor responses were assessed.

Results: Twenty-five dogs with a variety of cancers were enrolled. Toxicities were primarily gastrointestinal in nature consisting of diarrhea, vomiting, inappetence and lethargy. Upregulation of HSP70 protein expression was noted in both tumor specimens and PBMCs within 7 hours following drug administration. Measurable objective responses were observed in dogs with malignant mast cell disease (n=3), osteosarcoma (n=1), melanoma (n=1) and thyroid carcinoma (n=1), for a response rate of 24% (6/25). Stable disease (>10 weeks) was seen in 3 dogs, for a resultant overall biological activity of 36% (9/25).

Conclusions: This study provides evidence that STA-1474 exhibits biologic activity in a relevant large animal model of cancer.

About Ganetespib

Ganetespib (formerly STA-9090) is a potent, synthetic, 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 diarrhea, which has been manageable with standard supportive care. Information on clinical trials with ganetespib can be found at www.clinicaltrials.gov.

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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statements. Such statements, including statements relating to the timing, developments and progress of our clinical and preclinical programs, reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such forward-looking statements, including those described in "Risk Factors" of our Form 10-K for the year ended December 31, 2010 as filed with the Securities and Exchange Commission. Synta undertakes no obligation to publicly update forward-looking statements, whether because of new information, future events or otherwise, except as required by law.

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