

Abstract # **B199**

In vitro and *in vivo* efficacy of the novel Hsp90 inhibitor STA-9090 and its synergy with paclitaxel.

Weiwen Ying¹, Ronald K. Blackman¹, Dinesh Chimmanamada¹, Zhenjian Du¹, Kevin P. Foley¹, Suqin He¹, Takayo Inoue¹, David James¹, Jane Kepros¹, Tim Korbut¹, Luisa Shin Ogawa¹, Cong Peng², Teresa Przewloka¹, David Proia¹, Jim Sang¹, Donald Smith¹, Noriaki Tatsuta¹, Chin-Yu Yang¹, Chaohua Zhang¹, Haili Zhang¹, Shijie Zhang¹, Shaoguang Li², James Barsoum¹.

1. Synta Pharmaceuticals, Lexington, MA; 2. University of Massachusetts Medical School, Worcester, MA

Heat shock protein 90 (Hsp90) is a molecular chaperone that regulates the post-translational folding of its protein substrates ("client proteins"). Cancer cells contain elevated levels of active Hsp90 and, because many client proteins play critical oncogenic roles, cancer cells are especially sensitive to Hsp90 inhibition. Here we report on the initial characterization of STA-9090, a highly potent Hsp90 inhibitor that is currently in multiple Phase 1/2 clinical trials in solid tumor and hematological malignancies. STA-9090 is a small molecule drug that is structurally unrelated to the ansamycin Hsp90 inhibitor 17-AAG and binds the N-terminal ATP-binding pocket of the chaperone. *In vitro*, treatment with STA-9090 rapidly induced the degradation of known Hsp90 client proteins, such as HER2 and KIT, and growth inhibition IC₅₀ values typically ranged from 1 to 100 nM. STA-9090 demonstrated, on average, ~30-fold greater potency than 17-AAG for the ~60 hematological and solid tumor cell lines tested. STA-9090 also retained its potency against cell lines expressing mutated kinases that confer resistance to kinase inhibitors such as erlotinib and imatinib.

In vivo, STA-9090 demonstrated single-agent activity in a wide variety of human tumor cell line subcutaneous xenograft models in mice, including those representing solid tumor malignancies such as gastric carcinoma, nonsmall cell lung cancer, prostate carcinoma and melanoma, and hematological malignancies such as acute myeloid leukemia, B-cell lymphoma, chronic myeloid leukemia and multiple myeloma. In a mouse leukemia model in which wild type BCR-ABL or imatinib/dasatinib-resistant BCR-ABL^{T315I} was introduced into mouse bone marrow cells and then transplanted into host mice to induce the development of B-cell acute lymphoblastic leukemia, STA-9090 prolonged average survival from 27 to 37 days for BCR-ABL and from 29 to 57 days for BCR-ABL^{T315I}. STA-9090 also accumulated in tumors, with a half-life of 58 hr in tumors versus 3-5 hr in plasma and non-tumor tissues. To examine the potential for therapeutic synergy, STA-9090 was combined with the microtubule stabilizer paclitaxel. STA-9090 dramatically synergized with paclitaxel in *in vitro* cytotoxicity assays, particularly when paclitaxel treatment preceded treatment with STA-9090. Similarly, STA-9090 enhanced the activity of paclitaxel in the erlotinib-resistant NCI-H1975 lung cancer xenograft model, although this enhancement depended less on the order of dosing

than was observed *in vitro*. No significant pharmacokinetic interactions were observed between the two agents.

In conclusion, STA-9090 is a highly potent Hsp90 inhibitor that *in vitro* and *in vivo* rapidly induces the degradation of Hsp90 client proteins and apoptosis in a broad range of cancer types, including those resistant to targeted kinase inhibitors. It also demonstrates synergy with paclitaxel.