

Abstract # B105

Ganetespib, a unique resorcinolic Hsp90 inhibitor, exhibits potent antitumor activity and a superior safety profile in preclinical models.

Weiwen Ying, David A. Proia, Dan Zhou, Takayo Inoue, Noriaki Tatsuta, Jim Sang, Shuxia Ye, Jaime Acquaviva, Luisa Shin Ogawa, Yumiko Wada, Dinesh Chimmanamada, Shijie Zhang, Keizo Koya.. Synta Pharmaceuticals Corp., Lexington, MA

Background: Targeted inhibition of the molecular chaperone heat shock protein 90 (Hsp90) results in the simultaneous blockade of multiple oncogenic signaling pathways and has thus emerged as an attractive strategy for the development of novel cancer therapeutics. Ganetespib (STA-9090) is a unique resorcinolic inhibitor of Hsp90 currently in clinical trials for a number of human cancers.

Results: Here we describe the key interaction of ganetespib with a number of amino acid residues in the ATP binding pocket of Hsp90 which results in high affinity binding. Ganetespib exhibits potent *in vitro* cytotoxicity in a range of solid and hematological tumor cell lines. By using a novel isotope-labeling scheme and LC-MS/MS detection technique, we have determined that Hsp90 occupancy by ganetespib in cancer cells is relatively fast under saturating conditions, reaching equilibrium within 5 minutes of ganetespib exposure. *In vivo*, ganetespib demonstrated strong single-agent activity in solid and hematological xenograft models, as evidenced by significant tumor growth inhibition and/or regression. Of note, evaluation of the microregional activity of ganetespib in tumor xenografts showed that ganetespib efficiently distributed throughout tumor tissue, including hypoxic regions >150 μm from the microvasculature, to inhibit proliferation and induce apoptosis. Most importantly, ganetespib showed no evidence of cardiac or liver toxicity and exhibited minimal potential risk for CNS or ocular toxicities.

Conclusions: Taken together, this preclinical activity profile suggests that ganetespib may have broad application for a variety of human malignancies and mechanistic and safety advantages over other first- and second-generation Hsp90 inhibitors.