

In Vitro and In Vivo Efficacy of the Novel Hsp90 Inhibitor STA-9090 and its Synergy with Paclitaxel



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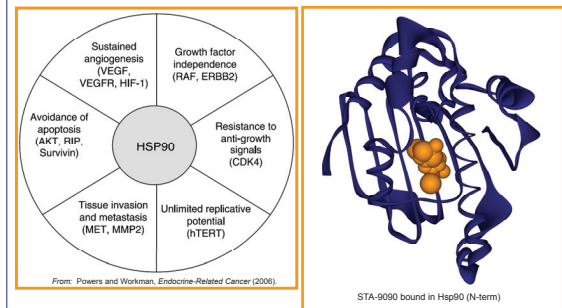
Abstract (#B199)

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.

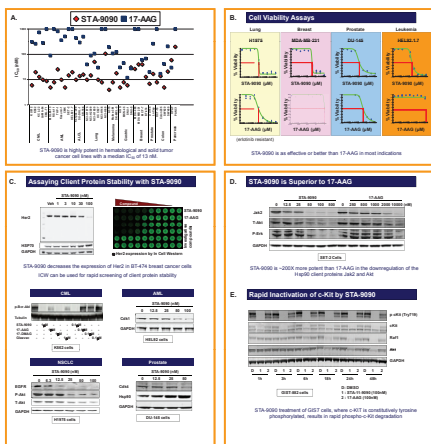
In vitro, treatment with STA-9090 rapidly induced the degradation of known Hsp90 client proteins, such as Her2 and Kit, and growth inhibition IC50 values typically ranged from 1 to 100 nM. STA-9090 demonstrated, on average, ~30-fold greater potency than 17-AAG for the ~60 hematological and solid tumor 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, non-small 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 33.5 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.

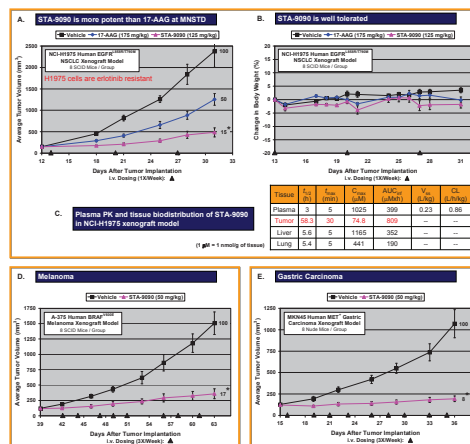
To examine the potential for therapeutic synergy, STA-9090 was combined with the microtubule stabilizer paclitaxel. STA-9090 synergized with paclitaxel in *in vitro* cytotoxicity assays, including when paclitaxel treatment preceded treatment with STA-9090. Similarly, STA-9090 enhanced the activity of paclitaxel in the erlotinib-resistant NCI-H1975 lung cancer xenograft model. No significant pharmacokinetic interactions were observed between the two agents.



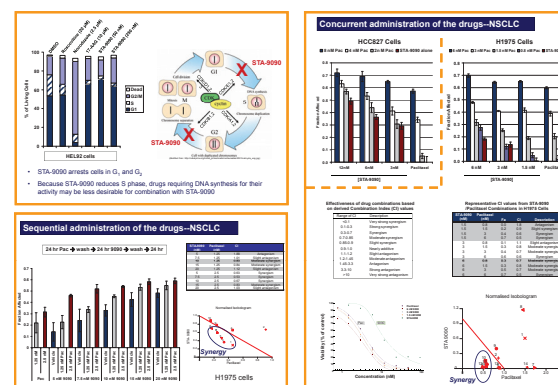
STA-9090 Is Highly Potent in a Wide Variety of Tumor Cells



STA-9090 Has In Vivo Activity in Solid Tumor Xenograft Models



Paclitaxel Synergizes With STA-9090 in In Vitro Studies

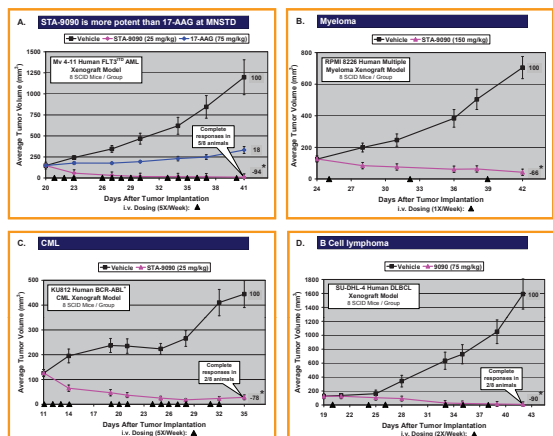


In vitro, combinations of STA-9090 and paclitaxel near or below their respective IC50s are synergistic

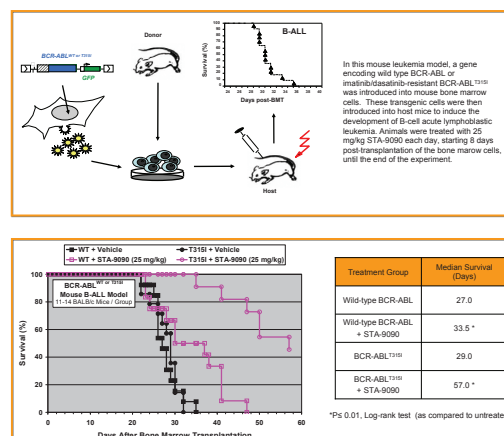
Summary

- STA-9090 has potent *in vitro* and *in vivo* efficacy in a broad range of hematological and solid tumor cell lines
- STA-9090 demonstrates superiority to 17-AAG and rapidly leads to the degradation of client proteins critical for oncogenic survival and proliferation
- In *in vivo* xenograft models, the drug is well tolerated and shows substantial accumulation and prolonged half-life in tumors
- In mouse models involving tumors resistant to targeted kinase inhibitors, STA-9090 treatment significantly increased survivability
- Combinations of STA-9090 and paclitaxel showed synergy both *in vitro* and *in vivo* and showed no PK interactions
- Future efforts: We are evaluating additional drug combinations and efficacy biomarkers to assist additional STA-9090 phase 2 clinical trials in solid tumor and hematological malignancies

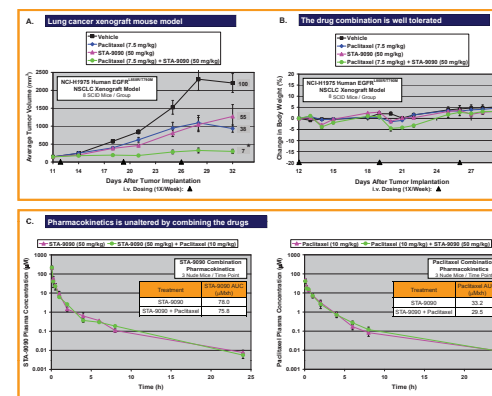
STA-9090 Has Potent In Vivo Activity in Hematological Subcutaneous Xenograft Models



STA-9090 Prolongs Survival in a TKI-Resistant B-ALL Mouse Model



Combination Efficacy In Vivo of STA-9090 and Paclitaxel



Once weekly dosing of STA-9090 enhances paclitaxel efficacy without increasing systemic toxicity

Additional Posters Presented on STA-9090

"HSP90 inhibitor STA-9090 potently suppresses heterogeneous KIT kinase domain mutations responsible for gastrointestinal stromal tumor progression during imatinib therapy"

Authors: J.A. Fletcher, et al.
 Abstract number: B184
 Poster session: B – Other Therapeutic Agents 1
 Date: Tuesday, 17 November 2009
 Time: 12:30 – 2:30 PM and 5:30 – 7:30 PM

"Pharmacodynamic analysis of the Hsp90 inhibitor STA-9090 in a lung cancer xenograft model supports an infrequent dosing schedule in the clinic"

Authors: K.P. Foley, et al.
 Abstract number: C91
 Poster session: C – Other Therapeutic Agents 2
 Date: Wednesday, 18 November 2009
 Time: 12:30 – 2:30 PM and 5:30 – 7:30 PM

