

Abstract # C91

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

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Background: Heat shock protein 90 (Hsp90) is a molecular chaperone that is required for the stability and function of many important signal transduction proteins that regulate the growth of cancer cells. Hsp90 inhibition results in ubiquitination and proteasomal degradation of these client proteins, which include clinically validated drug targets such as BCRABL, mutant EGFR, HER2, KIT and VEGFR. STA-9090 is a novel small molecule Hsp90 inhibitor that is currently in multiple Phase 1/2 clinical trials in solid tumor and hematological malignancies. STA-9090 is structurally unrelated to the first-generation anasamycin Hsp90 inhibitors 17-AAG and IPI-504 and inhibits Hsp90 by binding to its N-terminal ATP-binding pocket. Although Hsp90 inhibitors such as STA-9090 induce rapid client protein degradation, cell cycle arrest and apoptosis of cancer cells, it is possible that frequent drug dosing in the clinic may be needed to continuously maintain decreased client protein expression and avoid renewed tumor growth. To investigate this possibility, we conducted in vitro and in vivo studies using the human NCIH1975 non-small cell lung cancer cell line, which expresses the Hsp90 client protein EGFR^{L858R/T790M}, a mutationally activated and erlotinib-resistant form of the epidermal growth factor receptor.

Results: In an in vitro cytotoxicity assay using this cell line, STA-9090 and 17-AAG displayed IC₅₀ values of 10 and 40 nM after 72 hr drug exposure, respectively. These results closely correlated with decreased expression of EGFR^{L858R/T790M} and other Hsp90 client proteins. Unexpectedly, exposure to STA-9090 for only 1 hr still resulted in an IC₅₀ of 670 nM, suggesting that even brief drug exposure in vivo may be sufficient to affect tumor growth. Consistent with this, intravenous dosing of 125 mg/kg STA-9090 on a 1X/week x 3 week schedule (~80-100% of the highest non-severely toxic dose) induced stable disease in a NCI-H1975 xenograft model, whereas 175 mg/kg 17-AAG resulted in progressive disease, with %T/C values of 15 and 50, respectively. Inhibition of tumor growth was correlated with decreased expression of EGFR^{L858R/T790M} and other client proteins, and importantly, these effects persisted in tumors for 3-6 days after a single drug dose. Similarly, histological analysis of tumors indicated that STA-9090 inhibited cell proliferation by 7-fold and induced apoptosis by 9-fold, with maximal effects being observed at 1-3 days after treatment. Consistent with these observations, STA-9090

accumulated in tumors relative to normal tissues, with a tumor half-life of 58 hr versus 3-5 hr in liver, lung and plasma, and the tumor concentration remained 140-fold higher than the in vitro IC_{50} (72 hr) even 6 days after a single drug dose.

Conclusions: Taken together, these results demonstrate that STA-9090 is a highly potent Hsp90 inhibitor that selectively accumulates in tumors and induces long-lasting client protein degradation, cell cycle arrest, increased apoptosis and tumor growth inhibition in a lung cancer xenograft model. Our results suggest that an infrequent dosing schedule may have clinical activity in cancer patients.