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The novel Hsp90 inhibitor STA-9090 has potent anticancer activity in *in vitro* and *in vivo* models of lung cancer.

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We describe the anticancer activity of STA-9090, a novel non-geldanamycin heat shock protein 90 (HSP90) inhibitor, in non-small cell (NSCLC) and small cell lung cancer (SCLC) models. STA-9090 inhibited proliferation and induced apoptosis of a panel of human lung cancer cell lines with IC₅₀ values of 2- 30 nM (mean = 7.6±1.6 nM). In contrast, the geldanamycin HSP90 inhibitor 17-AAG was significantly less potent, with IC₅₀ values of 20-3,500 nM (mean = 229±159 nM). Similarly, STA-9090 inhibited association of HSP90 with its co-chaperone p23 at a 5-fold lower drug concentration than that observed for 17-AAG. Altered expression of biomarkers for HSP90 inhibition, such as induction of HSP70 and depletion of HSP90 client proteins, occurred with significantly faster kinetics following treatment with STA-9090 than 17-AAG. Complete depletion of HSP90 clients such as AKT, IGF-1R, MET and activated EGFR in the NCI-H1975 (EGFR^{L858R/T790M}) and HCC827 (EGFR^{del746-750}) cell lines was observed following treatment with 4 nM STA-9090 for 24 hours, whereas 3-12-fold higher concentrations of 17-AAG were required to achieve similar effects. To more fully assess the activity of STA-9090 against mutationally activated forms of EGFR, we utilized Ba/F3 cells converted to growth factor-independence by over-expression of oncogenic EGFR mutants that are commonly found in NSCLC patients. In this system, average IC₅₀ values for cell killing by STA-9090 were 9.9±2.9 nM, while the corresponding values for 17-AAG were 245.1±144.9 nM. Importantly, STA-9090 was also active in NSCLC and SCLC cell lines expressing high levels of MRP1, a known drug transporter of geldanamycins. To confirm these findings *in vivo*, STA-9090 was examined in the NCI-H1975 xenograft model in SCID mice. Treatment with 25 mg/kg STA-9090 dosed 5 times per week for 3 weeks resulted in significant tumor regression, with a %T/C value of -23. Pharmacodynamic studies also demonstrated that the induction of HSP70 and HSP27 expression, and the depletion of AKT, IGF-1R, MET and activated EGFR, were correlated with *in vivo* antitumor activity. Similarly, STA-9090 was found to be highly efficacious in a transgenic mouse model in which inducible expression of EGFR^{del746-750/T790M} results in erlotinib-resistant lung adenocarcinomas. STA-9090 demonstrated reduced toxicity on normal lung bronchial epithelial cells relative to 17-AAG and was well-tolerated in these animal models. Our results indicate that STA-9090 has greater potency and reduced toxicity relative to 17-AAG, and that HSP90 represents a relevant target for therapeutic intervention in lung cancer.

