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Hsp90 inhibitor STA-9090 enhances the activity of standard of care therapies in erlotinib-sensitive and -resistant NSCLC models.

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BACKGROUND: Heat shock protein 90 (Hsp90) is a molecular chaperone that regulates the folding, stability and activity of many kinases and signal transduction proteins that are critical for the proliferation and survival of cancer cells. These Hsp90 client proteins include wild type and drug-resistant forms of such clinically important drug targets as: BCR-ABL, BRAF, EGFR, HER2, KIT, MET and VEGFR1. STA-9090 is a highly potent and less toxic, next-generation Hsp90 inhibitor that is structurally unrelated to first-generation agents such as 17-AAG and IPI-504. STA-9090 induces proteasome-mediated degradation of Hsp90 client proteins preferentially in cancer versus normal cells, resulting in cell cycle arrest and apoptosis. STA-9090 is currently being evaluated in multiple Phase 1/2 clinical trials in solid tumor and hematologic malignancies, including an open-label, multi-center Phase 2 trial in patients with advanced NSCLC harboring wild type or activated forms of EGFR or KRAS. In anticipation of conducting clinical trials combining STA-9090 with therapeutic agents commonly employed to treat NSCLC, we have examined the ability of STA-9090 to enhance the *in vitro* and *in vivo* activity of paclitaxel, docetaxel, erlotinib and bevacizumab in preclinical models of lung cancer.

RESULTS: *In vitro* cytotoxicity studies were conducted with the erlotinib-sensitive HCC827 (expressing EGFR^{del746-750}) and erlotinib-resistant NCI-H1975 (expressing EGFR^{L858R/T790M}) NSCLC cell lines. Using the median-effect method of Chau and Talalay, STA-9090 was found to significantly enhance the *in vitro* cytotoxicity of the taxanes, paclitaxel and docetaxel, with combination index (CI) values ranging from 0.3-0.7, which is indicative of synergy rather than additive or antagonistic effects. Similarly, STA-9090 also displayed synergy (0.4-0.8 CI) with the EGFR inhibitor erlotinib against erlotinib-sensitive cells, but as expected, not against erlotinib-resistant cells. Consistent with these results, STA-9090 enhanced the *in vivo* efficacy of concomitantly dosed paclitaxel and docetaxel in the HCC827 and NCI-H1975 xenograft models. Further, STA-9090 also enhanced the *in vivo* efficacy of the anti-VEGF monoclonal antibody bevacizumab in these models. These combinations did not result in significant additional toxicity relative to the single agents alone, and pharmacokinetic analyses demonstrated that these findings were not due to drug-drug interactions.

CONCLUSIONS: Our results demonstrate that STA-9090 potently synergizes with paclitaxel, docetaxel, erlotinib and bevacizumab, which are widely employed to treat NSCLC in the clinic. Hsp90 inhibition using STA-9090 represents a novel and promising approach to combination therapy for NSCLC.