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Potent anticancer actions of the Hsp90 inhibitor STA-9090 in wild-type EGFR models of lung cancer.

Jaime Acquaviva², Jim Sang², Manuel Sequeira², Donald Smith², Chaohua Zhang², Christine Lovly¹, Yumiko Wada², Ronald K. Blackman², David A. Proia².

¹ Vanderbilt University School of Medicine, Nashville, TN

² Synta Pharmaceuticals Corp., Lexington, MA

Non-small cell lung cancer (NSCLC) is a heterogeneous disease that can be subclassified based on the specific alterations in oncogenes that drive it. While EGFR and KRAS are most often implicated in the molecular epidemiology of NSCLC, aberrations in several other genes have been shown to contribute to oncogenesis. These include mutation and/or amplification of MET, mutation in BRAF or chromosomal rearrangements involving ALK. Targeted therapy against these kinases has shown signs of therapeutic success; however, acquired drug resistance universally develops.

Heat Shock Protein 90 (Hsp90) is a molecular chaperone that mediates the post-translational stability of its protein substrates, many of which are validated oncogenes. Hsp90 is emerging as an important target in cancer therapy because its inactivation results in the abrogation of multiple signaling pathways simultaneously, irrespective of the mutational status of its substrate. STA-9090 is a second-generation, synthetic, small-molecule Hsp90 inhibitor that has shown potent and selective activity preclinically and is currently in Phase 2 trials in a number of indications.

We show here that in the presence of STA-9090, upregulation of the MET pathway, either through transient stimulation by its ligand, HGF, or through amplification of MET itself, is incapable of maintaining survival in EGFR-inhibitor-resistant NSCLC. To identify additional genetic lesions sensitive to Hsp90 inhibition, we screened a panel of wild-type EGFR NSCLC cell lines for viability in the presence of STA-9090. All the cell lines assayed, driven by mutations in genes such as PDGFR, BRAF, PI3K and EML4-ALK or amplification of wild-type EGFR, were sensitive to STA-9090, with IC₅₀ values between 10 and 150 nM. Further analysis demonstrated that STA-9090 potently destabilized the oncogenic driver for each cell line. In vivo, STA-9090 showed strong single-agent activity in xenograft models of human NSCLC carrying either a BRAF mutation or EML4-ALK fusion, in accordance with the sensitivity of these client proteins to the effects of STA-9090 action.

Inhibition of Hsp90 activity therefore presents a promising approach for combating NSCLC induced by mutations in genes other than EGFR, as well as by compensatory pathways upregulated in the context of EGFR-inhibitor resistance.