

#1638 Potent Anticancer Actions of the Hsp90 Inhibitor Ganetespib (STA-9090) in Wild-Type EGFR Models of Lung Cancer

Jaime Acquaviva¹, Jim Sang¹, Manuel Sequeira¹, Donald Smith¹, Chaohua Zhang¹, Christine Lovly², Julie Friedland¹, Suqin He¹, William Pao², Yumiko Wada¹, Ronald K. Blackman¹, David A. Proia¹

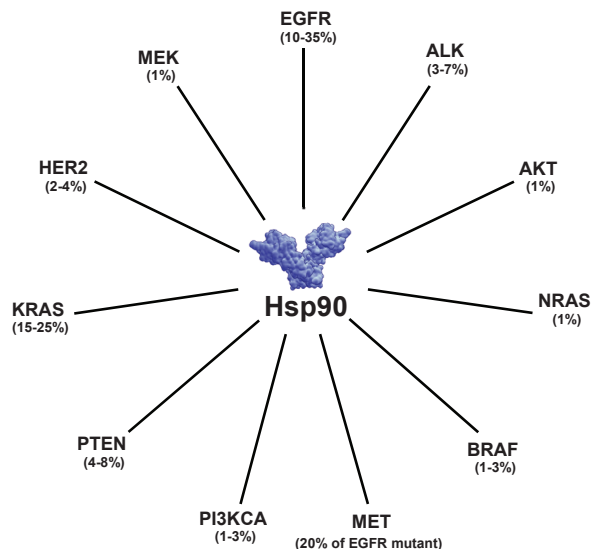
¹Synta Pharmaceuticals Corp., Lexington, Massachusetts USA; ²Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, USA

Abstract

Non-small cell lung cancer (NSCLC) is a heterogeneous disease that can be sub-classified 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 α , 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 potentially 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.

Introduction



Hsp90 is a central mediator in NSCLC tumorigenesis. Hsp90 is a molecular chaperone required for the folding and maturation of many clinically validated oncoproteins including the majority of those that drive NSCLC. The frequency of mutation for each gene in NSCLC is represented in parenthesis, compiled by Lovly, Horn and Pao (<http://www.vicc.org/mycancergenome/nsclc>).

Ganetespib Displays Broad Activity Against Multiple Validated Oncogenes

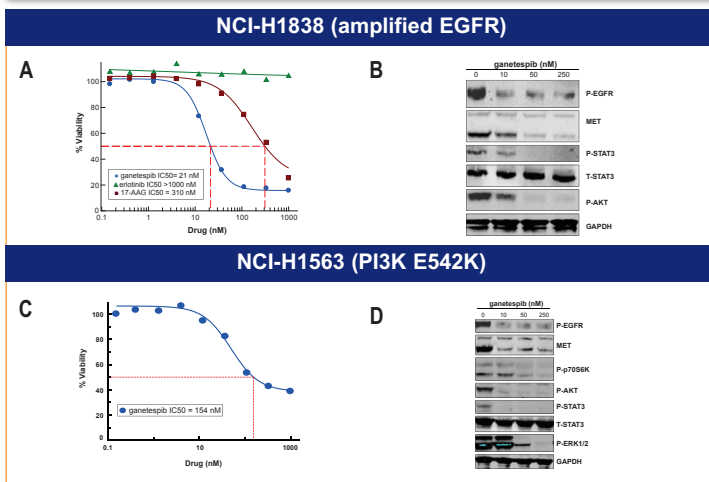


Figure 1. Hsp90 inhibition by ganetespib leads to the destabilization or deactivation of multiple clinically validated oncoproteins in NSCLC cells.

Ganetespib is Active in MET-induced Erlotinib Resistant NSCLC Cells

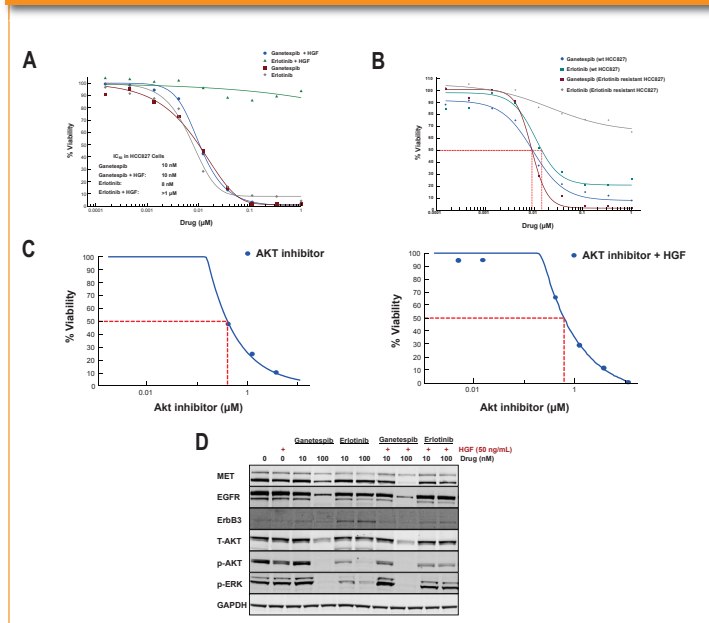


Figure 2. Ganetespib displays potent activity in NSCLC cells where erlotinib resistance is driven either by exogenous activation (A) or amplification (B) of c-MET. Inhibition of AKT is required for erlotinib resistance (C). Ganetespib abrogates MET/AKT signaling required for erlotinib resistance.

Multi-modal Actions of Ganetespib Contribute to Cytotoxicity in Mutant BRAF NSCLC Cells

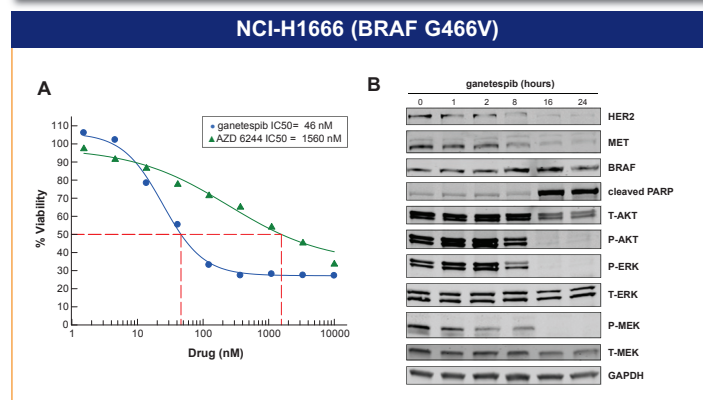


Figure 3. Disruption of multiple signaling cascades likely contributes to more pronounced cell death than targeted therapies.

Ganetespib Effectively Inhibits Oncogenic Signaling and Growth and in EML4-ALK Positive NSCLC cells

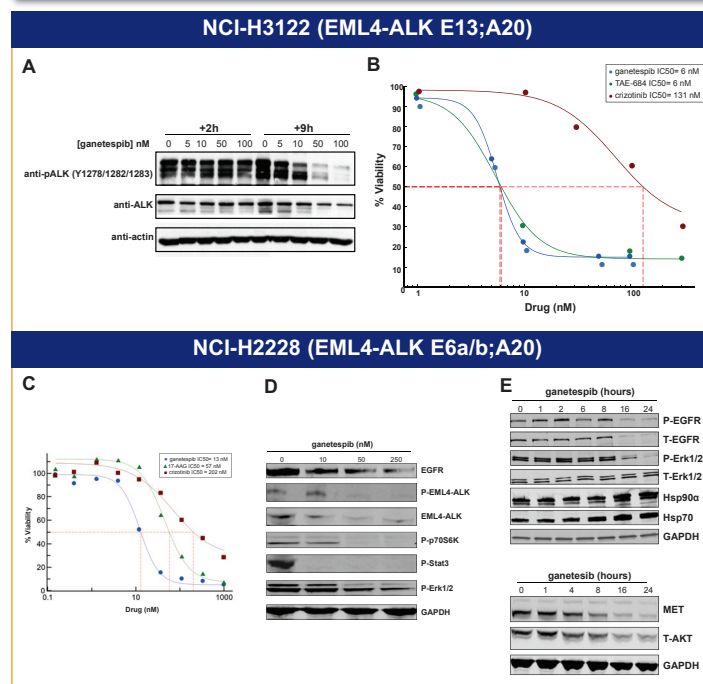


Figure 4. (A-B) Ganetespib fully inhibits phosphorylation of EML4-ALK leading to potent cytotoxicity in EML4-ALK driven H3122 NSCLC cells. In contrast, the ALK inhibitor crizotinib displays weak activity resulting in reduced cell killing. (C) Ganetespib displays more potent anticancer activity than 17-AAG and crizotinib in the EML4-ALK positive NSCLC cell line H2228. (D-E) Ganetespib induces downregulation of EML4-ALK, EGFR and c-MET leading to disruption of downstream signaling.

STA-9090 Destabilizes PDGFR α and Activates Apoptosis

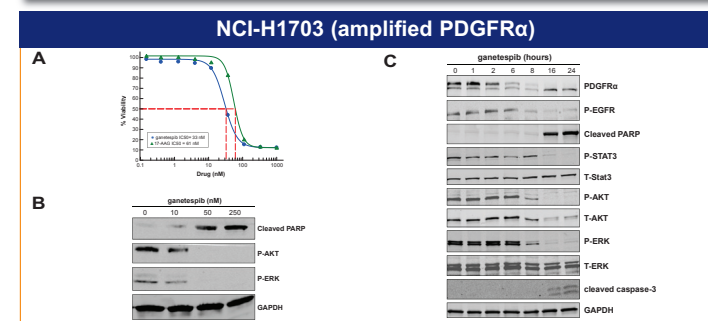


Figure 5. (A) Ganetespib decreases viability in H1703 NSCLC cells with amplified PDGFR α . (B) Activation of apoptosis and downregulation of MAPK and AKT activity correlate with the IC50 dose. (C) Ganetespib induces depletion of PDGFR α and EGFR activity followed by the disruption of oncogenic signaling and induction of apoptosis.

Ganetespib Suppresses Tumor Growth in Wild-type EGFR Xenograft Models

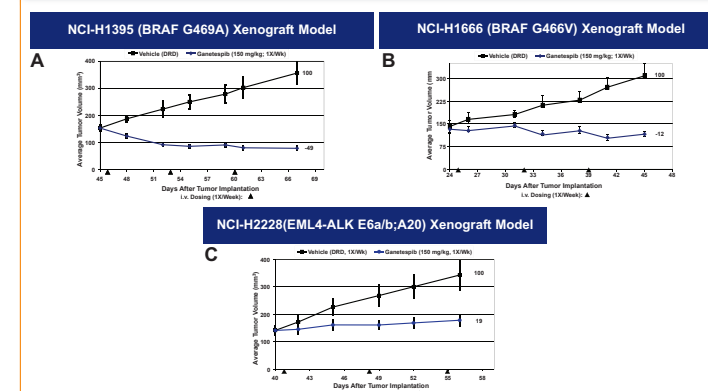


Figure 6. Ganetespib treatment induced tumor regression in mutant BRAF NSCLC xenograft models (A & B) and led to stable disease in EML4-ALK positive NSCLC xenograft models (C).

Summary

- Ganetespib promotes the destabilization of multiple clinically validated oncogenes present in NSCLC including EML4-ALK, PDGFR α , EGFR, MET, and HER2 resulting in potent cell death *in vitro*
- The multi-modal action of ganetespib makes it superior to targeted therapies
- In vivo*, ganetespib is highly efficacious in NSCLC xenografts expressing mutant BRAF or the EML4-ALK fusion oncoprotein
- A Phase 2b/3 clinical trial for ganetespib in patients with advanced NSCLC is currently being initiated



For further information on Ganetespib: www.syntapharma.com