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## Targeting KRAS mutant NSCLC with the Hsp90 inhibitor ganetes.

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**Background:** Mutant KRAS is detected in 20-25% of non-small cell lung carcinomas (NSCLC) and represents one of the most common oncogenic drivers of this disease. NSCLC tumors with oncogenic KRAS respond poorly to currently available therapies necessitating the pursuit of new treatment strategies. Heat shock protein 90 (Hsp90) is a molecular chaperone required for the maturation and stability of hundreds of client proteins, many of which are known oncogenic drivers or effectors of such proteins. Inactivation of Hsp90 results in the simultaneous inhibition of multiple oncogenic signaling pathways, making Hsp90 a highly attractive therapeutic target. Ganetespi is a second generation, small molecule Hsp90 inhibitor currently being evaluated in multiple clinical trials. Recent results from a Phase 2 trial with ganetespi revealed that >60% of patients with KRAS mutant NSCLC exhibited tumor shrinkage at 8 weeks, indicating that ganetespi has promising potential to benefit this disease.

**Aims:** To further understand the actions of ganetespi in mutant KRAS NSCLC tumors, preclinical studies were executed in a diverse panel of KRAS mutant NSCLC cell lines to: (1) Investigate whether ganetespi is effective in suppressing critical cell signaling nodes responsible for KRAS-driven NSCLC cell survival and (2) Assess whether ganetespi can synergize with both clinical agents targeted against these signaling nodes and standard of care chemotherapies.

**Results:** Ganetespi displayed potent anticancer activity across 15 KRAS mutant NSCLC cell lines assayed *in vitro*, with an average IC<sub>50</sub> of 24 nM. Combining ganetespi with anti-mitotics, alkylating agents or topoisomerase inhibitors resulted in an increase in cell death of up to 44, 61 and 26%, respectively, versus monotherapy. At the molecular level, ganetespi induced the destabilization of several KRAS substrates, including BRAF and CRAF, leading to inactivation of their downstream effectors followed by programmed cell death. Ganetespi effectively suppressed the growth of human KRAS mutant NSCLC tumor xenografts *in vivo*, however; ganetespi did not induce tumor regression. In light of this, we sought to investigate whether inhibitors targeting KRAS driven signaling nodes would confer greater sensitivity to ganetespi. *In vitro*, combinations of low dose ganetespi with either MEK or PI3K/mTOR inhibitors consistently resulted in greater activity than monotherapy, up to 77% and 42%, respectively. Furthermore, ganetespi suppressed activating feedback loops that occur in

response to MEK and PI3K/mTOR inhibition, providing a rationale for the enhanced combinatorial activity. To validate these results, *in vivo* combinations were performed with ganetespib and a PI3K/mTOR inhibitor in KRAS mutant NSCLC xenografts. While both agents promoted tumor shrinkage on their own, considerable improvement in tumor growth inhibition was observed in the combination arm.

**Conclusions:** Ganetespib, a potent inhibitor of Hsp90, has shown encouraging evidence of clinical activity, including tumor shrinkage in patients with KRAS mutant NSCLC. *In vitro*, ganetespib exhibited potent anticancer activity in NSCLC cells harboring a diverse spectrum of KRAS mutations due in part to degradation and inactivation of critical KRAS signaling effectors. Combination with targeted therapies that overlap with these signaling nodes led to enhanced anticancer activity *in vitro* and in mouse models of KRAS mutant NSCLC. Taken together, these results could have interesting clinical utility in patients with KRAS mutant NSCLC.