

Abstract #74

## **Combination of the Hsp90 inhibitor ganetespib (STA-9090) with docetaxel displays synergistic anticancer activity in solid tumor cells.**

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**Background:** Ganetespib (formerly STA-9090) is a synthetic, small-molecule inhibitor of Hsp90 that is currently in twelve Phase 1 or Phase 2 trials for solid and hematologic malignancies. Recent results from a Phase 2 trial in non-small cell lung carcinoma (NSCLC) show encouraging signs of clinical activity and is well tolerated in patients whose tumors are wild-type for EGFR and KRAS. Here, because of the accumulating evidence that Hsp90 inhibition sensitizes tumor cells to taxanes, we have now performed preclinical investigations on combinations of ganetespib with the taxane docetaxel in NSCLC, prostate and colon cancer cells.

**Results:** We observed potent single agent activity with ganetespib across a panel of NSCLC cell lines independent of EGFR status both *in vitro* and in mouse xenograft models. Similar activity was observed in patient-derived NSCLC tumor cells grown as tumor spheres *in vitro* or tumor grafts *in vivo*. Comparable results were demonstrated in prostate and colon cell lines regardless of androgen receptor or p53 status, respectively. To investigate the potential for therapeutic synergy, we measured the response of lung, prostate and colon cancer cells to the combination of ganetespib and docetaxel. By microscopy and proliferation assays, the combination resulted in enhanced cell death compared to either agent alone *in vitro*. Similarly, mouse xenograft models of NSCLC containing wild-type EGFR displayed greater efficacy with the combination of docetaxel and ganetespib than monotherapy.

**Conclusions:** Ganetespib is a highly potent Hsp90 inhibitor which displays nonclinical efficacy across a broad range of indications and genetic alterations, both in cancer cell lines as well as in primary human tumors. Combining ganetespib with docetaxel enhanced cell death in a synergistic fashion in multiple cancer cell types, and as a result, could expand the therapeutic potential of both drugs.