

## **Mechanism(s) of action and potency of Hsp90 inhibitor STA-9090 in small cell lung carcinoma cells.**

Dae-Ho Lee, Chien-Hao Lai, Yisong Wang, and Giuseppe Giaccone  
Medical Oncology Branch, Center for Cancer Research, National Cancer Institute,  
National Institutes of Health, Bethesda, MD 20892, USA

**Background:** STA-9090 (Synta Pharmaceuticals) is a second generation Hsp90 inhibitor, which is a resorcinol-containing triazole compound with a novel structure that is unrelated to the geldanamycin class of Hsp90 inhibitors. It binds to the ATP-binding domain of Hsp90 and is a potent Hsp90 inhibitor through degradation of Hsp90 client onco-proteins in cancer cells. At low nanomolar concentrations, STA-9090 potently inhibits cell proliferation and induces apoptosis in a variety of cancer cell lines including many receptor tyrosine kinase inhibitor- and 17-AAG (geldanamycin class of Hsp90 inhibitor)-resistant cell lines, and in several tumor xenograft models. Based on preclinical activity of other Hsp90 inhibitors, small cell lung cancer appears like a promising tumor target for this class of agents.

**Results:** Using 12 small cell lung carcinoma (SCLC) cell lines, we demonstrate that STA-9090 (IC<sub>50</sub>: 30.9± 16.6 nM) is much more potent than 17-AAG (IC<sub>50</sub>: 16±47 uM) in MTS assays. In addition, at the concentrations of IC<sub>50</sub> or 3-60 times over IC<sub>50</sub>, STA-9090 exhibits cytostatic effect by arresting cells at G2/M on all the SCLC cell lines studied so far. Cells survive for as long as 6 days in the presence of STA-9090. Intriguingly, cell viability precipitously drops upon STA-9090 withdrawal following 48-72 h treatment. We are investigating the mechanism of cell death occurring after drug withdrawal (mitotic catastrophe after release from G2 arrest or cell death in the next cell cycle). In addition we are evaluating the molecular mechanism(s) of STA-9090 action in xenograft models of SCLC.

**Conclusion:** Our study suggests that STA-9090 is a potent inhibitor of SCLC cell growth via induction of G2/M arrest. The fact that STA-9090 withdrawal induces precipitous cell death suggests that STA-9090 intermittent treatment strategy might be considered for the ongoing phase II studies in SCLC.