

Abstract # 2899

## **Preclinical Evaluation of A Potent 2nd Generation Small-Molecule Hsp90 Inhibitor STA-9090 in Hematological Cell Lines.**

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STA-9090 is a potent, second generation, small-molecule Hsp90 inhibitor, with a chemical structure unrelated to the first-generation, ansamycin family of Hsp90 inhibitors. In preclinical *in vitro* and *in vivo* studies, STA-9090 has shown potency up to 100 times greater than the first-generation Hsp90 inhibitors against a wide range of solid and hematological cancer types including those resistant to imatinib, sunitinib, erlotinib, and dasatinib. STA-9090 is currently being evaluated two Phase 1 and four Phase 2 trials (non-small cell lung, GIST, colon, and gastric) in solid tumor cancers; and two trials in hematologic cancers. Additional Phase 2 trials in several other indications are planned for 2H 2010.

Inhibition of Hsp90 by STA-9090 results in the destabilization of a broad range of oncogenic kinases often overexpressed or mutated in hematological cancers. For example, the nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) expressed in the anaplastic large cell lymphoma (ALCL) cell line Karpas 299, is degraded rapidly in the presence of STA-9090 *in vitro*, resulting in the loss of viability. Similar results were shown in other NPM-ALK driven ALCL cells including SU-DHL-1 and SR-786 with IC<sub>50</sub> less than 20 nM. Stability of other kinases common to hematological malignancies, such as Bcr-Abl, FLT3 and c-Kit, were also shown to be highly sensitive to STA-9090, resulting in potent cell death of cell lines addicted to signaling by these kinases.

*In vivo*, STA-9090 was highly effective in a subcutaneous xenograft model of diffuse large B-cell lymphoma SU-DHL-4 with resulting %T/C values of 26, 4, -90 and -93 when dosed at 25, 50, 75 and 100 mg twice per week, respectively. Importantly, 75 and 100 mg/kg STA-9090 dosed 2 times per week for a total of 3 weeks (150 and 200 mg/kg weekly) resulted in 25% and 50% of the animals in each group being free of tumors by the end of the study, respectively. MV4-11, an AML (FLT3ITD) cell line, turned out to be one of the most sensitive xenograft models to STA-9090 treatment. STA-9090 at 100 mg/kg or 125mg/kg once weekly was highly efficacious with 37.5% of mice achieving tumor free with acceptable toxicity at the end of the 3-week treatment period.

In conclusion, STA-9090 exhibits preferable biological profiles both *in vitro* and *in vivo* in treating hematological malignancies. Clinical studies for using STA-9090 both once weekly and twice weekly are ongoing.

