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### **Fragment to clinic: Translational biomarkers for clinical candidates derived from fragment-based drug design**

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Heat Shock Protein 90 (HSP90) is a member of a family of molecular chaperone proteins which directs the folding of polypeptides into functional configurations affecting stabilisation and activation. AT13387 is a small molecule inhibitor of HSP90 discovered using fragment-based drug discovery. Pharmacokinetic studies in tumor bearing mice showed that AT13387 exhibits a much extended tumor half life compared to that in plasma.

We characterised the kinetics of pharmacodynamic (PD) activity in mouse models and how they may correlate with efficacy on a particular dose schedule. These data were then used to validate and translate a number of laboratory assays into a biomarker platform for use on clinical samples. Plasma and tumour samples from a phase I clinical study were used to develop and confirm a set of PD biomarker assays to assess the level of HSP90 inhibition in patient samples.

We show that a xenograft tumor half life of up to 72 hours results in the modulation of markers of HSP90 inhibition; including an induction of HSP70 and a reduction in the levels of client proteins for between 6 and 96h. This extended PD effect predicted efficacy on both once or twice weekly dose schedules and this was confirmed in a number of xenograft models. An HSP70 ELISA assay in peripheral blood mononuclear cells (PBMCs) was developed and again, in the mouse model, HSP70 induction was observed at between 1 and 6h, consistent with the plasma half life of AT13387 at 4 hours. There was a dose dependent effect of AT13387 on HSP70 induction resulting in a significant increase at doses above 60mg/kg. We confirmed that the HSP70 ELISA effectively monitored HSP70 in human PBMCs in an ex vivo assay and used the dose and time dependency data to design a sampling procedure for the phase I clinical study.

Finally, we attempt to correlate these effects in GIST preclinical models using a soluble c-Kit ELISA assay from culture media and plasma samples and extend these findings to clinical samples from a Phase I clinical trial.