Heat Shock Protein 90 Inhibitor in Patients With Refractory Solid Tumors: A Phase I Pharmacokinetic And Pharmacodynamic Study Of AT13387

INTRODUCTION

- AT13387 is a highly potent heat shock protein 90 (Hsp90) inhibitor (Ki of 0.71 nM). Hsp90 is required for the functional stabilization of numerous oncoproteins, including tumor promoting growth factors, growth factor receptors, and proteins such as HER2, ER, IGF1R, EGFR, AKT, and RAF.

- In vitro preclinical experiments have shown that AT13387 can bind to the immunosuppressive activity of hsp90, resulting in up-regulation of hsp90, and down-regulation of key client proteins, causing growth arrest and apoptosis.

- In vivo experiments in murine xenograft models demonstrated that AT13387 causes prolonged knockdown of client proteins and has a half-life of 68-76 hours in the tumor xenographs.

- Due to the prolonged pharmacodynamic effect of AT13387, too closely spaced doses were being explored clinically. As a result, weekly administration, three times every four weeks, was chosen.

- The results of the ongoing Phase I dose escalation study, AT13387-0001, in which patients have been treated with the weekly dose escalation schedule are presented.

- We present preliminary data demonstrating that we achieve inhibition of HSP90 in tumor that results in an increase in the apoptotic marker, cleaved caspase 3.

OBJECTIVES

Primary

- To identify the MTD of AT13387 when administered both once and twice weekly for three weeks out of every four.

Secondary

- To characterize the safety and tolerability of AT13387 including the identification of DLTs.

- To define the pharmacokinetics of AT13387 in plasma and urine.

- To demonstrate the pharmacodynamic activity of AT13387 in plasma, correlating peripheral blood mononuclear cells (PBMC) and in tumor using PET scans and biopsies.

METHODS

Study Design

- Phase I study in which AT13387 is administered IV for 1 hr, either once and twice weekly for three weeks out of every four; patients with histologically confirmed metastatic solid tumors, including tumors, who are refractory to standard therapy.

- Dose escalation is performed in accordance with the modified Fibonacci principle.

- DLTs were defined as:
  - Neutropenia <3 x 10⁹/L for >5 days;
  - Neutropenia <1 x 10⁹/L with fever; Thrombocytopenia <25 x 10⁹/L accompanied by bleeding or thrombocytopenia <50 x 10⁹/L;
  - More than one individual dose omission during the first cycle of treatment due to the appearance of drug-related toxicity, where, in the investigator’s opinion, it is likely that administration of AT13387 is causally linked to the toxicity or observed effect.

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- DLTS were defined as:
  - Neutropenia <3 x 10⁹/L for >5 days;
  - Neutropenia <1 x 10⁹/L with fever; Thrombocytopenia <25 x 10⁹/L accompanied by bleeding or thrombocytopenia <50 x 10⁹/L;
  - More than one individual dose omission during the first cycle of treatment due to the appearance of drug-related toxicity, where, in the investigator’s opinion, it is likely that administration of AT13387 is causally linked to the toxicity or observed effect.

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PHARMACOKINETICS

- Hsp70 inhibition as demonstrated in both PBMC and tumor tissue following dosing with AT13387 in preclinical models.

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- This was associated with an increase in caspase-3, indicative of apoptosis within the tumor.

- These data suggest that we are achieving sufficient AT13387 levels in the tumor to elicit the low grade toxicities described above.

- In the examples above Akt, CDK4, Raf-1 and Lck levels were all reduced following infusion of AT13387, with levels recovering prior to administration of the next dose.

- The t1/2 mean cohort values ranged from 6.5 to 9.1 hr. There was no notable accumulation or reduction in exposure between Day 1 and Day 18 of the weekly schedule.

- In conclusion, no DLTs were recorded in Cohorts 1-5. Dose escalation beyond Cohort 5 (120 mg/m²) will be determined.

- The MTD for a once weekly dosing schedule (three weeks out of four) was defined as 120 mg/m² per dose.

DISEASE RESPONSE

- Patients with measurable disease had their tumor dimensions calculated according to RECIST at screening and every two months during the first 6 months of treatment.

- Stable disease for at least six months was observed in 221 (55%) of patients

- Patient 01-032 who had thyroid cancer and was treated with 30 mg/m² per dose and patient 01-072 who had metastatic uveal melanoma and was treated with 80 mg/m²

- Stable disease for 6-24 months was observed in 521 (24%) of patients.

CONCLUSIONS

Safety

- AT13387 is well tolerated between 10-120mg/m². The most commonly reported AEs were gastrointestinal toxicity, especially transient diarrhea and fatigue, which have been previously reported for geldanamycin (Hsp90), and reversible visual symptoms.

- The maximum tolerated dose of AT13387 for a twice weekly dosing schedule (three weeks out of four) was defined as 120 mg/m² per dose.

Pharmacodynamics

- Inhibition of Hsp70, as shown by induction of Hsp70 in a dose-dependent manner, was observed in PBMCs from patients treated with AT13387 across all cohorts.

- Similarly, upregulation of Hsp70 and caspase 3 was observed in post-dose biopsy samples collected from patients in the expansion cohort on the twice weekly schedule.

- The PK data demonstrate that we are achieving pharmacologically active levels of drug in both the plasma and in tumor, and suggest that consistent with preclinical data we can expect a prolonged tumor PD effect in comparison to the plasma half-life.

- The 100% mean cohort values ranged from 6.5 to 9.1 hr. Maximum t1/2 observed for any individual profile was 14hrs. There was no notable accumulation or reduction in exposure between Day 1 and Day 18 of the weekly schedule.

- Pharmacokinetics of AT13387 is independent of dose and showed a mean value of 283.6 micromolar (SD 54.4 micromolar).

- Excretion in urine was minimal.

- Response

- Stable disease for at least six months has been observed in 2 patients and in a further 5 patients beyond 2 cycles of treatment.

- Ongoing work

- Completion of the twice weekly dose escalation phase with associated tumor PD sampling (biopsy and PET imaging).

- Tumor biopsies will be assessed for client protein knockdown.

- The MTD for a once weekly dosing schedule will be determined.

Acknowledgments

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