AT13387, A Novel, Non-Ansamycin Inhibitor of Heat Shock Protein 90 is Active Against Gastrointestinal Stromal Tumors (GIST)

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AT13387 Overcomes Imatinib-Resistant In GIST Cell Lines

AT13387 is a promising agent in GIST, including TKI-resistant c-KIT positive and c-Kit negative GIST. AT13387 demonstrated clinical activity after failure of multiple TKI treatment in Phase 2 study in combination with imatinib is ongoing for imatinib-resistant GIST patients. AT13387 exhibits dose dependent systemic exposure and linear pharmacokinetics. Half-life of AT13387 in GIST patients across Phase 1 and Phase 2, range between 6.8 - 11.2 hours. AT13387 exhibits dose dependency on linear exposure and pharmacokinetics. AT13387 + 400 mg imatinib)

Phase 1: AT13387 PK Profile

- The pharmacokinetics of AT13387 following a 1h IV infusion show biphasic distribution with elimination half life of 9.9 h (N=8)
- Exposures (AUC(0-t), Cmax) increased dose proportionally from 10 to 310 mg, AT13387 was independent of dose, mean value of 1 L/h/g (m<sub>2</sub>/kg) based on data from all dose cohorts.

Phase 2: PR > 6 Months

- Patient 106-102 enrolled into Cohort 1 (180 mg/m<sup>2</sup>) AT13387 + 400 mg imatinib
- Initial disease stabilization November 2002
- Sample analyzed from February 2006 from recurrence of GIST
- After initial disease stabilization, patient received continued - CR Recurrence Feb 2006. Aug 2006 – Oct 2008 patient remained on therapy - SD
- Oct 2008 – May 2011 patient received sunitinib - CR Jun 2011 – Patient started AT13387 on 02/2012 - PR for 44 days
- No CR/IT mutations
- PDGFRα mutations
- Exon 18 deletion 842-845 (I982)

Phase 1: Drug-related Adverse Events > 10% by Frequency All Patients (N=53), All were Gr1 or 2 except pts Gr3(11%), No Gr4

Methods

- Key eligibility: advanced, untreated solid tumors including GIST, sarcoma and other solid tumors, 18 years of age or older, Eastern Cooperative Oncology Group (ECOG) PS 1-2
- No prior chemotherapy or radiation for the tumor being entered
- At least one local or metastatic lesion
- Prior TKIs: patients received a minimum of 8 weeks (4 cycles) of prior TKI therapy
- Optimal TKI therapy: no prior or ongoing systemic treatment with novel inhibitors of the PDGF or VEGF receptor
- Prior systemic treatment: metastatic only
- Maximum 3 lesions per subject

Results

- Key objective: maximum tolerated dose (MTD), dose limiting toxicities (DLTs), pharmacokinetics (PK), pharmacodynamics (PD), early anti-tumor activity
- AT13387 exhibits dose dependent systemic exposure and linear pharmacokinetics. Half-life of AT13387 in GIST patients across Phase 1 and Phase 2, range between 6.8 - 11.2 hours.
- AT13387 induction of HSP70, following a 1h IV infusion show biphasic distribution with elimination half life of 9.9 h (N=8)
- Exposures (AUC(0-t), Cmax) increased dose proportionally from 10 to 310 mg, AT13387 was independent of dose, mean value of 1 L/h/g (m<sub>2</sub>/kg) based on data from all dose cohorts.

Individual Gist Characteristic

- Plasma clearance of AT13387 was independent of dose; mean value of AT13387 following a 1h IV infusion show biphasic distribution with elimination half life of 9.9 h (N=8)