Encouraging Interim Data From A Phase I Study Of Astex's HSP90 Inhibitor AT13387 To Be Presented At ASCO

Cambridge, UK, 2 June 2010

Astex Therapeutics, the UK-based biotechnology company developing targeted therapies for oncology and virology, announced that interim data from an ongoing Phase I study of its novel HSP90 inhibitor, AT13387, is to be presented at the American Society of Clinical Oncology Annual Meeting, June 4-8, 2010, in Chicago, USA.

The Phase I study, in patients with refractory solid tumours, is being conducted at multiple sites in the US, with Dr Geoff Shapiro from the Dana-Farber Cancer Institute as Principal Investigator. The primary objective of the study is to determine the maximum tolerated dose of AT13387, with secondary objectives to investigate the safety and tolerability of the compound, its pharmacokinetic (PK) profile, and its pharmacodynamic (PD) activity in circulating blood cells and in tumours using PET scans and biopsies.

Interim clinical data, to be presented by Dr Shapiro, indicate that AT13387 is well tolerated, with no dose limiting toxicities observed at doses up to 120mg/m2/day. In addition, none of the hepatotoxicity seen with other compounds in this class has been observed in patients treated with AT13387. The data also demonstrate that AT13387 exhibits favourable PK and is associated with expected PD endpoints, including HSP70 up-regulation, in a dose dependent manner. Increases in caspase 3 in biopsy samples are indicative of induction of apoptosis in the tumour. The PD data demonstrate that the compound is achieving levels that are pharmacologically active in plasma and in tumour, consistent with the extended duration of action of the drug observed in preclinical testing. Stable disease has been observed in 24% of patients (5/21) for more than 2 cycles of treatment and in a further 10% of patients (2/21) for at least 6 months.

The Phase I study is designed to administer AT13387 as a one hour IV infusion, either once or twice weekly, for three weeks out of every four in patients with metastatic solid tumours, or with lymphoma, who are refractory to standard therapy. To date, a total of 26 patients have received AT13387 on a twice weekly schedule. Astex is currently planning for a Phase II study of AT13387 in patients with gastro-intestinal stromal tumours (GIST) to commence later this year and for a number of single agent and combination studies of AT13387 under its Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) that was entered into at the end of 2009.

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About AT13387

AT13387 is a highly potent, non-ansamycin, heat shock protein 90 (HSP90) inhibitor derived from Astex fragment chemistry platform, Pyramid™, with a potential best-in-class profile based on its long duration of action in tumour cells. HSP90 is required for the functional stabilization of numerous oncogenic client proteins such as HER-2, ER, c-MET, AKT, VEGF-R and B-RAF. AT13387 inhibition of HSP90 suppresses client proteins for greater than 7 days in tumor cells in preclinical models in vitro, making it the longest acting agent reported to date. A potential benefit of highly potent and long acting HSP90 inhibitors, such

as AT13387, is their ability to maintain their anti-tumour effect while minimising the potential for undesirable side effects associated with systemic exposure, thereby enhancing the therapeutic opportunities available to patients by reducing the requirement for frequent dosing.

AT13387 is the third drug candidate that Astex has discovered in house that has entered the clinic. Astex signed a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) to collaborate on the study of AT13387 for the treatment of cancer at the end of 2009.

About Astex Therapeutics

Astex is a UK-based biotechnology company that discovers and develops novel small molecule therapeutics. Using its pioneering fragment-based drug discovery platform Pyramid™, Astex has built a pipeline of five molecularly targeted oncology drugs, of which three are currently being tested in clinical trials and two are in pre-clinical development.

In addition to its proprietary research programmes, Astex's productivity in lead discovery has been endorsed through numerous partnerships with major pharmaceutical companies, including AstraZeneca, Bayer-Schering, Boehringer Ingelheim, GlaxoSmithKline, Novartis and Johnson & Johnson.

For further information on Astex please visit the Company's website at www.astex-therapeutics.com

Editors Notes: ASCO presentation

Presentation title: Phase I pharmacokinetic and pharmacodynamic study of the heat shock protein 90 inhibitor AT13387 in patients with refractory solid tumors.

Abstract Number: 3069
Session: Developmental Therapeutics - Experimental Therapeutics
Sub-category: Other Novel Agents
Time: Monday June 7, 8:00 AM to 12:00 PM
Location: S Hall A2

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Abstract:
Background: AT13387 is a highly potent heat shock protein 90 (HSP90) inhibitor (IC50 0.7 nM) derived from Astex fragment chemistry platform, Pyramid. AT13387 suppresses client proteins for greater than 7 days in tumor cells, making it the longest acting agent reported to date.
Methods: In this phase I dose escalation trial, AT13387 was administered as a 1-hr intravenous infusion on days 1, 4, 8, 11, 15 and 18 of a 28-day cycle in a standard "3+3" design in order to determine MTD. Secondary endpoints included PK, PD and tolerability.

Results:
Between May 2008 and December 2009, 21 patients with median age 57 (r 28-77) were treated with AT13387 over 5 dose levels, including 10, 20, 40, 80 and 120 mg/m2 twice weekly. No dose-limiting toxicities have been observed. The most frequent toxicities reported in the first eighteen patients were diarrhea (11/18, 61%) and fatigue (5/18, 28%) of mild or moderate severity. At the 120 mg/m2 dose level, reversible grade 1 visual changes were common, including blurred vision, flashes and delayed light dark/accommodation, occurring at day 11 or later. Evidence of HSP90 inhibition, manifest as an increase in HSP70 in PBMCs, was detected at all dose levels and exhibited dose dependence. Reductions in the expression of CDK4, raf-1 and phospho-AKT were also detected in PBMCs in a proportion of patients. PK parameters determined on days 1 and 18 of cycle 1 demonstrated exposure proportional to dose administered, without significant plasma accumulation with repeated administration. Clearance of AT13387 was independent of dose (mean 25 ml/min/kg). The best response in this heavily pre-treated population has been stable disease that persisted for at least six months in two patients (follicular cell carcinoma of the thyroid and metastatic uveal melanoma).

Conclusions:
Single-agent AT13387, administered as a twice-weekly infusion three weeks out of four, is well-tolerated at doses up to 120mg/m2. No hepatotoxicity has been observed. Favorable pharmacokinetics and expected pharmacodynamic endpoints

have been demonstrated. Further schedule refinement may involve evaluation of twice-weekly dosing two weeks out of every three, as well as weekly administration.