Astex Reports Positive Clinical Biomarker Data from its Phase I study on CDK Inhibitor AT7519 at the AACR Annual Meeting 2009

Cambridge, UK, 14th April 2009

Astex Therapeutics announced today that key biomarker data from the Company's first Phase I trial of its cyclin dependent kinase (CDK) inhibitor, AT7519, will be presented at the 100th American Association for Cancer Research (AACR) Annual Meeting 2009, to be held April 18-22, 2009, at the Colorado Convention Center in Denver, Colorado.

AT7519 was discovered using the Company's industry-leading fragment-based drug discovery platform, PyramidTM, and is a potent inhibitor of the cyclin dependent kinases (CDKs) 1, 2, 4, 5 and 9. A first Phase I dose escalation study of the compound in patients with refractory solid tumours using a daily times 5 every three weeks schedule was recently completed. The trial was conducted at the Northern Institute for Cancer Research in the UK and at the Arizona Cancer Center in the US. Trial endpoints included pharmacodynamic (PD) and pharmacokinetic (PK) sampling during and following infusion of AT7519. Results to be reported at this meeting demonstrate that direct inhibition of CDK was observed in skin biopsies or serum samples at all doses during the escalation phase. By monitoring phenotypic markers that occur only as a consequence of a pharmacologically relevant CDK inhibition, we were further able to determine a predicted Biologically Effective Dose (BED). Such a clear understanding of the dose dependent effects of AT7519 will be valuable to the further clinical development of the agent.

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Editors Notes

Abstract Number: 3588
Session Title: Early Clinical Trials
Presentation Title: Identification of a biologically effective dose of AT7519, a cyclin dependent kinase inhibitor, in a phase I study.
Presentation Start/End Time: Tuesday, Apr 21, 2009, 8:00 AM -12:00 PM
Location: Hall B-F, Poster Section 31
Poster Section: 31
Poster Board Number: 2

Authors

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Abstract

AT7519 is a potent inhibitor of the cyclin dependent kinases (CDKs) 1, 2, 4, 5 and 9 developed using Astex's fragment-based medicinal chemistry approach. A dose escalation study was performed in patients with refractory solid tumours using a 1 h intravenous infusion on days 1 through 5 of a 21 day cycle. Dose escalation proceeded through 6 dose levels (1.8 to 34 mg/m2/day) via a standard "3+3" design according to observed toxicity to define the maximum tolerated dose.

Trial endpoints included pharmacodynamic (PD) and pharmacokinetic (PK) sampling during and following infusion of AT7519. Biochemical markers (direct indicators of CDK inhibition), phospho-nuclephosmin (pNPM), proliferating cell nuclear antigen (PCNA) and functional markers (phenotypic markers of a consequence of CDK inhibition), Ki67 and cytokeratin were monitored in skin punch biopsies or serum samples. Skin punch biopsies were taken prior to patients receiving the first dose of AT7519 and on day 3 of cycle 1. Slides were prepared from formalin fixed, paraffin embedded sections of the epidermis and immunohistochemistry performed for PCNA, pNPM and Ki67. Serum samples were collected prior to patients receiving AT7519 and on day 5 of cycle 1. ELISA for cytokeratin-18 (M65) and its cleaved form (M30) were performed as an indirect marker of tumour cell apoptosis.

Inhibition of CDK, compared to pre-treatment levels, was indicated by reduction in pNPM and PCNA levels in skin biopsies and was observed across the dose range in 16 out of 18 patients treated at or above 3.6mg/m2/day. Changes in the functional markers were only observed in patients treated in cohort 5 (28.8mg/m2/day) and above with significant increases in the serum levels of cytokeratin and its caspase cleaved product in 7/8 and 6/8 patients respectively, treated at these doses. Four out of eight of these same patients exhibited inhibition of the proliferative marker Ki67 in skin samples. Pharmacokinetic data show that as dose escalation was performed plasma levels of AT7519 were rapidly achieved that would be expected to modulate CDK activity. However these levels were only maintained over a short period of time in initial cohorts. Patients receiving 28.8mg/m2/day and above maintained these levels out over a 24h period consistent with the observation that it was in these cohorts that a biological consequence of CDK inhibition was observed.

These data show that it is possible to monitor CDK inhibitory activity in surrogate tissue taken from patients receiving AT7519. AT7519 is pharmacologically active in these tissues and we show AT7519 must achieve a certain magnitude or duration of exposure before the biological effects of CDK inhibition manifest. AT7519 has a mechanism of action consistent with a CDK inhibitor in surrogate tissue and these markers offer the opportunity to determine a biologically effective dose for AT7519 and other inhibitors of the class.

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, Novartis and Johnson & Johnson.

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