Astex reports positive data from its Phase I study of AT9283 at the ASCO Annual Meeting 2009

Cambridge, UK, 16th May 2009

Astex Therapeutics announced today that it has successfully completed an initial Phase I trial of AT9283 in patients with refractory solid tumours and will be reporting key data from the study at the American Society for Clinical Oncology (ASCO) Annual Meeting, May 29- June 2nd in Orlando, Florida.

Treatment with AT9283, a multi-targeted kinase inhibitor, was found to be generally well tolerated in highly-refractory patients with solid tumours when administered as a 72 hour continuous intravenous infusion repeated every three weeks. Over 30% of patients derived clinical benefit from single agent treatment with AT9283. One patient with pre-treated non small cell lung cancer achieved a durable partial response and more than 13 patients experienced a best response of stable disease according to the RECIST criteria. Amongst these 13 patients three achieved prolonged disease stabilisation of at least six months duration. The study was conducted under the supervision of Professor Ian Judson, Principal Investigator, at the Cancer Research UK Centre for Cancer Therapeutics at the Royal Marsden Hospital, Sutton, UK and Professor Hilary Calvert at the Northern Institute for Cancer Research, Newcastle Upon Tyne, UK. Results from the study will be presented in a poster session (Abstract #2566).

A sub-study also confirmed the oral bioavailability of AT9283 in patients, an observation that opens up the potential for development of an oral formulation of the agent.

Biomarker data of biochemical and biological markers, such as p53, phospho-histone H3, PCNA and Ki67 from skin samples support the biological activity of AT9283 in this trial. Clinical pharmacokinetic data also support exposures consistent with this biological activity. “We were delighted to see target modulation in samples from patients at generally well tolerated doses, supporting the potential utility of AT9283 in the treatment of patients with solid tumours,” said John Lyons, Ph.D., VP of Translational Research & Development.

Additional Phase I trials are testing alternative dosing schedules of AT9283 in patients with solid tumours and haematological malignancies. Combination trials are also planned as a result of the positive outcome of this Phase I trial.

About AT9283

AT9283 is a small molecule inhibitor of Aurora kinases A and B, with potent activity also against c-ABL and JAK2. Aurora kinases have been demonstrated to be over-expressed in several high risk cancers. Exposure of cancer cell lines to AT9283 results in endoreplication leading to a polyploidy state and cell death by apoptosis. Preclinical activity has been demonstrated in xenografts of colorectal (HCT116), ovarian (A2780) carcinoma and leukaemia (HL60). Tumour growth delay and regressions were observed with an intermittent dosing schedule. Histone H3 phosphorylation has been demonstrated as an effective biomarker of AT9283 Aurora kinase B activity. Preclinical toxicity studies confirmed myelosuppresion as the main dose limiting toxicity.

Inhibitors of Aurora kinases, such as AT9283, represent attractive novel anti-cancer agents for the treatment of a broad range of solid tumours and haematological malignancies as evidenced by anticancer activity in tumour models and emerging early clinical data in adults. AT9283 has been found to be well tolerated in adult patients with haematological malignancies using an intravenous 72 hour infusion on a 21 day schedule. Furthermore, in an ongoing Phase I clinical trial, AT9283 has demonstrated early signals of efficacy in approximately one third of adult patients with relapsed/refractory acute myeloid leukemia.

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Editors Notes

Abstract Number: 2566
Session Title: Developmental Therapeutics: Cytotoxic Chemotherapy

Presentation Title: A phase I study of AT9283, an aurora kinase inhibitor, in patients with refractory solid tumors.
Presentation Start/End Time: Saturday May 30, 8:00 AM to 12:00 PM
Location: Level 2, West Hall C

Authors

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Abstract
Background: AT9283, a multitargeted kinase inhibitor, inhibits several closely related tyrosine and serine/threonine kinases with an IC50 of <10 nM including Aurora A and B, JAK and ABL. Exposure of solid tumour cell lines to AT9283 in vitro induces an "aurora inhibitory" phenotype. Cell survival decreases with increased duration of exposure. Methods: A phase I dose escalation study was performed using a 72 hour continuous intravenous (iv) infusion schedule repeated three weekly according to a stand ard "3+3" design. Results: Thirty-three patients have been treated with a median age of 61 (range 33 to 76 years). The maximum tolerated dose (MTD) was 9 mg/m2/day. Treatment was well tolerated with febrile neutropenia the only dose limiting toxicity. Other adverse events considered possibly related to AT9283 were reversible and included gastrointestinal disturbance and fatigue. Biological evidence of aurora B inhibition manifest as a reduction in histone H3 phosphorylation in skin biopsies during the infusion was observed at all dose levels. A plateau steady state plasma concentration of AT9283 was achieved within 24 hours of initiating drug infusion at all dose levels and exposure increased linearly with dose. Seven patients received an initial oral dose of AT9283 as an aqueous solution in a fasting state at a dose of 0.9 mg/m2 one week prior to starting iv treatment. Interim pharmacokinetic analysis indicated that the median oral bioavailability was 27% (range 17 to 45%) The best response to treatment was a partial response in one patient with NSCLC (ongoing). An additional 4 patients received at least six cycles of therapy (squamous cell carcinoma of the lung, adenocarcinoma of the esophagus and colorectal carcinoma [2]) with a best response of stable disease. Conclusions: The MTD of AT9283 when administered as a 72 hour continuous iv infusion was 9mg/m2/day. Febrile neutropenia is the dose limiting toxicity and evidence of anticancer activity was seen in heavily pre-treated patients.

Summary of dose escalation procedure

Dose (mg/m2/day), # patients treated, # cycles (median), Dose-limiting toxicities

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1 (1.5), 3, 2-7 (2), None
2 (3), 3, 1-4 (4), None
3 (6), 3, 1-2 (2), None
4 (12), 6, 1-6 (2), Febrile neutropenia (2)
5 (9), 25, 1-12(2)* (ongoing), Hickman line infection with grade 3 neutropenia

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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