Encouraging Data from Phase I Studies of Astex's Anti-Cancer Drugs AT7519, AT9283 and AT13387 to be Presented at EORTC-NCI-AACR Annual Meeting

Cambridge, UK, 11th November 2010

Astex Therapeutics, the UK-based biotechnology company developing targeted therapies for oncology and virology, today announced presentations of new clinical data on three of its novel anti-cancer agents and on an advanced drug discovery programme aimed at identifying non-peptidic selective inhibitors of the IAP (inducers of apoptosis) class of proteins. The presentations will be made during the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, being held from 16-19 November 2010 in Berlin, Germany.

AT7519 in Patients with Refractory Solid Tumours and Lymphoma

The presentation on AT7519, Astex's small molecule inhibitor of multiple cyclin dependent kinases, will report on a recently completed Phase I clinical study, sponsored by the NCIC Clinical Trials Group, to examine the safety and tolerability of AT7519 in patients with refractory solid tumours or lymphoma. The data demonstrate that AT7519 is safe and well tolerated with nine of twenty-nine patients treated at four dose levels having stable disease ranging from 2.5 to 11.1 months. The NCIC Clinical Trials Group, located at Queen's University in Kingston, Canada, is planning to commence Phase II trials of AT7519 in patients with chronic lymphocytic leukaemia and mantle cell lymphoma in 2011.

AT9283 in Patients with Refractory Solid Tumours and Lymphoma

A second presentation on AT9283, Astex's small molecule combinatorial kinase inhibitor will report on a Phase I trial, being sponsored by NCIC Clinical Trials Group, to examine the safety and tolerability of AT9283 in patients with refractory solid tumours or lymphoma. AT9283 was safe and well tolerated with evidence of Aurora inhibitory activity observed in tumour samples taken from patients. A partial response was reported in one patient while 4 patients had stable disease ranging from 2.1 to 3.5 months. The NCIC Clinical Trials Group has activated a Phase II trial of AT9283 in patients with refractory multiple myeloma.

AT13387 Biomarker Strategy for Clinical Development

Astex will present further data on the pharmacodynamic (PD) activity of AT13387, its small molecule inhibitor of HSP90, in tumour models and in samples taken from its Phase I clinical study in patients with refractory solid malignancies. These data demonstrate that pharmacologically active concentrations of AT13387 are achieved in the tumour as shown by HSP70 induction, modulation of client proteins and markers of apoptosis. The studies have been used by Astex to develop a biomarker strategy for clinical development of AT13387.

Drug Discovery Programme on IAP Inhibitors

Astex will also present data from a new drug discovery programme focused on the identification of novel, small molecule, selective antagonists of inhibitors of apoptosis (IAP) proteins; XIAP; cIAP1 and cIAP2. These IAP proteins are important regulators of cancer cell survival making them attractive targets for cancer therapy. Astex has used its fragment based drug discovery approach, Pyramid™, to identify novel compounds with selectivity for either XIAP or cIAP and which sensitise and/or promote apoptosis (programmed cell death) in cancer cells and inhibit tumor growth in vivo. These compounds represent promising start points for the development of selective IAP antagonists as novel therapeutic agents for the treatment of cancer

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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, GlaxoSmithKline, Novartis and Johnson & Johnson.

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

About NCIC Clinical Trials Group

The NCIC Clinical Trials Group (NCIC CTG) is a cancer clinical trials cooperative group that conducts phase I-III trials testing anti-cancer and supportive therapies across Canada and internationally. It is one of the national programmes and networks of the Canadian Cancer Society Research Institute (CCSRI), and is supported by the CCSRI with funds raised by the Canadian Cancer Society (CCS). The NCIC CTG's Central Office is located at Queen's University in Kingston, Ontario, Canada.

Editors Notes: EORTC- NCI- AACR presentations

Abstract Number: 491

Presentation Title: NCIC CTG IND.177: Phase I study of AT7519M given as a short infusion twice weekly

Presentation Time: 08:00-09:30, 19th November 2010

Poster Session: PP8: Cell cycle interactive agents

Author Block: S.J. Hotte[1], E.X. Chen[2], L. McIntosh[3], H.W Hirte[1], S Turner[1], A Jarvi[2], M.S. Squires[4], L. Seymour[3]

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Abstract Body:

Background: AT7519M is a small molecule inhibitor of multiple cdks (1, 2, 4, 5, 9) with lower potency against 3, 6 and 7. A recent phase I trial examined a daily short infusion for 5 days every three weeks. Dose dependent QTc prolongation was noted on this schedule. This study examines safety and tolerability of AT7519 delivered on an alternative schedule.

Material and Methods: Patients with refractory solid tumours or lymphoma were eligible and received escalating doses of AT7519M on days 1,4,8,11 every 3 weeks. A protocol amendment in 2007 excluded patients at risk of QTc prolongation and instituted serial EKG evaluation. Pharmacokinetics (PK) were planned for all patients. Patients at the recommended phase II dose level (RP2D) were planned for Holter monitoring and serial tumour and tissue acquisition to examine pharmacodynamic (PD) effects.

Results: 29 patients were treated at 4 dose levels from 14.4mg/m2 to 32.4mg/m2. RP2D was 27mg/m2. Dose limiting toxicity included mucositis, rash, fatigue and muscle weakness, renal dysfunction and febrile neutropenia. The most common toxicities were fatigue (46%;), mucositis (50%;), nausea or vomiting (36%;). Hematologic toxicity was mild other than 1 patient who had grade 4 neutropenia documented. There was no evidence of QTc prolongation, including in external review of EKGs. Nine patients have had stable disease (2.5–11.1 months). PK are dose proportional. Accrual continues to the expanded RP2D level and patients are undergoing Holter testing (QTc) and PDs.

Conclusions: AT7519M given in a short infusion appears to be tolerable and is not associated with QTc prolongation noted with other schedules. NCIC CTG plans phase II trials in mantle cell lymphoma and CLL.

Abstract Number: 512

Presentation Title: NCIC CTG IND.181: Phase I study of AT9283 given as a weekly 24 hour infusion

Presentation Time: 08:00-09:30, 19th November 2010

Poster Session: PP12: DNA repair and inhibitors

Author Block: K. Gelmon[1], S. Dent[2], K. Chi[1], D. Jonker[2], N. Wainman[3], R Simpson[2], K. Capier[1], E. Chen[4], M.S. Squires[5], L. Seymour[3]

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Abstract Body:

Background: AT9283 is a small molecule inhibitor of aurora kinases A and B.

Material and Methods: Patients with refractory solid tumours (up to 2 prior regimens for advanced disease) or lymphoma were eligible and received escalating doses of AT9283 (given as 24 hour infusion) on days 1,8 every 3 weeks. Pharmacokinetics (PK) were planned for all patients. Serial tumour and tissue acquisition to examine pharmacodynamic (PD) effects were planned at the recommended phase II dose level (RP2D), using Immunohistochemistry (IHC) evaluation of histone H3 phosphorylation, upregulation of p53 and the proliferation marker PCNA.

Results: 35 patients were treated at 9 dose levels from 1.5mg/m2 to 47mg/m2. RP2D was 40mg/m2. Dose limiting toxicity was febrile neutropenia. Other than myelosuppression, all other toxicities were mild and included fatigue (31%), alopecia (11%), anorexia (14%), and nausea (17%). Myelosuppression was dose proportional. One partial response was reported in a patient with anal cancer, while 4 patients had stable disease (r; 2.1–3.5 months). PK are dose proportional and neutropenia correlated with AUC, Cmax and clearance. Four patients had serial tumor and skin biopsies taken at the RP2D. Immunohistochemistry (IHC) was performed on these sections for evidence of biological activity of AT9283 in the tissue. Pharmacological evidence of Aurora inhibitory activity was noted, including reduction in PCNA in 3 out of 4 tumour samples following AT9283 administration. Multi-nucleated cells, a consequence of Aurora inhibition, were also observed.

Conclusions: AT9283 given as a weekly (day 1,8 every 21 days) 24 hour infusion has clinical activity and has a tolerable toxicity profile. NCIC CTG has activated a phase II trial in refractory multiple myeloma using this dose schedule.

Abstract Number: 596

Presentation Title: Design and validation of Pharmacodynamic Assays to measure the activity of the HSP90 inhibitor, AT13387 in surrogate tissue and tumor in a Phase I Study

Presentation Time: 08:00-09:30, 19th November 2010

Poster Session: PP6: Biomarkers

Author Block: J. Lyons[1], M. Squires[1], V. Lock[1], B. Graham[1], T. Smyth[1], E. Ong[2], D. Mahadevan[2], E. Kwak[3], G. Shapiro[3]

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Abstract Body:

Heat Shock Protein 90 (HSP90) is a member of a family of molecular chaperone proteins which directs the folding of polypeptides into functional configurations affecting stabilisation and activation. AT13387 is a small molecule inhibitor of HSP90 discovered using fragment-based drug discovery. Pharmacokinetic studies in tumor bearing mice showed that AT13387 exhibits a much extended tumor half life compared to that in plasma.

The studies presented here characterise the kinetics of pharmacodynamic (PD) activity in mouse models and how they may correlate with efficacy on a particular dose schedule. These data were then used to validate and translate a suite of laboratory assays into a biomarker platform for use on clinical samples. Plasma and tumour samples from a phase I clinical study were used to develop and confirm a set of PD biomarker assays to assess the level of HSP90 inhibition in patient samples.

We show here that a xenograft tumor half life of up to 72 hours results in the modulation of markers of HSP90 inhibition; including an induction of HSP70 and a reduction in the levels of client proteins for between 6 and 96h. This extended PD effect predicted efficacy on both once or twice weekly dose schedules and this was confirmed in a number of xenograft models. An HSP70 ELISA assay in peripheral blood mononuclear cells (PBMCs) was developed and again, in the mouse model, HSP70 induction was observed at between 1 and 6h, consistent with the plasma half life of AT13387 at 4 hours. There was a dose dependent effect of AT13387 on HSP70 induction resulting in a significant increase at doses above 60mg/kg. We confirmed that the HSP70 ELISA effectively monitored HSP70 in human PBMCs in an ex vivo assay and used the dose and time dependency data to design a sampling procedure for the phase I clinical study.

PD data generated during a phase I study with AT13387 in refractory solid malignancies confirmed pre-clinical observations of the dose and time dependency of HSP70 induction in patients PBMCs along with some examples of client protein knockdown. We conclude that we achieve sufficient plasma levels to inhibit HSP90 in PBMCs in all cohorts in this study. This level of inhibition results in client protein degradation in several instances. We go on to demonstrate in 5 paired tumor biopsies, taken in the MTD cohort, that we achieve pharmacologically active concentrations of AT13387 in the tumor as demonstrated by HSP70 induction, modulation of client proteins and markers of apoptosis. These data represent a case study in translating assays applied to pre-clinical models to clinical biomarker assays with the aim of demonstrating pharmacological activity of AT13387 in clinical samples and informing the minimally effective biological dose on a twice weekly dose schedule

Abstract Number: 592

Presentation Title: Characterisation of novel, small molecule antagonists of XIAP, cIAP1 and cIAP2 generated by fragment based drug discovery (FBDD)

Presentation Time: 08:00-09:30, 19th November 2010

Poster Session: PP4: Apoptosis, necrosis, autophagy

Author Block: G. Ward[1], G. Chessari[1], A. Woolford[1], P. Williams[1], K. Hearn[1], C. Richardson[1], J. Coyle[1], I. Buck[1], J. Day[1], E. Tamanini[1]

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Abstract Body:

The inhibitor of apoptosis (IAP) family of proteins are important regulators of cancer cell survival, making them attractive targets for cancer therapy. They are characterized by one to three baculovirus IAP repeat (BIR) domains, which are necessary for the antiapoptotic activity of most IAPs. Several small molecule BIR antagonists mimic the N-terminal sequence of SMAC (second mitochondrial activator of caspases), an endogenous inhibitor of the IAPs. These peptidomimetic compounds have the ability to sensitise and/or promote apoptosis in cancer cells and inhibit tumor growth in vivo.

Using our fragment-based screening approach, Pyramid™, we identified a range of diverse, non-peptidomimetic chemotypes which bind to the P1′–P2′ pocket in the BIR3 domain of XIAP. Alanine-like fragments have also been identified with excellent Ligand Efficiency (LE) values, which are superior to LE of Ala-Val (natural substrate) and to LEs of published competitor compounds. Optimisation of these hits using a structure based approach led to novel series (both alanine and non-alanine) which bound with sub μM potency to both XIAP and cIAP1. The most potent compounds were characterised further in proliferation assays using two sensitive human breast cancer cell lines EVSA-T and MDA-MB-231 (with an insensitive cell line, HCT116, as a control). Anti-proliferative compounds were investigated further for their ability to induce cIAP1 degradation and to increase the levels of cleaved caspase-3 in EVSA-T cells. cIAP1 degradation occurred rapidly at low compound concentrations in all cell lines tested; whilst caspase-3 induction closely paralleled the anti-proliferative data.

In conclusion fragment-based screening has enabled the identification of non-peptidomimetic ligands that inhibit this protein:protein interaction. These chemotypes represent promising start points for novel, selective IAP antagonists.