AT7519, a Selective Small Molecule Inhibitor of Cyclin Dependent Kinases: Pharmacodynamic Biomarker Activity in a Phase I Study.

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Introduction

Monitoring PD Endpoints in a Phase I Dose escalation trial in Patients with Advanced Solid Malignancies

The study is a Phase I, open label study in patients with advanced solid malignancies. Treatment cohorts are being dosed in escalating order to determine the safety and tolerability of AT7519 in this first in man trial.

Pre and post-dose samples are being taken for pharmacodynamic biomarker analysis as follows:

1. Skin punch biopsy for analysis by immunohistochemistry as a surrogate tissue (Post dose)
2. Serum samples for analysis of cleaved cytokeratin 18 (Post dose sample taken 1-2h following dosing).

Figure 5. Mean PK data from patients in cohort 1 on day 1 and 4 of dosing

Figure 6. Monitoring of PD Endpoints in Clinical Samples

A. Assay of Cytokinin-18 from serum samples
   - Assay is robust with little inter-patient variability
   - The lack of effect observed at this low dose was expected in this first treatment cohort.

B. PCNA staining in skin biopsy samples
   - Staining is robust with little intra-patient variation
   - Inter-patient variation is significant
   - The lack of effect observed at this low dose was expected in this first treatment cohort.

Conclusion

The selective CDK inhibitor AT7519, was shown to be highly efficacious in xenograft models and was used in the studies described to help develop biomarker methodologies that would be applicable to the clinical development of this and other cell cycle inhibitors. Pharmacodynamic markers of the compounds’ action, identified in cell based studies, were applied to xenograft and skin samples taken from tumour bearing mice. Immunochemistry showed that for certain markers down-regulation of a marker in the tumour correlated with down-regulation in the proliferating layer of the skin. Considered together these data represented a strategy for monitoring compound activity in skin samples taken from patients during early phase clinical development. Samples are currently being collected from an ongoing Phase I clinical trial aimed at characterising a number of assay systems and markers in the clinical setting in order to monitor pharmacodynamic activity of AT7519 and to suggest assays that may be useful in future clinical development.

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