

# A Phase I Study of AT9283, an Aurora Kinase inhibitor in Patients with Refractory Solid Tumours

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## BACKGROUND

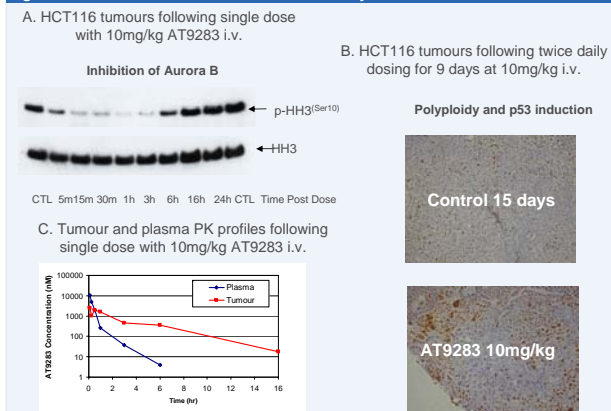
- Aurora kinases are key regulators of mitosis having roles in centrosome function, mitotic spindle formation, chromosome segregation and cytokinesis.
- Aurora A is thought to be involved in centrosome separation, maturation and bipolar spindle assembly through recruitment and phosphorylation of microtubule associated proteins. It also phosphorylates p53, targeting the phosphoprotein for degradation and thereby bypassing the G2/M checkpoint.
- Aurora B is a 'chromosome passenger protein', its localization changing throughout mitosis. During prophase and metaphase it is concentrated along the inner centromeres and at anaphase moves to the central spindle, mediating chromosome segregation and cytokinesis. It associates with specific proteins, such as survivin forming 'chromosome passenger' complexes and phosphorylates a number of targets, including histone H3.
- Over-expression of the Aurora kinases A and B have been linked to genetic instability and cancer, due to dysregulation of cell division.

## INTRODUCTION

- AT9283 is a small molecule inhibitor of several serine/threonine and tyrosine kinases with an  $IC_{50} < 10nM$  against the Aurora kinases A and B, Tyk2, JAK2, RSK2, Ret, Mer, Yes and GSK3 beta.
- The final results of a phase I and pharmacodynamic study of AT9283 administered as a continuous intravenous infusion over 72 hours every three weeks to patients with refractory solid tumours are presented here. Inclusion and exclusion criteria were standard. Dose escalation was performed according to a standard 3+3 design. In order to explore the bioavailability of an oral suspension of AT9283 a subset of patients treated at the MTD received an oral dose one week prior to starting a 72 hour infusion.

## PRECLINICAL DATA

Figure 1: Preclinical Pharmacokinetic/Pharmacodynamic Studies with AT9283



- HCT116 tumour bearing mice received either a single dose of AT9283 at 10mg/kg i.v. (Fig. 1A and 1C) or twice daily doses at 10mg/kg (Fig. 1B).
- Efficacious doses of AT9283 induced a transient knockdown of Aurora B markers (pHH3) for ~6h.
- Polyploidy and p53 induction was observed in tumours following several days dosing.

## PATIENT DEMOGRAPHICS

- A total of 40 patients received 125 cycles of treatment with AT9283 (median 2).

Table 1: Patient Demographics

Characteristic	Value
Age (median)	34 – 79 (64)
Sex	12 Female (30%)
Prior radiotherapy	20 (50%)
Number of previous lines of chemotherapy (median)	1-7 (2)
<b>Diagnoses</b>	
Colorectal cancer	13
NSCLC	7
Esophageal	6
Cholangiocarcinoma	2
Gastric adenocarcinoma	2
Others	SCLC, GIST, ovarian, mesothelial, thyroid, renal cell cancer, adenocarcinoma of the breast, appendix, duodenum, pancreas.

## DOSE ESCALATION

Table 2: Dose Escalation Scheme

Dose Level (mg/m <sup>2</sup> /day)	Number of Patients Treated	Number of Cycles Received (Median)	Dose Limiting Toxicities (DLT)
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)	Hickman Line Infection in the presence of Grade 3 neutropenia

- No evidence of DLT was observed until cohort four (12 mg/m<sup>2</sup> per day) where two of six patients experienced febrile neutropenia during their first cycle of treatment.
- The administered dose was reduced in cohort five (9 mg/m<sup>2</sup> per day) where only one patient of 18 treated experienced a DLT during their first cycle of treatment.
- 9 mg/m<sup>2</sup> per day was identified as the maximum tolerated dose (MTD).

## EFFICACY

Table 3: Best Response To Treatment with AT9283

Response	Best Response N (%)
Partial Response	1 (3%)
Stable Disease	12 (30%)
Treatment for at least 24 weeks	4 (10%)

- There was one partial response in a patient with pre-treated NSCLC (duration five months).
- Three other patients received at least six months of therapy with a best response of stable disease (colorectal carcinoma, adenocarcinoma of esophagus, NSCLC).
- Three of thirty-one (10%) patients treated at the MTD, or above, received at least six months of treatment.

## TOXICITY

- In general, treatment with AT9283 was well tolerated with the majority of patients discontinuing therapy as a consequence of progressive disease.
- Reversible toxicities included; alopecia, mild gastrointestinal disturbances, elevated liver function tests and myelosuppression, particularly neutropenia.

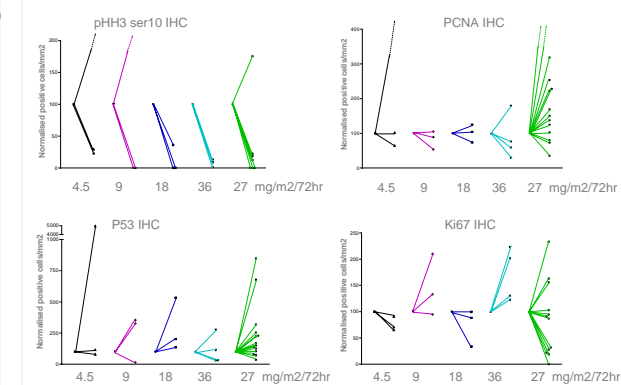
Table 4: Serious Adverse Events Considered To Be At Least Possibly Related To Treatment With AT9283

Event	Number of Patients
Febrile Neutropenia	3
Neutropenia	1
Hickman Line Infection	1
Pneumonia	1
Nausea and Vomiting	2

## PHARMACODYNAMICS

- Skin punch biopsies were taken at 0h and 48h prior to, and during, the infusion of AT9283 in cycle 1. Immunohistochemistry was performed on paraffin embedded sections.
- Serum samples were obtained at 0h, 24h, 48h, 72h and 8 days after commencement of infusion during cycles 1 and 2. M65 and M30 ELISA assays were performed to detect cytokeratin and its caspase-cleaved form as an indirect marker of tumour apoptosis.
- Table 5 summarises the numbers of patients per cohort that exhibited the changes in biological markers anticipated from pre-clinical studies following administration of AT9283.

Figure 2: Aurora Inhibitory Effects Are Observed Across The Dose Range

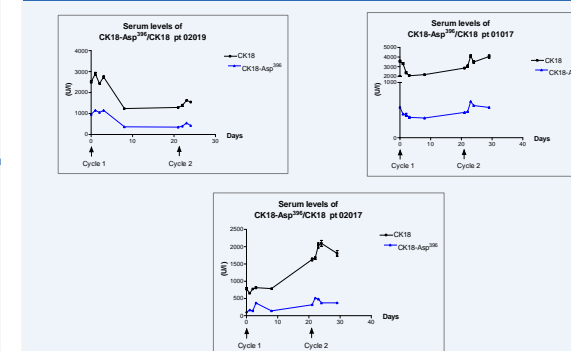


- Pharmacodynamic effects consistent with Aurora A and B inhibition and cell cycle arrest were observed at all dose levels.

Table 5: Skin Immunohistochemistry Summary Table

Dose mg/m <sup>2</sup> /day	ELISA		IHC			
	M30 increase	M65 increase	pHH3 inhibition	p53 stabilisation	PCNA reduction	Ki67 reduction
1.5	0/3	0/3	2/3	2/3	0/3	1/3
3	0/3	0/3	2/3	2/3	1/3	0/3
6	2/3	2/3	3/3	3/3	0/3	1/3
12	3/4	4/4	3/4	1/4	3/4	0/4
9	7/16	10/16	7/14*	11/14	6/14	7/14

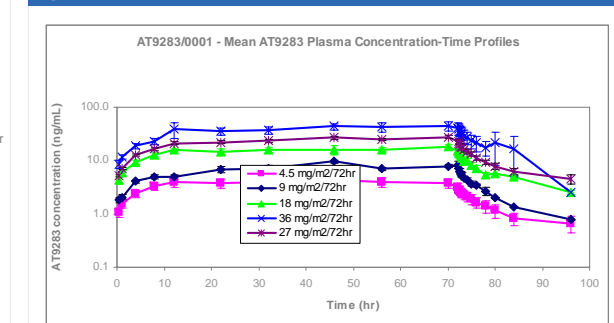
Figure 3: M30/M65 ELISA Cytokeratin Measurements



- 3 profiles observed - ELISA readout of biological effect of AT9283. Their significance is under investigation.
  - Profile 1 – Levels peak during infusion, then return to basal level.
  - Profile 2 – Levels peak during infusion, then increase before cycle 2.
  - Profile 3 – Levels peak during infusion, then decrease before cycle 2.

## PHARMACOKINETICS

Figure 4: Plasma Concentration-Time Profile Of Intravenous AT9283



- Steady state plasma concentrations were achieved at all dose levels.
- Plasma elimination was biphasic with only modest inpatient variation.

Table 6: Oral Bioavailability Of A Solution Of AT9283 In A Subgroup Of Patients

Patient	Cl (mL/min/kg)	Vdss (L/kg)	t <sub>1/2</sub> (hr) IV	PO t <sub>max</sub> (hr)	PO C <sub>max</sub> (ng/mL)	F (%)
01019	6.2	4.1	12	4.4	0.5	1.3
01020	10	4.1	3.6	2.8	2	0.8
01022	5.1	2.8	11	8.0	2	2.8
02023	3.9	1.4	5.6	9.2	2	4.9

## CONCLUSIONS

- The MTD of AT9283 when administered as a 72 hour continuous intravenous infusion is 9 mg/m<sup>2</sup>/day in patients with solid tumours.
- The dose limiting toxicity is febrile neutropenia.
- Treatment was otherwise well tolerated with occasional reports of self-limiting fatigue and gastrointestinal toxicity.
- Preliminary evidence of oral bioavailability was observed (median 25%; range 13 to 45).
- Pharmacodynamic evidence of Aurora kinase A and Aurora kinase B inhibition was observed at all dose levels.
- Significant anticancer activity was seen in patients with pre treated solid tumours.

