

A Phase I Trial of AT9283, a Multitargeted Kinase Inhibitor, in Patients with Refractory Hematological Malignancies

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INTRODUCTION

- AT9283 is a small molecule inhibitor of several serine/threonine and tyrosine kinases including the aurora kinases, JAK2 and 3, FIt3 and Abl (Table 1).
- Overactivity of several of these kinases has been implicated in the etiology of hematological malignancies and *in vitro* studies indicate that AML cell lines are highly sensitive to treatment with AT9283 (Figure 1).
- The initial results of a phase I study of AT9283 administered as a continuous intravenous infusion over 72 hours to patients with pre treated acute leukemias, chronic myeloid leukemia, high-risk myelodysplastic syndromes or myelofibrosis are presented here.
- A starting dose of 3 mg/m²/day (9 mg/m²/72 hours) was identified from preclinical toxicology studies.

Table 1: AT9283 *In Vitro* Kinase Inhibition

Protein Kinase	IC ₅₀ (nM)
Aurora A	52% @ 3nM
Aurora B	58% @ 3nM
JAK2	1.2
JAK3	1.1
T315I ABL	4
FIt3	57% @ 15 nM
RSK-1	37
Lck	63
Src	97
C-abl	110

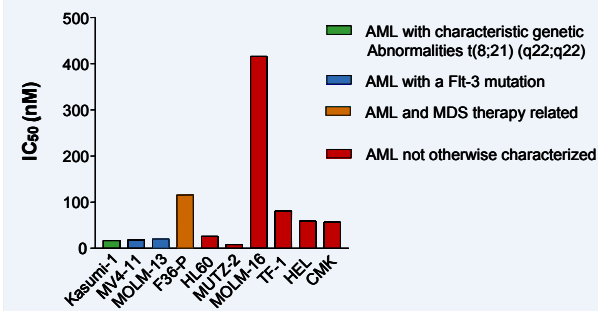


Figure 1: Growth Inhibitory Effect of AT9283 in AML Cell Lines

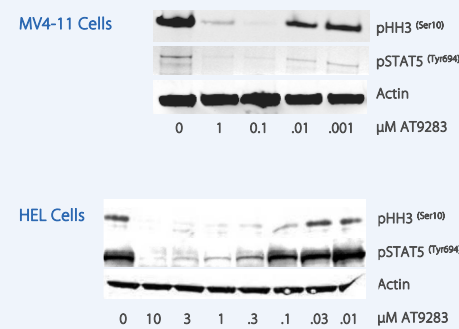


Figure 2: Mechanistic Effects of AT9283 in AML Cell Lines

IN VITRO CHARACTERIZATION

- AT9283 has potent anti-proliferative activity in a panel of AML cell lines comprising a variety of subtypes (Figure 1).
- The mechanism of action of AT9283 was investigated in 2 AML cell lines, MV4-11 and HEL that harbour the FIt3 ITD and JAK2 V617F mutations respectively.
- Figure 2 shows that 1h treatment with AT9283 inhibits substrates of Aurora B (Histone H3 (HH3)) and JAK 2 (STAT5). This inhibition is observed at doses consistent with the antiproliferative activity of the compound in these cell lines.

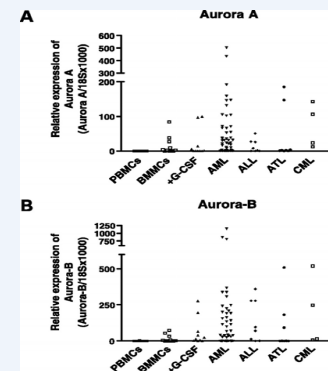


Figure 3: Aurora Kinase Expression in Leukemia (From Ikezoe T et al. Mol Can Ther 6(6):1851-7 (2007))

Table 2: Patient Demographics

Age	Median 54 years (range 22 – 86) Male: Female 1:1
Diagnoses	AML 19 (73%) AMML 1 (4%) MDS 1 (4%) Granulocytic sarcoma 1 (4%) CML 2 (7%) ALL 1 (4%) Myelofibrosis 1 (4%)
Number of Prior Lines of Therapy (Median 3)	One 3 (12%) Two 9 (35%) Three 11 (42%) Four 2 (7%) Five 1 (4%)
Previous Allograft	3 (12%)

Notes: To date 26 patients have been treated on seven different dose levels

Table 3: Dose Escalation Scheme

Dose level (mg/m ² /day)	Number of Patients Treated	Number of Cycles Received (Median)	Dose Limiting Toxicities
1 (3)	3	1 – 3 (1)	None
2 (6)	3	1 – 2 (1)	None
3 (12)	7	1 – 3 (2)	Tumour Lysis Syndrome/ Pulmonary Insufficiency Supraventricular arrhythmia (Considered to be a single event)
4 (24)	3	1 – 2 (2)	None
5 (48)	4	1 – 2 (1)	None
6 (72)	3	2 – 4 (ongoing)(tbc)	None
7 (108)	3	1 – 2 (ongoing)(1)	None

DOSE ESCALATION

- No evidence of DLT was observed until cohort three where one patient developed Grade 4 Tumour Lysis Syndrome requiring short term dialysis.
- This dose level was expanded to a total of seven patients and no further DLTs were observed.
- Dose escalation was reduced to 50% of the previous dose following the appearance of mucositis (Grade 2) at dose level 5.

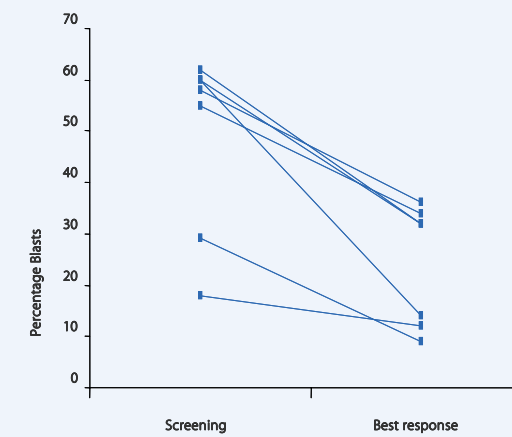


Figure 4: Reduction In Marrow Blasts In Seven Patients With Relapsed/Refractory AML (83% Of Patients) Following Treatment With AT9283

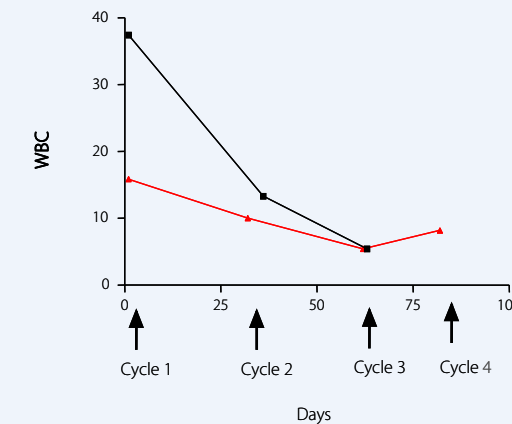


Figure 5: Reduction In WBC In Two Patients With Accelerated CML Who Have Failed Previous Therapy With Imatinib And Dasatinib

SERIOUS ADVERSE EVENTS

- The most common SAEs reported to date have been infectious complications of neutropenia including septicemia and pneumonia.
- Several patients experienced Grade II mucositis which in one case was associated with dehydration and delirium.
- One patient treated at 12 mg/m²/day developed tumour lysis necessitating temporary dialysis. Later during the first cycle of therapy this patient developed septicemia with subsequent multi-organ failure and later died from pneumonia.

Figure 6: Pharmacokinetic Profile

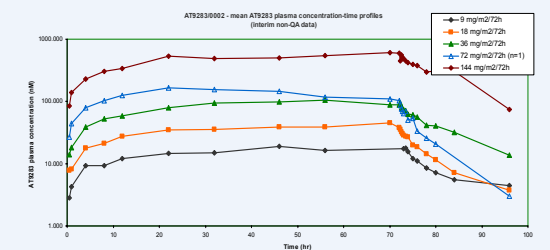


Figure 6a: Plasma Concentration-Time Profile Per Cohort

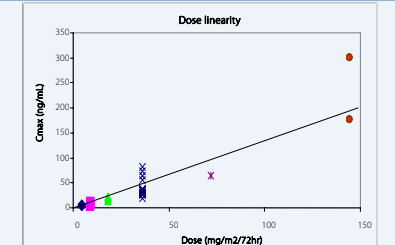


Figure 6b: Cmax Linearity Across The Range of Administered Doses

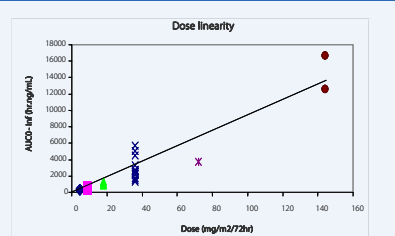


Figure 6c: AUC Linearity Across The Range of Administered Doses

CONCLUSIONS

- The mitotic kinase inhibitor AT9283 exhibits preliminary evidence of activity in patients with relapsed/refractory AML and accelerated CML with a predictable and reversible toxicity profile which is predominantly neutropenia.
- Dose escalation to establish a MTD for a 72-hour continuous infusion schedule is continuing.
- The mechanism of this antileukemic effect remains under investigation although the ability of AT9283 to inhibit multiple signalling pathways may mean that the drug induces different biological effects according to the importance of specific signalling pathways in the survival of specific leukemia.
- Preclinical combination studies with cytarabine and anthracyclines are planned.

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