ABSTRACT # 491

NCIC CTG IND.177: Phase I Study of AT7519M Given as a Short Infusion Twice Weekly

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ABSTRACT

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: 28 patients were treated at 4 dose levels from 14.4mg/m^2 to 32.4mg/m^2. RP2D was 27mg/m^2. 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 on 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 pharmacokinetic studies.

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.

RATIONALE

- Correct progression through the various phases of the cell cycle is critically dependent upon cyclin-dependent kinases (CDKs) and their cognate regulatory partners cyclins.
- A CDK complex controls passage through discrete cell cycle checkpoints.
- Failure of this process can lead to cell cycle arrest and/or apoptosis.
- Aberrant cellular proliferation, as is manifested in cancer, can often be attributed to loss of correct cell cycle control.
- CDK2/cyclin E, CDK4/cyclin D and CDK6/cyclin D primarily regulate progression from the G1 phase to the S phase of the cell cycle.
- The CDK1/cyclin B complex is a key initiator of mitosis.
- CDK2 and CDK1 therefore represent attractive targets for therapeutics designed to arrest, or recover control of, the cell cycle in aberrantly dividing cells.
- CDK2 was chosen by Astex Therapeutics as the target for an integrated crystallography-based approach for the detection of high efficiency binding of low molecular weight fragments and their subsequent optimization using structure-based drug design into potent novel lead compounds.
- Further refinement identified AT7519M as a potent inhibitor of CDK1 and CDK2.

AT7519M

- AT7519M is a novel, small molecule heterocyclic, organic compound. The mesylate salt was selected for clinical development because of its excellent water solubility, stability and crystalline structure.
- AT7519Mpotently inhibits CDKs 1, 2, 4 and 5 with IC_{50} values ranging from 11 to 220 nM and with lower potency against other CDKs tested (3, 6 and 7)
- The inhibition of CDK1 is competitive with ATP.
- X-ray structure of a complex of CDK2 and AT7519M confirms that the agent binds within the active site cleft of the enzyme overlapping with the ATP binding site
- AT7519M is inactive agains all of the non-CDK kinases tested to date (with the exception of GSK3beta).
- AT7519M has potent antiproliferative activity against a variety of human tumor cell lines, but not normal cell lines.
- Exposure of tumour cells to AT7519M results in cell cycle arrest and, ultimately, cell death by apoptosis.
- *In vivo*, studies have shown potent antitumor activity in three human tumor cell line xenograft models (HCT116 colon cancer, A2780 ovarian cancer and HT-20 colorectal cancer).

STUDY OBJECTIVES

Primary Objective:

- To determine the recommended phase II dose of AT7519M when given twice weekly for two weeks as a 1 hour infusion every 21 days in patients with advanced incurable malignancies.

Secondary Objectives:

- To determine the safety, tolerability, toxicity profile, dose limiting toxicities and pharmacokinetic profile of AT7519M in this schedule. The correlation, if any, between the toxicity profile and the pharmacokinetics will be determined.
- To assess preliminary evidence of the anti-tumour activity of AT7519M in patients with measurable disease.

PATIENTS AND METHODS

Key Eligibility Criteria:

- Histologically documented advanced and/or metastatic solid tumors OR non-Hodgkin lymphoma refractory to standard therapy, or for which no curative therapy exists
- ECOG PS $\leq$ 2
- Clinically or radiologically documented disease
- Adequate bone marrow, liver, renal, cardiac, and pulmonary function
- No more than two lines of systemic chemotherapy for metastatic disease for patients with solid tumors
- No pre-existing cardiovascular conditions and/or symptomatic cardiac dysfunction, including: QT and QTc > 460 msec on screening ECG or LVEF < 45% by MUGA
- No untreated CNS metastases (stable CNS mets allowed if off corticosteroids)
- No periopheral neuropathy > grade 1

AT7519M Administration:

- AT7519M given as a 1 hour infusion on Days 1, 4, 8, and 11, in a 3 week schedule

RESULTS

Table 1: Patient Characteristics

Characteristic	Patients (n)
Total number of patients	28
Male:Female	15:13
Median Age	59 years (40-77)
Measurable disease	27
Primary tumor type:	
NSCLC	3
Colon	3
Head and Neck	3
Gastric and Esophagus	3
Melanoma	2
Breast	2
Thyroid	2
Sarcoma – Uterine	2
Other	8

Table 2: Dose Levels

Dose Level	Dose (mg/m2)	# of Patients	# of Cycles Received
1	14.4	5	1, 1, 2, 2, 4 (2 patients replaced for PD in cycle 1)
2	21.6	7	1, 1, 2, 2, 4, 4, 10
3	27.0	11	1, 1, 1, 2, 2, 2, 2, 3, 3, 3, 4
4	32.4	5*	<1, <1, <1, <2, 5

* Of the 3 patients first accrued to DL4, two did not complete cycle 1. One had a possible DLT of increasing fatigue (grade 3). Two additional patients entered, both with DLT: The first had febrile neutropenia after first dose of ATM7519M and second had grade 3 hypokalemia, grade 3 mucositis and went on to have grade 4 muscle weakness and renal failure following their first cycle 2 dose.

Therefore DL4 was declared the MTD and DL3 was defined as the RP2D for expansion.

Adverse Events

Dose Limiting Toxicities:

- **DL2:** 1 pt - Gr. 3 rash, mucositis, infection (prior RTX to H/N)
- **DL3:** 1 pt - Gr. 3 mucositis, fatigue (prior RTX to H/N)
  1 pt - Gr. 3 elevation in LFTs (at time of viral infection – relation to AT7519M unclear)
- **DL4:** 1 pt - Gr. 3 fatigue, muscle weakness
  1 pt - Febrile neutropenia
  1 pt - Gr. 3 hypokalemia, mucositis

Table 3: Adverse Events Related to AT7519M (N=28)

Adverse Event	No. of pts with any Grade AE	No. of pts with Grade 3/4 AE
Non-hematologic Adverse Event (at least possibly related):		
Mucositis	14	3
Fatigue	13	3
Nausea	11	0
Vomiting	10	0
Dermatological	4	1
Infection	7	2
Musculoskeletal	6	2
Hematologic Adverse Event (all causalities):		
Lymphopenia	24	11
Hemoglobin	25	1
Neutropenia	4	1
Thrombocytopenia	8	0

QTc Interval:

In April 2007, study put on hold after another phase I study of AT7519M (using daily x 5 schedule) was suspended because of the observation of a progressive increase in QTc interval in a patient who died while on study. This study amended to increase ECG monitoring.

Among 24 patients with on-treatment values on this study:

- **16 patients had QTc interval < 450 ms**
- **8 patients had QTc interval between 450-499 ms**
- **0 patients had QTc interval > 500 ms**
- **No clinically significant drug-related arrhythmias**

Pharmacokinetics

Dose level	14.4 mg/m^2 (n = 5)	21.6 mg/m^2 (n = 7)	27.0 mg/m^2 (n = 7)	32.4 mg/m^2 (n = 1)
PK parameter	Mean +/- Std Dev			
C_{max} (ng/ml)	197 ± 114	432 ± 98	510 ± 134	701
$T_{1/2}$ (hr)	12.1 ± 4.3	12.7 ± 5.6	14.1 ± 1.5	12.7
$AUC_{0-\infty}$ (ng*hr.ml)	946 ± 682	1663 ± 807	2077 ± 363	4220
Vd (mL/m^2)	440200 ± 418075	267051 ± 169431	272949 ± 63972	140308
Clearance (mL/hr/m^2)	31070 ± 35483	15742 ± 7016	13333 ± 2254	7677

Efficacy

Patients Evaluable for Response: 16

- Partial or Complete Response: 0
- Stable Disease: 9

(Med. Duration SD: 3.3 mo (range 2.5 – 11.1)

CONCLUSIONS

- AT7519M given in a short infusion appears to be tolerable and is not associated with QTc prolongation noted with other schedules.
- Recommended Phase II Dose is 27 mg/m^2 given as 1 hour infusion twice weekly for 2 out of every 3 weeks. Expansion at RP2D continues
- Skin, tumour, and blood Pharmacodynamic studies are in progress in patients being enrolled at expansion of RP2D
- NCIC CTG plans phase II trials in mantle cell lymphoma and CLL.