A Dose Escalation, Pharmacokinetic and Pharmacodynamic Study of AT7519, a Cyclin-Dependent Kinase Inhibitor in Patients with Refractory Solid Tumours


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INTRODUCTION

Uncontrolled proliferation is characteristic of cancer cells and can often be attributed to an alteration in the regulatory mechanisms controlling the cell cycle. Disruption of cyclin dependent kinase (CDK) activity is frequently seen in human cancers, for example the overexpression of D-cyclins and loss of the inhibitory co-factor (INK) proteins or RB. The key role of CDKs in the different stages of the cell cycle means that their inhibition should limit uncontrolled proliferation in cancer cells. AT7519 is a small molecule inhibitor of multiple CDKs, including 1, 2, 4, 5 and 9. The results of a phase I and pharmacodynamic study of AT7519 administered as a one hour intravenous infusion on days one, two, three, four and five every three weeks to patients with refractory solid tumours is presented here. Inclusion and exclusion criteria were standard. Dose escalation was performed according to a standard 3 + 3 design.

Table 2: Patient Demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>Median (range)</th>
<th>Number of Patients</th>
<th>Treatment duration (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>18-86</td>
<td>50</td>
<td>1-25</td>
</tr>
</tbody>
</table>

Table 3: AT7519 IC50 (nM)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT116</td>
<td>250</td>
</tr>
<tr>
<td>BT-20</td>
<td>125</td>
</tr>
</tbody>
</table>

EFFICACY

Figure 2: Disappearance of Plural Deposit in a Patient with Pretreated NSCLC after Four Cycles of Treatment with AT7519

Four patients completed at least six cycles of treatment (adenocarcinoma of the lung, adenocarcinoma of the pancreas (2) and HER2 overexpressing adenocarcinoma of the breast). The best response to treatment in all of these cases was stable disease although one patient experienced a mixed response with a maximum reduction in the sum of unidimensional measurements of approximately 80%.

TOXICITY

Patients treated in cohorts five and seven developed Grade 2 thrombocytopenia and early Grade 3/4 neutropenia and lymphopenia. Fatigue and stomatitis were reported in a dose dependent manner but were not dose limiting. The study was discontinued following evidence of a dose-related increase in QTc on day 5 of treatment. Similar toxicity has not been reported from studies of alternative administration schedules.

Figure 5: Plasma Concentration-time Profiles Across all Administered Doses

*AT7519 undergoes multiphasic elimination with a long terminal half-life and only modest inter-patient variation.

CONCLUSIONS

This study was unable to identify a maximum tolerated dose of AT7519 when administered as a one hour intravenous infusion on days one, two, three, four and five every three weeks to patients with refractory solid tumours. Anti-proliferative activity and tumour apoptosis (cytobrin 16 cleavage) were consistently observed in the majority of patients treated at a dose of 28.8 mg/m² per day.

Poster can be downloaded from www.astex-therapeutics.com