First in human phase I study - results of a second-generation non-ansamycin Heat Shock Protein 90 (HSP90) inhibitor AT13387 in refractory solid tumors

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ABSTRACT

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BACKGROUND

- HSP90s required for functional stabilization of numerous client proteins which function as oncogenes in many cancer settings.
- Inhibition of HSP90 results in degradation of those client proteins including mutant forms thus holding the promise of downregulating multiple aberrant signaling pathways in a wide range of cancers.
- The first generation ansamycins (HSP90 inhibitors 60-600 nM) with good tissue distribution, excellent in vivo antitumor activity and long tumor half life in preclinical models (65-78 hours).
- This study is the First in human (1st) phase I study in refractory solid tumors.

OBJECTIVES

- To identify the Maximum Tolerated Dose (MTD) of AT13387 when administered either twice weekly or once weekly on 3 consecutive weeks of a 4-week cycle.
- To characterize the safety and tolerability of AT13387 including the identification of Dose Limiting Toxicity (DLT).
- To define the Pharmacokinetics (PK) of AT13387 in plasma and urine.
- To demonstrate the Pharmacodynamic (PD) activity of AT13387 in plasma, circulating PBMC and optional tumor biopsies.
- To identify an optimal schedule to test preliminary antitumor activity of AT13387 in refractory solid tumor patients.

METHODS AND STUDY DESIGN

- Standard 3 + 3 design
- Main Eligibility Criteria:
  - Adults with metastatic solid tumor refractory to standard therapy or with metastatic melanoma or cardiac dysfunction.
  - Adequate bone marrow, hematopoietic, and cardiac functions.
- Dose Limiting Toxicity (DLT):
  - Neutropenia <0.5 x 10(9) for 5 days or with fever.
  - Thrombocytopenia <25 x 10(9) by bleeding or thrombocytopenia <10 x 10(9).
  - Any Grade 3 or 4 non-hematological toxicity which is not a consequence of tumor progression.
- More than one individual dose omission of AT13387 during the first cycle of treatment due to the appearance of drug related toxicity.
- AT13387 was given as an intravenous bolus over one hour.

The MTD of the twice weekly regimen was identified prior to further dose escalation according to a once weekly regimen.

AT13387 DOSE LEVELS AND EXPOSURE

<table>
<thead>
<tr>
<th>Dose Level (twice weekly/3x4 weeks)</th>
<th>N of Patients (N=11)</th>
<th>N of Cycles Received (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1: 120 mg/m2 (MTD)</td>
<td>3</td>
<td>3 (1 - 12)</td>
</tr>
<tr>
<td>Cohort 2: 20 mg/m2</td>
<td>3</td>
<td>2 (1 - 5)</td>
</tr>
<tr>
<td>Cohort 3: 60 mg/m2</td>
<td>3</td>
<td>2 (0 - 8)</td>
</tr>
<tr>
<td>Cohort 4: 80 mg/m2</td>
<td>3</td>
<td>2 (0 - 5)</td>
</tr>
<tr>
<td>Cohort 5: 120 mg/m2 (MTD)</td>
<td>3</td>
<td>2 (0 - 6)</td>
</tr>
</tbody>
</table>

Dose Level (once weekly/6x4 weeks)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>N of Patients</th>
<th>N of Cycles Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 7: 120 mg/m2 (MTD)</td>
<td>4</td>
<td>3 (1 - 4)</td>
</tr>
<tr>
<td>Cohort 8: 20 mg/m2</td>
<td>3</td>
<td>2 (1 - 2)</td>
</tr>
<tr>
<td>Cohort 9: 80 mg/m2</td>
<td>4</td>
<td>2 (1 - 2)</td>
</tr>
<tr>
<td>Cohort 10: 120 mg/m2 (MTD)</td>
<td>5</td>
<td>2 (0 - 6)</td>
</tr>
</tbody>
</table>

N of Patients Treated (N=11)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>N of Patients Treated</th>
<th>N of Cycles Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 mg/m2 (twice weekly)</td>
<td>5</td>
<td>3 (1 - 12)</td>
</tr>
<tr>
<td>120 mg/m2 (once weekly)</td>
<td>5</td>
<td>3 (1 - 12)</td>
</tr>
</tbody>
</table>

PHARMACOKINETICS

PK Profile at Different Dose Levels of AT13387

Trend of AUC. Dose proportionality maintained up to 310 mg/m2

PHARMACODYNAMICS

HSP70 Inhibition

Twice Weekly

Once Weekly

Dose (mg/m2)

Maximum fold increase of HSP70 at all dose levels, 2.7 fold increase in HSP70 was observed with highest evidence of dose dependent effect in Cohort 4.

DISCUSSIONS AND CONCLUSIONS

- AT13387 was well tolerated.
- Twice-weekly regimen 120 mg/m2 dose in 3 weeks in 4 cycles cycle.
- Once-weekly regimen 260 mg/m2 dose in 3 weeks in 4 cycles cycle.
- DLTs consisted mainly of multiple Grade 2 adverse events of GI toxicities (diarrhea, vomiting), systemic infusion reactions, and fatigue. Few patients had Grade 3 toxicities and no Grade 4 were reported.
- Visual disturbances were all Grade 1 with only 1 patient reported as Grade 3 due to ERG changes, all were transient and reversible. Visual disturbances are considered on target pharmacological class effects of potential HSP90 inhibition.
- PK exposures were dose-dependent and linear.
- HSP70 inhibition of 27 fold magnitude was observed representing pharmacodynamic evidence of target engagement.
- Objective and durable partial response in HSP90 was observed in 5 patients (including 3 GIST patients).
- Additional patients were being enrolled at 480 mg/m2 once weekly and a Phase 2 study in relapsed/refractory GIST patients in combination with imatinib is ongoing.

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