First-In-Man Study of 4SC-205 (AEGIS), a novel oral inhibitor of Eg5 kinesin spindle protein

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Introduction

• 4SC-205 is an orally available, anti-mitotic small molecule (MW 448.5 Da)
  - The compound potently inhibits human kinesin Eg5 (K6P7) with an IC50 ~ 3nM and > 30,000 fold selectivity towards other kinesins
  - 4SC-205 demonstrates excellent preclinical efficacy in a diverse set of solid tumor models in vitro and in vivo

Target Rationale

• Kinesin Eg5 motor protein is essential for separation of spindle poles during mitosis
• Target is exclusively expressed during mitosis in dividing cells
• Inhibition of Eg5 causes failure of bipolar spindle formation, mitotic arrest & induction of apoptosis
• Mitosis-confined cytotoxicity does not affect silent somatic tissue

Data Evaluation

• Preliminary results are based on 56 patients. Currently, 3 more patients will be enrolled in the 20mg continuous dose level

Study Design

• Open label, dose escalation trial of oral 4SC-205 in patients with advanced malignancies
• Study objectives comprised analysis of safety and tolerability, determination of the maximum tolerated dose (MTD) and pharmacokinetics of 4SC-205
• Secondary objects comprise assessment of biomarker response (pH3 in skin biopsies, M30/M65 cytokeratin in blood).

Demographics and baseline characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%       )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.5 ± 11.4</td>
</tr>
<tr>
<td>Gender</td>
<td>31 (57)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>57.5</td>
</tr>
<tr>
<td>Male</td>
<td>26 (46)</td>
</tr>
<tr>
<td>Race</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.5 (1/7)</td>
</tr>
<tr>
<td>Race – %</td>
<td>31 (7)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>56 (100)</td>
</tr>
<tr>
<td>ECOG performance status – % (N=33)</td>
<td>21 (63)</td>
</tr>
<tr>
<td>ECOG performance status – % (N=33)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

Rational for Continuous Dosing

Proliferation Rate Paradox

• Eg5 target is expressed exclusively during cell mitosis
• Mitosis represents a timely restricted event in human tumours

• An optimal dosing scheme should establish continuous exposure of the Eg5 target to 4SC-205. Once or twice weekly dosing is insufficient to ensure permanent target coverage.

• In contrast, daily dosing using actual dose levels will result in neutropenia and other dose limiting toxicities.

Targeting Hypothesis for Continuous Dosing

Clinical Trial Simulation using Population PK/PD Modeling

• Model is based on interim data of 33 patients (287 observations for AIC)
  - The final model was used to simulate continuous dosing schemes
  - Risk of neutropenia was calculated as % of simulated patients that develop
    • grade 3 neutropenia, based on 1000 simulated patients

Patient Enrollment & Dose Schedules

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Patients (N)</th>
<th>Median dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg continuous</td>
<td>20 (36)</td>
<td>10mg</td>
</tr>
<tr>
<td>15mg continuous</td>
<td>16 (28)</td>
<td>15mg</td>
</tr>
<tr>
<td>20mg continuous</td>
<td>20 (36)</td>
<td>20mg</td>
</tr>
<tr>
<td>25mg continuous</td>
<td>3 (5)</td>
<td>25mg</td>
</tr>
<tr>
<td>30mg continuous</td>
<td>6 (10)</td>
<td>30mg</td>
</tr>
</tbody>
</table>

Pharmacokinetics

• PK is linear with respect to Cmax and AUC over entire dose range
  - f0 = 10% Cs = 12h
• No accumulation observed from day 1 to day 8
• No significant variation in exposure between cycles

Efficacy / Treatment Duration

• MoA demonstrated in skin biopsies
  - pH3 as marker of mitotic arrest (N=28)
  - 10mg (N=1); 15mg (N=2); 20mg (N=3) & 30mg (N=2)

Biomarker Response

• No long-term effects observed on M30/M65 levels
• Sporadic reduction in leasion size

Conclusions

• Several dose schemes were evaluated in 56 patients. 3 more patients will be enrolled
  - DLT was reached at 200 mg (ow) and at 100mg (tw). MTD is established at 150mg (ow) and at 75mg (tw)
  - 4SC-205 exhibits linear pharmacokinetics within the tested dose range
  - pH3 biomarker response demonstrates intended mode-of-action
  - No objective response was observed. Continuous dosing schedule is still under evaluation, but so far no objective response was observed
  - Observed side effects (Neutropenia) expected for given mode-of-action
  - Stabilization of 28% of patients in follow-up (> 2 cycles)

Acknowledgments

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