In Vivo Activities of TP-2846: A Novel Tetracycline Antileukemia Agent

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Introduction

TP-2846, a novel tetracycline derivative, has been identified as a highly potent antileukemia agent through high-throughput screening, medicinal chemistry studies, and in vitro profiling based on mechanistic rationales, as shown in 18817 and 4802. This poster presents data from in vivo evaluations of TP-2846.

Methods

PK Studies

PK studies were performed at WuXi AppTec or Charles River Laboratories. Animals (male CD-1 mice, Sprague Dawley rats, or cynomolgus monkeys) were dosed with TP-2846 by IP, IV, or PO administration. Blood samples were collected into heparin tubes and processed to plasma. Concentrations of TP-2846 in plasma were determined using a validated LC-MS/MS method, and PK parameters were calculated using WinNonLin.

In Vivo Efficacy Studies

In vivo efficacy studies were performed at WuXi AppTec. Nude mice (n = 5, BALB/c or CD-17 SCID) were inoculated subcutaneously at the right flank with MV4-11 or HL-60 cell suspensions (1 × 10⁶ cells in 0.2 mL of PBS with Matrigel (1:1)) for tumor development.

Results

Table 1. PK Parameters of TP-2846 in Mice, Rats, and Monkeys

<table>
<thead>
<tr>
<th>Species</th>
<th>Volume of Distribution (Vdss)</th>
<th>Clearance (Cl)</th>
<th>AUC0-last</th>
<th>Tmax</th>
<th>Tlast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>12170 (L/kg)</td>
<td>3624</td>
<td>628</td>
<td>16.0</td>
<td>9.80</td>
</tr>
<tr>
<td>Rat</td>
<td>4.39</td>
<td>4.31</td>
<td>9.41</td>
<td>6.92</td>
<td>9.80</td>
</tr>
<tr>
<td>Monkey</td>
<td>4.39</td>
<td>4.31</td>
<td>9.41</td>
<td>6.92</td>
<td>9.80</td>
</tr>
</tbody>
</table>

Note: the last dose was skipped due to significant body weight loss on one day for 2 out of 5 tigecycline treated animals, and one animal was euthanized after the 1st dose.

Table 2. Number of Animals (Out of N=10) Achieving >50% Tumor Shrinkage in Efficacy Study of TP-2846

<table>
<thead>
<tr>
<th>Species</th>
<th>TP-2846</th>
<th>Cytarabine</th>
<th>Cytarabine (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>5/10</td>
<td>4/10</td>
<td>3/10</td>
</tr>
<tr>
<td>Rat</td>
<td>5/10</td>
<td>4/10</td>
<td>3/10</td>
</tr>
<tr>
<td>Monkey</td>
<td>5/10</td>
<td>4/10</td>
<td>3/10</td>
</tr>
</tbody>
</table>

Note: dosing was suspended due to significant body weight loss on one day for 2 (out of 5) cytarabine treated animals and on 1-5 days for 4 tigecycline treated animals during the course of the study, while only one animal from the TP-2846 to AUC group skipped one dose for the last cycle.

Discussion

TP-2846 displayed favorable pharmacokinetic profiles across multiple species. TP-2846 demonstrated potent, dose-dependent in vivo efficacy in acute myeloid leukemia xenograft models. In two studies presented, >50% tumor shrinkage was observed in TP-2846 treated animals treated with TP-2846, while none of the comparator-treated animals achieved >50% tumor shrinkage. Pharmacokinetic/pharmacodynamic modeling indicates that TP-2846’s efficacy is driven primarily by AUC.

References


AAAR (American Association for Cancer Research), March 29 – April 3, 2019, Atlanta, Georgia