3. Results: OS PDX model dose response to Eribulin

Eribulin was evaluated in 10 PPTC models, 8 models were treated at 1mg/kg IP injection on days 1 & 4, repeated at day 21.  From primary OS specimens (OS46, OS51, OS55, OS56) and 2 from relapsed specimens (OS17, OS56).  Response to treatment was determined based on a PPTP-established endpoints throughout study period.  Minimum relative tumor volumes also showed a dose-response effect from 0.25 to 1.0mg/kg.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Dose [mg/kg]</th>
<th>EFS T-C (Days)</th>
<th>EFS T/C</th>
<th>P Median</th>
<th>ORM</th>
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</thead>
<tbody>
<tr>
<td>OS-1</td>
<td>0.25</td>
<td>24.1 &gt;41 &gt;14.9</td>
<td>1.61</td>
<td>0.001</td>
<td>PD1</td>
</tr>
<tr>
<td>OS-17</td>
<td>0.25</td>
<td>16.0 &gt;43 &gt;27</td>
<td>2.69</td>
<td>&lt;0.001</td>
<td>PD2</td>
</tr>
<tr>
<td>OS-51</td>
<td>0.25</td>
<td>38.6 &gt;41 &gt;2.4</td>
<td>1.06</td>
<td>0.003</td>
<td>PR</td>
</tr>
<tr>
<td>OS-33</td>
<td>0.50</td>
<td>20.9 &gt;41 &gt;20.1</td>
<td>1.96</td>
<td>&lt;0.001</td>
<td>PR</td>
</tr>
<tr>
<td>OS-60</td>
<td>0.50</td>
<td>34.4 &gt;42 &gt;7.6</td>
<td>1.22</td>
<td>&lt;0.001</td>
<td>SD</td>
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<tr>
<td>OS-1</td>
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<td>1.67</td>
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<td>2.69</td>
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<td>PD2</td>
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<td>1.22</td>
<td>&lt;0.001</td>
<td>SD</td>
</tr>
</tbody>
</table>

3. Results: New PPTC model response to eribulin at single dose treatment

Eribulin was supplied to the PPTC by Eisai Inc.  Pharmacokinetic studies from the COG phase 2 study are ongoing to understand the disparate tumor responses seen in the in vivo studies and the phase 2 clinical trial.

5. References


Eribulin was supplied to the PPTC by Eisai Inc. www.nci-pptc.org

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Wendong Zhang, E. Anders Kobel, Richard Gorlick, Michael Roth, Jonathan Gillis, Sudhe Roshan, Stephen Erickson, Raushan Kumaresha, Peter Houghton, Beverly Teicher, and Malcolm A. Smith.

MD Anderson, Houston, TX; Nemours Center for Cancer and Blood Disorders, Wilmington, DE; RTI International, Research Triangle Park, NC; Gorgeney Children’s Cancer Research Institute, San Antonio, TX; National Cancer Inst., Bethesda, MD.

3. Results: Categorical response to single dose eribulin

Eribulin demonstrated antitumor activity against OS PDX models generated from primary and relapsed tumors at a dose level of 1mg/kg.  Eribulin showed a clear dose-response effect in terms of its ability to induce SD/PR responses, highlighting the importance of dose selection. This dose response effect suggests the possibility that an inability to achieve comparable serum drug concentrations in human clinical trials may explain the limited tumor responses observed in the COG phase 2 trial of eribulin.  Pharmacokinetic studies from the COG phase 2 study are ongoing in an effort to understand the disparate tumor responses seen in the in vivo studies and the phase 2 clinical trial.

4. Discussion and Conclusions

Eribulin is a synthetic analogue of halichondrin B and inhibits cancer cell proliferation via blockade of microtubule function. It is FDA approved for patients with breast cancer with two prior chemotherapy regimens for the treatment of metastatic disease and for previously treated patients with inoperable or metastatic liposarcoma. In vivo testing of eribulin against osteosarcoma (OS) Pediatric Preclinical Testing Program (PPTP) PDX models, developed from primary tumors, demonstrated significant single agent activity. However, a Children’s Oncology Group (COG) phase 2 trial of eribulin in patients with relapsed OS did not demonstrate significant responses to single agent eribulin (Isakoff M et al.). In the current study, the efficacy of eribulin in PDX models generated from primary and relapsed tumors, as well as dose-response, were assessed.

1. Introduction

Eribulin was evaluated in 10 PPTC models. 8 models were treated at 1mg/kg IP injection on days 1 & 4, repeated at day 21.  From primary OS specimens (OS46, OS51, OS55, OS56) and 2 from relapsed specimens (OS17, OS56).  Response to treatment was determined based on PPTP-established endpoints throughout study period.  Minimum relative tumor volumes also showed a dose-response effect from 0.25 to 1.0mg/kg.

2. Study Methods

Eribulin was evaluated in 10 PPTC models. 8 models were treated at 1mg/kg IP injection on days 1 & 4, repeated at day 21.  From primary OS specimens (OS46, OS51, OS55, OS56) and 2 from relapsed specimens (OS17, OS56).  Response to treatment was determined based on PPTP-established endpoints (Houghton PJ, et al.) (Kolb EA, et al.). In an additional 4 models, 3 dose levels of eribulin were evaluated in 3 primary tumors (OS1, OS17, OS33) and 1 relapsed tumor (OS66).  In the dose response studies, eribulin was administered IP at 1mg/kg, 0.5mg/kg, and 0.25mg/kg on day 1 & 4, repeated at day 21 with follow up through day 42.

3. Results: Categorical response to single dose eribulin

The Kaplan-Meier curves were used to compare time-to-event between groups. A p-value of 0.0167 for declaring significance was used to correct for the multiple comparisons.

The objective response categories as described by Houghton, et al. 2007:

- PR = partial response, ≥50% tumor regression at any point during study but measurable tumor through study period
- SD = stable disease, <50% tumor regression throughout study and ≤25% tumor growth at end of study
- PD1 = when PD and the mouse’s time to event ≤ 200% the KM median time-to-event in control group
- PD2 = when PD but, additionally, time-to-event is > 200% of the KM median time-to-event in control group

3. Results: Dose response and single dose response to eribulin

The Kaplan-Meier curves were used to compare time-to-event between groups. A p-value of 0.0167 for declaring significance was used to correct for the multiple comparisons.  The Kaplan-Meier curves were used to compare time-to-event between groups. A p-value of 0.0167 for declaring significance was used to correct for the multiple comparisons.