Introduction

- Osteosarcoma (OS) is the most common primary bone malignancy in adolescents and young adults
- Overall survival rate for patients with metastatic or recurrent disease is <30%
- Survival outcomes have remained stagnant for the past 3 decades and new agents are needed to improve outcomes
- Eltrombopag (EP) is a small molecule thrombopoietin receptor (TPO-R) agonist and polyvalent cation chelator
- FDA-approved to treat chronic immune thrombocytopenia purpura (ITP) and severe aplastic anemia
- EP reduces leukemia cell proliferation via the depletion of intracellular iron levels, independent of TPO-R binding
- EP’s inhibits osteosarcoma cell growth in vitro in a dose-dependent manner
- The PPTC sought to evaluate the potential anti-cancer efficacy of EP against in vivo osteosarcoma models

Methods

EP Administration:
- 5 mg/kg/day (low-dose) via oral gavage for 5 days per week over 4 weeks
- 50 mg/kg/day (high-dose) administered to 2 models (OS2, OS9) per the same schedule

Study Design and Analysis:
- Six OS patient-derived xenograft (PDX) models (OS-2, OS-9, OS-31, OS-33, OS-36, and OS-60-SJ) were heterotopically injected into the flanks of CB17SCid− mice
- A control cohort that received vehicle was included for each PDX model
- Tumor volume was monitored in all cohorts
- Events defined as 4x initial tumor growth
- Tumor growth, Event Free Survival (EFS) compared between treatment and control groups
- p-values were two-sided and considered statistically significant if p < 0.05

Results

- No toxic deaths with either dose of EP
- EP dose 5 mg/kg/day:
  - No significant prolongation of time to event observed
  - No objective responses observed
  - All mice met criteria for PD1 (Table 1)
- EP dose 50 mg/kg/day:
  - Resulted in a small, but significant prolongation in time to event for both models tested No objective responses observed
  - All mice met criteria for PD1 (Table 1)

Table 1: Osteosarcoma PDX model response to EP

<table>
<thead>
<tr>
<th>Model</th>
<th>OS-2</th>
<th>OS-9</th>
<th>OS-31</th>
<th>OS-33</th>
<th>OS-36</th>
<th>OS-60-SJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Event</td>
<td>26.0</td>
<td>23.0</td>
<td>16.1</td>
<td>21.1</td>
<td>18.1</td>
<td>24.9</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>0.9</td>
<td>1.5</td>
<td>0.6</td>
<td>2.2</td>
<td>2.8</td>
<td>3.7</td>
</tr>
<tr>
<td>p-value</td>
<td>0.137</td>
<td>0.881</td>
<td>0.407</td>
<td>0.109</td>
<td>0.170</td>
<td>0.603</td>
</tr>
<tr>
<td>Gehan-Breslow-Yates &amp; Logrank</td>
<td>1.134±0.09</td>
<td>1.686±0.46</td>
<td>1.774±0.18</td>
<td>1.472±0.23</td>
<td>2.019±0.35</td>
<td>1.403±0.24</td>
</tr>
<tr>
<td>p-value</td>
<td>0.631</td>
<td>0.739</td>
<td>0.011</td>
<td>0.125</td>
<td>0.684</td>
<td>0.520</td>
</tr>
</tbody>
</table>

Discussion and Conclusions

- EP failed to exhibit significant anti-tumor activity in the osteosarcoma PDX models
- EP did not enhance tumor growth in any of the models tested
- Lack of meaningful EP anti-tumor activity suggests that leukemia and osteosarcoma may exhibit different dependencies on intracellular polyvalent cations
- EP may be considered as a potential supportive care agent in stimulating platelet recovery following chemotherapy-induced myelosuppression in patients with osteosarcoma

References