In vivo evaluation of the menin inhibitor VTP-50469 against Ewing sarcoma preclinical models – A report from the Pediatric Preclinical Testing Consortium (PPTC)

Raushan T. Kurmasheva1, Stephen W. Erickson2, Gerald M. McGeehan3, Beverly A. Teicher4, Malcolm A. Smith4, Peter J. Houghton1
1Greehey Children’s Cancer Research Institute, San Antonio, TX; 2RTI International, Research Triangle Park, NC; 3Syndax Pharmaceuticals, Waltham, MA; 4National Cancer Inst., Bethesda, MD

1. Introduction

- MLL1 (KMT2A), a lysine methyltransferase, binds promoters of HOX genes resulting in H3 Lys 4 methylation and H3 and H4 acetylation.
- While the role of MLL1 translocations is well established for leukemia, less is known regarding the role of MLL1 in solid tumors.
- Posterior HOXD genes are overexpressed in Ewing sarcoma (EwS). Promoter regions for these genes are characterized by MLL1-mediated H3K4me3 marks and are devoid of repressive H3K27me3 marks (Svoboda, et al. 2014).
- In leukemias, the oncogenic activity of MLL1 fusion proteins is dependent on association with menin, a scaffolding protein that binds MLL1 and MLL4 (KMT2B) in the context of TrxG COMPASS complexes (Yokoyama, et al. 2005).
- Small molecules that inhibit the Menin-MLL1 interaction have potential therapeutic value for treatment of MLL1 rearranged leukemia (Borkin, et al. 2015).
- Recently, evidence has been presented that the tumorigenicity of EwS cells is dependent on the Menin-MLL1 interaction (Svoboda, et al. 2015).

2. Study Methods

Agent Administration: VTP-50469 was administered by oral gavage at 130 mg/kg or 100 mg/kg twice daily for a planned 28 days.

3. Results

3.4. Summary of VTP-50469 Activity Against Ewing Sarcoma In Vivo Models

<table>
<thead>
<tr>
<th>Tumor Line</th>
<th>Treatment</th>
<th>KM Median (days)</th>
<th>EFS T/C (days)</th>
<th>EFS T/C</th>
<th>0.1628 - 0.5000 Wilcoxon</th>
<th>Median Response</th>
<th>Minimum Relative Tumor Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHL258</td>
<td>Control</td>
<td>12.4 2.066</td>
<td>1.01 0.665</td>
<td>PD1</td>
<td>0.0167 for declaring significance to correct for the multiple comparisons made.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES-1</td>
<td>Control</td>
<td>10.4 3.047</td>
<td>0.93 0.084</td>
<td>PD1</td>
<td>2.333</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES-4</td>
<td>Control</td>
<td>10.7 2.494</td>
<td>1.93 0.198</td>
<td>PD1</td>
<td>1.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES-5</td>
<td>Control</td>
<td>16.2 1.971</td>
<td>1.93 0.198</td>
<td>PD1</td>
<td>2.333</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EW-5</td>
<td>Control</td>
<td>12.2 1.5 1.14 0.186</td>
<td>0.665</td>
<td>PD1</td>
<td>1.01 0.665</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EW-6</td>
<td>Control</td>
<td>13.1 1.709</td>
<td>1.93 0.198</td>
<td>PD1</td>
<td>1.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EW-S</td>
<td>Control</td>
<td>10.6 4.5</td>
<td>1.74 0.915</td>
<td>PD1</td>
<td>3.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCH-EWS-1</td>
<td>Control</td>
<td>10.4 0.1</td>
<td>1.01 0.665</td>
<td>PD1</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Discussion and Conclusions

- VTP-50469 caused a statistically significant growth delay in 4 of 7 EwS models.
- Among models with significant slowing of tumor growth, the ratio of median time to event for the treated versus control groups (EFS T/C) ranged from 1.24 to 1.74.
- There were no tumor regressions, and the mean minimum relative tumor volumes (RTV) for treated groups ranged from 1.2 to 3.5.
- At the same dose and schedule at which VTP-50469 shows remarkably high in vivo activity against MLL-rearranged leukemia xenograft lines, it shows minimal levels of in vivo activity against EwS models.
- Our results and an examination of existing literature for menin inhibitors suggest that EwS cells are less dependent on the Menin-MLL1 interaction for survival in comparison to MLL-rearranged leukemias.

5. References


MLL-mediated H3K4me3 marks and are devoid of recessive H3K27me3 marks (Svoboda, et al. 2014). Our results and an examination of existing literature for menin inhibitors suggest that EwS cells are less dependent on the Menin-MLL1 interaction for survival in comparison to MLL-rearranged leukemias.

More Information

*Corresponding author: Raushan T. Kurmasheva | Presented at: AACR 2019
Supported by: U01 CA190897 and U01 CA190823
www.ncipptc.org