Briciclib and its oral derivative (ON 013100) exhibit comparable anticancer activity in various preclinical cancer models

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INTRODUCTION

- Eukaryotic translation initiation factor 4E (eIF4E) is a master regulator that controls translation of mRNAs in mammalian cells. eIF4E is potent proto-oncogene that promotes translation of several genes essential for cellular proliferation (cyclin D1, c-Myc, mTOR), survival (Akt, survivin), angiogenesis (VEGF), and metastasis (MMP9)1.

- Overexpression of eIF4E has been observed in almost all major groups of cancers and has been shown to induce increased expression of cyclin D1 and c-Myc2.

- In this study we investigated and compared the anticancer activity of Briciclib (ON 013105), a novel investigational eIF4E-selective inhibitor, to its precursor ON 013100. Briciclib, a water-soluble derivative of ON 013100, is designed for intravenous therapy whereas ON 013100 is a small molecule inhibitor that can be administered orally. We determined the susceptibility of various breast, mantle cell leukemia (MCL), gastric, and esophageal cancer cell lines to treatment with Briciclib or ON 013100. In addition, we also investigated the effect of Briciclib or ON 013100 on expression of markers associated with eIF4E activity (cyclin D1 and c-Myc) and apoptosis (P53 and Cleaved Caspase 3).

METHODS

- MTT cell viability assay, Western blot analysis, and ELISA were done to evaluate cellular viability, survival, and protein expression levels.

RESULTS

**Figure 1. Treatment with Briciclib or ON 013100 significantly inhibits cell viability of various cancer cell lines:**

**Table 1. IC50 values for Briciclib and ON 013100**

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Briciclib</th>
<th>ON 013100</th>
</tr>
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<tbody>
<tr>
<td>AGS</td>
<td>10.2 ± 0.4</td>
<td>6.8 ± 0.6</td>
</tr>
<tr>
<td>FLO-1</td>
<td>12.3 ± 0.3</td>
<td>10.1 ± 0.5</td>
</tr>
<tr>
<td>JEKO-1</td>
<td>9.7 ± 0.7</td>
<td>4.8 ± 0.2</td>
</tr>
<tr>
<td>MINO</td>
<td>9.8 ± 0.05</td>
<td>6.7 ± 0.1</td>
</tr>
<tr>
<td>MCF-7</td>
<td>15.1 ± 0.8</td>
<td>7.9 ± 0.3</td>
</tr>
<tr>
<td>MDA MB 231</td>
<td>13.5 ± 1.2</td>
<td>10.8 ± 0.7</td>
</tr>
</tbody>
</table>

**Figure 2. Treatment with Briciclib or ON 013100 significantly inhibits survival of cancer cells lines:**

**Figure 3. Treatment with Briciclib or ON 013100 reduces endogenous levels of C-MYC and CYCLIN D1:**

**CONCLUSION**

- Overall our findings indicate that both Briciclib and ON 013100 exhibit similar anticancer activity in various cancer cell lines. Our in vitro data emphasize the potential of aforementioned eIF4E- inhibitors in selectively treating hematopoietic and solid cancers.

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REFERENCES
