The gamma secretase inhibitor AL101 combined with other drugs for dual targeting of Notch dysregulated tumors

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Selection of Compounds for In Vivo Combo Studies

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Ratiosame</th>
<th>Drug Compound</th>
<th>Dose &amp; Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notch</td>
<td>Genomic hallmark of Notch dependency for ACC &amp; breast cancer</td>
<td>AL101</td>
<td>3mg/kg PO QD</td>
</tr>
<tr>
<td>HDAC</td>
<td>Genomic hallmark of HDAC dependency for ACC &amp; breast cancer</td>
<td>Vorinostat (SAHA)</td>
<td>3mg/kg IP QD</td>
</tr>
<tr>
<td>Bcl2</td>
<td>Notable biomarker of differentially expressed pathways in ACC</td>
<td>Venetoclax (ABT-199)</td>
<td>50mg/kg PO QD</td>
</tr>
<tr>
<td>CDK4/6</td>
<td>Notable biomarker of differentially expressed pathways in ACC</td>
<td>Palbociclib (PD0332991)</td>
<td>60mg/kg PO QD</td>
</tr>
<tr>
<td>FGFR</td>
<td>Notable biomarker of differentially expressed pathways in ACC</td>
<td>Erlotinib (AZD4805)</td>
<td>25mg/kg PO QD</td>
</tr>
</tbody>
</table>

Table 1: Compounds selected for in vivo combination studies. The doses were selected after completing a 14-day tolerability study in non-tumor bearing Nude mice, comparing each drug alone to combination with AL101 for the effect on body weight and survival. Combinations were purchased at LC Labs or MedChemExpress.

Conclusions

- Additive or synergistic activity of GSI combined with agents of various mechanisms of action, indicates that cross-talk between signaling pathways may increase the effectiveness of AL101 in recurrent/metastatic ACC regardless of Notch mutational status.
- This may also be a promising approach for expansion to other cancer indications in which Notch is dysregulated.

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