**Anti-Tumor Activity of CUDC-101, a Novel Small Molecule Inhibitor of HDAC, EGFR and Her2, in Hepatocellular Cancer (HCC)**

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**Introduction**

Hepatocellular cancer (HCC) is the 5th most common cancer and the 3rd leading cause of cancer death worldwide. Its incidence in industrialized countries is increasing due to hepatitis C virus infection. The late diagnosis and inherent resistance of this disease to available treatments generally leave HCC patients with few effective therapeutic options, so that an unmet medical need exists.

**CUDC-101 Potently Inhibits HDAC, EGFR and Her2**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM) in Enzyme Assays</th>
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<tbody>
<tr>
<td>SAHA</td>
<td>HDAC 60.0, EGFR NA, Her2 NA</td>
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<td>Erlotinib</td>
<td>NA 48.0, 134.5</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>NA 10.2</td>
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<tr>
<td>CUDC-101</td>
<td>4.4</td>
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</tbody>
</table>

- HDAC inhibition: 5-10 fold more potent than SAHA
- EGFR inhibition: 10-20 fold more potent than Erlotinib
- Her2 inhibition: 10-fold more potent than Erlotinib & similar to lapatinib

**Selectivity of CUDC-101 Against a 72-Kinase Panel**

- 72 kinases screened
- Weak inhibitor of VEGFR2, Lyn, Abl-1, FGR2, Fh3, Ret and Lck kinases (IC50 values are within the range of 1-5 mM)
- Inhibition of other kinases is less than 50% at 10 mM

**Proposed Mechanism for Synergistic Multi-Targeting of HDAC, EGFR & Her2**

- EGFRi and/or Her2i often results in Her2C-met/AKT survival pathway upregulation and evasion of apoptosis by cancer cells
- HDACi blockade of survival pathways improves efficacy

**CUDC-101 Simultaneously Inhibits 3 Clinically Validated Cancer Targets: HDAC, EGFR & Her2**

**CUDC-101 Effectively Inhibits Proliferation of Human Liver Cancer Cell Lines**

**Intermittent Dosing of CUDC-101 Induces Tumor Growth Inhibition in HepG2 Xenografts**

**CUDC-101 Induces Tumor Growth Inhibition in Hep3B Xenografts**

**Conclusions**

- CUDC-101, a selective small molecule inhibitor of HDAC, EGFR and Her2, displays anti-proliferation activities in vitro against human HCC cell lines
- CUDC-101 induces tumor regression/stasis in HCC tumor xenografts in nude mice without overt toxicity
- CUDC-101 displays potent inhibition of both HDAC activity and EGFR phosphorylation in HCC tumor xenografts in nude mice
- CUDC-101 displays a favorable safety profile (data not shown)
- The simultaneous inhibition of HDAC, EGFR, and Her2 by CUDC-101 in a single small molecule may have PK and safety advantages over treatment with 2-3 separate agents
- CUDC-101 is being prepared for a Ph I trial in oncology against solid tumors