DCC-3116, a first-in-class selective inhibitor of ULK1/2 kinases and autophagy, synergizes with EGFR inhibitors osimertinib and afatinib in NSCLC preclinical models

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I have the following financial relationships to disclose:

Stockholder in: Deciphera Pharmaceuticals
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Strategies for blocking autophagy in cancer

- Autophagy is important during homeostasis of the cell for recycling of nutrients and damaged organelles
- Once tumors are established, autophagy can be used as a survival mechanism
- Inhibition of autophagy, in combination with a targeted treatment, could drive cancer cells to cell death

**ULK**
- ULK1/2 are druggable serine/threonine kinases that initiate autophagy
- Receives and processes key input from nutrient and stress sensors
- ULK activation leads to phosphorylation of protein substrates such as ATG13 and can be used as measure of autophagy initiation
- DCC-3116 is a potent & selective first-in-class ULK1/2 inhibitor designed to inhibit autophagy

**VPS34**
- Druggable lipid kinase target
- Has roles in autophagy and endocytic sorting
DCC-3116 is an investigational, potent & selective first-in-class ULK inhibitor designed to inhibit autophagy

- Highly Potent in biochemical and cellular assays
- Highly Selective
- No off-target kinases within 30-fold of ULK1
- Only 5 kinases within 100-fold of ULK1
- Designed to avoid CNS exposure
- Low Brain/Plasma free fraction ratio (4.3%) to avoid CNS autophagy
- Current Status: Phase 1 study initiated in 2Q 2021
  - NCT04892017

### Enzyme assay (1 mM ATP) & Cellular assay (NanoBRET) IC₅₀ (nM)

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Enzyme IC₅₀</th>
<th>Cellular IC₅₀</th>
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<tbody>
<tr>
<td>ULK1</td>
<td>4.7</td>
<td>6</td>
</tr>
<tr>
<td>ULK2</td>
<td>35</td>
<td>9</td>
</tr>
</tbody>
</table>

Source and Notes: Composite of enzyme and cellular kinase phosphorylation data was used. The size of the red circle corresponds to the IC₅₀ value obtained. No circles are plotted for kinases with IC₅₀ > 1 μM. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).
Targeting autophagy may confer sensitivity to anti-EGFR treatments and prevent resistance to EGFR TKIs

DCC-3116 Combination Opportunities: MAPK inhibitors

- Strong scientific rationale to combine DCC-3116 with inhibitors of the MAPK pathway
  - Three publications in 2019 (Kinsey et al, Bryant et al and Lee et al) demonstrated that the combination of MAPK and autophagy inhibitors may be a valid approach for RAS mutant cancers
- Literature and preclinical studies support combinations with inhibitors upstream of MAPK pathway

DCC-3116 Combination Opportunities: EGFR inhibitors

- Epidermal Growth Factor Receptor (EGFR) is a member of the ErbB family which consist of EGFR, HER2, HER3 and HER4
- EGFR is mutated in ~30% of patients with NSCLC
- Multiple generations of small molecule inhibitors against EGFR have been approved, however resistance causes cancer progression
  - Osimertinib has been approved for patients with EGFR exon 19 deletion or L858R mutations, as well as for the EGFR resistance mutation T790M
  - Afatinib has activity against both EGFR and HER2
- Enhanced autophagy is associated with resistance to osimertinib both in vitro and in vivo (Kwon et al. 2019)
EGFR inhibitors gefitinib, erlotinib and osimertinib all activate the ULK pathway as measured by pATG13 induction in the HCC827 cell line.

The ErbB-family inhibitor afatinib also activates the ULK pathway.
Osimertinib and afatinib induce autophagy in the H1975 cell line, which is inhibited by DCC-3116.

In the H1975 cell line which contains the T790M EGFR resistance mutation, EGFR inhibitors (gefitinib and erlotinib) that are not able to inhibit the T790M mutation, do not induce ULK-mediated ATG13 phosphorylation, as expected.
DCC-3116 combines with osimertinib and afatinib in the EGFR mutant cell line, H1975 (T790M/L858R)

- DCC-3116 decreased tumor burden in combination with osimertinib and afatinib in the H1975 EGFR mutant xenograft model

**Combination with Osimertinib**

**Combination with Afatinib**
EGFR and EGFR family inhibitors induce autophagy through activation of ULK1/2 in multiple EGFR-mutant NSCLC cell lines

DCC-3116, a specific and potent inhibitor of ULK1/2, inhibits EGFR and EGFR family inhibitor-induced autophagy in multiple EGFR-mutant NSCLC cell lines

DCC-3116 decreased tumor burden in combination with osimertinib and afatinib in the H1975 EGFR mutant xenograft model

These data provide a strong scientific rationale to combine DCC-3116 with EGFR inhibitors such as osimertinib and afatinib in NSCLC cancer patients

DCC-3116 is currently in a Phase 1 clinical trial in patients with advanced solid tumors with a documented RAS or RAF mutation (NCT04892017)