DCC-3116, a first-in-class selective ULK1/2 inhibitor of autophagy, in combination with the KIT inhibitor ripretinib induces complete regressions in GIST preclinical models

Madhumita Bogdan, Mary J Timson, Hibikat Al-Hashimi, Bryan D Smith, and Daniel L Flynn

Deciphera Pharmaceuticals, LLC, Waltham, MA, USA

Introduction

- Cancer cells activate autophagy as an adaptive stress response (ASR) escape mechanism to therapies targeting the RTK/RAS/MAPK/PI3K pathways, limiting antitumor response1-2
- ULK1/2 kinases are key regulators that initiate autophagy in response to stress, such as RTK pathway inhibition1-2
- Most gastrointestinal stromal tumors (GISTs) are driven by mutations in KIT3-5
- KIT signals through MAPK/PI3K pathways, suppressing ULK1/2 kinases and autophagy2-3
- Inhibitors targeting KIT reverse this suppression, activating autophagy and cancer cell survival2
- Approved therapies for mutant KIT,,dipretinib, also contain sunitinib, sorafenib, and ripretinib5
- Avapritinib is approved for PDGFRα exon 11 mutation-driven GIST6, however, drug resistance can develop6 through secondary mutations or activation of ASR pathways, however, drug resistance can develop7 through RTK/RAS/MAPK/PI3K pathways, limiting antitumor activity and generating tumor drug resistance and cancer cell survival.7
- ULK1/2 kinases are key regulators that initiate autophagy
- Cancer cells activate autophagy as an adaptive stress response8

Methods

- Inhibition of ULK1/2 in cell assays was measured using an ELISA for the ULK substrate pATG13
- Autophagic flux was measured by monitoring mCherry/GFP-tagged LC3 protein in GIST cells
- Xenograft studies were performed at a CRO with the approval of Animal Care and Use committees

Results

DCC-3116 synergizes with ripretinib to inhibit autophagy and block tumor growth in GIST preclinical models

DCC-3116 reverses ripretinib-induced ULK activation in multiple GIST cell lines

DCC-3116 reverses ripretinib-induced autophagic flux

Synergy of DCC-3116 in combination with ripretinib in the GIST-T1 xenograft model

Table 2. Combination treatment resulted in regressions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% TGI</th>
<th>% regression</th>
<th>Regressions (n/N)</th>
<th>Complete regressions (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle control</td>
<td>0</td>
<td>0/5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
| Monotherapy  
Ripretinib 25 mg/kg (chow) | -100 | 9/9 | 9/9 |
| Ripretinib 100 mg/kg (chow) | 5/5 | 5/5 |
| DCC-3116 50 mg/kg | -8 | 0/10 | 0 |
| DCC-3116 100 mg/kg | -9 | 0/10 | 0 |
| Combination  
Ripretinib 25 mg/kg (chow) + DCC-3116 50 mg/kg | -100 | 9/9 | 9/9 |
| Ripretinib 25 mg/kg (chow) + DCC-3116 100 mg/kg | -100 | 10/10 | 10/10 |
| Ripretinib 100 mg/kg (chow) + DCC-3116 50 mg/kg | -100 | 10/10 | 10/10 |
| Ripretinib 100 mg/kg (chow) + DCC-3116 100 mg/kg | -100 | 9/9 | 9/9 |

Conclusions

- DCC-3116 strongly synergizes with the KIT inhibitor ripretinib, resulting in complete regressions in the GIST-T1 exon 11 deletion xenograft model
- These data demonstrate preclinically that, like other RTK inhibitors, ripretinib activates ULK1/2-mediated autophagy as an ASR escape mechanism, which is inhibited by DCC-3116
- This provides the rationale to study DCC-3116 in combination with ripretinib in patients with GIST
- DCC-3116 is currently in a phase 1 clinical trial in patients with advanced solid tumors (NCT04892017), and initiation of a new combination escalation study with ripretinib is expected in the second half of 2023

REFERENCES