DCC-3116, a first-in-class selective inhibitor of ULK1/2 kinases and autophagy, synergizes with encorafenib and cetuximab in BRAFV600E–mutant colorectal cancer models

Madhumita Bogdan, Mary J Timson, Hikmat Al-Hashimi, Bryan D Smith, and Daniel L Flynn
Deciphera Pharmaceuticals, LLC, Waltham, MA, USA

**Introduction**

- Cancer cells activate autophagy through ULK1/2 kinases as an adaptive stress response (ASR) escape mechanism to therapies targeting the RTK/RAS/MAPK/PI3K pathways, limiting antitumor response.
- BRAF signals through the MAPK pathway while EGFR signals upstream through both the MAPK and PI3K pathways, suppressing ULK1/2 kinases and autophagy; treatment with BRAF and EGFR inhibitors reverses this suppression, activating autophagy
- Approved treatments for patients with CRC harboring BRAF signals through the MAPK pathway while EGFR pathways, suppressing ULK1/2 kinases and autophagy; treatment with BRAF and EGFR inhibitors reverses this suppression, activating autophagy
- DCC-3116 is a selective, investigational, potent, first-in-class inhibitor of ULK1/2 kinases in clinical development in combination with targeted therapies that activate the autophagic ASR escape pathway.
- Here, we demonstrate that ULK1/2 kinases and autophagy are activated in BRAFV600E–mutant CRC models upon treatment with encorafenib + cetuximab and that the ULK1/2 inhibitor DCC-3116 deepened responses to encorafenib + cetuximab in BRAFV600E–mutant CRC xenograft models

**Results**

DCC-3116 synergizes with encorafenib and cetuximab to inhibit ULK activity and block tumor growth in vitro

**DCC-3116 reverses encorafenib- and cetuximab–induced ULK activity and autophagic flux in vitro**

**CONCLUSIONS**

- These preclinical data demonstrated that ULK-mediated autophagy was activated as an ASR escape mechanism in response to BRAF inhibitors in combination with EGFR blockade.
- Inhibition of ULK1/2 with DCC-3116 deepened control of tumor growth in combination with encorafenib + cetuximab, with the triple combination resulting in regression in 10 out of 10 mice in the Colo-205 model.
- These data provide the rationale to study the combination of DCC-3116 with encorafenib + cetuximab in patients with CRC harboring the BRAFV600E mutation.
- 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 in combination with encorafenib and cetuximab in the second half of 2023.