DCC-3116, a first-in-class selective inhibitor of ULK1/2 kinases and autophagy, synergizes with encorafenib and cetuximab in *BRAF*^{V600E}–mutant colorectal cancer models

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

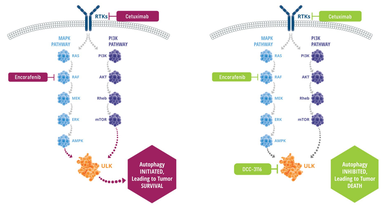
Deciphera Pharmaceuticals, LLC, Waltham, MA, USA

decīphera®

Poster: 1377

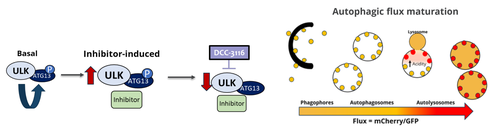
Introduction

- 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[1,2]
- 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[3-6]
- Approved treatments for patients with CRC harboring *BRAF*^{V600E} mutations include the BRAF inhibitor encorafenib in combination with the EGFR antibody cetuximab[7]
- Treatment with encorafenib + cetuximab is initially successful; however, drug resistance can develop[7] either through RTK/MAPK-resistant mutations and/or ASR pathways, including 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[1,2]
- Here, we demonstrate that ULK1/2 kinases and autophagy are activated in *BRAF*^{V600E}–mutant CRC models upon treatment with encorafenib + cetuximab and that the ULK1/2 inhibitor DCC-3116 deepened responses to encorafenib + cetuximab in *BRAF*^{V600E}–mutant CRC xenograft models



Methods

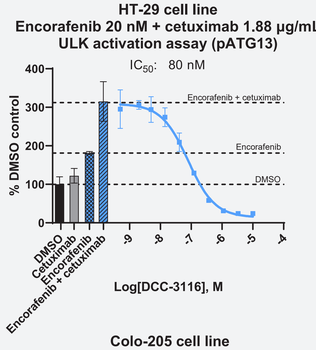
- ULK1/2 activity was measured in cells using an ELISA for the ULK substrate pATG13
- Autophagic flux was measured by monitoring mCherry/GFP-tagged LC3 in HT-29 and Colo-205 cells
- Xenograft models were performed at a CRO with the approval of Animal Care and Use committees

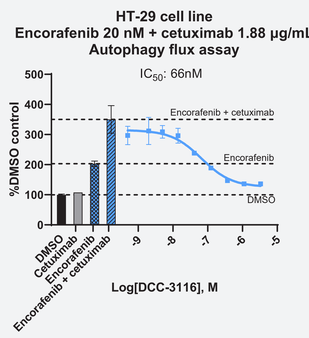


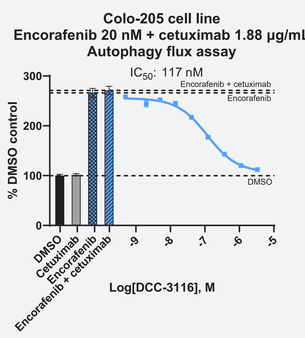
Results

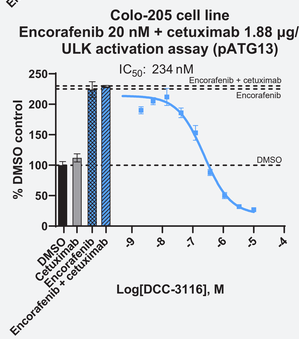
DCC-3116 synergizes with encorafenib and cetuximab to inhibit autophagy and block tumor growth in *BRAF*^{V600E} colorectal cancer

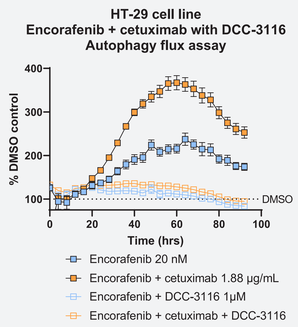
DCC-3116 reverses encorafenib– and cetuximab–induced ULK activity and autophagic flux *in vitro*

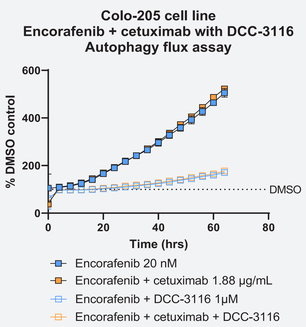




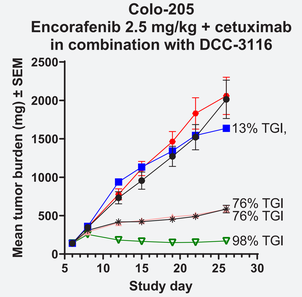


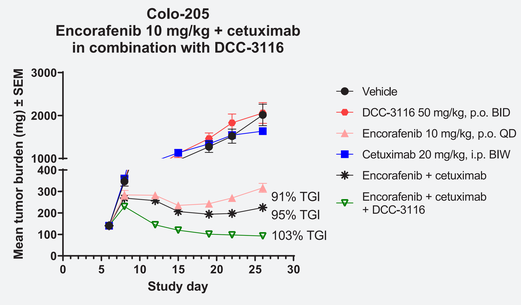




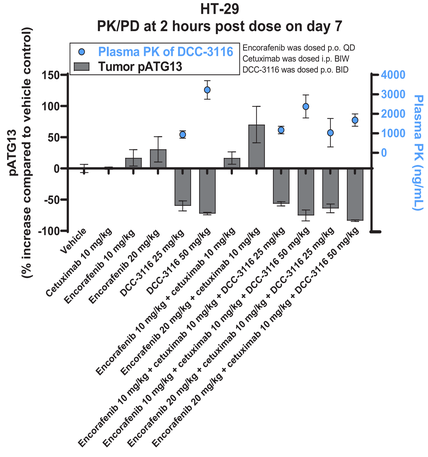


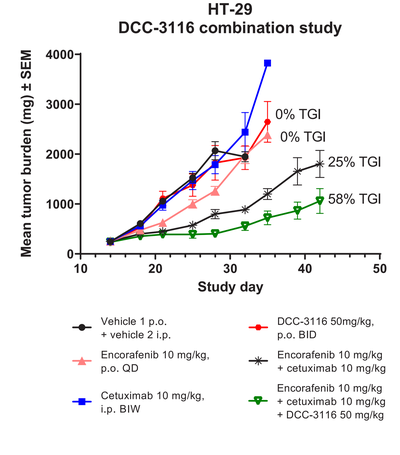
DCC-3116 synergizes with encorafenib and cetuximab combination to inhibit tumor growth in the Colo-205 colorectal model





DCC-3116 combines with encorafenib and cetuximab to inhibit ULK activity and tumor growth in the HT-29 colorectal model





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 *BRAF*^{V600E} 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

PRESENTED AT THE AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR) ANNUAL MEETING
ORLANDO, FL, APRIL 14–19, 2023

CORRESPONDING AUTHOR/DISCLOSURES

Madhumita Bogdan (mbogdan@deciphera.com)
All authors are/were full time employees of Decipher Pharmaceuticals, LLC and own/owned Decipher Pharmaceutical, LLC stock or options.

ACKNOWLEDGMENTS

We thank Fred Reu and Cheryl Gradziel for contributions to this project. Editorial support was provided by AlphaBioCom, a Red Nucleus company, and was funded by Decipher Pharmaceuticals, LLC.

ABBREVIATIONS

AKT, protein kinase B; AMPK, adenosine monophosphate–activated protein kinase; ASR, adaptive stress response; ATG13, autophagy-related protein 13; BID, twice daily; BIW, 2 times a week; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CRC, colorectal cancer; CRO, clinical research organization; DMSO, dimethyl sulfoxide; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal–regulated kinase; GFP, green fluorescent protein; IC_{50}, half maximal inhibitory concentration; i.p., intraperitoneally; LC3, microtubule-associated protein light chain 3; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; mTOR, mammalian target of rapamycin; pATG13, phosphorylated ATG13; PD, pharmacodynamics; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetics; p.o., orally; QD, once daily; RAF, rapidly accelerated fibrosarcoma serine/threonine kinase; RAS, rat sarcoma small GTPase protein; Rheb, Ras homolog enriched in brain; RTK, receptor tyrosine kinase; SEM, standard error of the mean; ULK, unc-51–like autophagy-activating kinase.

REFERENCES

1. Lee JJ, et al. *Int J Mol Sci*. 2021;22(22):12402.
2. Karmacharya U and Jung JW. *Int J Mol Sci*. 2023;24(2):953.
3. Bogdan M, et al. *Mol Cancer Ther*. 2021;20(suppl 12):P084.
4. Gupta A, et al. *Proc Natl Acad Sci U S A*. 2010;107(32):14333-8.
5. Li Y-Y, et al. *Lung Cancer*. 2013;81(3):354-61.
6. Mehnert JM, et al. *Clin Cancer Res*. 2022;28(6):1098-106.
7. Mauri G, et al. *Cancers (Basel)*. 2021;13(1):137.