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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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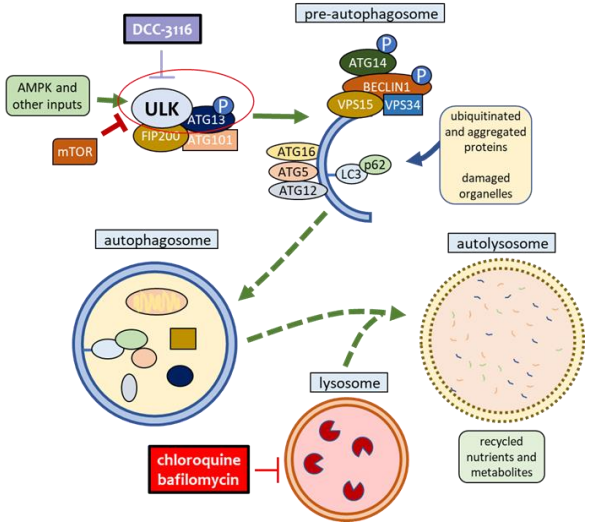
Strategies for blocking autophagy in cancer

- 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

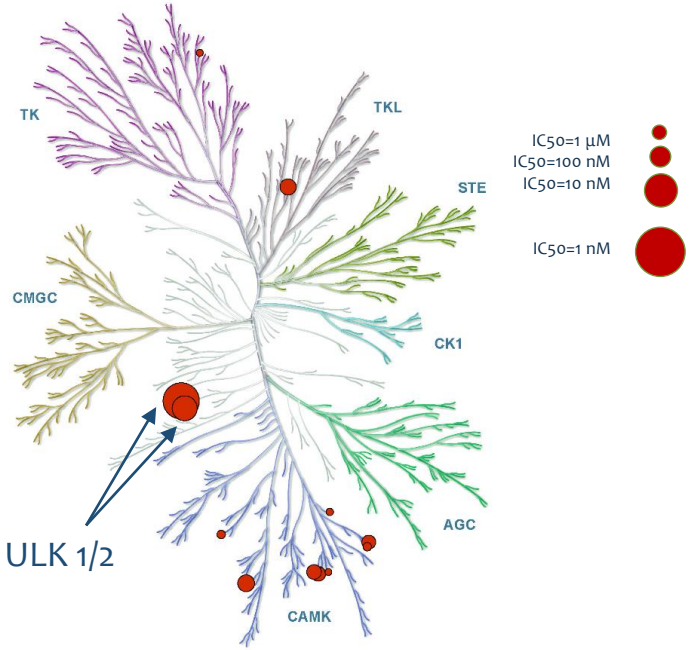
- Highly Potent in biochemical and cellular assays

	Enzyme assay (1 mM ATP)	Cellular assay (NanoBRET)
	IC_{50} (nM)	
ULK1	4.7	6
ULK2	35	9

- 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



Source and Notes: Composite of enzyme and cellular kinase phosphorylation data was used. The size of the red circle corresponds to the IC_{50} value obtained. No circles are plotted for kinases with IC_{50} > 1 µM; Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

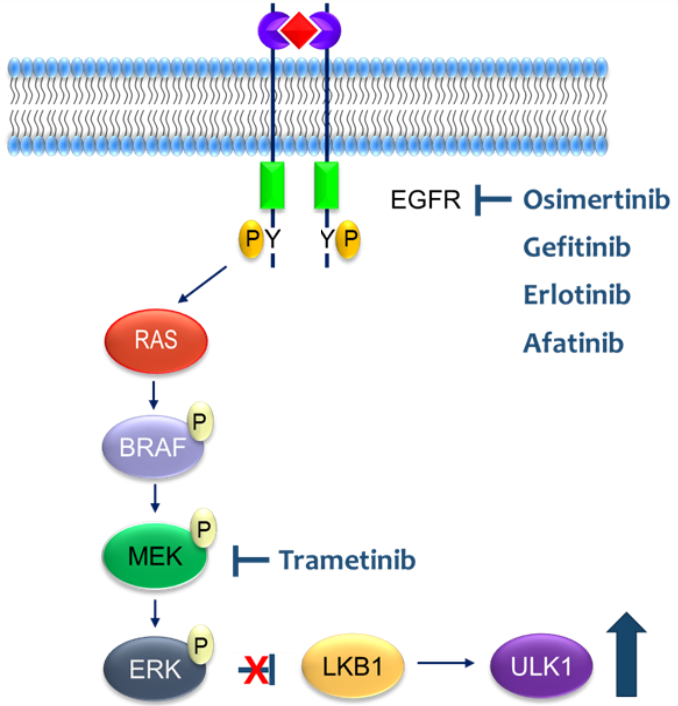
Targeting autophagy may confer sensitivity to anti-EGFR treatments and prevent resistance to EGFR TKIs

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

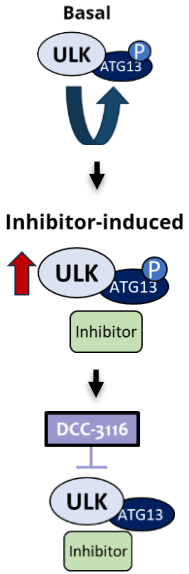
DCC-3116 Combination Opportunities: EGFR inhibitors

- 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)

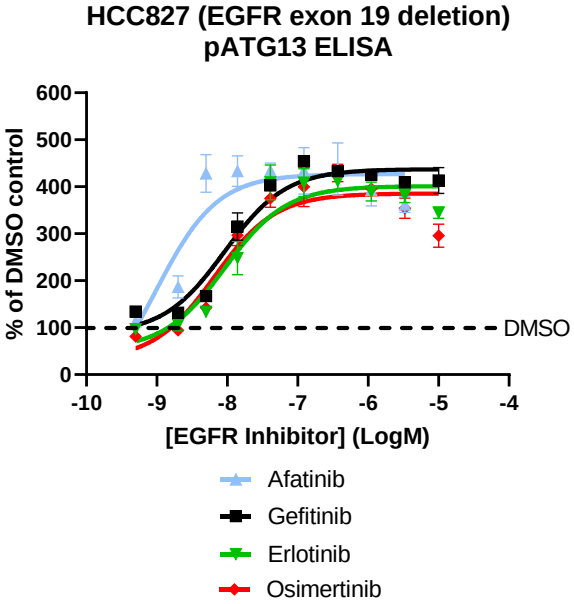


Kwon et al. 2019
Kinsey et al. 2019
Bryant et al. 2019
Lee et al. 2019

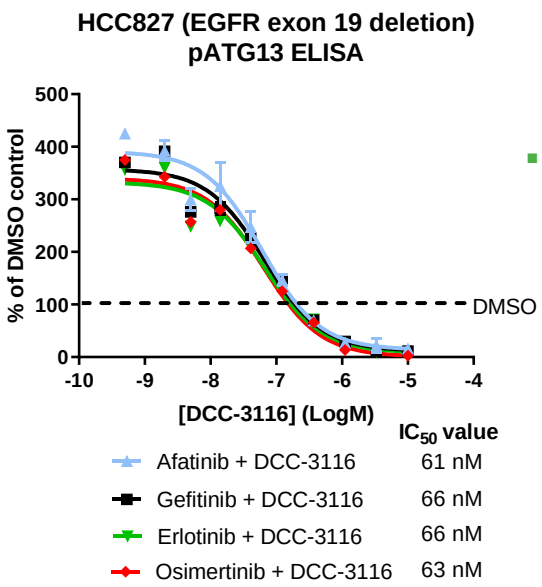
DCC-3116 inhibits EGFR and EGFR-family inhibitor-induced pATG13 and formation of autophagic vesicles in the exon19 deletion cell line HCC827



EGFR inhibitors induce ULK activity

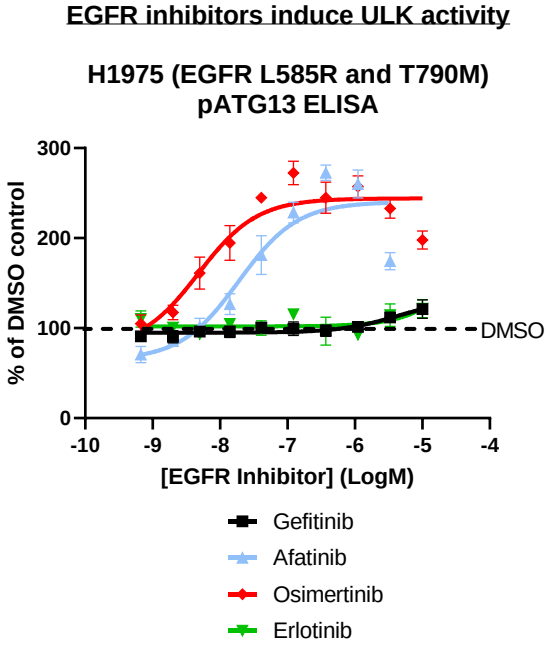


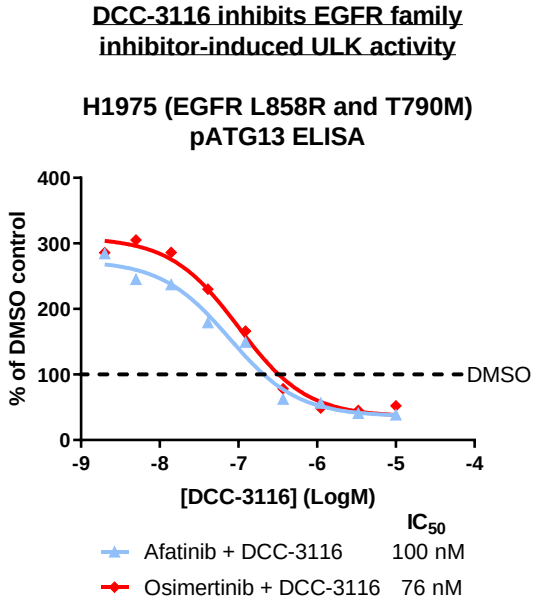
DCC-3116 inhibits EGFR inhibitor-induced ULK activity

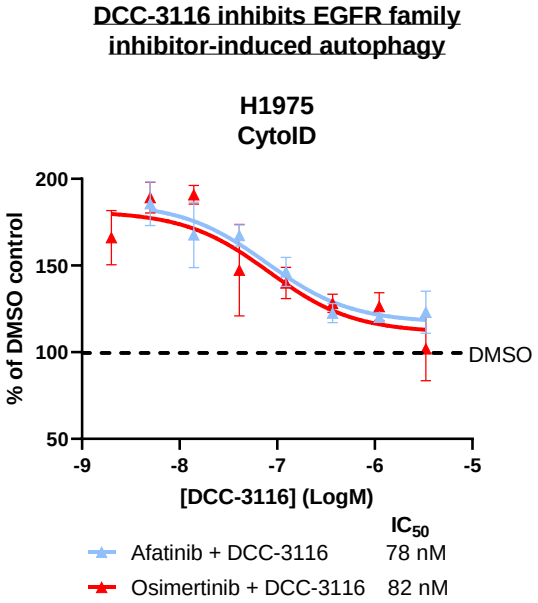


- EGFR inhibitors gefitinib, erlotinib and osimertinib all activate the ULK pathway as measured by pATG13 induction in the HCC827 cell line
- The ErbB-family inhibitor afatinib also activates the ULK pathway

DCC-3116 inhibits osimertinib and afatinib-induced pATG13 and autophagy in the EGFR gatekeeper T790M mutant cell line, H1975



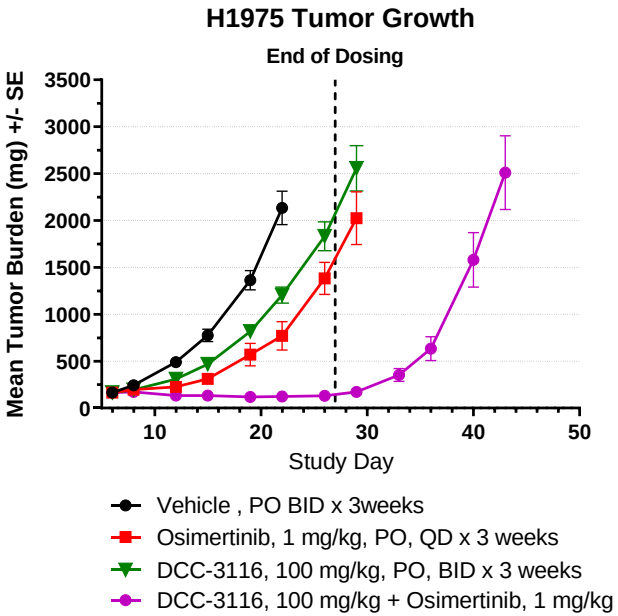




- Osimertinib and afatinib induce autophagy in the H1975 cell line, which is inhibited by DCC-3116.
- In the H1975 cell line which contains the T790M EGFR resistance mutation, EGFR inhibitors (gefitinib and erlotinib) that are not able to inhibit the T790M mutation, do not induce ULK-mediated ATG13 phosphorylation, as expected.

DCC-3116 combines with osimertinib and afatinib *in vivo* in the EGFR mutant cell line, H1975 (T790M/L858R)

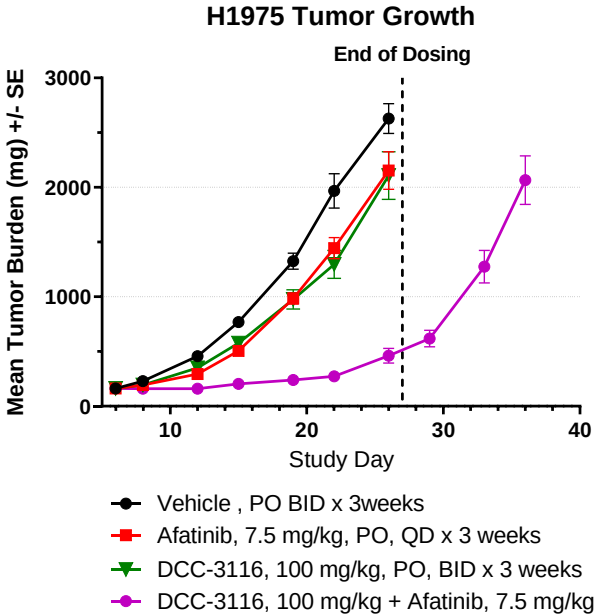
Combination with Osimertinib



Osimertinib vs. Combination p = 0.0005

Vehicle vs. Combination p=0.0001

Combination with Afatinib



Afatinib vs. Combination p= 0.0001

Vehicle vs. Combination p=0.0001

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

Conclusions

- 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)