DCC-3116, a First-in-Class Selective Inhibitor Of ULK1/2 Kinases and Autophagy, Combines with the KRAS$^{G12C}$ Inhibitor Sotorasib Resulting in Tumor Regression in NSCLC Xenograft Models
Martin McMahon, Disclosures:

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Mutationally activated H-, K- or NRAS genes encode oncoproteins that drive the aberrant and lethal behavior of ~20% of all human cancers.

Once considered “undruggable”, RAS oncoproteins are now at the center of a massive effort to develop direct pharmacological inhibitors of RAS.GDP or RAS.GTP, representing a major advance for cancer therapy.

However, as with most/all single-agent, pathway-targeted cancer therapies, the durability of patient response is limited by the emergence of drug resistant disease generally due to on-target reactivation of the RAS-regulated RAF>MEK>ERK MAP kinase and/or the PI3’-kinase>AKT signaling pathways.

Hence, the depth and durability of patient responses will likely be greatly improved by the development of novel combination therapies whether it be RAS inhibitors plus: 1. Conventional chemoRx; 2. Radiation therapy; 3. immuno-oncology or; 4. Pathway-targeted agents.
Inhibition of KRAS>RAF>MEK>ERK signaling with trametinib in RAS-driven cancers induces cytoprotective autophagy

McMahon Lab

Der Lab

**Lee et al., (2019) PNAS**
Luo Lab

- Inhibition of KRAS>RAF>MEK>ERK signaling in RAS-driven cancer cell lines leads to induced autophagy

- Combined inhibition of KRAS>RAF>MEK>ERK signaling plus lysosome function (HCQ) promotes regression of established xenografts

- Patient 1 showed a striking anti-tumor response to the combination of trametinib plus HCQ (T2,HCQ1200)

A trametinib/HCQ combination elicits regression of a KRAS-mutated pancreatic cancer PDX

PDX 220 (Pancreatic Cancer)

- Control
- Trametinib
- Hydroxychloroquine
- Trametinib plus Hydroxychloroquine
- Gem + Abraxane

N=6 for all groups

Gem + Abraxane
Trametinib + 400 mg HCQ
Trametinib + 800 mg HCQ
Everolimus
Gem + Abraxane

Trametinib

Pre-treatment 2 months T/HCQ
MEK1/2 inhibition leads to activation of the LKB1►AMPK►ULK1 signaling axis

Oncogenic B-RAF Negatively Regulates the Tumor Suppressor LKB1 to Promote Melanoma Cell Proliferation

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ULK1/2 Inhibitor (DCC-3116) Inhibits Autophagy Pathways Activated by Tumor-Targeted Therapies

- Inhibitors of tumor driver pathways activate ULK-dependent tumor survival pathways that mediate resistance through autophagy.
- ULK inhibition leads to striking pre-clinical anti-cancer activity in combination with tumor driver inhibitors within the RTK/RAS/MAPK pathway.
- DCC-3116 is a First-in-Class target opportunity in RTK, RAS, MAPK mutant cancers. DCC-3116 is currently under clinical investigation (NCT04892017).
- Deciphera is on track to initiate combination cohorts by the end of 2022.

>70% of human cancers depend on RTK/RAS/MAPK signaling.

ULK1 and ULK2 kinases are initiating factors for activation of autophagy.

DCC-3116 is the only selective and potent ULK kinase inhibitor in clinical development.

Phase 1 dose escalation includes rational combination cohorts.
DCC-3116 is a Potent & Selective, First-In-Class ULK1/2 Inhibitor Designed to Inhibit Autophagy

Summary

Highly Potent (IC\textsubscript{50} cellular NanoBRET)

- ULK1: \textbf{6nM}
- ULK2: \textbf{9nM}

High Kinome Selectivity

- No off-target kinases within 30-fold of ULK1
- Only 5 kinases within 100-fold of ULK1

Designed to avoid CNS exposure

- Low Ratio Brain\textsubscript{ff}/Plasma\textsubscript{ff} (4.3%) to avoid CNS autophagy

Phase 1 study initiated in June 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\textsubscript{50} value obtained. No circles are plotted for kinases with IC\textsubscript{50} > 1 \muM; Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).
DCC-3116 inhibits ULK1/2 activity and autophagic flux in a KRAS\textsuperscript{G12C} mutated NSCLC cell line

DCC-3116 inhibits KRAS\textsuperscript{G12C} inhibitor-induced ULK → pATG13 signaling

**Diagram:**
- **Basal autophagy:**
  - ULK1/2 → ATG13
- **Soto/adagrasib-induced autophagy:**
  - ULK1/2 → ATG13
- **DCC-3116:**
  - ULK1/2 → ATG13

**Graphs:**
- **H358 pATG13 ELISA:**
  - Adagrasib
  - Sotorasib
  - Soto/adagrasib
- **H358 pATG13 ELISA (IC\textsubscript{50}):**
  - Adagrasib + DCC-3116 50 nM
  - Sotorasib + DCC-3116 59 nM
DCC-3116 inhibits ULK1/2 activity and autophagic flux in a KRAS<sup>G12C</sup> mutated NSCLC cell line

**DCC-3116 inhibits KRAS<sup>G12C</sup> inhibitor-induced ULK → pATG13 signaling**

**DCC-3116 inhibits KRAS<sup>G12C</sup> inhibitor-induced autophagy flux**

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**Basal autophagy**

**Soto/adagrasib-induced autophagy**

**DCC-3116**

**ULK1/2**

**P**

**ATG13**

**H358**

**pATG13 ELISA**

**DCC-3116 inhibits KRAS<sup>G12C</sup> inhibitor-induced autophagy flux**

**Autophagic Flux maturation**

**Flux = mCherry/GFP fused LC3-II**

**H358**

**mCherry-GFP tagged LC3**

**100nM Sotorasib**

**Sotorasib + DCC-3116**

**50 nM**

**IC<sub>50**

**100nM Adagrasib**

**Adagrasib + DCC-3116**

**59 nM**

**DMSO**
DCC-3116 produces deeper and longer regressions in combination with sotorasib in a KRAS\textsuperscript{G12C}-mutated NSCLC xenograft model.

Spaghetti plots demonstrating sustained regressions in combination cohorts.

Sotorasib dosed QD and DCC-3116 dosed BID.
DCC-3116 Outperformed Lysosomal Inhibitor Chloroquine as a Combination Partner to Sotorasib in a KRAS\textsuperscript{G12C} NSCLC Model

Calu-1 is a NSCLC xenograft model with a heterozygous KRAS\textsuperscript{G12C} mutation

- DCC-3116 cooperates with sotorasib for superior control of Calu-1 KRAS\textsuperscript{G12C}-driven xenografts
- Combination sotorasib plus DCC-3116 elicits tumor regression
DCC-3116 Exhibits Combination Efficacy with Sotorasib and Adagrasib in a PDX Lung Cancer KRAS\textsuperscript{G12C} Model

LU11554 is a KRAS\textsuperscript{G12C}-driven NSCLC PDX model with KEAP1 and CDKN2A mutations.
Summary & Conclusions

• Inhibitors targeting mutant RTK>RAS>BRAF cancers activate ULK1/2-mediated autophagy as an adaptive treatment resistance mechanism.

• Sotorasib and adagrasib activate ULK1/2-mediated autophagy that is inhibited by DCC-3116 \textit{in vitro}. Combination therapy with DCC-3116 translates to deeper and longer tumor regressions \textit{in vivo}.

• These data demonstrate a compelling rationale to evaluate DCC-3116 in combination with KRAS$^{G12C}$ inhibitors in NSCLC patients.

• DCC-3116 is currently in a Phase 1 clinical trial in patients with advanced solid tumors with documented KRAS, NRAS or BRAF mutations (NCT04892017).
Cooperation between DCC-3116, a First-in-Class, Selective Inhibitor Of ULK1/2 Kinases, & KRAS\textsuperscript{G12C} Inhibition in Preclinical Models of NSCLC

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