DCC-3116 Overview and Preclinical Data

April 15, 2022
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ULK-MEDIATED AUTOPHAGY AND METABOLIC REWIRING FORM THE FOUNDATION OF A GENERAL TUMOR SURVIVAL PATHWAY
- A broad range of targeted therapeutics that inhibit tumor drivers also activate ULK-mediated tumor survival pathways as a general treatment resistance mechanism
- Addressable market targets ~70% of all human cancers

DCC-3116 COMBINATION WITH RTK INHIBITORS TARGETING MUTANT RTK-DRIVEN CANCERS
- DCC-3116 + osimertinib combination in mEGFR NSCLC
- DCC-3116 + afatinib combination in mEGFR NSCLC
- Combination exhibits deeper and more durable responses compared to single agent therapy

DCC-3116 COMBINATION WITH KRAS INHIBITORS TARGETING MUTANT RAS-DRIVEN CANCERS
- DCC-3116 + sotorasib combination in mKRAS<sup>G12C</sup> NSCLC
- DCC-3116 + adagrasib combination in mKRAS<sup>G12C</sup> NSCLC
- Combination exhibits deeper and more durable regressions compared to single agent therapy

DCC-3116 COMBINATION WITH MAPK INHIBITORS TARGETING MUTANT RAS/RAF-DRIVEN CANCERS
- DCC-3116 + trametinib combination in mKRAS NSCLC, mKRAS PDAC, mKRAS CRC, and mBRAF Melanoma
- Combination exhibits synergy or additivity compared to single agent therapy

DCC-3116 PHASE 1 TRIAL UNDERWAY
- Single dose escalation underway
- Safety, pharmacokinetic, pharmacodynamic readouts
- Identification of recommended dose for Phase 1b combination studies
- Identification of MTD

Notes: BRAF=proto-oncogene b-RAF; CRC=colorectal cancer; EGFR=epidermal growth factor receptor; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=Kirsten rat sarcoma virus; MTD=maximum tolerated dose; NSCLC=non-small-cell lung cancer; PDAC=pancreatic ductal adenocarcinoma; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.
Autophagy is a catabolic process in which cells recycle components to generate energy.

RTK-, RAS-, and RAF-mutant cancer cells activate autophagy in order to survive stresses or damage due to anti-cancer therapeutic intervention with MAPK and PI3K pathway inhibitors.

The ULK kinase initiates the autophagy pathway and provides a potential targeted approach to selectively inhibit autophagy in these cancers.

DCC-3116 is a first-in-class small molecule designed to inhibit cancer autophagy by inhibiting ULK kinase.

Notes: ATG13=Autophagy-related protein 13; MAPK=mitogen-activated protein kinase; PI3K=phosphatidylinositol-3 kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.
DCC-3116 | POTENTIAL BACKBONE OF COMBINATION THERAPY

CENTRAL ROLE FOR AUTOPHAGY IN THE RAS/MAPK AND PI3K PATHWAYS

Growing Preclinical Validation for Role of Autophagy in Cancer

DCC-3116 In Combination with RTK Inhibition
- DCC-3116 exhibits synergy with osimertinib and afatinib resulting in tumor regression in EGFR-mutant NSCLC in vivo

DCC-3116 In Combination with KRAS G12C Inhibition
- DCC-3116 exhibits synergy with AMG-510 resulting in tumor regression in KRAS G12C-mutant NSCLC in vivo

DCC-3116 In Combination with MEK Inhibition
- DCC-3116 exhibits synergy in combination with trametinib and inhibited pancreatic, lung, and melanoma xenograft tumor growth

Other targets where therapeutic intervention activates ULK and autophagy

Notes: AKT=protein kinase B; AMPK=AMP-activated protein kinase; EGFR=epidermal growth factor receptor; ERK=extracellular signal-regulated kinase; G12C=single point mutation with a glycine to cysteine substitution at codon 12; KRAS=kirsten rat sarcoma virus; LKB1=liver kinase B1; MAPK=mitogen-activated protein kinase; MEK=mitogen-activated extracellular signal-regulated kinase; mTOR=mammalian target of rapamycin; NSCLC=non-small cell lung cancer; PI3K=phosphatidylinositol-3-kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; Rheb=ras homolog enriched in brain; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.
ULK Inhibition
- ULK is initiating factor of autophagy
- Druggable serine/threonine kinase
- Receives and processes key input from nutrient and stress sensors

Lysosomal Inhibition
- Indirect and non-selective inhibition by preventing degradation of the contents
- Elevated pH inactivates hydrolases
- Interference with normal lysosomal house-keeping functions

Notes: ATG13=autophagy-related protein 13; ULK=unc-51-like kinase.
**DCC-3116 | OVERVIEW**

**POTENT AND SELECTIVE ULK INHIBITOR DESIGNED TO INHIBIT AUTOPHAGY**

**First-in-Class Switch-Control ULK Kinase Inhibitor**
- Potent and selective inhibitor of ULK, the initiating factor in autophagy
- Strong preclinical data in combination with RTK/RAS/MAPK inhibitors
- Potential backbone combination agent across >70% of cancers

**Highly Potent (Cellular IC\textsubscript{50} values for ULK inhibition)**
- ULK1 6 nM
- ULK2 9 nM

**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 ratio brain\textsubscript{ff}/plasma\textsubscript{ff} (4.3%) to avoid CNS autophagy

Notes: MAPK=mitogen-activated protein kinase; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.
SIGNIFICANT POTENTIAL OPPORTUNITY EXISTS AS MUTATIONS IN RAS/RAF/RTK SIGNALING OCCURS IN ~70% OF HUMAN CANCERS

RAS Mutations
~32% of Human Cancers

- KRAS 18.2%
- NRAS 5.3%
- HRAS 2.2%
- NF1 6.2%
- Non-RAS Mutated 68.1%

RAF Mutations
~18% of Human Cancers

- BRAF 18.3%
- Non-RAS/RAF Mutated 49.8%

- RAS 31.9%

RTK Mutations
~20% of Human Cancers

- BRAF 18.3%
- RTK Mutated ~20.0%

- RAS 31.9%
- Non-RAS/RAF/RTK Mutated ~30.0%

RTK Known Tumor Driver Mutations
• EGFR
• KIT
• TRK A
• ALK
• FGFR 2
• BCR-ABL
• HER2
• PDGFrα
• TRK B
• ROS
• FGFR 3
• BTK
• HER3
• FLT3
• TRK C
• RET
• FGFR 4
• cMET exon 14 skipping

Source: COSMIC (Catalogue of Somatic Mutations in Cancer) Database, v90. Notes: RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; KRAS=kirsten rat sarcoma virus; BRAF=proto-oncogene b-raf; HRAS=Harvey rat sarcoma gene; NRAS=neuroblastoma ras viral oncogene homolog; EGFR=epidermal growth factor receptor; HER2=human epidermal growth factor receptor 2; HER3=human epidermal growth factor receptor 3; PDGFRα=platelet derived growth factor receptor alpha; FLT=ferm-like tyrosine kinase; TRK=Tropomyosin receptor kinase; ALK=Anaplastic lymphoma kinase; RET=Rearranged during transfection; FGFR=Fibroblast growth factor receptor; cMET=tyrosine-protein kinase Met.
GROWING PRECLINICAL DATA SUPPORT MULTIPLE COMBINATION PARTNERS

**DCC-3116 Preclinical Combination Data**

**RTKs**
- Osimertinib (EGFRi)
- Afatinib (EGFRi)

**RAS**
- Sotorasib (KRAS G12Ci)
- Adagrasib (KRAS G12Ci)

**MAPK**
- Trametinib (MEKi)
- Binimetinib (MEKi)
- Ulixertinib (ERKi)

Notes: EGFR=epidermal growth factor receptor; ERK=extracellular signal-regulated kinase; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=kirsten rat sarcoma virus; MAPK=mitogen-activated protein kinase; MEK=mitogen-activated extracellular signal-regulated kinase; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase.
DCC-3116 inhibits KRAS\(^{G12C}\) inhibitor-induced ULK activity

**Notes:** EGFR=epidermal growth factor receptor; \(G12C\)=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=Kirsten rat sarcoma virus; MAPK=mitogen-activated protein kinase; NSCLC=non–small-cell lung cancer; PDAC=pancreatic ductal adenocarcinoma; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.
**DCC-3116 | PRECLINICAL DATA**

**DCC-3116 OBSERVED PRECLINICALLY TO DURABLY AND POTENTLY INHIBIT AUTOPHAGY INDUCED BY MULTIPLE PATHWAY INHIBITORS**

- **RTK/RAS/MAPK** induces significant autophagy flux
- **DCC-3116** can sustainably inhibit this induction

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**Autophagic Flux Maturation**

**DCC-3116 + EGFR Inhibitor**

NSCLC: H1975 Osimertinib-induced Autophagy Induction Over Time (mCherry/GFP Tagged LC3)

**DCC-3116 + KRAS\(^{G12C}\) Inhibitor**

NSCLC: H358 Sotorasib vs. Adagrasib-induced Autophagy Induction Over Time (mCherry/GFP Tagged LC3)

**DCC-3116 + Trametinib (MEK)**

PDAC: MiaPaca-2 Trametinib-induced Autophagy Induction Over Time (mCherry/GFP Tagged LC3)

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Notes: EGFR=epidermal growth factor receptor; \(G12C\)=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=Kirsten rat sarcoma virus; MAPK=mitogen-activated protein kinase; NSCLC=non-small-cell lung cancer; PDAC=pancreatic ductal adenocarcinoma; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase.
DCC-3116 EXHIBITED ADDITIVITY OR SYNERGY IN COMBINATION WITH MULTIPLE RTK, RAS, & MAPK PATHWAY INHIBITORS

DCC-3116 + Osimertinib (EGFR)

NSCLC: H1975 Tumor Growth

DCC-3116 + Sotorasib (KRAS)

NSCLC: H358 Tumor Growth

DCC-3116 + trametinib (MEK)

PDAC: MiaPaca-2 Tumor Growth

Notes: BID=twice daily; EGFR=epidermal growth factor receptor; KRAS=Kirsten rat sarcoma virus; MAPK=mitogen-activated protein kinase; MEK=mitogen-activated extracellular signal-regulated kinase; NSCLC=non-small-cell lung cancer; PDAC=pancreatic ductal adenocarcinoma; PO=by mouth; QD=once daily; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase.
DCC-3116 demonstrated deeper and longer regressions in combination with Sotorasib in KRAS\textsuperscript{G12C} H358 NSCLC

Notes: Data presented at the AACR Meeting 2022; AMG510 was dosed QD and DCC-3116 was dosed BID; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=Kirsten rat sarcoma virus; NSCLC=non-small-cell lung cancer.
**DCC-3116 | PHASE 1 STUDY**

MULTICENTER, OPEN-LABEL, FIRST-IN-HUMAN STUDY AS A SINGLE AGENT AND IN COMBINATION WITH A MEK INHIBITOR

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**Part 1**

**Dose Escalation Phase (3 + 3 design)**

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<tr>
<th>DCC-3116</th>
<th>Single agent dose escalation cohorts</th>
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<tr>
<td><strong>DCC-3116 + MEK inhibitor (trametinib)</strong></td>
<td>Combination dose escalation cohorts</td>
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**RP2D or MTD of DCC-3116 as a single agent**

**RP2D of the combination**

**Dose Escalation Phase Inclusion Criteria**
- Histologically confirmed diagnosis of an advanced or metastatic solid tumor with a documented RAS or RAF mutation
- KRAS G12C inhibitor combination in NSCLC planned, subject to feedback from regulatory authorities

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**Part 2**

**Dose Expansion Phase**

- **Cohort 1 (n=20)**
  - Pancreatic ductal adenocarcinoma

- **Cohort 2 (n=20)**
  - Non-small cell lung cancer

- **Cohort 3 (n=20)**
  - Colorectal cancer

- **Cohort 4 (n=20)**
  - Melanoma

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**Notes:**
- G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=kirsten rat sarcoma virus; MEK=MAPK/ERK kinase; MTD=maximum tolerated dose; NSCLC=non-small-cell lung cancer; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase; RAS=rat sarcoma gene; RP2D=recommended Phase 2 dose; (1) with a documented mutation in KRAS or BRAF; (2) with a documented mutation in KRAS, NRAS, or BRAF; (3) with a documented mutation in NRAS or BRAF.
ULKi decreases pATG14 in PBMNCs
PUBLICATIONS AND PRESENTATIONS
SELECTED THIRD-PARTY AUTOPHagy PUBLICATIONS

A. Reviews


B. Mutant RAS cancers


3. Lee, Chih-Shia et al. MAP kinase and autophagy pathways cooperate to maintain RAS cancer cell survival. PNAS 2019; 16(10): 4508-4517. https://www.pnas.org/content/116/10/4508


C. RTK mutated cancers

D. Immuno-oncology


E. Non-cancer cell systemic effects of autophagy in oncology


59-8290.CD-17-0952.full-text.pdf


F. Cancer stemness and persistence states


G. Glucose metabolism/regulation of Reactive Oxygen Species (ROS)


3. Smith B. et al. Preclinical studies with DCC-3116, an ULK kinase inhibitor designed to inhibit autophagy as a potential strategy to address mutant RAS cancers. AACR-NCI-EORTC. 2019. (Linked here)


5. McMahon M. et al. DCC-3116, a first-in-class selective inhibitor of ULK1/2 kinases and autophagy, synergizes with the KRASG12C inhibitor sotorasib resulting in tumor regression in KRAS mutant NSCLC xenograft models. AACR Annual Meeting. 2022. (Linked here)
DCC-3116 INHIBITS OSIMERTINIB AND AFATINIB-INDUCED pATG13 AND AUTOPHagy

**Notes:**

- Osimertinib and afatinib induce autophagy in the H1975 cell line, which is inhibited by DCC-3116.
- EGFR inhibitors (gefitinib and erlotinib) do not induce ULK-mediated ATG13 phosphorylation in the H1975 cell line (with a T790M mutation) as expected since they do not inhibit T790M mutation.

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**Notes:**

Data presented at the AACR-NCI-EORTC Meeting 2021; ATG13=autophagy-related protein 13; EGFR=epidermal growth factor receptor; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=kirsten rat sarcoma virus; MAPK=mitogen-activated protein kinase; NSCLC=non–small-cell lung cancer; PDAC=pancreatic ductal adenocarcinoma; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.
DCC-3116 EXHIBITS SYNERGY IN COMBINATION WITH OSIMERTINIB AND AFATINIB

DCC-3116 + Osimertinib

NSCLC: H1975 Tumor Growth

DCC-3116 + Afatinib

NSCLC: H1975 Tumor Growth

Notes: Data presented at the AACR-NCI-EORTC Meeting 2021; BID=twice daily; NSCLC=non-small-cell lung cancer; PO=by mouth; QD=once daily.
DCC-3116 OUTPERFORMED LYSOSOMAL INHIBITOR CHLOROQUINE AS A COMBINATION PARTNER TO SOTORASIB IN A KRAS$^{G12C}$ NSCLC MODEL

DCC-3116 + Sotorasib Exhibits Regressions In a Resistant Calu-1 Model

NSCLC: Calu-1 (KRAS$^{G12C}$-driven) Xenograft

- Vehicle
- DCC-3116 100 mg/kg/day chow
- Chloroquine 50 mg/kg
- Sotorasib 30 mg/kg
- Chloroquine + Sotorasib
- DCC-3116 + Sotorasib

P = 0.002  
P = 0.001

Notes: Data presented at the AACR Meeting 2022; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=Kirsten rat sarcoma virus; NSCLC=non-small-cell lung cancer.
**DCC-3116 EXHIBITS COMBINATION EFFICACY WITH SOTORASIB AND ADAGRASIB IN A PDX LUNG CANCER KRAS\(^{G12C}\) MODEL**

**Notes:** Data presented at the AACR Meeting 2022; BID=twice daily; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=Kirsten rat sarcoma virus; NSCLC=non-small-cell lung cancer; QD=once daily.
**DCC-3116 POTENTLY INHIBITS TRAMETINIB-INDUCED ATG13**

**KRAS Lung Cancer**
- A549 – DCC-3116
  - IC\(_{50}\) 52 nM

**KRAS\(^{G12C}\) Pancreatic Cancer**
- MiaPaca-2 – DCC-3116
  - IC\(_{50}\) 28 nM

**KRAS Colorectal Cancer**
- HCT116 – DCC-3116
  - IC\(_{50}\) 57 nM

**BRAF Melanoma Cancer**
- A375 – DCC-3116
  - IC\(_{50}\) 40 nM

**Basal and MAPK Inhibitor-mediated Compensatory Increased Autophagy are Inhibited**

**Notes:** Data presented at Deciphera’s 2019 R&D Day; ATG13=Autophagy-related protein 13; BRAF=proto-oncogene b-RAF; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; KRAS=Kirsten rat sarcoma virus; MAPK=mitogen-activated protein kinase.
DCC-3116 exhibits additivity or synergy in combination with trametinib

DCC-3116 + Trametinib

PDAC: MiaPaca-2 Tumor Growth

NSCLC: A549 Tumor Growth

Melanoma: A375 Tumor Growth

Notes: Data presented at the AACR-NCI-EORTC Meeting 2019; BID=twice daily; NSCLC=non-small cell lung cancer; PO=by mouth; PDAC=pancreatic ductal adenocarcinoma; QD=once daily.