One Mission, Inspired by Patients: Defeat Cancer.™

April 18, 2023
OPENING REMARKS

Steve Hoerter
President and Chief Executive Officer
Forward-Looking Statements

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**Opening Remarks**

Steve Hoerter  
President and Chief Executive Officer

Dan Flynn, Ph.D.  
Chief Scientific Officer and Founder

**Our Switch-Control Platform**

Stacie Bulfer, Ph.D.  
Sr. Director, Biological Sciences

Madhumita Bogdan, Ph.D.  
Sr. Principal Investigator, Biological Sciences

**Pan-RAF (DCC-3084)**

Bryan Smith, Ph.D.  
Vice President, Biological Sciences

**ULK (DCC-3116)**

Gada Al-Ani, Ph.D.  
Sr. Principal Investigator, Biological Sciences

**Pan-KIT (DCC-3009)**

**GCN2 (DP-9149)**

**Closing Remarks**

Steve Hoerter  
President and Chief Executive Officer

**Q&A**

Notes: GCN2=general control-nonderepressible 2; KIT=KIT proto-oncogene receptor tyrosine kinase; RAF=rapidly accelerated fibrosarcoma; ULK=unc-51-like autophagy-activating kinase.
Executing on our mission to discover, develop, and commercialize important new medicines to **improve the lives of people with cancer**.

- **Over $1 Billion**
- **Peak Worldwide Sales** Potential for QINLOCK® (ripretinib) and Vimseltinib
- **Two Phase 3 Programs**
- **MOTION Top-line Data** and INSIGHT Initiation Planned for 2023
- **Potential First-in-Class Autophagy Program**
- **Multi-billion Dollar Opportunity** Targeting Autophagy
- **Proven Discovery Engine**
- **High-Value Research Pipeline** of Switch-Control Kinase Inhibitors
STRATEGIC PRIORITIES FOR 2023

QINLOCK™ (ripretinib)
- Initiate INSIGHT Phase 3 study in 2L KIT exon 11+17/18 GIST patients
- Drive continued 4L adoption in US and expansion in key European markets

Vimseltinib
- Announce top-line results from the MOTION Phase 3 study
- Present longer-term follow up from Phase 1/2 study

DCC-3116
- Initiate one or more MEK/G12C expansion cohorts in the Phase 1/2 study
- Initiate new combination study with encorafenib/cetuximab and with ripretinib

DCC-3084
- Submit IND to FDA

Proprietary Drug Discovery Platform
- Nominate development candidate for pan-KIT inhibitor (DCC-3009)

Notes: 2L=second-line; 4L=fourth-line; FDA=U.S. Food and Drug Administration; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; GIST=gastrointestinal stromal tumor; IND=Investigational New Drug Application; KIT=KIT proto-oncogene receptor tyrosine kinase; MEK=mitogen-activated extracellular signal-regulated kinase.
OUR SWITCH-CONTROL PLATFORM

Dan Flynn, Ph.D.
Chief Scientific Officer and Founder
DECIPHERA IS A LEADER IN KINASE BIOLOGY

Two Decades of Pioneering Research in Kinase Biology

Proven Track Record of Advancing Novel Drug Candidates from Research to the Clinic and to Patients

Novel Library of Switch Control Inhibitors

Focused Investment in Next Gen Research Programs to Provide First- or Best-in-Class Treatments
High Kinome Selectivity

Ability to Target Broad Spectrum of Kinase Mutations

Hinders Development of Mutational Resistance

Extended Residency Times (Measured in Hours, Not Minutes)

High Cellular Potency (Cellular ATP Levels do not Compete)

Alternative Manipulation of Switches to Activate Kinases

Notes: ATP=Adenosine Triphosphate.
Notes: CSF1R=colony-stimulating factor 1 receptor; GCN2=general control nondepressible 2; KIT=KIT proto-oncogene receptor tyrosine kinase; RAF=rapidly accelerated fibrosarcoma; ULK=unc-51-like autophagy-activating kinase.
Kinases are regulated by changes in their shapes controlled by various switch regions.

Unlike classical approaches to kinase inhibition, Deciphera’s approach does not focus on binding into a pocket.

Deciphera’s candidates bind to Switch Control Amino Acids to prevent kinase activation.

We take advantage of variation in the Switch Control Amino Acid environment to design highly specific molecules.
DECIPHERA | KIT INHIBITOR QINLOCK (RIPRETINIB)
DUAL SWITCH KIT RECEPTOR TYROSINE KINASE ORCHESTRATES SHAPE CHANGES THAT REGULATE KINASE ACTIVITY

Main Switch in “OFF” State

Main Switch
Blocks ATP and Substrate Pockets

Phe 811
Trp 557
Tyr 823

Main Switch in “ON” State

ATP
Substrate
Phe 811
Tyr 823
Trp 557

Turn “ON”

Turn “OFF”

Notes: Chan et al, Mol Cell Biol. (2003) 23(9): 3067-78; ATP=Adenosine Triphosphate; KIT=KIT proto-oncogene receptor tyrosine kinase; Phe=phenylalanine; Trp=tryptophan; Tyr=tyrosine.
RIPRETINIB SOLVES FOR LOSS OF KIT INHIBITORY SWITCH IN GIST

**Restoration of the Inhibitory Spine**

- **OFF State Inhibitory Spine**: Normal wild type KIT with intact inhibitory switch.
- **ON State Dysregulated Active Spine**: Loss of exon 11 inhibitory switch.
- **OFF State Restored Inhibitory Spine**: Ripretinib is surrogate for deleted inhibitory switch.

Ripretinib ejects main switch to turn OFF kinase activity.

Notes: Kornev et al. PNAS 2006;103(47):17783-17788; Smith et al, Cancer Cell (2019) 35: 738-51; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase.
Ripretinib stabilizes the inhibitory hydrogen bond macroswitch network. In the KIT OFF state, sacrosanct amino acids form an inhibitory network of 11 hydrogen bonds to maintain the inactive conformation. Ripretinib forms 4 direct hydrogen bonds to nucleate and further stabilize the inhibitory hydrogen bond macroswitch network.

**Notes:** ATP=Adenosine Triphosphate; KIT=KIT proto-oncogene receptor tyrosine kinase; Phe=phenylalanine; Tyr=tyrosine.
Ripretinib Inhibits KIT Mutations Across Exons 9, 11, 13, 14, 17, and 18

Ripretinib KIT Inhibition is Resilient to 4 mM ATP Concentration

Ripretinib Off-rate Analysis

Notes: ATP=Adenosine Triphosphate; KIT=KIT proto-oncogene receptor tyrosine kinase; T_{1/2}=half-life.
Vimseltinib Stabilizes Inhibitory Spine Macroswitch, Ejecting Main Switch to the OFF State

Vimseltinib Nucleates Hydrogen Bond Macroswitch and Stabilizes Main Switch to the OFF State

Vimseltinib
- High Target Selectivity
- Noncompetitive with ATP Concentrations
- Long Residency Time. $T_{1/2}$ 3 hours

Notes: ATP=Adenosine Triphosphate; CSF1R=colony-stimulating factor 1 receptor; Phe=phenylalanine; $T_{1/2}$=half-life; Tyr=tyrosine.

Green: Main Switch
Gold: C-Helix Switch
CSF1R has an Unusual Amino Acid Sequence in the Switch that was Mined for Selectivity

Glycine (G)  Small amino acid
Cysteine (C)  Large amino acid

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Main Switch Region</th>
<th>IC₅₀ (nM)</th>
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</thead>
<tbody>
<tr>
<td>CSF1R</td>
<td>-G-D-F-G-</td>
<td>3.0</td>
</tr>
<tr>
<td>KIT</td>
<td>-C-D-F-G-</td>
<td>1,600</td>
</tr>
<tr>
<td>FLT3</td>
<td>-C-D-F-G-</td>
<td>&gt;3300</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>-C-D-F-G-</td>
<td>&gt;3300</td>
</tr>
<tr>
<td>PDGFRB</td>
<td>--C-D-F-G-</td>
<td>&gt;3300</td>
</tr>
</tbody>
</table>

2-methyl Group of Vimseltinib Occupies Switch “Glycine 795 Hole” Not Available in other RTK Family Members

CSF1R Accommodates Vimseltinib at the Switch “Glycine 795 Hole” Whereas KIT does not Accommodate Due to Large Cys 809

Notes: CSF1R=colony-stimulating factor 1 receptor; Cys=cysteine; FLT3=fetal liver kinase-2; Gly=glycine; KIT=KIT proto-oncogene receptor tyrosine kinase; PDGFRA=platelet-derived growth factor receptor α; PDGFRB= platelet-derived growth factor receptor β; RTK=receptor tyrosine kinase.

Cyan: CSF1R
Salmon: KIT
ULK has Unusual Main Switch

Unique Selectivity Region Created by ULK Switch

DCC-3116
- Highly Potent
- Highly Selective
- Extended Residency Time. $T_{1/2}$ 5 hours

Notes: $T_{1/2}$=half-life; ULK=unc-51-like kinase.
Cancer Cell

Inhibition of RAF Isoforms and Active Dimers by LY3009120 Leads to Anti-tumor Activities in RAS or BRAF Mutant Cancers

Authors: Sheng-Bin Peng, James R. Henry, Michael D. Kaufman, ..., Gregory D. Plowman, James J. Starling, and Daniel L. Flynn

Graphical Abstract:

In Brief:
Peng et al. show that LY3009120 inhibits all RAF isoforms and inhibits BRAF and CRAF homodimers and heterodimer. Moreover, LY3009120 induces minimal paradoxical activation in BRAF wild type cells. Importantly, LY3009120 exhibits anti-tumor activities in models carrying oncogenic KRAS, NRAS, or BRAF mutations.

Note pan-RAFT Inhibitor LY3009120 Bound into Both RAF Protomers

C-Helix Switch must be in the IN state

Main Switch must be in the DFG OUT state

Notes: BRAF=proto-oncogene b-RAF; CRAF=proto-oncogene c-RAF; DFG=DFG activation loop motif; KRAS=Kirsten rat sarcoma virus; NRAS=neuroblastoma RAS viral oncogene homolog; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.
**Notes:** RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.
For **RAF inhibition**, DCC-3084 designed to induce a **C-Helix IN state** to facilitate **binding to BOTH monomers** and block dimer signaling....

For **GCN2 activation**, DP-9149 designed to induce a **C-Helix OUT state** to facilitate **binding to ONE monomer**, transactivating unoccupied monomer to signal.

**Notes:** GCN2=general control nonderepressible 2, RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.
Notes: DFG=aspartic acid-phenylalanine-glycine, GCN2=general control nonderepressible 2.
Cancer cells activate Adaptive Stress Response pathways in order to enable their survival and continued proliferation under stressful conditions.

Kinases involved in Adaptive Stress Responses resolve the stressors caused by tumor drivers.

Cancers can become addicted to both tumor driver pathway and Adaptive Stress Response pathway signaling.

Modulation of cancer Adaptive Stress Response pathways are an important emerging field in targeted therapy.

Notes: 
1. ATF4=activating transcription factor 4; CSF1R=colony stimulating factor 1 receptor; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; KIT=KIT proto-oncogene receptor tyrosine kinase; MAPK=mitogen-activated protein kinase; PERK=protein kinase R-like endoplasmic reticulum kinase; PI3K=phosphatidylinositol-3 kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.
### DECIPHERA | OVERVIEW

**ROBUST PIPELINE OF SWITCH-CONTROL KINASE INHIBITORS**

<table>
<thead>
<tr>
<th>Program</th>
<th>Initiator</th>
<th>Phase 1</th>
<th>Phase 1/2</th>
<th>Phase 3 Planned for 2H 2023</th>
<th>Regulatory Submission</th>
<th>Approved</th>
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<tbody>
<tr>
<td><strong>Qinlock</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>KIT Inhibitor</td>
<td>GIST ≥4&lt;sup&gt;th&lt;/sup&gt; Line</td>
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<td></td>
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<tr>
<td></td>
<td>GIST 2&lt;sup&gt;nd&lt;/sup&gt; Line KIT Exon 11 + 17/18 (INSIGHT Phase 3 Study)&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Phase 3</td>
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<td><strong>Vimseltinib</strong></td>
<td>CSF1R Inhibitor</td>
<td>TGCT (MOTION Phase 3 Study)</td>
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<td></td>
<td>TGCT (Phase 1/2 Study)</td>
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<tr>
<td><strong>DCC-3116</strong></td>
<td>ULK Inhibitor</td>
<td>+ MEK Inhibitors (Trametinib or Binimetinib)</td>
<td>+ KRAF&lt;sup&gt;12C&lt;/sup&gt; Inhibitor (Sotorasib)</td>
<td>Planned for 2H 2023&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>+ BRAF inhibitor / EGFR inhibitor (Encorafenib / Cetuximab)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>+ KIT Inhibitor (Ripretinib)</td>
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<td><strong>DCC-3084</strong></td>
<td>Pan-RAF Inhibitor</td>
<td>Solid Tumors and Hematologic Malignancies</td>
<td></td>
<td>Planned for 2H 2023&lt;sup&gt;3&lt;/sup&gt;</td>
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<td><strong>DCC-3009</strong></td>
<td>Pan-KIT Inhibitor</td>
<td>GIST</td>
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<td>Planned for 1H 2024</td>
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<td><strong>Additional Programs</strong></td>
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<td>GCN2</td>
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<tr>
<td></td>
<td></td>
<td>VPS34&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
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### Notes:
- BRAF=proto-oncogene b-RAF; CSF1R=colony-stimulating factor 1 receptor; EGFR=epidermal growth factor receptor; GCN2=general control nonderepressible 2; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase; MAPK=mitogen-activated protein kinase; RAF=rapidly accelerated fibrosarcoma; RAS=rat sarcoma gene; TGCT=tenosynovial giant cell tumor; ULK=unc-51-like autophagy-activating kinase.
- 1) Exclusive development and commercialization license with Zai Lab in Greater China for Qinlock.
- 2) The patient population for the planned INSIGHT study consists of second-line GIST patients with mutations in KIT exon 11 and 17 and/or 18 and the absence of mutations in KIT exon 9, 13, and/or 14 (also referred to as KIT exon 11 + 17/18 patients).
- 3) Qinlock is approved for 4th line GIST in the United States, Australia, Canada, China, the European Union, Hong Kong, Israel, Macau, New Zealand, Switzerland, Taiwan, and the United Kingdom.
- 4) 2023 Corporate Goal.
- 5) Agreement with Sprint Bioscience for exclusive in-license worldwide rights to a research-stage program targeting VPS34.
DCC-3084 (PAN-RAF INHIBITOR)

Stacie Bulfer, Ph.D.
Sr. Director, Biological Sciences

Notes: RAF = rapidly accelerated fibrosarcoma.
- DCC-3084 is a potential best-in-class pan-RAF inhibitor engineered using Deciphera's proprietary switch-control platform.
- Potent and selective inhibitor of BRAF and CRAF kinases, shown preclinically to target all relevant aberrant signaling mechanisms (monomers, homodimers, heterodimers).
- High permeability, CNS penetrance, and solubility at gastric pH to facilitate tumor access.
- Long residency time, low efflux, and transporter inhibition to enable durable efficacy.
- Strong pre-clinical data supports single agent use in RAF and RAS mutant cancers, and deeper responses in combination with MEK inhibitors.

Notes: BRAF=proto-oncogene b-RAF; CNS=central nervous system; CRAF=proto-oncogene c-RAF; MEK=mitogen-activated extracellular signal-regulated kinase; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase; RAS=rat sarcoma gene.
POTENTIAL BEST-IN-CLASS BRAF/BRAF HOMODIMER AND BRAF/CRAF HETERODIMER INHIBITOR

Notes: BRAF=proto-oncogene b-RAF; CRAF=proto-oncogene c-RAF; GTP=guanosine triphosphate; MEK=mitogen-activated extracellular signal-regulated kinase; RAS=rat sarcoma gene.
DCC-3084 | PRECLINICAL DATA
KEY PROPERTIES FOR A BEST-IN-CLASS PAN-RAF INHIBITOR

Potency & Selectivity

- BRAF/CRAF inhibition of signaling via monomers, homodimers, and heterodimers
- Long on-target residency time
- Limited inhibition of off-target kinases

Pharmaceutical Properties

- High permeability, low efflux and inhibition of resistance transporters to maximize efficacy
- Improved solubility to enhance target inhibition

Tissue Distribution

- High accumulation in tumor cells
- CNS penetration for primary and secondary brain tumors

Notes: BRAF=proto-oncogene b-RAF; CNS=central nervous system; CRAF=proto-oncogene c-RAF; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.
DCC-3084 Limits Paradoxical Stimulation by Binding into Both Monomers Using Switch Control Approach

DCC-3084 Binds Both Monomers of a RAF Dimer

DCC-3084 Forces the Main Activation DFG Switch in an OUT State and the C-Helix Switch to an IN State

HCT-116: KRAS G13D Colorectal Cell Lines

DCC-3084 Limits Perk Activity Due to Paradoxical Pathway Activation Observed with First Generation BRAF Inhibitors

Notes: Data presented at the AACR Annual Meeting 2023; BRAF=proto-oncogene b-RAF; DFG=aspartic acid–phenylalanine–glycine; KRAS=Kirsten rat sarcoma virus.
# DCC-3084 | PRECLINICAL DATA

DCC-3084 EXHIBITS OVERALL BEST-IN-CLASS INHIBITION OF CLASS I, II, AND III BRAF-MUTANTS AND RAF FUSION CELL LINES

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>A375</th>
<th>HT-29</th>
<th>BxPC-3</th>
<th>H2405</th>
<th>WM3928</th>
<th>WM3629</th>
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<tr>
<td>DCC-3084</td>
<td>54</td>
<td>13</td>
<td>61</td>
<td>74</td>
<td>42</td>
<td>3</td>
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<tr>
<td>tovorafenib</td>
<td>3,000</td>
<td>5,270</td>
<td>1,100</td>
<td>603</td>
<td>669</td>
<td>305</td>
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<td>naporafenib</td>
<td>438</td>
<td>228</td>
<td>19</td>
<td>465</td>
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<td>belvarafenib</td>
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<td>128</td>
<td>59</td>
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<tr>
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<td>170</td>
<td>101</td>
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<td>549</td>
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<td>JZP815</td>
<td>141</td>
<td>47</td>
<td>200</td>
<td>47</td>
<td>133</td>
<td>2</td>
</tr>
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</table>

**IC\(_50\) (nM)**

**Notes:** Data presented at the AACR Annual Meeting 2023; BRAF=proto-oncogene b-RAF; NRAS=neuroblastoma RAS viral oncogene homolog; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.
DCC-3084 HAS EXCELLENT PERMEABILITY, LOW EFFLUX AND IS A STRONG INHIBITOR OF THE MDR1 AND BCRP DRUG RESISTANCE TRANSPORTERS

**Notes:** BCRP=breast cancer resistance protein transporter; MDR1=multidrug resistance mutation transporter; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase.
DCC-3084 | PRECLINICAL DATA

DCC-3084 SHOWED OPTIMIZED PHARMACEUTICAL PROPERTIES FOR ORAL ADMINISTRATION

- DCC-3084 has **good solubility** at gastric pH to allow for oral absorption
- DCC-3084 has **high cellular permeability** and **low efflux** to aid accumulation in tumor tissue
- Inhibition of **drug resistant transporters** enables durable efficacy
- DCC-3084 does **not inhibit human liver cytochrome P450** isoforms (CYPs).

Notes: Data presented at the AACR Annual Meeting 2023; BCRP=breast cancer resistance protein transporter; MDR1=multidrug resistance mutation transporter.

<table>
<thead>
<tr>
<th>Pharmaceutical Property</th>
<th>Result</th>
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<tbody>
<tr>
<td>Solubility, pH 1.6</td>
<td>408 µM</td>
</tr>
<tr>
<td>Caco2 Cell Permeability</td>
<td>10x10^-6 cm/s</td>
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<tr>
<td>Caco2 Efflux Ratio</td>
<td>0.9</td>
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<tr>
<td>MDCK1-MDR1 Permeability</td>
<td>21x10^-6 cm/s</td>
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<tr>
<td>MDCK1-MDR1 Efflux Ratio</td>
<td>0.9</td>
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<tr>
<td>MDCKII - BCRP Permeability</td>
<td>33x10^-6 cm/s</td>
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<td>MDCKII - BCRP Efflux Ratio</td>
<td>0.8</td>
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<tr>
<td>MDR1 Inhibition</td>
<td>IC50 = 79 nM</td>
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<tr>
<td>BCRP Inhibition</td>
<td>IC50 = 74 nM</td>
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<tr>
<td>CYP inhibition (1A2, 2D6, 3A4-M)</td>
<td>&gt;50,000 nM</td>
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<tr>
<td>CYP inhibition (3A4-T, 2B6)</td>
<td>&gt;9,000 nM</td>
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<td>CYP inhibition (2C19)</td>
<td>&gt;5,000 nM</td>
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<tr>
<td>CYP inhibition (2C8, 2C9)</td>
<td>&gt;2,000 nM</td>
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DCC-3084 | PRECLINICAL DATA

DCC-3084 EXHIBITS STRONG ACCUMULATION IN TUMORS AND SUPERIOR CNS PENETRATION

- DCC-3084 accumulated in tumor tissue at a ratio between 1.7x and 1.9x (tumor/plasma)
- DCC-3084 had higher CNS penetration enabled by inhibition of efflux transporters
- Enables potential for use in brain metastases (i.e. lung and melanoma) or primary brain cancer, areas with high unmet medical needs

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>AUC [brain] / AUC [plasma]</th>
<th>Kp\textsubscript{u/u}</th>
<th>Classification</th>
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<tbody>
<tr>
<td>DCC-3084</td>
<td>0.49</td>
<td>0.30</td>
<td>Moderate</td>
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<tr>
<td>tovorafenib</td>
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<tr>
<td>exarafenib</td>
<td>0.02</td>
<td>0.01</td>
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Notes: Data presented at the AACR Annual Meeting 2023; AUC=area under the concentration time curve; CNS=central nervous system; Kp\textsubscript{u/u}=unbound partition coefficient (free brain concentration/free plasma concentration).
DCC-3084 PRODUCES TUMOR REGRESSIONS IN BRAF MUTANT CANCER MODELS AS A SINGLE AGENT

**BRAF Class I**

**A375**: BRAF Mutant Melanoma Model

**BxPC-3**: BRAF Mutant Pancreatic Model

**WM3928**: SKAP2-BRAF Fusion Melanoma Model

**WM3629**: BRAF plus NRAS G12D Melanoma Model

Notes: Data presented at the AACR Annual Meeting 2023; BID=twice daily; BRAF=proto-oncogene b-RAF; NRAS=neuroblastoma RAS viral oncogene homolog.
DCC-3084 PRODUCES SINGLE AGENT TUMOR REGRESSION OR TUMOR GROWTH INHIBITION IN MUTANT RAS MODELS DRIVEN BY BRAF/CRAF

**Notes:** Data presented at the AACR Annual Meeting 2023; BID=twice daily; BRAF=proto-oncogene b-RAF; CRAF=proto-oncogene c-RAF; KRAS=Kirsten rat sarcoma virus; RAS=rat sarcoma gene; Reg.=regression; TGI=tumor growth inhibition.

**Calu-6:** KRAS Q61K Lung Cancer
**H358:** KRAS G12C Lung Cancer
**HPAF-II:** KRAS G12D Pancreatic Cancer
DCC-3084 PRODUCES DEEPER TUMOR REGRESSION IN KRAS MUTANT CANCER MODELS IN COMBINATION WITH MEK INHIBITORS

**Calu-6: KRAS Q61K Lung Cancer**

**H358: KRAS G12C Lung Cancer**

**HPAF-II: KRAS G12D Pancreatic Cancer**

Notes: Data presented at the AACR Annual Meeting 2023; BID=twice daily; KRAS=Kirsten rat sarcoma virus; MEK=mitogen-activated extracellular signal-regulated kinase; QD=once daily; Reg.=regression; TGI=tumor growth inhibition.
DCC-3084 is a potent and selective inhibitor of BRAF and CRAF kinases, shown preclinically to target all relevant aberrant signaling mechanisms (monomers, homodimers, heterodimers).

DCC-3084 exhibits high permeability, good central nervous system penetrance, and tumor tissue accumulation.

DCC-3084 exhibits long residency time, low efflux, and transporter inhibition to enable durable efficacy.

Strong pre-clinical data in cancers driven by RAF or RAS mutations supports exploration of single agent and combination opportunities.

★ IND Submission Expected in 2H 2023

Notes: Data presented at the AACR Annual Meeting 2023; BRAF=proto-oncogene b-RAF; CRAF=proto-oncogene c-RAF; RAF=rapidly accelerated fibrosarcoma serine/threonine protein kinase; RAS=rat sarcoma gene.
DCC-3116 (ULK INHIBITOR)

Madhumita Bogdan
Sr. Principal Investigator, Biological Sciences

Notes: ULK=unc-51-like autophagy-activating kinase.
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 IC₅₀ 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 brain/plasma ratio (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.
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.

**Notes:**
- G12C = single point mutation with a glycine-to-cysteine substitution at codon 12; 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; ATG13 = Autophagy-related protein 13.
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 ripretinib, osimertinib, and afatinib, resulting in tumor regression in EGFR-mutant NSCLC and GIST in vivo

DCC-3116 In Combination with KRAS<sup>G12C</sup> Inhibition
- DCC-3116 exhibits synergy with sotorasib and adagrasib resulting in tumor regression in KRAS<sup>G12C</sup>-mutant NSCLC in vivo

DCC-3116 In Combination with RAF Inhibition
- DCC-3116 exhibits synergy in combination with encorafenib in BRAFm CRC 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; GIST=gastrointestinal stromal tumor; 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.
DCC-3116 SYNERGIZES WITH ENCORAFENIB AND CETUXIMAB IN BRAF\textsuperscript{V600E} MUTANT COLORECTAL CANCER MODELS

- BRAF\textsuperscript{V600E} mutation occurs in ~10% of colorectal cancer patients and approved treatments include encorafenib (BRAFi) and cetuximab (EGFRi)
- Inhibition of mutant BRAF and EGFR activates autophagy and promotes cancer cell survival
- Drug resistance develops through RTK/MAPK resistant mutations and/or adaptive stress response pathways including autophagy
- Preclinically, DCC-3116 synergizes with encorafenib and cetuximab to increase tumor growth inhibition or tumor regressions by reducing autophagy through inhibition of the ULK kinase

Notes: AKT=protein kinase B; AMPK=AMP-activated protein kinase; BRAF=proto-oncogene b-RAF; BRAFi=BRAF inhibitor; EGFR=epidermal growth factor receptor; EGFRi=EGFR inhibitor; ERK=extracellular signal-regulated kinase; LKB1=liver kinase B1; MAPK=mitogen-activated protein kinase; mTOR=mammalian target of rapamycin; 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.
DCC-3116 INHIBITS CETUXIMAB- AND ENCORAFENIB-INDUCED pATG13 IN COLORECTAL CANCER CELL LINES

**Notes:** Data presented at the AACR Annual Meeting 2023; ULK activation is measured by pATG13 by ELISA; DMSO=dimethyl sulfoxide; ELISA=enzyme-linked immunosorbent assay; pATG13=phosphorylated ATG13.
DCC-3116 INHIBITS CETUXIMAB- AND ENCORAFENIB-INDUCED AUTOPHAGIC FLUX IN COLORECTAL CANCER CELL LINES

**HT-29:** BRAF\(^{V600E}\) Colorectal Cancer Model

- **IC\(_{50}\):** 66 nM

**Colo-205:** BRAF\(^{V600E}\) Colorectal Cancer Model

- **IC\(_{50}\):** 117 nM

**Notes:** Data presented at the AACR Annual Meeting 2023; Autophagic flux assay uses cell lines generated by tagging LC3 with mCherry and GFP; Assay measures the loss of GFP fluorescence in the lysosome and normalizes to mCherry signal which is unchanged in the lysosome; BRAF=proto-oncogene b-RAF; DMSO=dimethyl sulfoxide.
DCC-3116 INCREASES TUMOR GROWTH INHIBITION IN COMBINATION WITH ENCORAFENIB AND CETUXIMAB IN VIVO

HT-29: DCC-3116 Exposure and Target Engagement

HT-29: BRAFV600E Colorectal Cancer Model

Notes: Data presented at the AACR Annual Meeting 2023; % reg is the percent of mice that had regressions; %TGI and %Reg were calculated at the last day of dosing; BID=twice daily; BIW=2 times a week; BRAF=proto-oncogene b-RAF; pATG13=phosphorylated ATG13; PD=pharmacodynamics; PK=pharmacokinetics; PO=orally; QD=once daily; Reg=regression; TGI=tumor growth inhibition.
DCC-3116 INDUCES TUMOR REGRESSIONS IN COMBINATION WITH ENCORAFENIB AND CETUXIMAB IN VIVO

**Colo-205: BRAF^{V600E} Colorectal Cancer Model**

![Graph showing tumor burden over study days for different treatments](image)

**Notes:** Data presented at the AACR Annual Meeting 2023; % reg is the percent of mice that had regressions. %TGI and %Reg were calculated at the last day of dosing; BID=twice daily; BIW=2 times a week; BRAF=proto-oncogene b-RAF; PO=orally; QD=once daily; Reg=regression; TGI=tumor growth inhibition
Most gastrointestinal stromal tumors (GIST) are driven by mutations in KIT kinase and approved treatments include imatinib, sunitinib, regorafenib, and ripretinib.

Inhibition of mutant KIT activates autophagy and promotes cancer cell survival.

Drug resistance generally develops through secondary mutations in KIT as well as through the adaptive stress response pathway, including autophagy.

Preclinically, DCC-3116 synergizes with ripretinib to induce tumor regressions by reducing ULK-mediated autophagy.

Notes: AKT=protein kinase B; AMPK=AMP-activated protein kinase; EGFR=epidermal growth factor receptor; ERK=extracellular signal-regulated kinase; KIT=KIT proto-oncogene receptor tyrosine kinase; LKB1=liver kinase B1; MAPK=mitogen-activated protein kinase; mTOR=mammalian target of rapamycin; PI3K=phosphatidylinositol-3 kinase; RAF=rapidly accelerated fibrosarcoma; RTK=receptor tyrosine kinase; ULK=unc-51-like kinase.
DCC-3116 INHIBITS RIPRETNIB-INDUCED ULK ACTIVATION AND AUTOPHAGIC FLUX IN KIT-MUTATED GIST CELL LINES

**GIST Mutated Cell Lines: Ripretinib**

**GIST Mutated Cell Lines: 50 nM Ripretinib + DCC-3116**

**GIST-T1: GIST Exon 11 Mutated Cell Line**

Notes: Data presented at the AACR Annual Meeting 2023; DMSO=dimethyl sulfoxide; GIST=gastrointestinal stromal tumor; GIST-Mutated Cell Lines: 50 nM Ripretinib + DCC-3116; GIST-48; IC<sub>50</sub> (nM) 40; GIST-T1 Juke=Exon 11 del/Exon 14 T670I; GIST-T1 5R=Exon 11 del/Exon 14 T670I; GIST-882=Exon 11 del/Exon 13 V654A; GIST-430=Exon 11 del/Exon 13 K642E; GIST-48=Exon 11 del/Exon 14 T670I; KIT=KIT proto-oncogene receptor tyrosine kinase; ULK=unc-51-like kinase.
DCC-3116 SHOWS 100% TUMOR REGRESSIONS IN COMBINATION WITH RIPRETINIB IN KIT EXON 11 MUTATED GIST XENOGRRAFT MODEL

**GIST-T1:**

**PK/PD**

**GIST-T1:**

**Tumor Growth Inhibition**

**GIST-T1:**

**Tumor Volume**

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**Notes:** Data presented at the AACR Annual Meeting 2023; % reg is the percent of mice that had regressions; %TGI and %Reg were calculated at the last day of dosing; BID=twice daily; GIST=gastrointestinal stromal tumor; GIST-T1=Exon 11 del; KIT=KIT proto-oncogene receptor tyrosine kinase; PD=pharmacodynamics; PK=pharmacokinetics; Reg.=regression; TGI=tumor growth inhibition.

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**Pharmacodynamic inhibition of ULK in the GIST-T1 model**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Percent of Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

**Vehicle Control**
- Ripretinib Chow 25mg/kg
- DCC-3116 50mg/kg BID

**Ripretinib 25mg/kg**

**DCC-3116 50mg/kg BID**

**Ripretinib 25mg/kg Chow + DCC-3116 50mg/kg**

---

**Days Post Tumor Implant**

**Mean Tumor Burden (mg)**

**Days Post Tumor Implant**

**Tumor Volume mm**

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DCC-3116 + Encorafenib + Cetuximab

- DCC-3116 blocked BRAF$^{V600E}$ inhibitor and cetuximab-induced ULK activation and autophagic flux in preclinical models
- DCC-3116 exhibited combination efficacy in preclinical cancer models, leading to superior inhibition of tumor growth or to tumor regression

DCC-3116 + Ripretinib

- DCC-3116 blocked ripretinib-induced ULK activation and autophagic flux in preclinical models
- DCC-3116 exhibited combination efficacy in preclinical cancer models, leading to strong tumor regressions

Initiation of DCC-3116 dose escalation cohorts in combination with ripretinib and with encorafenib + cetuximab expected in 2H 2023

Notes: Data presented at the AACR Annual Meeting 2023; BRAF=proto-oncogene b-RAF; ULK=unc-51-like kinase.
Combination Dose Escalation Cohorts

Dose Expansion Cohorts

**Combination Dose Escalation Cohorts**

- **Trametinib**
  (MEK inhibitor)

- **Binimetinib**
  (MEK inhibitor)

- **Sotorasib**
  (KRAS\(^{G12C}\) inhibitor)

- **Encorafenib / Cetuximab\(^1\)**
  (BRAF inhibitor / EGFR inhibitor)

- **Ripretinib\(^1\)**
  (KIT inhibitor)

---

**Dose Expansion Cohorts**

- **2\(^{nd}\) Line PDAC\(^3\)**
  (KRAS-driven)

- **3\(^{rd}-5\(^{th}\) Line NSCLC\(^4\)**
  (RAF/RAS/NF1-driven)

- **≥3\(^{rd}\) Line CRC\(^4\)**
  (RAF/RAS/NF1-driven)

- **2\(^{nd}-3\(^{rd}\) Line Melanoma\(^5\)**
  (NRAS-driven)

- **2\(^{nd}-4\(^{th}\) Line NSCLC\(^6\)**
  (KRAS\(^{G12C}\)-driven)

- **2\(^{nd}-3\(^{rd}\) Line CRC\(^7\)**
  (BRAF-driven)

- **2\(^{nd}\) Line GIST**
  (KIT exon 11-driven)

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**Notes:**
CRC = colorectal cancer; 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; NRAS = neuroblastoma RAS viral oncogene homolog; NSCLC = non-small-cell lung cancer; PDAC = pancreatic ductal adenocarcinoma; RAF = rapidly accelerated fibrosarcoma serine/threonine protein kinase; RAF = RAF kinase; RP2D = recommended Phase 2 dose; (1) Corporate goal planned for 2H 2023; (2) Under the terms of the clinical trial collaboration and supply agreement with Pfizer, Inc., Deciphera will sponsor the trial and Pfizer will supply encorafenib at no cost; (3) with a documented mutation in KRAS; (4) with a documented mutation in KRAS, NRAS, NF1, or BRAF; (5) with a documented mutation in NRAS; (6) with a documented mutation in KRAS\(^{G12C}\); (7) with a documented mutation in BRAF\(^{V600E}\).
DCC-3009 (PAN-KIT INHIBITOR)

Bryan Smith, Ph.D.
Vice President, Biological Sciences

Notes: KIT proto-oncogene receptor tyrosine kinase.
DCC-3009 is a potential best-in-class pan-KIT inhibitor engineered using Deciphera’s proprietary switch-control platform.

Unmet medical need remains for a pan-KIT inhibitor that can broadly and potently inhibit the spectrum of KIT mutations that drive GIST.

Potent inhibitor of primary KIT mutations in exons 9 and 11 and secondary mutations across exons 13, 14, 17, and 18.

Highly selective for KIT with optimized pharmaceutical and ADME properties.

Strong pre-clinical efficacy data in xenograft models driven by drug resistant KIT mutations.

Notes: ADME=absorption, distribution, metabolism, and excretion; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase.
GIST PROGRESSION DRIVEN BY SECONDARY RESISTANCE MUTATIONS IN KIT

**DCC-3009 | OVERVIEW**

KIT-DRIVEN MUTATIONS

Primary Mutations
Driving Tumor Development

Resistance Mutations
Enabling Treatment Escape

Exon 9
*In 10% of Patients*

Exon 11
*In 70% of Patients*

Exon 13/14
ATP Binding Pocket

Exon 17/18
Activation Loop

NOTES: ATP=Adenosine Triphosphate; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase; (1) Oppelt et al. J Gastrointest Oncol 2017;8(3):466-473.
DCC-3009 POTENTLY INHIBITS THE SPECTRUM OF KNOWN PRIMARY AND SECONDARY DRUG-RESISTANT MUTATIONS IN GIST

Notes: GIST=gastrointestinal stromal tumor; GIST-T1=exon 11 del; (1) exon 9 primary is A502/Y503 duplication; (2) exon 11 primary mutations include deletions or the Y560D point mutation.
### DCC-3009 PRECLINICAL DATA

DCC-3009 SHOWED OPTIMIZED PHARMACEUTICAL AND ADME PROPERTIES FOR ORAL ADMINISTRATION

<table>
<thead>
<tr>
<th>Property</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Microsomal Stability</td>
<td>$t_{1/2} &gt; 145$ min</td>
</tr>
<tr>
<td>Human Plasma Protein Binding</td>
<td>96.3% bound</td>
</tr>
<tr>
<td>Caco2 Permeability</td>
<td>$11 \times 10^{-6}$ cm/s</td>
</tr>
<tr>
<td>Caco2 Efflux Ratio</td>
<td>7.8</td>
</tr>
<tr>
<td>CYP Inhibition (3A4, 2D6, 2C9, 2C19, 1A2)</td>
<td>$IC_{50} &gt; 10$ µM</td>
</tr>
<tr>
<td>CYP3A4 time-dependent Inhibition</td>
<td>Negative</td>
</tr>
<tr>
<td>hERG inhibition</td>
<td>$IC_{50} &gt; 20$ µM</td>
</tr>
<tr>
<td>Ames test (3 strains)</td>
<td>Negative</td>
</tr>
<tr>
<td>Rat oral bioavailability</td>
<td>87%</td>
</tr>
<tr>
<td>Dog oral bioavailability</td>
<td>100%</td>
</tr>
<tr>
<td>Rat brain penetration $K_{pu/u}$</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Notes:** Data presented at the AACR Annual Meeting 2023; CYP=cytochrome P450; hERG=human ether-a-go-go-related gene; $K_{pu/u}$=unbound partition coefficient (free brain concentration/free plasma concentration); $T_{1/2}$=half-life.
DCC-3009 exhibits a favorable kinome selectivity profile.

Notes: Evaluation in a ~400 kinase panel — all IC50 values < 1 µM are shown.
DCC-3009 RESULTED IN TUMOR REGRESSIONS IN GIST XENOGRAFT MODELS, INCLUDING KIT EXONS 9, 11, 13 AND 17 MUTATIONS

**V654A:** BaF3 KIT Exon 9
AY dup / Exon 13

**V654A:** GIST PDX KIT
Exon 11 delWK / Exon 13

**Y823D:** GIST PDX KIT Exon 11
delWK / Exon 17

**Notes:** Data presented at the AACR Annual Meeting 2023; BID=twice daily; GIST=gastrointestinal stromal tumor; KIT=KIT proto-oncogene receptor tyrosine kinase; PDX=patient-derived xenograft.
DCC-3009 is a pan-KIT inhibitor exhibiting high potency for KIT mutants in pre-clinical models spanning exons 9, 11, 13, 14, 17, and 18.


DCC-3009 is highly selective for KIT and has a high free fraction to enable exposures above levels needed to suppress the broad spectrum of KIT mutations in GIST.

DCC-3009 has optimized pharmaceutical and ADME properties for oral administration.

**DCC-3009 IND expected in 1H 2024**

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**Notes:** Data presented at the AACR Annual Meeting 2023; ADME=absorption, distribution, metabolism, and excretion; GIST=gastrointestinal stromal tumor; IND=Investigational New Drug Application; KIT=KIT proto-oncogene receptor tyrosine kinase.
DP-9149 (GCN2 ACTIVATOR)

Gada Al-Ani, Ph.D.
Sr. Principal Investigator, Biological Sciences

Notes: GCN2=general control nonrepressible 2.
DP-9149 IS A POTENT AND SELECTIVE ACTIVATOR OF THE GCN2 KINASE

Compelling Preclinical Data
- Potent and selective activator of GCN2 kinase
- Strong single agent activity in solid tumor models \textit{in vivo}
- Tumor regressions in combination with standard of care agents \textit{in vivo}

Novel Mechanism of Action
- Leveraging the cytotoxic arm of the Integrated Stress Response pathway enables the engagement of cancer cell death pathways
- GCN2 overexpression in solid tumors provides a favorable therapeutic window as evident by tolerability in preclinical models
- Synergizes with other stress-inducing therapies (anti-angiogenics/tumor driver-targeting agents) and effective in RAS/MAPK driven cancers

Notes: GCN2=general control nonderepressible 2; MAPK=mitogen-activated protein kinase; RAS=rat sarcoma gene.
The Integrated Stress Response (ISR) is a major adaptive stress response pathway in cancer and plays an important role in cell fate determination.

Oncogene addicted solid tumors are under high stress levels and are dependent on a well-balanced ISR pathway for accelerated growth.

Inhibition or stimulation of GCN2 in solid tumors can be pharmacologically leveraged to induce anti-tumoral effects.

Deciphera’s GCN2 activator (DP-9149) has shown anti-tumoral effects in solid tumors in vitro and in vivo.
Binding of GCN2 activator to only one monomer *selectively and potently transactivates* the unbound GCN2 protomer

Robust upregulation of ISR genes: ATF4 upregulation, expression of CHOP, and apoptotic signals

Persistent activation of the cytotoxic arm of the ISR leading to unresolved stress and *cancer cell death*

Notes: ATF4=activating transcription factor 4; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response.
GCN2 KINASE ACTIVATOR | OVERVIEW

GCN2 ACTIVATOR INDUCES CELL DEATH AS A SINGLE AGENT AND PROMOTES TUMOR REGRESSION IN COMBINATION

Single Agent Activity
Oncogene-driven cancer cells are vulnerable to activation of cytotoxic arm of the ISR

Combination Opportunities
Therapy induced cytotoxicity (e.g. anti-angiogenics, MAPKi) further sensitizes cancer cells to ISR pathway activation

Notes: ATF4=activating transcription factor; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; MAPKi=mitogen-activated protein kinase inhibitor.
DP-9149 SELECTIVELY AND POTENTLY ACTIVATES GCN2 AND HAS AN OPTIMIZED PHARMACEUTICAL AND SELECTIVITY PROFILE

DP-9149 Upregulates the ISR Pathway and Potently Inhibits Cell Growth as a Single Agent

786-O: Renal Cell Carcinoma ATF4 Upregulation

LoVo: KRAS G13D Colorectal ATF4 Upregulation

786-O: Renal Cell Carcinoma Spheroid Growth Inhibition

LoVo: KRAS G13D Colorectal Spheroid Growth Inhibition

Notes: Data presented at the AACR Annual Meeting 2023; ATF4=activating transcription factor; DMSO=dimethyl sulfoxide; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; KRAS=Kirsten rat sarcoma virus; PD=pharmacodynamic; PK=pharmacokinetic; VHL=Von Hippel-Lindau.
DP-9149 RESULTS IN TUMOR GROWTH INHIBITION AS A SINGLE AGENT AND TUMOR REGRESSIONS IN COMBINATION IN VIVO

**HT-1080: NRAS Fibrosarcoma Model**  
DP-9149 + Cobimetinib

**LoVo: KRAS G13D CRC Model**  
DP-9149 + Bevacizumab

**786-O: VHL Mutant RCC Model**  
DP-9149 + Axitinib

*Notes: Data presented at the AACR Annual Meeting 2023; HT-1080 TGI was calculated on Day 6; LoVo TGI was calculated on Day 21; 786-O TGI was calculated on Day 19; BID=twice daily; CRC=colorectal cancer; GCN2=general control nonderepressible 2; QD=once a day; TIW=3 times a week.*
The Integrated Stress Response is a novel Adaptive Stress Response mechanism in oncogene addicted solid tumors targetable through activation of GCN2.

DP-9149 was designed as a potent and selective activator of GCN2 with an optimized pharmaceutical and selectivity profile.

DP-9149 Exhibited Robust Activity in RAS mutant cancers and in VHL-mutant renal cell cancers as a single agent and in combination with standard-of-care agents *in vivo*.

Upregulating the ISR by activation of GCN2 through DP-9149 represents a novel anti-tumor approach in solid tumors *in vitro* and *in vivo* both as a single agent and in combination.

**DP-9149 is currently undergoing further preclinical studies**

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Notes: Data presented at the AACR Annual Meeting 2023; GCN2=general control nonderepressible 2; ISR=Integrated Stress Response; RAS=rat sarcoma gene; VHL=Von Hippel-Lindau.
CLOSING REMARKS

Steve Hoerter
President and Chief Executive Officer
DECIIPHERA
EXPECTED 2023 MILESTONES

QINLOCK
✓ Present additional data from Phase 3 INTRIGUE ctDNA analysis at an ASCO Plenary Session
  ■ Initiate INSIGHT Phase 3 study in 2L KIT exon 11+17/18 GIST patients (2H 2023)
  ■ Continue geographic expansion with launches in key European markets (2023)

VIMSELTINIB
✓ Complete enrollment in the Phase 3 MOTION study
  ■ Announce top-line results from MOTION study (4Q 2023)
  ■ Present updated Phase 1/2 data in TGCT patients (2H 2023)

DCC-3116
✓ Present preclinical data on new combinations
  ■ Present updated Phase 1 single agent and initial combination dose escalation data (2H 2023)
  ■ Initiate MEK/G12C expansion cohort(s); initiate escalation cohort for encorafenib/cetuximab (2H 2023)

DCC-3084
✓ Present data on preclinical profile
  ■ Submit IND to FDA (2H 2023)

PROPRIETARY DRUG DISCOVERY PLATFORM
✓ Nominate development candidate for pan-KIT inhibitor (DCC-3009 pan-KIT inhibitor)
✓ Present new preclinical data from research programs

Notes: 2L=second-line; ASCO=American Society of Clinical Oncology; ctDNA=circulating tumor deoxyribonucleic acid; FDA=U.S. Food and Drug Administration; G12C=single point mutation with a glycine-to-cysteine substitution at codon 12; GIST=gastrointestinal stromal tumor; IND=Investigational New Drug Application; KIT=KIT proto-oncogene receptor tyrosine kinase; MEK=mitogen-activated extracellular signal-regulated kinase; TGCT=tenosynovial giant cell tumor.
THANK YOU