BDTX-1535, a CNS penetrant MasterKey inhibitor of common, uncommon and resistant EGFR mutations, demonstrates in vivo efficacy and has potential to treat patients with NSCLC harboring osimertinib-resistant mutations with or without brain metastases.

Matthew C Lucas, Melinda Merchant, Matthew O’Connor, Carl Cook, Sherri Smith, Anthony Trombino, Wu-Yan Zhang, Irache Visiers, Christopher Roberts, Rachel Humphrey, Kate Tith, Reza Foroughi, Nigel Waters, Iwona Wrona, Michael Pickard, Sudharshan Eathiraj, Karsten Witt, Elizabeth Buck

Black Diamond Therapeutics, Cambridge, USA
Expanding the Reach of Precision Medicine Through the Development of Novel MasterKey Therapies

Addressing significant unmet need for novel precision oncology therapies for patients with genetically defined cancers with limited treatment options

Uniquely de-orphaning oncogenic mutations to develop single therapies designed to inhibit specific mutation families

Our proprietary computational Mutation Allostery Pharmacology (MAP) drug discovery engine is designed to:

- Analyze population-level genetic sequencing data to identify oncogenic mutations that promote cancer across tumor types
- Aggregate these mutations into families
- Develop a spectrum-selective (MasterKey) small molecule therapy

Robust pipeline of oral, potent and selective small molecule kinase inhibitors across a range of indications and target groups including EGFR, HER2, BRAF and FGFR
Targeting Unmet Medical Need in EGFR-mutated NSCLC

Acquired Resistance to 3rd generation EGFR TKIs

- EGFR Mutations Resistant to First line Osimertinib

Leonetti et al., Br J Cancer 2019

Intrinsic Resistance to EGFR TKIs

- Rare
- Exon 19 Deletion
- Other Deletion Mutations
- Other Frame Shift Mutations
- Complex

Harrison et al., Semin Cancer Biol. 2020

Brain Metastasis Occurrence with NSCLC

- EGFR-mutant (N=200)
  - 31% Never
  - 16% At diagnosis
  - 53% On treatment

Offin et al., Cancer 2019

BDTX-1535

EGFR Mutant with NSCLC
BDTX-1535: A Brain Penetrant, Potent Inhibitor of Oncogenic EGFR Mutations

- **Potent EGFR Inhibitor**
  - Designed to inhibit broad spectrum of oncogenic EGFR mutations

- **Selectivity Over WT-EGFR**
  - Designed with balanced selectivity versus EGFR-WT to deliver efficacy coupled with favorable safety profile

- **Brain Penetration**
  - Designed to be brain penetrant to ensure adequate free drug exposure in CNS
Optimized to Address a Wide Range of Oncogenic EGFR Mutations and Variants

**EGFR Variants and Mutations Found in GBM**

- WT-EGFR
- EGFR variants
- EGFR point mutations

**EGFR Mutations of Intrinsic Resistance and Acquired Resistance in NSCLC**

- WT-EGFR
- Non-Canonical EGFR KD mutations
- Canonical EGFR mutations

**Anti-proliferation Ba/F3 IC50 (nM)**

- >10-fold selectivity vs WT-EGFR

**Expanding**

AACR-NCI-EORTC VIRTUAL INTERNATIONAL CONFERENCE ON MOLECULAR TARGETS AND CANCER THERAPEUTICS
BDTX-1535 Is a CNS-penetrant Inhibitor of Canonical and Drug-Resistance Mutations

<table>
<thead>
<tr>
<th>MOA</th>
<th>Erlotinib</th>
<th>Gefitinib</th>
<th>Afatinib</th>
<th>Dacomitinib</th>
<th>Osimertinib</th>
<th>BDTX-1535</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS Kpuu (r)</td>
<td>Reversible</td>
<td>Reversible</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td></td>
<td>0.08</td>
<td>0.29</td>
<td>*</td>
<td>0.21</td>
<td>0.29</td>
<td>0.45</td>
</tr>
<tr>
<td>EGFR-WT (H292) IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>878</td>
<td>418</td>
<td>29</td>
<td>28</td>
<td>454</td>
<td>119</td>
</tr>
<tr>
<td>EGFR Ex19del (Ba/F3) IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>19</td>
<td>10</td>
<td>0.5</td>
<td>0.3</td>
<td>2.5</td>
<td>0.6</td>
</tr>
<tr>
<td>EGFR Ex19del/C797S (Ba/F3) IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>9</td>
<td>&gt;1000</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Selectivity over WT H292 (fold)

<table>
<thead>
<tr>
<th></th>
<th>Selectivity over WT H292 (fold)</th>
<th>CNS exposure (average Kpuu, m/r)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;10x</td>
<td>&gt;0.3</td>
</tr>
<tr>
<td></td>
<td>5-10x</td>
<td>0.3-0.1</td>
</tr>
<tr>
<td></td>
<td>&lt;5x</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

*Rat Kpuu not measured, but mouse Kpuu = 0.03
BDTX-1535 Achieves Excellent Kinome Selectivity and Drug Like Properties

- Not a hERG inhibitor at projected clinical concentrations
- Good blood & moderate liver stability
- Good GSH T\(_{1/2}\)
- Low Risk for CYP Inhibition with no TDI
- No CYP induction
- No unique human metabolites
- Weak Pgp substrate

*DiscoverX Kinome Panel of 468 kinases, at test concentration of 100 nM; Kd for EGFR and DDR1 0.17 and 3.8 nM, respectively
Preclinical Data Supports Opportunity in NSCLC Harboring Osimertinib Resistant C797S

Retains irreversible binding against C797S mutant

%Inhibition of pEGFR (C797S)

34nM BDTX-1535
1000nM Osimertinib

Washout

>24h inhibition of pEGFR Ex19del/C797S

Regression in Ba/F3-EGFR Exon19del/C797S Mouse allograft

Regression across range of allograft and EGFRvII and C595F PDX models

Dose dependent TGI in without loss of body weight

% change from baseline capped at 100%; Vehicle control and osimertinib from EGFR Ex19del/C797S study
CNS Exposure, Sustained Target Engagement and TGI in Intracranial PDX Tumors

Exposure in Rat Blood, Brain, CSF after single oral dose of 30 mg/kg

>24h Inhibition of pEGFR in Ba/F3 Allograft Tumors expressing EGFRvIII

Survival increase in Intracranial EGFRvIII PDX Tumors

- **Exposure in Rat Blood, Brain, CSF**
  - Time (h): 1.0, 2.0, 4.0, 8.0
  - Concentration (ng/mL or ng/g)

- **Single oral dosing of BDTX-1535** (50 mg/kg) in mice

- **Oral dosing of BDTX-1535** (50 mg/kg) daily in mice
  - GBM6 model expressing EGFRvIII/amplified EGFR WT conducted at UCSF Brain Tumor Center

- **Kpuu = 0.45**
Conclusions

Black Diamond Therapeutics is Developing BDTX-1535 as a Brain Penetrant, Potent Inhibitor of Oncogenic EGFR Mutations

- Excellent free drug exposure in the CNS
- Highly efficacious in intracranial PDX tumor model with an intact BBB and across a range of allograft and PDX models
- Potential to treat patients with NSCLC harboring osimertinib-resistant C797S mutation with or without brain metastases