BDTX-1535 – A MasterKey EGFR Inhibitor Targeting Classical, Non-Classical and the C797S Resistance Mutation to Address the Evolved Landscape of EGFR Mutant NSCLC

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Etienne Dardenne

*I have the following financial relationships to disclose:*

- Stockholder in: Black Diamond Therapeutics
- Employee of: Black Diamond Therapeutics

*I will not discuss off-label use and/or investigational use in my presentation.*
Small molecules directed against oncogenic EGFR mutations expressed in NSCLC is a 20-year success story.

The EGFR mutational landscape in NSCLC continues to evolve – today we present real world data that reveals new mutations and treatment opportunities.

BDTX-1535: potentially first- and best-in-class fourth-generation EGFR inhibitor designed to address the evolved mutational landscape; previously disclosed pre-clinical and clinical data for BDTX-1535 is put into context.

BDTX-1535: Phase 1 clinical proof-of-concept achieved, Phase 2 trial in progress across 1L, 2L, and 3L NSCLC patients.
Real World Data Describe a Broad EGFR Mutational Landscape in NSCLC & Reveal New Opportunities for EGFR Targeting

**2004**

Two classical EGFR oncogenic mutations first described\(^1\)

\[ L858R \; & \; \text{Ex19del} \; (\text{classical}) \]

**Today**

Real World Data reveals a broad landscape of classical & non-classical EGFR oncogenic mutations in NSCLC

Black Diamond examined 235,761 sequenced NSCLC cases

- >100 EGFR mutations (classical & non-classical*)
- Distinct co-mutational profiles for L858R vs Ex19del
- Resistance mutations evolve with TKI therapies

\*non-classical EGFR mutations also referred to as: atypical, second-site, uncommon, intrinsic, or PACC mutations

1. Paez et al. Science 2004
20-30% of Newly Diagnosed EGFRm NSCLC Patients Carry Non-Classical Mutations; Are Not Adequately Addressed by Current Therapies

Classical and non-classical driver mutations are distributed across EGFR structure

- **Ectodomain-Juxtamembrane (non-classical)**
  - 50+ mutations
  - R108X
  - R222X
  - A289X
  - C598X
  - S645X
  - ...

- **PACC1 & others (non-classical)**
  - 60+ mutations
  - E709X
  - G719X
  - T725M
  - L754E
  - L747X
  - S768I
  - V769X
  - L861X
  - L833X
  - ...

22-30% of newly diagnosed EGFRm NSCLC express non-classical mutations

- **GUARDAN**
  - Black Diamond Therapeutics analyses of 94,939 sequencing reports from treatment naïve NSCLC
  - Adapted from Du et al. 2023. Analysis of the AACR GENIE database of 22,050 cases of NSCLC

- **INFORM**
  - Current therapies do not adequately address non-classical EGFR mutations

1. Borgeaud M. JTO 2024
C797S and Non-Classical Mutations are Major Mechanisms of Acquired On-Target EGFR Resistance

On-target EGFR resistance mechanisms have shifted since approval of 3G TKI osimertinib in 1L setting

- Decreasing T790M
- Increasing C797S

Black Diamond Therapeutics analyses of Foundation Medicine’s FoundationInsights™ platform

C797S & non-classical mutations are major mechanisms of on-target EGFR resistance in patients post-osimertinib

*either more than 1 non-classical mutation, or non-classical + C797

Real-World Genomic Profile of EGFR Second-Site Mutations and Other Osimertinib Resistance Mechanisms and Clinical Landscape of NSCLC Post-Osimertinib

Julia K. Rotow, MD, Jessica K. Lee, MS, Russell W. Nadim, MS, Geoffrey R. Demard, MD, Pati A. Jaine, MD, PhD, Alexa B. Schrock, PhD

1. Adapted from Rotow, JK, et al., Journal of Thoracic Oncology, 2023. (non-classicals represented as L792, G796, G724, L718).
BDTX-1535 Potently Targets Non-Classical EGFR Mutations Commonly Co-Expressed with L858R Which are Insensitive to Osimertinib

EGFR-L858R tumors more frequently co-express non-classical EGFR mutations before exposure to EGFR TKI

Patients with L858R do less well on osimertinib therapy vs Ex19del

Non-classical mutations co-expressed with L858R are insensitive to osimertinib but sensitive to BDTX-1535

Black Diamond Therapeutics analyses of 94,939 sequencing reports from treatment naïve NSCLC (Guardant Health)

Gijtenbeek et al 2023. Overall survival by type of mutation in patients with stage IV EGFR mutated NSCLC and brain metastasis who received first-line treatment with osimertinib

EGFR mutation frequently associated with L858R

Pre-clinical data; EGFR mutations are engineered in Ba/F3 cells
BDTX-1535: A MasterKey EGFR Inhibitor Achieving Potent Inhibition of *EGFR Classical* (Ex19del and L858R) & *Non-Classical* Mutations while Sparing EGFR-WT

- Potent cellular IC\textsubscript{50} across all non-classical subtypes, complex mutations, and C797S resistance
- ≤10nM potency across >90% of validated oncogenic mutations and complex mutations
- Selective over wild type EGFR

Pre-clinical data IC50 potency data generated in collaboration with Heymach Lab, MD Anderson Cancer Center

EGFR-WT: H292 Cell line. All other EGFR mutations are engineered in Ba/F3 cells
BDTX-1535: A MasterKey EGFR Inhibitor Achieving Potent Inhibition of EGFR *Classical* (Ex19del and L858R) & *Non-Classical* Mutations while Sparing EGFR-WT

Activity against mutations acquired following progression on 3G EGFR TKIs (osimertinib / furmonertinib / lazertinib)
BDTX-1535 Achieves Coverage of the EGFR Mutation Spectrum at the Well-Tolerated Oral Doses of 100-200mg QD

*PK data from Phase 1 dose escalation trial*

*Cmax at 100mg and 200mg QD doses plotted for human PK. PK data adapted from poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023*
BDTX-1535 Drives Clearance of Mutant EGFR VAF and ctDNA in Phase 1 Trial

Clearance of plasma ctDNA (9/9 patients)

Clearance classical mutations (7/7 patients)

Clearance of C797S (6/6 patients)

Clearance of non-classical mutations (4/4 patients)

Data adapted from poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023. Select patients expressed more than one mutation and are represented on multiple plots.
BDTX-1535 Achieves Radiographical Responses in Efficacy-Evaluable NSCLC Patients Across Relevant Mutations in Phase 1 Trial

**Best overall response**

<table>
<thead>
<tr>
<th>On treatment</th>
<th>20</th>
<th>0</th>
<th>-20</th>
<th>-40</th>
<th>-60</th>
<th>-80</th>
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<tbody>
<tr>
<td>PD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
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<tr>
<td>PR</td>
<td>PR**</td>
<td>uPR*</td>
<td>PR</td>
<td>PR</td>
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**Assigned dose level, mg QD**

<table>
<thead>
<tr>
<th>300</th>
<th>400</th>
<th>200</th>
<th>200</th>
<th>200</th>
<th>200</th>
<th>400</th>
<th>400</th>
<th>300</th>
<th>200</th>
<th>200</th>
<th>300</th>
<th>100</th>
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</thead>
<tbody>
<tr>
<td>EGFR mutation (retrospective central testing)</td>
<td>Classical</td>
<td>L858R</td>
<td>Ex19del</td>
<td>L858R#</td>
<td>Ex19del</td>
<td>Ex19del</td>
<td>Ex19del</td>
<td>Ex19del</td>
<td>L858R</td>
<td>L858R</td>
<td>L858R</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-classical</td>
<td>L833V</td>
<td>G719A</td>
<td>E709V#</td>
<td>G724S</td>
<td>S768I</td>
<td>E709V</td>
<td>L747P</td>
<td>L718Q</td>
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</tr>
<tr>
<td></td>
<td>Acquired</td>
<td>C797S</td>
<td>C797S</td>
<td>C797S</td>
<td>C797S</td>
<td>C797S</td>
<td>C797S</td>
<td>C797S</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Prior lines of therapy</td>
<td>1st line</td>
<td>Osi</td>
<td>Osi</td>
<td>Gefi</td>
<td>Osi</td>
<td>Osi</td>
<td>Erlo</td>
<td>CPI</td>
<td>Osi</td>
<td>Osi</td>
<td>Osi</td>
<td>Osi</td>
</tr>
<tr>
<td></td>
<td>2nd line</td>
<td>Daco, Osi</td>
<td>C</td>
<td>CPI, C</td>
<td>C</td>
<td>Osi</td>
<td>Osi+Gefi</td>
<td>C</td>
<td>CPI/C</td>
<td>Osi</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>&gt;2 line</td>
<td>CPI, C</td>
<td>Afa</td>
<td></td>
<td></td>
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<td></td>
<td>C</td>
<td>BLU-701</td>
<td>C</td>
<td>C</td>
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</tr>
</tbody>
</table>

**Efficacy-Evaluable Patients**

5 cPR, 1 uPR of 13 by RECIST
5 cPR, 1 uPR of 11 by RECIST post osimertinib

Osi = Osimertinib; Afa = Afatinib; Gefi = Gefitinib; Daco = Dacomitinib; Erlo = Erlotinib; CPI = Checkpoint inhibitor, C = Chemotherapy; # - mutations were absent on confirmatory test; * uPR=unconfirmed partial response-patient had a PR on a post baseline scan, but a radiologist was unable to confirm a response on a subsequent scan; this patient remains on study treatment without evidence of PD. **%SoD was updated to -50% from prior data release

BDTX-1535-101 clinical data extract

Data adapted from Poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023
BDTX-1535 Achieves Radiographical Responses in Efficacy-Evaluable NSCLC Patients Across Relevant Mutations in Phase 1 Trial

Best overall response

On treatment

PR = Partial response
SD = Stable disease
PD = Progressive disease

Best % SoD change

Assigned dose level, mg QD

EGFR mutation (retrospective central testing)

Classical

Non-classical

Acquired

Prior lines of therapy

1st line

2nd line

>2 line

Pre-clinical data; EGFR mutations are engineered in Ba/F3 cells

BDTX-1535: potent inhibition of non-classical mutations that are insensitive to osimertinib
Evolution of the EGFR mutation landscape over the past 20 years

**BDTX-1535: Potential First- and Best-in-Class Therapy to Address Major Unmet Medical Needs in EGFRm NSCLC (Classical, Non-Classical, and C797S Resistance Mutation)**

**Evolution of the EGFR mutation landscape over the past 20 years**

- **2005**: Classical EGFR mutations described
- **2013**: L858R / Ex19del
- **2015**: Non-classical drivers
- **2018**: Classical drivers
- **2024**: C797S resistance
- **2024**: T790M resistance

**Treatments**
- **2005**: erlotinib (2/3L)
- **2013**: erlotinib (1L)
- **2015**: osimertinib (2L)
- **2018**: osimertinib (1L)
- **2024**: BDTX-1535 (1/2/3L)

**Sequencing practices**
- **Mutation specific sequencing**
- **NGS revolution** → **Realization of >100 EGFR non-classical driver mutations**

**BDTX-1535: opportunity to address all relevant mutations—critical for a 4th generation EFGR TKI**
BDTX-1535: Currently in Phase 2 Trial for 1L/2L/3L EGFRm NSCLC; Multiple Additional Opportunities

<table>
<thead>
<tr>
<th></th>
<th>Non-Classical</th>
<th>Classical (L858R)</th>
<th>Classical (Ex19del)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2/3L</strong></td>
<td>Ongoing P2</td>
<td>Ongoing P2 C797S</td>
<td>Ongoing P2 C797S</td>
</tr>
<tr>
<td><strong>1L</strong></td>
<td>Ongoing P2</td>
<td><strong>Potential opportunity</strong></td>
<td><strong>Potential opportunity</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(patients co-expressing non-classical or following adjuvant osimertinib)</td>
<td>(following adjuvant osimertinib)</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td><strong>Potential opportunity</strong></td>
<td><strong>Potential opportunity</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(patients co-expressing non-classical)</td>
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</tr>
</tbody>
</table>

We thank the patients and investigators who are participating in our clinical trials