BLU-285: A potent and highly selective inhibitor designed to target malignancies driven by KIT and PDGFRα mutations

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New Drugs on the Horizon
2017 AACR Annual Meeting
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Disclosures

- Employee and shareholder of Blueprint Medicines
- BLU-285 is an investigational agent currently in development by Blueprint Medicines
Activating mutations in KIT and PDGFRα are disease drivers

**KIT and PDGFRα**

- Highly-related class III receptor tyrosine kinases
- Kinase activity normally requires ligand-induced dimerization
- PDGFRα activity: organogenesis, angiogenesis, vascular integrity
- KIT activity: hematopoiesis, melanocytes, germ cells

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGFRα Fusion</td>
<td>MDS, MPN, Eosinophilic leukemia</td>
</tr>
<tr>
<td>PDGFRα Exon 12</td>
<td>GIST</td>
</tr>
<tr>
<td>PDGFRα Exon 18</td>
<td>GIST</td>
</tr>
<tr>
<td>KIT Exon 9</td>
<td>GIST</td>
</tr>
<tr>
<td>KIT Exon 11</td>
<td>GIST, Melanoma</td>
</tr>
<tr>
<td>KIT Exon 13</td>
<td>GIST, Melanoma</td>
</tr>
<tr>
<td></td>
<td>imatinib-resistant GIST</td>
</tr>
<tr>
<td>KIT Exon 17</td>
<td>Systemic Mastocytosis</td>
</tr>
<tr>
<td></td>
<td>Acute Myeloid Leukemia</td>
</tr>
<tr>
<td></td>
<td>Germ Cell Tumors</td>
</tr>
<tr>
<td></td>
<td>imatinib/sunitinib-resistant GIST</td>
</tr>
</tbody>
</table>

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)
KIT activation loop mutations abrogate type II inhibitor binding

*Imatinib binds inactive conformation of KIT/PDGFRα*

Inactive conformation
- Activation loop closed, DFG-out
- Type II inhibitors active

Active conformation
- Activation loop open, DFG-in
- Type II inhibitors inactive
Annotated library highlights type 1 inhibitor activity on KIT exon 17 and exon 11 activating mutations

**UNIQUE KINASE-DIRECTED COMPOUND LIBRARY**

- Designed to balance novelty, potency, selectivity
- Broad and deep kinome coverage
- High quality, differentiated medicinal chemistry starting points fully annotated across human kinome
BLU-285 is a potent type 1 KIT/PDGFRα inhibitor that binds to the active conformation of the kinase.

Imatinib
Activation loop open

BLU-285
Activation loop open
BLU-285 is a potent, highly selective inhibitor of KIT and PDGFRα activation loop mutants

<table>
<thead>
<tr>
<th>Compound</th>
<th>PDGFRα D842V IC_{50} nM</th>
<th>KIT D816V IC_{50} nM</th>
<th>KIT V560G/D816V IC_{50} nM</th>
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<tbody>
<tr>
<td>BLU-285</td>
<td>0.24</td>
<td>0.27</td>
<td>0.10</td>
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<tr>
<td>imatinib</td>
<td>759</td>
<td>8150</td>
<td>6145</td>
</tr>
<tr>
<td>sunitinib</td>
<td>120</td>
<td>207</td>
<td>97.2</td>
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<tr>
<td>regorafenib</td>
<td>810</td>
<td>3640</td>
<td>1685</td>
</tr>
<tr>
<td>midostaurin</td>
<td>4.9</td>
<td>2.8</td>
<td>1.4</td>
</tr>
<tr>
<td>crenolanib</td>
<td>0.2</td>
<td>1.5</td>
<td>1.2</td>
</tr>
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</table>

Exon 17

<table>
<thead>
<tr>
<th>Compound</th>
<th>Exon 17/18 Activation loop</th>
<th>JM domain/activation loop</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLU-285</td>
<td></td>
<td></td>
</tr>
<tr>
<td>imatinib</td>
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<td>crenolanib</td>
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</tr>
</tbody>
</table>

Type II inhibitors

Non-selective Type I inhibitors

Kinome screening at 3 µM
BLU-285 potently inhibits a broad spectrum of disease relevant KIT mutants.
BLU-285 inhibits a broad spectrum of disease relevant KIT mutants more potently than imatinib
BLU-285 biochemical activity is recapitulated in cells

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>KIT mutation</th>
<th>Exon</th>
<th>Tissue</th>
<th>BLU-285</th>
<th>Imatinib</th>
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</thead>
<tbody>
<tr>
<td>M-07e</td>
<td>Wild type</td>
<td>-</td>
<td>human megakaryoblastic leukemia</td>
<td>192</td>
<td>336</td>
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<tr>
<td>HMC1.1</td>
<td>V560G</td>
<td>11</td>
<td>human mast cell leukemia</td>
<td>100</td>
<td>31</td>
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<tr>
<td>Kasumi</td>
<td>N822K</td>
<td>17</td>
<td>human acute myeloid leukemia</td>
<td>40</td>
<td>126</td>
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<td>P815</td>
<td>D816Y</td>
<td>17</td>
<td>murine mastocytoma</td>
<td>22</td>
<td>1235.6</td>
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<tr>
<td>HMC1.2</td>
<td>V560G/D816V</td>
<td>11/17</td>
<td>human mast cell leukemia</td>
<td>4</td>
<td>9143.5</td>
</tr>
<tr>
<td>CHO</td>
<td>PDGFRα D842V</td>
<td>18</td>
<td>engineered</td>
<td>30</td>
<td>3145</td>
</tr>
</tbody>
</table>

**HMC1.2**
KIT V560G/D816V

**M-07e**
Wild-type KIT

**P-KIT inhibition**

<table>
<thead>
<tr>
<th>IC50 (nM)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>300</td>
</tr>
<tr>
<td>1000</td>
</tr>
</tbody>
</table>

**nM**

| 0         |
| 1         |
| 3         |
| 10        |
| 30        |
| 100       |
| 300       |
| 1000      |
BLU-285 is active in a primary activation loop mutant in vivo model

**Tumor Growth**

- **Vehicle QD**
- **BLU-285 0.3 mg/kg QD**
- **BLU-285 1 mg/kg QD**
- **BLU-285 3 mg/kg QD**
- **BLU-285 10 mg/kg QD**
- **BLU-285 30 mg/kg QD**

**PK-PD**

**Plasma Concentration**

**% Phospho-KIT**

**Concentration (ng/ml)**

**BLU-285**

KIT Exon 17-driven P815 mastocytoma allograft:

- Mutation in KIT exon 17 equivalent to human **KIT D816Y**
- Tumor regression observed with 10 and 30 mg/kg BLU-285 once daily, oral dosing
- BLU-285 well tolerated at all doses
BLU-285 is active in imatinib-resistant GIST PDX models

**KIT Exon 11/17 mutant (del556-558/Y823D) GIST PDX:**
- Tumor regression observed with 10 and 30 mg/kg BLU-285

**KIT Exon 11/13 mutant (V559D/V654A) GIST PDX:**
- Tumor regression observed with 30 mg/kg BLU-285
BLU-285 is active in a primary exon 11 mutant GIST PDX model

KIT Exon 11 mutant (del557-559insF) GIST PDX:
- Tumor regression observed with 30 mg/kg BLU-285, stasis with 10 mg/kg BLU-285 once daily, oral dosing
- BLU-285 active against primary KIT exon 11 mutants, suggests reemergence of primary clone is unlikely
- Collaboration with P. Schoffski, (KU Leuven) Abstract #687 Monday April 3, 1-5pm.
BLU-285 Achieves Rapid Clinical Proof of Concept in Diseases Driven by KIT/PDGFRα Mutants
Advanced systemic mastocytosis is a rare and severe disease that shortens life expectancy with a wide range of debilitating symptoms and organ damage.

- MC degranulation
- MC mediator Sx
- ↑tryptase
- Osteolytic bone lesions
- Cytopenias
- Liver function abnormalities, Ascites, or Hypersplenism
- Hypoalbuminemia
- Weight loss
- Urticaria pigmentosa

KIT D816V is a key driver in 90-95% of systemic mastocytosis.
Encouraging clinical activity in phase 1 AdvSM study

Objective decreases in mast cell burden and serum tryptase

Decreased bone marrow mast cells in 6 of 8 patients

Decreased serum tryptase in 10 of 12 patients

Data cut-off date: November 11, 2016
Drummond et al. 2016 ASH Annual Conference
Molecular response observed in blood and bone marrow of SM patients treated with BLU-285

Droplet digital PCR with allele specific primers measures KIT D816V allele burden in blood and BM aspirate.

Data cut-off date: November 11, 2016

Drummond et al. 2016 ASH Conference
Activating KIT or PDGFRα mutations drive metastatic GIST

Most common GI sarcoma

- Cancer of the interstitial cells of Cajal
- Chemotherapy has no impact

- Stomach 60%
- Duodenum 5%
- Small intestine 30%
- Colon and rectum 5%

KIT ~ 80%

- Primary mutational hotspots
  - KIT Exons 9 or 11
  - PDGFRα Exons 12 and 18 (D842V)

PDGFRα ~ 8%

- Resistance mutations
  - KIT Exons 13 and 17
  - PDGFRα Exon 18 (D842V)
65 year old female, Primary Gastric GIST, PDGFRα D842V
- Previous surgical de-bulking: stomach; peritoneal metastases x 2; colon
- Prior response to crenolanib followed by progression
- Progression on prior dasatinib (no response)
- Ongoing at Cycle 13 with confirmed partial response (-52% per RECIST1.1)
Strong clinical activity against PDGFRα D842-mutant GIST at all dose levels

- 14 out of 14 D842-mutant patients with tumor reductions
- ORR = 42%, DCR = 100%

Maximum reduction – sum of diameter change from Baseline (%)

Data cut-off date: November 1, 2016
Heinrich et al. 2016 EORTC-NCI-AACR Conference
Imatinib/sunitinib-resistant GIST are enriched for KIT exon 17 mutants

<table>
<thead>
<tr>
<th>KIT Exon 9</th>
<th>Exon 11</th>
<th>Exon 13</th>
<th>Exon 14</th>
<th>Exon 17</th>
<th>Exon 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>9%</td>
<td>67%</td>
<td>60-70%</td>
<td>20%</td>
<td>1%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Significant anti-tumor activity in TKI-resistant KIT-driven GIST at higher doses

The values above/below the bars denote the dose level (mg) QD received by each patient.

- 4 of 6 patients with tumor reduction
- 5 of 6 patients remain on treatment ≥ 5 cycles

Data cut-off date: November 1, 2016
Heinrich et al. 2016 EORTC-NCI-AACR Conference
BLU-285 demonstrates dose dependent human pharmacokinetics
PDX studies suggest clinical exposures in therapeutic range

- PDX data suggest active dose range for KIT mutant GIST at levels ≥ 135 mg
- Expansion cohorts for GIST phase 1 trial recently initiated with RP2D of 400 mg QD

*Exposures adjusted for free fraction
- KIT/PDGFRα activation loop mutants are unaddressed by approved therapies
- Insights from BPMC library catalyzed design of BLU-285, a potent, highly-selective type 1 inhibitor of KIT/PDGFRα activating mutants
- Potent activity of BLU-285 on KIT/PDGFR activation loop mutants has informed initial clinical development strategy resulting in early clinical proof of concept in several patient populations

In summary, mechanistic and structural understanding of disease-driving mutations paired with tailored inhibitors can accelerate drug development
Acknowledgements

- Thanks to all participating patients and their families
- Thanks to all study investigators, nurses and research coordinators
  - Abramson Cancer Center at the University of Pennsylvania
  - Dana-Farber Cancer Institute
  - Fox Chase Cancer Center
  - MD Anderson Cancer Center
  - Oregon Health & Science University
  - Stanford University
  - University of Colorado
  - University of Michigan Comprehensive Cancer Center
  - University of Utah, Huntsman Cancer Institute
  - Centre Leon Berard
  - Erasmus MC Cancer institute
  - Gartnavel General Hospital, Beatson West of Scotland Cancer Center
  - Guy's & St Thomas NHS Trust
  - Institut Gustave Roussy
  - Leuven Cancer Institute
  - Royal Marsden Hospital / Institute for Cancer Research
  - University of Essen
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- Thanks to all colleagues at Blueprint Medicines