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

Erica Evans Ph.D.
New Drugs on the Horizon
2017 AACR Annual Meeting
April 2, 2017
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

### Kinome Illustration

![Kinome Illustration](www.cellsignal.com)

<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>
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

Type I

- KIT WT
- KIT Exon 11 V559D
- KIT Exon 17 D816V

Type II

- imatinib
- regorafenib
- sunitinib

“Selectivity” pocket

Gatekeeper

To solvent

UNIQUE KINASE - DIRECTED
COMPOUND LIBRARY

Hinge
BLU-285 is a potent type 1 KIT/PDGFRα inhibitor that binds to the active conformation of the kinase.
BLU-285 is a potent, highly selective inhibitor of KIT and PDGFRα activation loop mutants

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activation loop</th>
<th>JM domain/activation loop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exon 18</td>
<td>Exon 17</td>
</tr>
<tr>
<td>PDGFRα D842V IC₅₀ nM</td>
<td>KIT D816V IC₅₀ nM</td>
<td>KIT V560G/D816V IC₅₀ nM</td>
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<tr>
<td>BLU-285</td>
<td>0.24</td>
<td>0.27</td>
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<tr>
<td>imatinib</td>
<td>759</td>
<td>8150</td>
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<tr>
<td>sunitinib</td>
<td>120</td>
<td>207</td>
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<td>regorafenib</td>
<td>810</td>
<td>3640</td>
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<tr>
<td>midostaurin</td>
<td>4.9</td>
<td>2.8</td>
</tr>
<tr>
<td>crenolanib</td>
<td>0.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Type II inhibitors

Non-selective Type I inhibitors

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)
BLU-285 potently inhibits a broad spectrum of disease relevant KIT mutants

ATP binding pocket
Exons 13 and 14

Activation Loop
Exons 17 and 18

JM Domain
Exon 11
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>
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<td>336</td>
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<tr>
<td>HMC1.1</td>
<td>V560G</td>
<td>11</td>
<td>human mast cell leukemia</td>
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<td>Kasumi</td>
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<td>P815</td>
<td>D816Y</td>
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<td>HMC1.2</td>
<td>V560G/D816V</td>
<td>11/17</td>
<td>human mast cell leukemia</td>
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<td>9143.5</td>
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<tr>
<td>CHO</td>
<td>PDGFRα D842V</td>
<td>18</td>
<td>engineered</td>
<td>30</td>
<td>3145</td>
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</table>

**HMC1.2**

<table>
<thead>
<tr>
<th>KIT V560G/D816V</th>
<th>P-KIT inhibition</th>
<th>IC₅₀ (nM)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>BLU-285</td>
<td>Imatinib</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>30</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>

**M-07e**

<table>
<thead>
<tr>
<th>Wild-type KIT</th>
<th>P-KIT inhibition</th>
<th>IC₅₀ (nM)</th>
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<tbody>
<tr>
<td></td>
<td>BLU-285</td>
<td>Imatinib</td>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
<td>3</td>
<td>10</td>
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<tr>
<td>3</td>
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<td>10</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>30</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>
BLU-285 is active in a primary activation loop mutant in vivo model

Tumor Growth

- 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

**Tumor Growth**
**Exon 11/17 mutant GIST PDX**

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

**Tumor Growth**
**Exon 11/13 mutant GIST PDX**

- **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
Kit D816V is a key driver in 90-95% of systemic mastocytosis

- Advanced systemic mastocytosis is a rare and severe disease that shortens life expectancy with a wide range of debilitating symptoms and organ damage.
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

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

KIT ~ 80%  PDGFRα ~ 8%

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

- 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%

Data cut-off date: November 1, 2016
Heinrich et al. 2016 EORTC-NCI-AACR Conference

The values above/below the bars denote the dose level (mg) QD received by each patient.
Imatinib/sunitinib-resistant GIST are enriched for KIT exon 17 mutants

<table>
<thead>
<tr>
<th>Exon</th>
<th>ORR (%)</th>
<th>PFS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>60-70%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>60-70%</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

1L imatinib → ORR ~60% PFS 19 mo
2L sunitinib → ORR ~7% PFS 6 mo
3L regorafenib → ORR ~5% PFS 4.8 mo
4L BSC or trial
Significant anti-tumor activity in TKI-resistant KIT-driven GIST at higher doses

BLU-285
30 – 90 mg

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

BLU-285
135 – 300 mg

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

Data cutoff date: November 1, 2016
Heinrich et al. 2016 EORTC-NCI-AACR Conference

The values above/below the bars denote the dose level (mg) QD received by each patient.
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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  - Patrick Schöffski (Leuven Cancer Institute)
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