Preliminary safety and activity in a first-in-human Phase 1 study of BLU-285, a potent, highly selective inhibitor of KIT and PDGFRα activation loop mutants in advanced gastrointestinal stromal tumor (GIST)

Michael Heinrich\textsuperscript{1}, Robin Jones\textsuperscript{2}, Patrick Schoffski\textsuperscript{3}, Sebastian Bauer\textsuperscript{4}, Margaret von Mehren\textsuperscript{5}, Ferry Eskens\textsuperscript{6}, Philippe Cassier\textsuperscript{7}, Olivier Mir\textsuperscript{8}, Hongliang Shi\textsuperscript{9}, Terri Alvarez-Diez\textsuperscript{9}, Mary Ellen Healy\textsuperscript{9}, Beni Wolf\textsuperscript{9}, Suzanne George\textsuperscript{10}

\textsuperscript{1}Oregon Health & Sciences University, Oregon, USA; \textsuperscript{2}Royal Marsden Hospital/Institute of Cancer Research, London, UK; \textsuperscript{3}Leuven Cancer Institute, Leuven, Belgium; \textsuperscript{4}University of Essen, Essen, Germany; \textsuperscript{5}Fox Chase Cancer Center, Pennsylvania, USA; \textsuperscript{6}Erasmus MC Cancer Institute, Rotterdam, Netherlands; \textsuperscript{7}Centre Leon Berard, Lyon, France; \textsuperscript{8}Institut Gustave Roussy, Paris, France; \textsuperscript{9}Blueprint Medicines Corporation, Massachusetts, USA; \textsuperscript{10}Dana-Farber Cancer Institute, Massachusetts, USA

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Disclosures

- BLU-285 is an investigational agent currently in development by Blueprint Medicines Corporation (Blueprint Medicines)

- Dr. Michael Heinrich is an investigator for Blueprint Medicines’ ongoing Phase 1 study in unresectable gastrointestinal stromal tumor

- Dr. Michael Heinrich has the following disclosures:
  - Consultant: Blueprint Medicines, Novartis, MolecularMD
  - Equity interest: MolecularMD
  - Research funding: Blueprint Medicines, Deciphera, Ariad
  - Expert testimony: Novartis
  - Patents: four patents on diagnosis and treatment of PDGFRα-mutant GIST
Gastrointestinal Stromal Tumor (GIST)

Most common GI sarcoma

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

- Cancer of the interstitial cells of Cajal
- Primary tumor usually presents as a stomach or intestinal mass
- Metastatic recurrences spread to liver, peritoneum, and other distant sites
- Chemotherapy has no impact

Activating RTK mutations drive metastatic GIST

- KIT ~ 80%
- PDGFRα ~ 8%

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

- Resistance mutations
  - KIT Exons 13 and 17
  - PDGFRα D842V Exon 18

GI, gastrointestinal; JM, juxtamembrane; KIT, receptor tyrosine kinase protein; PDGFRα, platelet-derived growth factor receptor; RTK, receptor tyrosine kinase; TM, transmembrane.


Study sponsored by Blueprint Medicines
Advanced GIST has high medical need

Primary resistance

1L imatinib → ORR ~60% PFS 19 mo

Secondary resistance

2L sunitinib → ORR ~7% PFS 6 mo

3L regorafenib → ORR ~5% PFS 4.8 mo

4L BSC or trial

<table>
<thead>
<tr>
<th>Resistance mutation</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT Exon 17</td>
<td>~ 1%</td>
<td>2L ~ 20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3L ~ 90%</td>
</tr>
<tr>
<td>PDGFR&lt;sub&gt;α&lt;/sub&gt; D842V</td>
<td>~ 5-6%</td>
<td>rare</td>
</tr>
</tbody>
</table>

- Activation loop mutations are associated with resistance to therapy
- Approved agents are ineffective against PDGFR<sub>α</sub> D842V
  - ORR ~ 0%
  - mPFS ~ 3 months

mPFS, median progression-free survival; ORR, objective response rate; PFS, progression-free survival

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

### Biochemical profiles

<table>
<thead>
<tr>
<th>Compound</th>
<th>PDGFRα D842V IC₅₀ nM</th>
<th>KIT D816V IC₅₀ nM</th>
<th>KIT V560G/D816V IC₅₀ nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLU-285</td>
<td>0.24</td>
<td>0.27</td>
<td>0.10</td>
</tr>
<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>
</tr>
<tr>
<td>regorafenib</td>
<td>810</td>
<td>3640</td>
<td>1685</td>
</tr>
</tbody>
</table>

### Tumor regression in KIT exon 11/17* mutant GIST PDX

- **Vehicle QD**
- **Imatinib 50 mg/kg BID**
- **BLU-285 3 mg/kg QD**
- **BLU-285 10 mg/kg QD**
- **BLU-285 30 mg/kg QD**

*del556-558/Y823D

BID, twice daily; IC₅₀, half maximal inhibitory concentration; PDX, patient derived xenograft; QD, once daily.

Kinome Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)
**BLU-285 Phase 1 study**

### Enrolling

**Dose escalation**

- **Advanced GIST**
- **MTD**

**First patient enrolled**
- October 2015

**Dose expansion**

- **PDGFRA D842-mutant GIST**
- **Unresectable GIST after imatinib and ≥ 1 other TKI**

**Anticipated initiation first half 2017**

**BLU-285 continuous once daily oral dosing**

- **Primary objectives** – determine the MTD and RP2D, and assess safety and tolerability
- **Secondary objectives** – PK, mutational status, anti-tumor activity

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MTD: maximum tolerated dose; PK: pharmacokinetics; RP2D: recommended Phase 2 dose; TKI: tyrosine-kinase inhibitor

NCT02508532

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## Demography and baseline patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients, N = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>61 (41 – 77)</td>
</tr>
<tr>
<td>GIST subtype</td>
<td></td>
</tr>
<tr>
<td>KIT mutant</td>
<td>18 (50)</td>
</tr>
<tr>
<td>PDGFRα mutant</td>
<td>18 (50)</td>
</tr>
<tr>
<td>Metastatic Disease</td>
<td>35 (97)</td>
</tr>
<tr>
<td>Largest target lesion size (cm)</td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>8 (22)</td>
</tr>
<tr>
<td>&gt; 5 – ≤ 10</td>
<td>12 (33)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>14 (39)</td>
</tr>
<tr>
<td>pending</td>
<td>2 (6)</td>
</tr>
<tr>
<td>#Prior TKI, median (range)</td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>12 (33)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>24 (67)</td>
</tr>
</tbody>
</table>

Data are preliminary and based on a cut off date of 1 November 2016
Initial dose escalation results

- Patients with unresectable GIST
  - Prior imatinib and ≥ 1 TKI
  - PDGFRα D842 mutation regardless of prior therapy

- 3 + 3 dose escalation with additional accrual to dose levels declared safe at a dose escalation meeting

- 36 patients enrolled over 12 months

- MTD has not been reached

<table>
<thead>
<tr>
<th>BLU-285 mg/day</th>
<th>Patients treated by dose N = 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3 + 2 enrichment</td>
</tr>
<tr>
<td>60</td>
<td>3 + 3 enrichment</td>
</tr>
<tr>
<td>90</td>
<td>3 + 3 enrichment</td>
</tr>
<tr>
<td>135</td>
<td>3 + 3 enrichment</td>
</tr>
<tr>
<td>200</td>
<td>3 + 2 enrichment</td>
</tr>
<tr>
<td>300</td>
<td>3 + 1 enrichment</td>
</tr>
<tr>
<td>400</td>
<td>4</td>
</tr>
</tbody>
</table>

- 75% (n=27) of patients remain on treatment, range 0.8 – 12.3 months
- All PDGFRα patients remain on treatment
- 9 patients off treatment (all due to progressive disease)
BLU-285 pharmacokinetics support once daily dosing

- Half-life > 24 hour, supporting QD dosing
- Relatively rapid absorption: $T_{\text{max}} \sim 2 - 8 \text{ hr}$
- Accumulation in plasma: 2.5 – 4.7 -fold after 15 days
- Exposure at 300 mg is at low end of predicted therapeutic range based on KIT Exon 17 mutant xenograft studies
Radiographic response per RECIST 1.1 in PDGFRα D842V GIST (dose level 1, 30 mg)

- 65 yo female, Primary Gastric GIST, PDGFRα D842V
  - Previous surgical de-bulking: stomach; peritoneal metastases × 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 RECIST 1.1)

CT, computerized tomography; ct-DNA, circulating tumor DNA; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors
Strong clinical activity against PDGFRα D842-mutant GIST at all dose levels

- 14 out of 14 D842-mutant patients with tumor reductions
- All PDGFRα patients remain on treatment

The values above/below the bars denote the dose level (mg) QD received by each patient.
SD, stable disease; PD, progressive disease; PR, partial response

Study sponsored by Blueprint Medicines
Radiographic response per RECIST 1.1 in heavily pretreated KIT Exon 11/17 GIST (dose level 4, 135 mg)

- 57 year old male, KIT Exon 11 (delWK557-8)/Exon 17 (D816V) mutations
  - Prior imatinib, sunitinib, nilotinib, sorafenib, imatinib + BKM120
  - Ongoing at Cycle 8 with confirmed partial response per RECIST 1.1
KIT GIST - early dose-response relationship

- BLU-285 30 – 90 mg
- BLU-285 135 – 300 mg

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

NB: The values above/below the bars denote the dose level (mg) QD received by each patient.
# Best radiographic response with BLU-285 per RECIST 1.1

<table>
<thead>
<tr>
<th>Best response (per investigator)</th>
<th>PDGFR(\alpha) N=15 n (%)</th>
<th>KIT N=13 n (%)</th>
<th>Total N=28 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>6 (40)</td>
<td>1 (8)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (60)</td>
<td>6 (46)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>DCR (PR +SD)</td>
<td>15 (100)</td>
<td>7 (54)</td>
<td>22 (79)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>6 (46)</td>
<td>6 (21)</td>
</tr>
</tbody>
</table>

- Of 7 partial responses, 6 confirmed; 1 pending (still on treatment)

DCR, disease control rate
Adverse events associated with BLU-285

- No DLTs or treatment-related Grade 4 – 5 AEs
- No patient discontinued BLU-285 due to treatment-related toxicity
- 11 (31%) patients had Grade 3 or higher AEs; of these, 3 were considered treatment-related:
  - 1 patient with Grade 3 nausea and vomiting
  - 1 patient with Grade 3 anemia and intratumoral hemorrhage
  - 1 patient with Grade 3 hypophosphatemia
- AEs occurring in ≥ 20% of patients
  - Nausea (42%)
  - Vomiting (33%)
  - Peripheral edema (31%)
  - Fatigue (28%)
  - Constipation (22%)
BLU-285 has been well tolerated on a QD schedule at doses of 30 – 400 mg

Half-life > 24 hours, supports QD dosing

BLU-285 demonstrates strong clinical activity in PDGFRα D842-mutant GIST at all dose levels

Significant anti-tumor activity in TKI-resistant, KIT-mutant GIST observed at doses ≥ 135 mg with tumor reduction in 4 of 6 patients, including 1 PR

Dose escalation continues with the goal of maximizing clinical activity in KIT-mutant GIST and to define the MTD and RP2D

Anticipate initiation of expansion cohorts in first half of 2017
We thank the participating patients, their families, all study co-investigators, and research coordinators at the following institutions:

- Oregon Health & Sciences University
- Royal Marsden Hospital/Institute for Cancer Research
- Leuven Cancer Institute
- University of Essen
- Fox Chase Cancer Center
- Erasmus MC Cancer Institute
- Centre Leon Berard
- Institut Gustave Roussy
- Dana-Farber Cancer Institute