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)

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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%

**Activating RTK mutations drive metastatic GIST**
- KIT ~ 80%
- PDGFRα ~ 8%

**Exons**
- Extracellular Domain
- TM Domain
- JM Domain
- Kinase Domain-1
- Kinase Domain-2 (activation loop)

**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

**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>Prevalence</th>
<th>Prevalence</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>PDGFRα 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 PDGFRα 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**

![Graph showing tumor regression](image)

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

PDGFRα 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

MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended Phase 2 dose; TKI, tyrosine-kinase inhibitor
NCT02508532
# 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><strong>GIST subtype</strong></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><strong>Metastatic Disease</strong></td>
<td>35 (97)</td>
</tr>
<tr>
<td><strong>Largest target lesion size (cm)</strong></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)

- **Baseline**
- **After 8 weeks, partial response (-42%)**
- **Rapid PDGFRα D842V ct-DNA decline**

- **65 yo 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 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

Baseline

After 24 weeks, partial response (-62%)
KIT GIST - early dose-response relationship

BLU-285 30 – 90 mg

- 90
- 60
- 30
- #
- #
- #
- #

BLU-285 135 – 300 mg

- 300
- 300
- 200
- 135
- #

- #Off treatment

- PD

- SD

- PR

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

Patient

NB: 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
### Best radiographic response with BLU-285 per RECIST 1.1

<table>
<thead>
<tr>
<th>Best response (per investigator)</th>
<th>PDGFRα 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)
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%)

AE, adverse event; DLT, dose limiting toxicity
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
Ackowledgments

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  - Erasmus MC Cancer Institute
  - Centre Leon Berard
  - Institut Gustave Roussy
  - Dana-Farber Cancer Institute