Preliminary Safety and Activity in a Phase 1 study of BLU-285, a Potent, Highly-Selective Inhibitor of KIT D816V in Advanced Systemic Mastocytosis (SM)

Mark Drummond¹, Daniel DeAngelo², Michael Deininger³, Deepti Radia⁴, Albert Quiery⁵, Elizabeth Hexner⁶, Hongliang Shi⁷, Terri Alvarez-Diez⁷, Erica Evans⁷, Mary Ellen Healy⁷, Beni Wolf⁷, Srdan Verstovsek⁸

¹Beatson West of Scotland Cancer Centre, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; ²Dana-Farber Cancer Institute, Boston, MA; ³Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, The University of Utah, Salt Lake City, UT; ⁴Guy’s & St Thomas NHS Trust, London, United Kingdom; ⁵University of Michigan, Ann Arbor, MI; ⁶Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; ⁷Blueprint Medicines, Cambridge, MA; ⁸Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

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Advanced Systemic Mastocytosis

- Mast cell neoplasm with poor prognosis and no effective treatments
  - Aggressive Systemic Mastocytosis (ASM); SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (MCL)
- KIT mutation D816V is a key driver in ~90-95% of patients¹

Mast cell accumulation and organ infiltration

**Blood**
- MC degranulation
- MC mediator Sx
- tryptase

**Skin**
- MC degranulation
- Urticaria pigmentosa

**Bone and bone marrow**
- Osteolytic bone lesions
- Cytopenias

**Liver and spleen**
- Liver function abnormalities, Ascites, or Hypersplenism

**GI tract**
- Hypoalbuminemia
- Weight loss

\[¹\] MC, mast cell; MCL, mast cell leukemia; SM, systemic mastocytosis; C-findings, clinical findings

Advanced SM has High Medical Need

Current therapy does not eradicate KIT D816V

- **Symptomatic therapy**
  - Anti-histamines
  - Corticosteroids
  - MC stabilizing agents

- **Cytoreductive therapy**
  - Cladribine
  - Interferon-α

- **TKI therapy**
  - Imatinib
  - Midostaurin

- **Experimental therapy**
  - Clinical trials

- **Life expectancy with current therapy**
  - ASM: ~41 months
  - SM-AHN: ~24 months
  - MCL: ~2 months

- **Morbidity via C-findings**
  - Cytopenias
  - Osteolytic bone lesions
  - Hepatomegaly with liver dysfunction
  - Hypersplenism
  - Malabsorption with weight loss

KIT, receptor tyrosine kinase protein; TKI, tyrosine-kinase inhibitor

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BLU-285: Potent, Highly Selective KIT D816V Inhibition

### Biochemical profiles

<table>
<thead>
<tr>
<th></th>
<th>KIT D816V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC$_{50}$ (nM)</td>
</tr>
<tr>
<td><strong>BLU-285</strong></td>
<td>0.27</td>
</tr>
<tr>
<td><strong>imatinib</strong></td>
<td>8,150</td>
</tr>
<tr>
<td><strong>masitinib</strong></td>
<td>&gt; 10K</td>
</tr>
<tr>
<td><strong>midostaurin</strong></td>
<td>2.8</td>
</tr>
</tbody>
</table>

### Anti-tumor activity in KIT-driven mastocytoma model

![Graph showing tumor volume over days after start of treatment for different treatments with BLU-285, imatinib, masitinib, and midostaurin.]

Model driven by KIT mutation equivalent to human KIT D816V mutation

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IC$_{50}$, half maximal inhibitory concentration; K$_D$, dissociation constant; PO, orally

1Evans E et al (2014)

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

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Key Entry Criteria

- Any of the following diagnoses:
  - Aggressive Systemic Mastocytosis (ASM)\(^1\)
  - SM with associated hematologic disorder (SM-AHN)\(^1\) with \(\geq 1\) C-finding
  - Mast Cell Leukemia (MCL)\(^1\)
  - Relapsed or refractory myeloid malignancy (dose escalation only)\(^2\)

- Age \(\geq 18\)

- ECOG performance status 0–3

- Platelet count \(\geq 25 \times 10^{9} /L\)

- ANC \(\geq 0.5 \times 10^{9} /L\)

- Adequate hepatic and renal function

ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group
\(^1\)ASM, SM-AHNMD, or MCL per WHO criteria via local diagnosis and retrospective central pathology to confirm mastocytosis subtype. \(^2\)Per IWG-MRT or WHO diagnostic criteria
BLU-285 Phase 1 Objectives and Design

Dose expansion
- Response rate per IWG-MRT-ECNM criteria
- D816V allele burden
- Advanced SM-PRO

Enrolling
3 + 3 dose escalation
- MTD and safety profile
- PK, PD, anti-neoplastic activity
- D816V allele burden

Advanced SM → MTD → ASM, N = 15
Advanced SM → MTD → SM-AHN, N = 15
Advanced SM → MTD → MCL, N = 5

FPI March 2016

BLU-285 continuous once-daily oral dosing

FPI, first patient-in; IWG-MRT-ECNM, International working group – myeloproliferative neoplasms research and treatment – European; competence network on mastocytosis; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; SM-PRO, systemic mastocytosis patient reported outcomes

1Gotlib J et al (2013); NCT02561988

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# Demography and Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Parameter (all data are preliminary as of 11 November 2016 cutoff)</th>
<th>All patients, N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease subtype per local assessment, n (%)</td>
<td></td>
</tr>
<tr>
<td>ASM</td>
<td>8 (67)</td>
</tr>
<tr>
<td>MCL</td>
<td>1 (8)</td>
</tr>
<tr>
<td>SM-AHN (all AHN are CMML)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>KIT D816V mutation, n (%)</td>
<td>11 (92)¹</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (17)</td>
</tr>
<tr>
<td>1</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Prior anti-neoplastic therapy, n (%)</td>
<td>6 (50)²</td>
</tr>
<tr>
<td>Number of C-findings median (range)</td>
<td>1 (1–3)</td>
</tr>
<tr>
<td>Cytopenias, n (%)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Osteolytic bone lesions</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Hepatomegaly with liver dysfunction</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Malabsorption with weight loss</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Urticaria Pigmentosa / Other SM-related skin rash, n (%)</td>
<td>8 (67)</td>
</tr>
</tbody>
</table>

SM-CMML, systemic mastocytosis with chronic myelomonocytic leukemia; pt, patient

¹One pt had no detectable KIT D816V mutation in blood or bone marrow; ²2 pts had midostaurin; 1 pt had cladribine; 1 pt had Pegasys; 1 pt had interferon alpha-2; 1 pt had hydroxyurea and 5-azacitidine
### Initial Dose Escalation and PK Results

<table>
<thead>
<tr>
<th>BLU-285 mg/day</th>
<th>Patients treated N = 12</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>130</td>
<td>Enrolling</td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**
- **C1D1**
  - Mean plasma concentration (ng/mL) vs. Nominal time (hours)
  - Dose levels: 30 mg, 60 mg, 100 mg

- **Key Findings:**
  - Dose-dependent increase in exposure
  - Rapid absorption: $t_{\text{max}}$ 2–4 hours
  - Half-life > 19 hours supports QD dosing

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*C1D1, cycle 1 day 1; DLT, dose limiting toxicity; $t_{\text{max}}$, time at which $C_{\text{max}}$ is observed; QD, once daily*

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*Study sponsored by Blueprint Medicines Corporation*
**Adverse Events**

<table>
<thead>
<tr>
<th>Non-hematological adverse events ≥ 2 patients (safety population, N = 12)</th>
<th>Hematological adverse events (safety population, N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
<td><strong>Any grade n (%)</strong></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (33)</td>
</tr>
<tr>
<td>↑ Alkaline Phosphatase</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
</tr>
</tbody>
</table>

- Most AEs were CTCAE Grade 1 or 2
- No Grade 4 or 5 treatment-related events and no dose reductions required for toxicity
- 1 DLT: Grade 3 alkaline phosphatase elevation
- MTD has not been reached
Alkaline Phosphatase Elevation is Likely a PD Effect on Bone Marrow Mast Cells

- Asymptomatic, transient Grade 3 alkaline phosphatase elevation occurred in the 3 patients with highest baseline bone marrow (BM) MC burden
- No associated transaminase or bilirubin elevation
- Confirmed bone origin in 1 patient (2 others not assessed)
- May represent a PD effect on BM MCs
- Protocol amended to consider only Grade 4 alkaline phosphatase elevation a DLT
BLU-285 Markedly Reduces Bone Marrow Mast Cells

Aggressive Systemic Mastocytosis
BLU-285 30 mg PO QD

Baseline – 80% mast cells
Cycle 7 – 10% mast cells

Aggressive Systemic Mastocytosis
BLU-285 60 mg PO QD*

Baseline – 20% mast cells
Cycle 7 – 5% mast cells

*Dr. Mohamed E. Salama, Hematopathology, Huntsman Cancer Institute, University of Utah

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Decreased BM Mast Cells in 6 of 8 Patients

BM, bone marrow
NB: The values above/below the bars denote the dose level (mg) QD received by each patient.
Decreased Tryptase in 10 of 12 Patients

Baseline value (ng/mL)

Best percentage change from baseline (%)

Patient

100

55.9

169.7

102.4

14.4

684.8

226.6

78.7

50

1414.3

146.8

562.6

30

30

60

60

30

60

100

100

60

60

60

60

NB: The values above/below the bars denote the dose level (mg) QD received by each patient.
Molecular Response in Blood and BM

30 mg dose level

KIT D816V Mutant Allele Fraction

Mutant Allele Fraction (% baseline)

Blood
BM

Days on study

60 mg dose level

Mutant Allele Fraction (% baseline)

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All available data as of data cutoff date shown
Decreased Malabsorption and Rash

- Maximum weight gain from baseline (n = 12):
  - Increase median 4.3 kg, range -0.5 – 12.9 kg
  - % increase median 4.7%, range -0.5 – 19.2%

- Maximum albumin gain from baseline (n = 12):
  - Increase median 0.45 g/dL, range 0 – 1.4 g/dL
  - % increase median 10.7%, range 0 – 40.0%

- Rash improved per investigator assessment in all 5 patients with Urticaria Pigmentosa for whom data are available
10 (83%) patients remain on study, range 1 – 8.1 months
Summary

- BLU-285 has demonstrated encouraging clinical activity in advanced SM with marked decreases in mast cell burden and improved patient symptoms
- Data support the hypothesis that KIT D816V is a key disease driver in SM
- Half-life > 19 hours supports QD dosing
- BLU-285 has been well tolerated over a dose range of 30 to 100 mg - dose escalation (currently at 130 mg QD)
- BLU-285 deserves continued investigation in advanced SM, and further investigation in other KIT-driven diseases; Phase 1 study of BLU-285 in GIST is ongoing

GIST, gastrointestinal stromal tumor

Study sponsored by Blueprint Medicines Corporation
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  - Dana-Farber Cancer Institute
  - University of Utah, Huntsman Cancer Institute
  - MD Anderson Cancer Center
  - University of Colorado
  - Stanford University
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  - Liver and spleen
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  - GI tract