Clinical activity in a Phase 1 study of BLU-285, a potent, highly-selective inhibitor of KIT D816V in advanced systemic mastocytosis

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Systemic mastocytosis (SM)

Diagnostic Criteria for systemic mastocytosis

WHO Criteria

• Major (+1 minor)
  Mast cell aggregates (≥ 15) in BM or other tissue

• Minor (or 3 of 4)
  Spindle-shaped mast cells
  c-KIT D816V mutation present
  CD2 or CD25 expression on mast cells
  Serum tryptase > 20 ng/mL

KIT D816V drives systemic mastocytosis

- Indolent (ISM) 16,100 cases
- Smoldering (SSM) 1,800 cases
- Advanced (AdvSM) 2,600 cases

KIT D816V
- Debilitating symptoms
- Organ damage
- ↓Survival

*Represents estimated prevalence in US, EU5, Japan, WHO, World Health Organization; AdvSM, advanced SM; ISM, indolent SM; SSM, smoldering SM

Systemic mastocytosis (SM)

Advanced systemic mastocytosis
ASM, SM-AHN and MCL

Bone and bone marrow*
Liver and spleen†
GI tract‡

C-findings

Osteolytic bone lesions
Cytopenias

Liver function abnormalities,
Ascites, or Hypersplenism

Hypoalbuminemia
Weight loss

BLU-285 was designed to treat systemic mastocytosis

BLU-285 provides highly potent and selective targeting of KIT D816V

<table>
<thead>
<tr>
<th>Kinome selectivity*</th>
<th>BLU-285</th>
<th>Midostaurin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical IC_{50} (nM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIT D816V</td>
<td>KIT wild type</td>
<td></td>
</tr>
<tr>
<td>BLU-285</td>
<td>0.27</td>
<td>73</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>2.9</td>
<td>26</td>
</tr>
</tbody>
</table>

• Multikinase inhibitor midostaurin is the only approved treatment for AdvSM
• Midostaurin provides CR+PR of 17% per IWG-MRT-ECNM criteria; mPFS 14.1 months

*Reproduced courtesy of Cell Signalling Technology, Inc. (www.cellsignal.com). The website is maintained by CSTI, Blueprint Medicines is not responsible for its content. IC_{50}, concentration causing 50% inhibition; CR, complete response; PR, partial response; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis; mPFS, median progression free survival

1. Evans E et al Science Translational Medicine (2017) 1;9(414);
2. Midostaurin US Prescribing information;
Phase 1 study of BLU-285 in advanced systemic mastocytosis: study design

Primary objectives: MTD/RP2D and safety profile
Secondary objectives: pharmacokinetics and preliminary anti-tumor activity

Part 1 (N=32)
Dose escalation completed
AdvSM or refractory myeloid malignancy
Dose levels: 30, 60, 100, 130, 200, 300, 400 mg per day

Part 2*
Dose expansion enrolling
ASM (n=15)
SM-AHN (n=15)
MCL (n=5)

BLU-285 continuous oral once-daily dosing

*As of November 27, 2017, 7 patients have been enrolled in dose expansion (data not shown); MTD, maximum tolerated dose; RP2D, recommended Part 2 dose
Key entry criteria

- Disease entities:
  - Advanced systemic mastocytosis per **WHO diagnostic criteria** via local assessment:
    - One of the following three histologic subtypes:
      - Aggressive systemic mastocytosis
      - Systemic mastocytosis with associated hematologic neoplasm with ≥1 C-finding
      - Mast cell leukemia
    - Relapsed or refractory myeloid malignancy (dose escalation only)
  - Age ≥18 years
  - ECOG performance status 0–3
  - Platelet count ≥ 25 x 10^9 /L
  - ANC ≥ 0.5 x 10^9 /L
  - Adequate hepatic and renal function

**WHO Criteria for SM**

- **Major**
  - Mast cell aggregates (≥ 15) in BM or other tissue
- **Minor**
  - Spindle-shaped mast cells
  - c-KIT D816V mutation present
  - CD2 or CD25 expression on mast cells
  - Serum tryptase > 20 ng/mL

ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group.
### Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63 (34–83)</td>
</tr>
<tr>
<td>Disease subtype per local assessment, n (%)*</td>
<td></td>
</tr>
<tr>
<td>ASM</td>
<td>17 (53)</td>
</tr>
<tr>
<td>SM-AHN</td>
<td>9 (28)</td>
</tr>
<tr>
<td>MCL</td>
<td>3 (9)</td>
</tr>
<tr>
<td>KIT mutation, n (%)</td>
<td>28 (88)</td>
</tr>
<tr>
<td>High risk mutation positive,(^1,2) n (%)</td>
<td>14 (44)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>Median number (range)</td>
<td>27 (84)</td>
</tr>
<tr>
<td>0-1</td>
<td>5 (16)</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Prior anti-neoplastic therapy</td>
<td></td>
</tr>
<tr>
<td>Median number (range)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Any, n (%)</td>
<td>22(^\wedge) (69)</td>
</tr>
<tr>
<td>Midostaurin</td>
<td>4 (13)</td>
</tr>
<tr>
<td>C-findings per WHO Criteria</td>
<td></td>
</tr>
<tr>
<td>Median number (range)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>Cytopenias, n (%)</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Hepatomegaly with liver dysfunction</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Malabsorption with weight loss</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Osteolytic bone lesions</td>
<td>6 (19)</td>
</tr>
</tbody>
</table>

*Other, SSM (n=2); telangiectasia macularis eruptive perstans (n=1); \(^\wedge\) Patients could have more than one S/A/R gene mutated, SFSR2 (n=22), ASXL1 (n=7), RUNX1 (n=5). S/A/R, mutations potentially associated with a poorer prognosis\(^1,2\);\(^\wedge\) Prior therapy taken by ≥2 pts, cladribine (n=6), imatinib (n=4), interferon (n=4), midostaurin (n=4), azacitidine (n=3), hydroxyurea (n=2), ibrutinib (n=2)

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Data cut-off: 4 Oct 2017

BLU-285 pharmacokinetics (PK) and dose escalation cohorts

**Steady state PK**

Mean plasma concentration (ng/mL)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Patients (n)</th>
<th>DLT (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
<td>1 Grade 3 alk phos</td>
</tr>
<tr>
<td>100</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>130</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>200</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>300</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>400</td>
<td>7</td>
<td>1 Grade 4 vomiting</td>
</tr>
</tbody>
</table>

**3+3 dose escalation with enrichment**

PK support QD dosing

Steady state $t_{1/2} > 20$ h

Xenograft $IC_{90} = 189$ ng/mL

Mean plasma concentration (ng/mL)

Nominal time (h)

PK support QD dosing

QD, once daily; DLT, dose-limiting toxicity

MTD not reached

300 mg daily selected as the RP2D
Treatment-emergent adverse events

Non-hematological AEs ≥20% (N=32)

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Any grade</th>
<th>≥Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periorbital edema</td>
<td>19 (59)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (41)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11 (34)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (28)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (22)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>7 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (22)</td>
<td>0</td>
</tr>
</tbody>
</table>

Hematological AEs ≥10% (N=32)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Any grade</th>
<th>≥Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>9 (28)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (28)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (13)</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

Most adverse events were CTCAE grade 1 or 2

≥ Grade 3 treatment-related AE in 16 (50%) patients

No deaths on study

30 of 32 patients remain on treatment (Median 9 months [range: 4–19])

1 discontinued due to PD (AML)
1 investigator decision (wild type KIT)
None discontinued due to BLU-285-related AE

AE, adverse event; AML, acute myeloid leukemia; CTCAE, Common Terminology Criteria for Adverse Events; PD, progressive disease

Data cut-off: 4 Oct 2017
Rapid and durable decline in tryptase and KIT D816V variant allele fraction across all dose levels

![Graph showing serum tryptase and blood KIT D816V VAF over time with different dose levels.](image)
Tryptase decrease in all patients

Baseline median 124 µg/L, range 14 to 1414 µg/L
All 32 patients achieved >50% reduction from baseline

* Prior midostaurin + S/A/R positive

• ASM
• SM-AHN
• MCL
• Other

Other, SSM (n=2): telangiectasia macularis eruptiva perstans (n=1)
Bone marrow mast cell decrease in all patients

- Baseline median 20%, range 1.5 to 95%
- ^n=25 evaluable patients with baseline bone marrow mast cells ≥ 5%
- 15/25 (60%) patients achieved bone marrow CR

Other, SSM (n=2); telangiectasia macularis eruptive perstans (n=1)
Spleen volume decrease in all patients

- Baseline median 633 mL, range 130 to 1952 mL
- \(^n=25\) patients with splenomegaly as per central assessment
- 15/25 (60%) patients achieved >35% reduction of spleen volume

* Prior midostaurin  + S/A/R positive
ASM  SM-AHN  MCL  Other

* Other, SSM (n=2); telangiectasia macularis eruptive perstans (n=1)
45-year-old female with ASM

*BLU-285 60 mg; remains on treatment at cycle 18 with confirmed PR per IWG-MRT-ECNM

Bone marrow tryptase

Baseline

Cycle 18

~50% MCs

<5% MCs

Colon CD25

Baseline

Cycle 7

>100 MCs/hpf

~100 MCs/hpf

Images courtesy of Dr Deepti Radia, Guy’s and St. Thomas NHS Trust
64-year-old male with MCL

Progressive clearance of bone marrow mast cells

Baseline

Cycle 3

Cycle 7

Bone marrow CD117

*BLU-285 200 mg; remains on treatment at cycle 9 with confirmed PR per IWG-MRT-ECNM
# Response analysis per IWG-MRT-ECNM criteria

<table>
<thead>
<tr>
<th>Complete response (CR)&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No bone marrow mast cell aggregate</td>
</tr>
<tr>
<td>• Serum tryptase &lt;20 ng/mL</td>
</tr>
<tr>
<td>• Peripheral blood count remission</td>
</tr>
<tr>
<td>• Complete resolution of C-findings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Partial response (PR)&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥50% reduction in bone marrow mast cell aggregate</td>
</tr>
<tr>
<td>• ≥50% reduction in serum tryptase</td>
</tr>
<tr>
<td>• Resolution of 1 or more C-findings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical improvement (CI)&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1 or more response criteria in absence of CR, PR or PD</td>
</tr>
</tbody>
</table>

IWG-MRT-ECNM evaluable patients

Part 1 dose escalation (all dose levels) (n=32)

Patients with AdvSM per WHO diagnostic criteria (n=28)

Patients excluded (n=10)
- n=6 only had osteolytic bone disease at baseline
- n=4 not measurable per IWG-MRT-ECNM criteria at baseline

Patients inevaluable (n=4)
- n=3 non-SM myeloid malignancy
- n=1 KIT WT; discontinued prior to post baseline response assessment

Patients with AdvSM evaluable per IWG-MRT-ECNM criteria¹ (n=18)

WT, wild type; ¹. Gotlib J et al Blood (2013) 121:2393
### Best overall response per IWG-MRT-ECNM criteria

<table>
<thead>
<tr>
<th>Best response* n (%) (confirmed and unconfirmed)</th>
<th>ASM (n=7)</th>
<th>SM-AHN# (n=8)</th>
<th>MCL (n=3)</th>
<th>Overall (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (CR + PR + CI)</td>
<td>6 (86)</td>
<td>5 (63)</td>
<td>2 (67)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>CR + PR</td>
<td>5 (71)</td>
<td>4 (50)</td>
<td>1 (33)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>2 (29)</td>
<td>0</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>3 (43)</td>
<td>4 (50)</td>
<td>1 (33)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Clinical improvement (CI)</td>
<td>1 (14)</td>
<td>1 (13)</td>
<td>1 (33)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>1 (14)</td>
<td>3 (38)</td>
<td>1 (33)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- 17 of 18 patients remain on treatment with median duration 9 months (range: 4–19)

BLU-285 has potent, clinically important activity in AdvSM

- Data validate *KIT* D816V as a key disease driver
- Selective targeting of *KIT* D816V with BLU-285 is well tolerated
  - 30 of 32 patients remain on treatment with median duration of 9 months (range: 4–19)
  - RP2D is 300 mg once daily, and expansion is ongoing
- BLU-285 demonstrates high preliminary response rates and durable activity
  - 72% ORR (CR + PR + CI) with 56% CR + PR per IWG-MRT-ECNM criteria
- Additional clinical development with BLU-285, now avapritinib, across the spectrum of systemic mastocytosis is planned for 2018
  - Phase 2 trial in AdvSM
  - Dose finding and Phase 2 trial in ISM and SSM
Acknowledgments

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  – Albert Quiery, University of Michigan Comprehensive Cancer Center
  – Dan DeAngelo, Dana-Farber Cancer Institute
  – Michael Deininger, University of Utah, Huntsman Cancer Institute
  – Srdan Verstovsek, MD Anderson Cancer Center
  – William Robinson, University of Colorado
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