GIST: imatinib and beyond

Clinical activity of BLU-285 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 studies 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
Imatinib revolutionized Gastrointestinal Stromal Tumor (GIST) treatment

- KIT mutations drive ~75–80% of GIST
- PDGFRα mutations drive ~5–10% of GIST

- Imatinib binds the inactive kinase conformation and inhibits many primary mutants
- Imatinib is a highly effective first-line GIST therapy
Beyond imatinib, there are no highly effective therapies\textsuperscript{1–6}

<table>
<thead>
<tr>
<th>Primary resistance</th>
<th>Secondary resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L imatinib ORR ~60% PFS 19 mo</td>
<td>2L sunitinib ORR ~7% PFS 6 mo</td>
</tr>
<tr>
<td>3L regorafenib ORR ~5% PFS 4.8 mo</td>
<td>4L no approved therapy ORR ~0% PFS ≤1.8 mo*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resistance mutation</th>
<th>Prevalence\textsuperscript{7,8}</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGFR(\alpha) D842V</td>
<td>~5–6%</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>KIT exon 17/18</td>
<td>~1%</td>
<td>2L ~23% ≥3L ~90%</td>
<td></td>
</tr>
<tr>
<td>KIT exon 13</td>
<td>N/A</td>
<td>2L ~40%</td>
<td></td>
</tr>
</tbody>
</table>

- Primary and secondary mutations cause therapeutic resistance
- Approved agents are ineffective against PDGFR\(\alpha\) D842V

*Imatinib re-challenged
BLU-285: highly potent and selective targeting of KIT/PDGFRα GIST mutants

- High kinome selectivity*
- Binds active conformation

*Image reproduced courtesy of CSTI (www.cellsignal.com)
BLU-285: highly active against imatinib-resistant GIST patient derived xenografts

**KIT exon 11/17 mutant**
- Tumor regression at 10 and 30 mg/kg QD

**KIT exon 11/13 mutant**
- Tumor regression at 30 mg/kg QD
BLU-285 Phase 1 study

Key objectives
- Part 1: MTD, safety, pharmacokinetics, ctDNA analyses, anti-tumor activity
- Part 2: response rate, duration of response, safety

Part 1: Dose escalation *completed*
- Advanced GIST
- 3+3 design with enrichment
- Dose levels: 30, 60, 90, 135, 200, 300, 400 and 600 mg QD
- MTD determined to be 400 mg PO QD

Part 2: Dose expansion *enrolling*
- PDGFRα D842V-mutant GIST (n=50)
- Unresectable GIST after imatinib and ≥1 other TKI (n=50)
### Demography and baseline patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients, N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>61 (25–85)</td>
</tr>
<tr>
<td><strong>GIST subtype</strong></td>
<td></td>
</tr>
<tr>
<td>KIT mutant</td>
<td>40 (56)</td>
</tr>
<tr>
<td>PDGFRα mutant</td>
<td>32 (44)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>69 (96)</td>
</tr>
<tr>
<td><strong>Largest target lesion size (cm)</strong></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>18 (25)</td>
</tr>
<tr>
<td>&gt;5–≤10</td>
<td>25 (35)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>29 (40)</td>
</tr>
<tr>
<td><strong>No. prior kinase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>PDGFRα</td>
</tr>
<tr>
<td>≥3</td>
<td>1.5 (0–6)</td>
</tr>
<tr>
<td>Prior regorafenib</td>
<td>KIT</td>
</tr>
<tr>
<td></td>
<td>10 (31)</td>
</tr>
<tr>
<td></td>
<td>4 (2–11)</td>
</tr>
<tr>
<td></td>
<td>8 (25)</td>
</tr>
<tr>
<td></td>
<td>36 (90)</td>
</tr>
</tbody>
</table>

Data are preliminary and based on a cut off date of 28 April 2017.
BLU-285 pharmacokinetics support QD dosing and broad mutational coverage

- Relatively rapid absorption $T_{max} \sim 2–8$ hours and long half-life $>24$ hours
- Exposure at the 300 and 400 (MTD) mg provides broad coverage of primary and secondary $KIT/PDGFR_\alpha$ mutations based on patient derived xenografts (PDX)

*includes escalation and expansion data
Radiographic response per RECIST 1.1 in PDGFRα D842V-mutant GIST

BLU-285 300 mg (dose escalation)

- Ongoing at cycle 5
- Prior imatinib and sunitinib
- Confirmed PR, -63% target sum

BLU-285 400 mg (dose expansion)

- Ongoing at cycle 3
- Prior imatinib
- PR (pending confirmation), -85% target sum
Tumor regression across all dose levels in PDGFRα D842-mutant GIST (central radiology review)

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

- Mutational status:
  - PD
  - SD
  - PR
  - PDGFRα N659K
  - D842V
  - D842I
  - D842V
  - D842V
  - D842V
  - D842V
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*per archival tumor and cfDNA

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High response rate and prolonged PFS in PDGFRα D842-mutant GIST

Central radiographic review

<table>
<thead>
<tr>
<th>Best response (N=25)</th>
<th>Choi Criteria  n (%)</th>
<th>RECIST 1.1  n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>25 (100%)</td>
<td>15* (60%)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>DCR (PR + SD)</td>
<td>25 (100%)</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* 12 confirmed, 3 pending confirmation

- Approved agents are ineffective\(^1,2\)
  - ORR ~0%

Median PFS not reached
PFS 25th percentile 11.2 months (95% CI: 5.9 – NE)

Probability of progression-free survival (%)

Approved agents are ineffective\(^1,2\) mPFS ~3 months

* 12 confirmed, 3 pending confirmation
Radiographic response in heavily pre-treated KIT-mutant GIST

- Ongoing at cycle 12
- 6 prior TKIs; exon 11, 13, and 18 mutations
- CHOI PR (density -53%); RECIST SD (-21%)

BLU-285 300 mg (dose escalation)

- Ongoing at cycle 4
- 5 prior TKIs; 1° exon 11 mutation; ctDNA pending
- CHOI PR (density -76%); RECIST PR (-41%)

BLU-285 400 mg (dose expansion)
Dose-dependent tumor reduction across multiple KIT genotypes (central radiographic review)

*ctDNA results pending

**per archival tumor and ctDNA
Important clinical activity in heavily pre-treated KIT-mutant GIST

Central radiographic review

<table>
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<th>Best response (N=25)</th>
<th>Choi Criteria n (%)</th>
<th>RECIST 1.1 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>8 (32)</td>
<td>2* (8)</td>
</tr>
<tr>
<td>SD</td>
<td>6 (24)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>DCR (PR + SD)</td>
<td>14 (56)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>PD</td>
<td>11 (44)</td>
<td>11 (44)</td>
</tr>
</tbody>
</table>

* 1 confirmed, 1 pending confirmation

• Beyond third-line regorafenib there are no approved therapies
  - Imatinib re-treatment in ≥third-line GIST
    • ORR ~0%

↑ PFS with BLU-285 ≥300 mg

1 confirmed, 1 pending confirmation

Probability of progression-free survival (%)

Median PFS 9.3 months (95% CI: 4.0 – NE)

Median PFS 2 months (95% CI: 1.9 – 4.4)

Imatinib re-treatment
PFS ~1.8 months

Months from first dose
Adverse events (AE) associated with BLU-285

<table>
<thead>
<tr>
<th>Safety population, N=72</th>
<th>Severity, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs in ≥20% of patients</td>
<td>n (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (60)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (53)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30 (42)</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>26 (36)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (33)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>22 (31)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Anemia</td>
<td>18 (25)</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (22)</td>
</tr>
</tbody>
</table>

- 18 (25%) patients had Grade (G) ≥3 treatment-related (Fatigue [8%], hypophosphatemia [6%], anemia [4%], nausea, vomiting, hyperbilirubinemia [3% each])
- DLT in 2 patients at 600 mg: 1 G2 hyperbilirubinemia; 1 G2 rash, hypertension, memory impairment
- BLU-285 discontinuations: disease progression n=19, treatment-related toxicity (G3 hyperbilirubinemia) n=1, and investigator’s decision n=1
Conclusions

• BLU-285 is well tolerated on a QD schedule at doses up to the MTD of 400 mg
• Exposure at 300–400 mg QD provides broad coverage of primary and secondary KIT / PDGFRα mutants
• BLU-285 has strong clinical activity in PDGFRα D842-mutant GIST with an ORR of 60% per central review and median PFS not reached
  – Potential expedited paths for approval are being evaluated
• BLU-285 demonstrates important anti-tumor activity including radiographic response and prolonged PFS in heavily pre-treated, KIT-mutant GIST at doses of 300–400 mg QD
  – Based on these encouraging data, planning is underway for a Phase 3 randomized study of BLU-285 in third-line GIST
Acknowledgments

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

We also thank Sarah Jackson, PhD, of iMed Comms, an Ashfield company, who provided editorial writing support funded by Blueprint Medicines
References

5. Demetri et al. Lancet. 2006;368:1329