**Efficacy of a highly potent and selective KIT V654A inhibitor for treatment of imatinib-resistant GIST**

Alexandra Grassl,1 Joseph Kim,1 Omar Ahmad,1 Kevin Batrivan,1 Alison Davis,1 Tom Dineen,1 Wei Hu,2 Eddy Job,3 Ludivine Moine,4 Kate Newberry,2 Maria Roche,4 Doug Shorten,4 Yeon Sook Choi,1 Francis Wolenski,1 Sebastian Bauer,1 César Serrano,1 Jonathan Trent,1 Suzanne George1

1Blueprint Medicines Corporation, Cambridge, MA, USA; 2Westmeade, Translational Sciences, Department of Medical Oncology, Essen, Germany; 3Vail of Nevada Institute of Oncology, Medical Oncology Department, Vail of Western University Hospital, Barcelona, Spain; 4University of Bristol, Translational Cancer Center, Bristol, UK. 111111

**Background**

- Gastrointestinal stromal tumor (GIST) is the most common type of sarcoma with an annual incidence of 0.75 per 100,000 people in the United States.
- Approximately 80% of patients with GIST present with primary inactivations in the c-kit oncogene at exon 11 or 17 (Table 1), which leads to constitutive, ligand-independent activation of the KIT receptor tyrosine kinase.1
- For patients with metastatic GIST, frontline therapy with imatinib is effective, with a response rate of approximately 51–56% and median progression-free survival (PFS) of 19–23 months, in a molecularly unselected population.2
- Agents that are approved for advanced GIST, without molecular selection, after progression on imatinib, include sunitinib, regorafenib, and ripretinib; however, response rates are less than 10% with PFS of approximately 3.6 months.3
- On-target resistance mutations in the KIT oncogene frequently occur following treatment with kinase-inhibitors (TKIs), such as those in exon 17, exon 13, and less commonly in exon 11 (Figure 1).4

**Table 1: Molecular classification of GIST**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Primary mutation (frequency)</th>
<th>Secondary mutation (frequency)</th>
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<tbody>
<tr>
<td>11</td>
<td>V654A (50%)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
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<td>13</td>
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<td>14</td>
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**Conclusions**

- Several agents are approved for advanced GIST, without molecular selection, after progression on imatinib, including sunitinib, regorafenib, and ripretinib; however, there are no potent and specific inhibitors that target the KIT-V654A resistance mutation.

**Results**

- Figure 2: Patients with GIST harboring the KIT V654A mutation had poorer outcomes when treated with sunitinib.
- Figure 3: Exposure and inhibition of STATS phosphorylation with BLU647 (Figure 3A–B) and BLU7444 (Figure 3C–D) were dose-dependent.

**References**


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