Avapritinib (BLU-285), a Selective KIT Inhibitor, is Associated with High Response Rate and Tolerable Safety Profile in Advanced Systemic Mastocytosis: Results of a Phase 1 Study

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Methods

Study design and assessments

EXPLORER is a two part, Phase 1, multicenter study of avapritinib in adult patients with AdvSM or relapsed/refractory myeloid malignancies (Figure 1, Table 1). Part 1 assessed single dose escalation and dose expansion in AdvSM. Part 2 assessed a dose of 400 mg QD in adults with AdvSM and high-risk Philadelphia chromosome–positive malignancy.

Background

Systemic mastocytosis (SM) encompasses a spectrum of mast cell disorders characterized by the accumulation of neoplastic mast cells in tissues/vascular organs.1

Constitutively active mutant KIT (typically D816V) is present in 90–95% of SM cases and is central to disease pathogenesis.2

Advanced systemic mastocytosis (AdvSM) is the most severe form of SM comprising three subtypes, aggressive SM (ASM), SM with an associated hematopoietic neoplasm (SM-AHN), and mast cell leukemia (MCL).3,4 classified using the World Health Organization (WHO) diagnostic criteria.5

The multi-kinase inhibitor midostaurin is currently the only approved treatment for all subtypes of AdvSM, but is not optimized for selective KIT D816V inhibition.6

Avapritinib is a highly potent and selective kinase inhibitor, developed to specifically target the active conformation of KIT, containing potent and selective inhibition of KIT D816V and other activation loop mutants.7

Antineoplastic activity was assessed by: Changes in percentage of bone marrow mast cells, spleen size, and skin thickness at baseline and each dose level; and an overall response assessment by modified International Working Group–Myeloid Neoplasms Research and Treatment and European Competence Network on Mastocytosis criteria (m-IWG-MRT-ECNM)8

Number of prior cytoreductive therapies

Average complete response (CR) with partial recovery of peripheral blood counts (CRi) added to accommodate CR with residual cytopenias due to avapritinib.

- Response is confirmed 12 weeks after first documentation of response
- Response adjudicated by a Response Adjudication Committee (RAC), composed of subset of study investigators

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Excluded patients with a history of bleeding, cardiac, renal, or hepatic dysfunction, uncontrolled hypertension, or uncontrolled diabetes mellitus

Antineoplastic activity: changes in measures of mast cell burden

Table 3. Antineoplastic activity: changes in measures of mast cell burden

<table>
<thead>
<tr>
<th>Best Response, n (%)</th>
<th>No response</th>
<th>Partial response</th>
<th>Complete response</th>
<th>CR</th>
<th>PR</th>
<th>CRh</th>
<th>CRi</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>25 (42)</td>
<td>13 (22)</td>
<td>9 (15)</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Improvement based on Investigator assessment for response</td>
<td>23 (40)</td>
<td>12 (21)</td>
<td>8 (13)</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions

Avapritinib has potent antineoplastic activity across all subtypes of AdvSM, with an ORR of 83% per m-IWG-MRT-ECNM criteria, and responses were durable

Avapritinib treatment resulted in deep and durable reductions in levels of bone marrow mast cells, serum tryptase, splenomegaly and KIT D816V mutant allele burden, as well as reversal of organ damage, in all subtypes of AdvSM, regardless of prior treatment

50% or greater reduction in both BM mast cells and cytoreduction occurred in 81% of patients, including those not evaluable for response by m-IWG-MRT-ECNM criteria

Avapritinib was well-tolerated, and the majority of patients remain on study treatment

Data support further evaluation of avapritinib across the spectrum of SM, including indolent SM and smoldering SM; a Phase 2 clinical study (PIONEER) is planned to start enrolment by the middle of 2018 to further investigate efficacy and tolerability of avapritinib in AdvSM

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References