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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Background
- Systemic mastocytosis (SM) encompasses a spectrum of mast cell disorders characterized by an accumulation of neoplastic mast cells in tissues/visceral organs.
- Constitutively active mutant KIT (typically D816V) is present in 90–95% of SM cases and is central to disease pathogenesis.
- Advanced systemic mastocytosis (AdvSM) is the most severe form of SM comprising three subtypes: aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL),2,3 classified using the World Health Organization (WHO) classification.
- The multi-kinase inhibitor midostaurin is currently the only approved treatment for all subtypes of AdvSM, but is not optimally selected for selective KIT D816V inhibition.4

Methods

Study design and assessments
EXPLORER is a two part, Phase 2 multicenter study of avapritinib in adult patients with AdvSM or relapsed/refractory myeloid malignancies (Figure 1, Table 1).

Results
- Of 30 patients accrued, 32 in Part 1 and 20 in Part 2 (Figure 2)
- Median duration of treatment was 14 months (range 1-26 months) in Part 1 and 5 months (range 1-9 months) in Part 2. (2) patients remain on treatment
- Baseline demographics and disease characteristics for all patients are shown in Table 2

Conclusions
- Avapritinib has potent antineoplastic activity across all subtypes of AdvSM, with an 9 (17) response rate in Part 1 and 4 (8) in Part 2. Of 32 patients treated, 22 (69%) achieved a confirmed response (CR/CRh) and 5 (16%) a nonconfirmed response (nCR/nCRh), including 4 patients with SM-AHN. The median time to response was 11 days (range 5-35 days)
- Overall response rate per modified IWG-ECM criteria in Part 1 and 2 of the study, 16 and 7 patients, respectively, was evaluable for response per m-IWG-MRT ECM criteria. Response data are presented in Table 4. In Part 1, all responses were confirmed at 12 weeks.
- In Part 2, all responses were confirmed (pending 12 week confirmation).
- Of 32 patients treated across Part 1 and 2 (n=16), 50% had ≥50% decrease in bone marrow mast cell burden, 35% decrease in spleen size by imaging, ≥50% decrease in serum tryptase, and ≥50% decrease in KIT D816V MAF, respectively

References
- Avapritinib has potent antiproliferative activity across all subtypes of AdvSM, with an ORR of 83% per m-IWG-MRT criteria, and responses were durable.
- Avapritinib treatment resulted in deep and durable reductions in levels of bone marrow mast cells, serum tryptase, splanchnectomy and KIT D816V mast cell 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 tryptase occurred in 81% of patients, including those not evaluable for response by m-IWG-ECM criteria
- Avapritinib was well tolerated, and the majority of patients remained on study treatment. EXPLORE is an ongoing and Phase 2 PATHFINDER study planned to start enrollment by the middle of 2018 to further investigate efficacy and tolerability of avapritinib in AdvSM.
- 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 in these indications by the end of 2018.

Table 1. Patient population

<table>
<thead>
<tr>
<th>Key population criterion</th>
<th>Diagnosis of AdvSM (ASM, SM-AHN or MCL) where KIT-IAV &gt;50%</th>
<th>Diagnosis of acute mast cell leukemia</th>
<th>High-risk myelodysplastic syndrome or chronic myelomonocytic leukemia</th>
<th>Age ≥18 years</th>
<th>ECOG performance score (PS) of 0-3</th>
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<tbody>
<tr>
<td>Diagnosis of AdvSM (ASM, SM-AHN or MCL) where KIT-IAV &gt;50%</td>
<td>32/30</td>
<td>30/30</td>
<td>11/11</td>
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Table 2. Key patient population

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<thead>
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<th>Diagnosis of AdvSM (ASM, SM-AHN or MCL) where KIT-IAV &gt;50%</th>
<th>Diagnosis of acute mast cell leukemia</th>
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<td>32/30</td>
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Table 3. Antineoplastic activity: changes in measures of mast cell burden

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<tr>
<th>Best Response, in n (%)</th>
<th>CR/CRh</th>
<th>Overall response</th>
<th>n (%)</th>
<th>No response</th>
<th>n (%)</th>
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<td>CR/CRh</td>
<td>22 (69%)</td>
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<td>1 (31%)</td>
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<tr>
<td>Overall response</td>
<td>25 (78%)</td>
<td>25 (78%)</td>
<td>25 (78%)</td>
<td>5 (17%)</td>
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<td>14 (44%)</td>
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<td>OR</td>
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<td>8 (25%)</td>
<td>8 (25%)</td>
<td>17 (50%)</td>
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Table 4. Best overall response per m-IWG-MRT ECM criteria

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<th>Response, n (%)</th>
<th>ASM</th>
<th>SM-AHN</th>
<th>MCL</th>
<th>All</th>
<th>ASM</th>
<th>SM-AHN</th>
<th>MCL</th>
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<td>22</td>
<td>22</td>
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