Pure Pathologic Response is associated with improved overall survival in patients with advanced systemic mastocytosis receiving avapritinib in the phase I EXPLORER study


*Equally contributing senior authors

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Disclosures

Dr. Gotlib is the Chair of the BLU-285-2101 Study Response Adjudication Committee, received research funding, served on advisory boards, and received honoraria and travel support from Blueprint Medicines Corporation.

Dr. Gotlib is the co-chair of the Study Steering Committee, received research funding, and served on advisory boards for Deciphera.

Study sponsored by Blueprint Medicines Corporation.

AYVAKIT™ (avapritinib) is approved by the US Food and Drug Administration (FDA) for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

In Europe, AYVAKYT® (avapritinib) is approved by the European Medicines Agency (EMA) for the treatment of adult patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation.

Avapritinib is not approved as safe or effective for use in systemic mastocytosis or any other indication by the FDA, EMA, or any healthcare authority in any jurisdiction.
AdvSM is a clonal hematologic neoplasm driven by *KIT* D816V

- AdvSM is characterized by elevated mast cell (MC) burden and organ damage (C-findings)\(^1\)
- Complete remissions are rare (<1%) and the median overall survival is 29 months with the multikinase inhibitor midostaurin, the only approved therapy for AdvSM\(^2\)
  - Estimated 1-, 2-, and 3-year overall survival rates were 72%, 53%, and 46%, respectively
  - Landmark analysis of response\(^a\) after 6 cycles was not significantly associated with improved survival (\(P=0.18\))

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*Neoplastic MC aggregates* 

Serum tryptase (and other MC mediators) 

*KIT D816V mutation* 

*Organ damage (C-findings)*

- Cytopenias
- Liver dysfunction
- Ascites, pleural effusions
- Splenomegaly with hypersplenism
- Malabsorption with weight loss
- Large osteolytic lesions/pathologic fractures
Avapritinib, a potent and selective inhibitor of KIT D816V, induces deep reductions in MC burden and resolution of organ damage\(^1\)

Highly potent against KIT D816V

- Biochemical IC\(_{50}\)=0.27 nM\(^2\)

Highly selective kinome profile

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**Bone marrow MCs**

- Maximum percent change from baseline

- <50% decrease from baseline
- MC aggregates cleared from marrow

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**KIT D816V mutation allele fraction**

- Maximum percent change from baseline

- <50% decrease from baseline
- ≥50% decrease from baseline
- Decreased to <1%
- Decreased to <0.17%

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**Serum tryptase**

- Maximum percent change from baseline

- >50% decrease in tryptase
- Tryptase decreased to <20 ng/mL
- Tryptase normalized to <11.4 ng/mL

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**Resolution of organ damage (C-findings)**

- Patient with SM-CMML-1
- Baseline
- Cycle 6 Day 1

- Weight loss of >50 pounds
- Hypoalbuminemia (2.3 mg/dL)
- Ascites with paracentesis (15 L/week)
- All weight gained back
- Albumin normalized
- Ascites resolved

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Overall response rate by modified IWG-MRT-ECNM criteria

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<tr>
<th>Best confirmed central response, n (%)</th>
<th>All evaluable (n=53)</th>
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<td>ORR (CR + CRh + PR + CI)</td>
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</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable (NE)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

All data in this presentation is as of a data cut-off of May 27, 2020

- BM MC aggregates eliminated
- Serum tryptase <20 ng/mL
- Resolution of palpable hepatosplenomegaly
- Full (CR) or partial (CRh) hematologic recovery
- Full resolution of all evaluable C-findings

- ≥50% reduction in BM MCs, serum tryptase
- Full resolution of ≥1 evaluable C-findings

- Full resolution of ≥1 evaluable C-findings

- Not in a CR, PR, CI or PD

- Worsening of evaluable C-findings or
- Progression to AML

All shown criteria for CR/CRh and PR need to be fulfilled

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*aPartial hematologic recovery: ANC >0.5 ×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) and platelet count >50 ×10^9/L and Hgb level >8.0 g/dL
*bNot evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks).
*cResponse duration must be ≥12 weeks. ANC, absolute neutrophil count; AML, acute myeloid leukemia; BM, bone marrow; CRh, complete remission with partial hematologic recovery; Hgb, hemoglobin; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment; ORR, overall response rate.
Overall response rate by modified IWG-MRT-ECNM criteria

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<th>Post midostaurin (n=17)</th>
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<td>ORR (CR + CRh + PR + CI)</td>
<td>40 (75)</td>
<td>3 (100)</td>
<td>28 (76)</td>
<td>9 (69)</td>
<td>30 (83)</td>
<td>10 (59)</td>
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<td>CR or CRh</td>
<td>19 (36)</td>
<td>2 (67)</td>
<td>14 (38)</td>
<td>3 (23)</td>
<td>16 (44)</td>
<td>3 (18)</td>
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<td>8 (15)</td>
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aPartial hematologic recovery: ANC >0.5×10^9/L, with normal differential (absence of neoplastic MCs and blasts <1%) and platelet count >50×10^9/L and Hgb level >8.0 g/dL.
bNot evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks).
ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.
Overall survival on avapritinib (efficacy population)

**Patients at risk:**

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<tr>
<td><strong>1-year OS</strong></td>
<td>100%</td>
<td>92%</td>
<td>84%</td>
<td>76%</td>
</tr>
<tr>
<td><strong>2-year OS</strong></td>
<td>100%</td>
<td>75%</td>
<td>68%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>3-year OS</strong></td>
<td>100%</td>
<td>NR</td>
<td>NR</td>
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**Median OS, months**

- **All AdvSM (n=53):** 46.9
- **ASM (n=3):** NR
- **SM-AHN (n=37):** 46.9
- **MCL (n=13):** NR

**95% CI**

- **All AdvSM (n=53):** 46.9–NE
- **ASM (n=3):** NE–NE
- **SM-AHN (n=37):** 24.5–NE
- **MCL (n=13):** 31.2–NE

**Months from first dose**

NR, not reached; NE, not estimable; OS, overall survival.
Primary basis of response in current AdvSM criteria is anchored to evaluable organ damage

**IWG-MRT-ECNM criteria (2013)**

*Measures full resolution in:*

- **“Evaluable” C-findings**
  - Cytopenias (ANC, Hgb, platelets)
  - Liver dysfunction (Dbil, AST/ALT, ALP)
  - Hypoalbuminemia
  - Ascites and pleural effusions
  - Symptomatic splenomegaly (>5 cm)

*Reductions in MC burden only sub-classifies response*

**Challenges**

- Defining response by C-findings is complex and challenging due to their heterogenous nature
  
- Geared more for clinical trials; more challenging in clinical practice

- Potential discordance between lingering non-hematologic C-findings but clearance of BM MCs

- Applicable to AdvSM patients who exhibit evaluable C-findings at baseline limiting the evaluable population

- Pathological or molecular responses may be more strongly associated with clinical outcomes such as survival and favored by regulatory agencies

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ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; Dbil, direct bilirubin.
mIWG-MRT-ECNM response trends toward association with improved survival: Landmark analysis starting at end of Cycle 6
Proposed **Pure Pathologic Response (PPR)** criteria focuses on histopathological and molecular responses

**PPR criteria**

*Measures resolution in:*

**Mast Cell Burden**
- Neoplastic MC aggregates
- Serum tryptase
- KIT D816V mutation

**Advantages**
- Avoids challenges of complex C-finding assessments
- Can be easily used in routine clinical practice
- Can be used in any patient with measurable MC burden

**Complete remission with full (CR) or partial (CRh) hematologic recovery**
- BM MC aggregates eliminated and tryptase <20 ng/ml

**Molecular complete remission (mCR/mCRh)**
- and KIT D816V mutant allele fraction falls below LOD by sensitive assay

**Partial remission (PR)**
- ≥50% reduction in BM MCs and tryptase

**Stable disease (SD)**
- Not in a CR, PR, or PD

**Progressive disease (PD)**
- Transformation to AML

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*Partial hematologic recovery: ANC >0.5×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) and platelet count >50×10^9/L and Hgb level >8.0 g/dL.*

*KIT D816V allele-specific polymerase chain reaction or digital droplet assay with sensitivity ~0.1%.*

*LOD, limit of detection; mCR, molecular complete remission; mCRh, molecular complete remission with partial hematologic recovery; PPR, pure pathologic response.*
Partial hematologic recovery: ANC >0.5 ×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) and platelet count >50 ×10^9/L and Hgb level >8.0 g/dL.

Not evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks).

PPR criteria highlight depth of pathologic and molecular responses

- Similar ORR overall, but higher rate of CR/CRh rate by PPR compared with mIWG-MRT-ECNM criteria, demonstrating discordance between pathologic responses and assessment of clinical responses
- Molecular CR + CRh in 25% of patients by PPR criteria

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<th>PPR criteria in mIWG population (n=53)</th>
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PPR molecular CRs

- In addition, 11 additional AdvSM patients lacking evaluable mIWG C-findings are evaluable by PPR: 3 CR, 3 CRh, 3 PR, and 2 SD

¹Partial hematologic recovery: ANC >0.5×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) and platelet count >50×10^9/L and Hgb level >8.0 g/dL.
²Not evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks).
PPR response is significantly associated with improved survival: *Landmark analysis starting at end of Cycle 6*

**2-year OS**

- **CR/CRh vs PR vs SD:** 
  - **CR/CRh:** 81%
  - **PR:** 58%
  - **SD:** 20%

- **Responders vs non-responders:** 
  - **Responders:** 86%
  - **Non-responders:** 58%

**Patients at risk:**
- **CR/CRh:** 9 9 9 9 9 9 7 6 4 4 4 4 2 1 1 1 0
- **PR:** 25 25 25 23 21 20 20 14 12 9 6 3 2 1 1 1 0
- **SD:** 16 16 16 11 9 8 6 6 6 6 6 5 5 5 4 3 1 0

**Patients at risk (second graph):**
- **Responder:** 34 34 34 32 30 29 27 20 16 13 10 7 4 2 2 1 1 0
- **Non-responder:** 16 16 16 11 9 8 6 6 6 6 6 5 5 5 4 3 1 1 0

Landmark analysis limited to mIWG-MRT-ECNM evaluable patients alive at end of Cycle 6 (n=50) for comparison purposes of PPR to mIWG-MRT-ECNM criteria. In all PPR evaluable AdvSM patients alive at end of Cycle 6 (n=61), response is also **significantly associated with improved survival (P=0.005).**
Conclusions

- Proposed PPR criteria are simple, can be utilized in clinical practice, increases the number of evaluable patients, and are applicable to all AdvSM patients with measurable disease burden (e.g. BM mast cells and serum tryptase level)
- PPR response versus no response at end of Cycle 6 is correlated with overall survival ($P=0.013$)
- PPR should be explored as a primary endpoint for future trials
- Further analyses are required to compare overall survival using mIWG-MRT-ECNM versus PPR in specific subgroups (e.g. SM-AHN; midostaurin-naïve vs. prior midostaurin)
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• Avapritinib investigators and research coordinators
• Colleagues at Blueprint Medicines Corporation

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