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**Supplementary information**

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**Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial**

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# **Efficacy and Safety of Avapritinib in Advanced Systemic Mastocytosis: Interim Analysis of the Phase 2 PATHFINDER trial**

## **Supplementary Information**

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**Supplementary Table 1 | mIWG-MRT-ECNM Definition of Evaluable Organ Damage**

**(C-Findings)**

<b>Non-hematologic C-Findings</b>	
Ascites or pleural effusion	<p>Symptomatic ascites or pleural effusion requiring medical intervention such as:</p> <ol style="list-style-type: none"> <li>1. Use of diuretics (Grade 2) or</li> <li>2. <math>\geq 2</math> therapeutic paracenteses <i>or</i> thoracenteses (Grade 3) <math>\geq 28</math> days apart over 12 weeks before C1D-8 with 1 procedure performed during the 6 weeks before C1D-8</li> </ol>
Liver function abnormalities	<p>Grade <math>\geq 2</math> abnormalities in direct bilirubin (<math>&gt;1.5 \times \text{ULN}</math>), AST (<math>&gt;3.0 \times \text{ULN}</math>), ALT (<math>&gt;3.0 \times \text{ULN}</math>) or AP (<math>&gt;2.5 \times \text{ULN}</math>) in the presence of:</p> <ul style="list-style-type: none"> <li>• Ascites <i>and/or</i></li> <li>• Clinically relevant portal hypertension, <i>and/or</i></li> <li>• Liver MC infiltration that is biopsy-proven <i>or</i></li> <li>• No other identified cause of abnormal liver function</li> </ul>
Hypoalbuminemia	Grade $\geq 2$ hypoalbuminemia ( $<3.0 \text{ g/dL}$ )
Splenomegaly	A spleen that is palpable $\geq 5 \text{ cm}$ below the left costal margin
<b>Hematologic C-Findings</b>	
ANC	Grade $\geq 3$ ANC ( $<1.0 \times 10^9/\text{L}$ )
Anemia (transfusion-independent)	Grade $\geq 2$ Hgb ( $<10 \text{ g/dL}$ )
Anemia (transfusion-dependent)	<ul style="list-style-type: none"> <li>• Transfusion of <math>\geq 6</math> units PRBCs in the 12 weeks before C1D-8 <i>and</i></li> <li>• Most recent transfusion occurring during the 4 weeks before C1D-8 <i>and</i></li> <li>• Transfusions administered for Hgb <math>\leq 8.5 \text{ g/dL}</math> <i>and</i></li> </ul>

	<ul style="list-style-type: none"> <li>Reason for transfusions is not bleeding, hemolysis, or therapy-related</li> </ul>
Thrombocytopenia (transfusion-independent)	Grade $\geq 2$ thrombocytopenia ( $<75 \times 10^9/L$ )
Thrombocytopenia (transfusion-dependent)	<ul style="list-style-type: none"> <li>Transfusion of <math>\geq 6</math> units of apheresed platelets (or <math>\geq 6</math> pools of random donor or buffy coat) 12 weeks before C1D-8 <i>and</i></li> <li><math>\geq 2</math> units transfused 4 weeks before C1D-8 <i>and</i></li> <li>Transfusions administered for platelet count <math>&lt;20 \times 10^9/L</math></li> </ul>

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; C, cycle; D, day; Hgb, hemoglobin; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment; MC, mast cell; PBRC, packed red blood cell; ULN, upper limit of normal.

$\geq 1$  C-finding is required for eligibility. Grade is based on the Common Terminology Criteria for Adverse Events, Version 5.0.

**Supplementary Table 2 | mIWG-MRT-ECNM Response Criteria in Advanced Systemic Mastocytosis**

Response	Criteria for Response
CR	<p>Requires all four of the following criteria, and response duration must be ≥12 weeks:</p> <ul style="list-style-type: none"> <li>• No presence of compact neoplastic MC aggregates in the BM or other biopsied extracutaneous organ</li> <li>• Serum tryptase level &lt;20 ng/mL</li> <li>• Peripheral blood count remission defined as:               <ul style="list-style-type: none"> <li>○ ANC ≥1 × 10<sup>9</sup>/L with normal differential (absence of neoplastic MCs and blasts &lt;1%) <i>and</i></li> <li>○ Platelet count ≥100 × 10<sup>9</sup>/L <i>and</i></li> <li>○ Hgb level ≥11 g/dL</li> </ul> </li> <li>• Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (C-findings)</li> </ul>
CRh	<p>Requires all criteria for CR be met and response duration must be ≥12 weeks; however, patient may have residual cytopenias. The following minimum recovery of peripheral blood counts is required:</p> <ul style="list-style-type: none"> <li>• ANC &gt;0.5 × 10<sup>9</sup>/L with normal differential (absence of neoplastic MCs and blasts &lt;1%) <i>and</i></li> <li>• Platelet count &gt;50 × 10<sup>9</sup>/L <i>and</i></li> <li>• Hgb level &gt;8.0 g/dL</li> </ul>
PR	<p>Requires all three of the following criteria, and response duration must be ≥12 weeks, in the absence of CR/CRh and PD:</p> <ul style="list-style-type: none"> <li>• Reduction by ≥50% in neoplastic MCs in the BM <i>and/or</i> other extracutaneous</li> </ul>

	organ at biopsy demonstrating eligible SM-related organ damage <ul style="list-style-type: none"> <li>• Reduction of serum tryptase level by <math>\geq 50\%</math></li> <li>• Resolution of one or more biopsy-proven or suspected SM-related organ damage (C-findings)</li> </ul>	
Clinical improvement	<ul style="list-style-type: none"> <li>• Response duration must be <math>\geq 12</math> weeks</li> <li>• Requires one or more of the non-hematologic and/or hematologic response criteria to be fulfilled in the absence of CR, CRh, PR, or PD</li> </ul>	
SD	Not meeting criteria for CR/CRh, PR, CI, or PD	
PD	Requires $\geq 1$ element from the criteria below; duration must be $\geq 4$ weeks:	
	<b>Baseline</b>	<b>Post Baseline</b>
	Any Grade 2 non-hematologic organ damage	<ul style="list-style-type: none"> <li>• Worsening by 1 grade <i>and</i></li> <li>• Minimum 100% increase (doubling) of laboratory abnormality</li> </ul>
	Grade $\geq 2$ albumin	<ul style="list-style-type: none"> <li>• Worsening by 1 grade <i>and</i></li> <li>• Decrease by <math>\geq 0.5</math> g/dL</li> </ul>
	Grade $\geq 3$ non-hematologic organ damage	Minimum 100% increase (doubling) of laboratory abnormality
	Grade $\geq 2$ transfusion-independent anemia or thrombocytopenia	New transfusion dependence for an 8-week period of $\geq 4$ units of PRBCs or platelets

ANC, absolute neutrophil count; BM, bone marrow; CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts; Hgb, hemoglobin; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment; MC, mast cells; PRBCs, packed red blood cells; PD, progressive disease; PR, partial remission; SD, stable disease; SM, systemic mastocytosis.