



# Suspecting and Diagnosing Advanced SM

Advanced SM is a clonal mast cell neoplasm caused by the KIT D816V mutation in ~95% of cases.<sup>1-3</sup>

## INDICATION

AYVAKIT™ (avapritinib) is indicated for the treatment of adult patients with Advanced SM (AdvSM) including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

Limitations of Use: AYVAKIT is not recommended for the treatment of patients with AdvSM with platelet counts of  $<50 \times 10^9/L$ .

**Please see Important Safety Information on pages 6 & 7 and [click here](#) to see full Prescribing Information for AYVAKIT.**

# Patient experience: Disease burden and diagnostic delay

Advanced SM is a clonal mast cell neoplasm **caused by the KIT D816V mutation in ~95% of cases.**<sup>1-3</sup> There are 3 different subtypes of Advanced SM: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).<sup>4,5</sup>

**People living with Advanced SM can experience significant symptom burden (including organ damage) and impact to their quality of life.**<sup>6,7</sup>

Organ damage caused by mast cell infiltration is considered a “C” finding—part of the WHO diagnostic criteria for Advanced SM.<sup>5</sup>

## DIAGNOSING ADVANCED SM CAN TAKE YEARS

**3  
YEARS**

The median time from symptom onset to diagnosis for patients with Advanced SM is 3 years.<sup>6,\*</sup>

**36%**

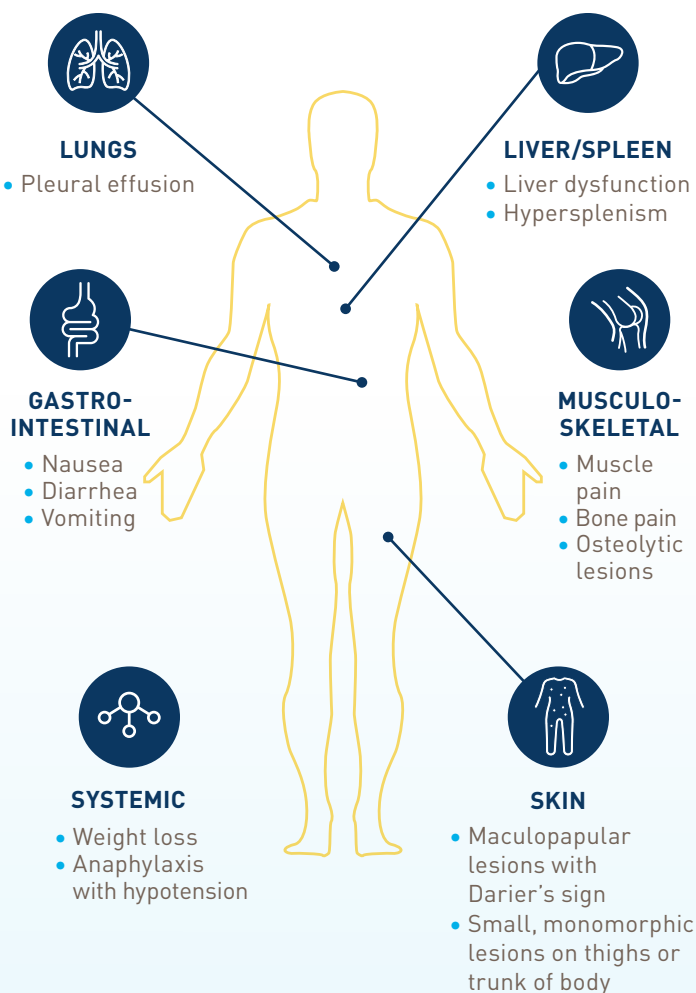
In a retrospective analysis of patients with Advanced SM, about 36% (51/140) were misdiagnosed.<sup>8</sup>

\*Based on a survey in patients with Advanced SM (n=13).

# Identifying Advanced SM in your practice

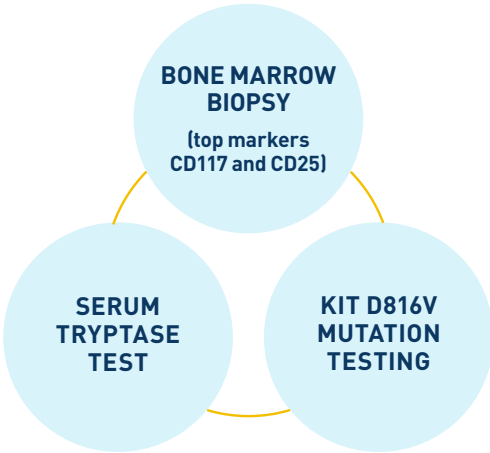
Knowing the symptoms of Advanced SM may help you shorten a patient's time to diagnosis.

Common mast cell mediator symptoms of Advanced SM include maculopapular rash and life-threatening anaphylaxis.<sup>6</sup> Additionally, patients can experience organ damage and related symptoms depicted below<sup>1,5,6,9,10</sup>:



# Testing for and diagnosing Advanced SM

Accurately evaluating a patient for Advanced SM is a multistep process. The diagnostic workup for suspected Advanced SM includes<sup>7,11</sup>:



**Advanced SM may be missed in patients with suspected myeloid neoplasms. Incidental KIT mutation findings should prompt a full diagnostic workup for Advanced SM.**<sup>8,12</sup>

Myeloid mutation panels alone may fail to detect KIT D816V, as NGS assays can exhibit low sensitivity. Higher-sensitivity assays can be used to detect KIT D816V in most patients with Advanced SM.<sup>11,13</sup>

Confirming a diagnosis of Advanced SM can help you determine the treatment course that may be best for your patient.



**Performing a high-sensitivity (<1%) KIT D816V assay is recommended** for patients where Advanced SM is suspected.<sup>7,11</sup>

NGS=next-generation sequencing.

# WHO diagnostic criteria

DIAGNOSIS OF ADVANCED SM REQUIRES THE PRESENCE OF 1 MAJOR CRITERION AND  $\geq 1$  MINOR CRITERION, OR  $\geq 3$  MINOR CRITERIA<sup>14</sup>

## MAJOR CRITERION

Multifocal aggregates of  $\geq 15$  mast cells in bone marrow sections and/or other extracutaneous organ(s)

## MINOR CRITERIA

- In biopsy sections of bone marrow or other extracutaneous organs,  $>25\%$  of mast cells in the infiltrate are spindle-shaped or have atypical morphology; or  $>25\%$  of all mast cells in bone marrow aspirate smears are immature or atypical
- Detection of an activating point mutation at codon 816 in KIT in bone marrow, blood, or another extracutaneous organ
- Mast cells in bone marrow, blood, or other extracutaneous organs express CD25, with or without CD2, in addition to normal MC markers
- Serum total tryptase persistently  $>20$  ng/mL (if the patient has an associated myeloid neoplasm, then this parameter is not valid)

ADDITIONALLY FOR DIAGNOSIS, CRITERIA FOR ONE OF THE ADVANCED SM SUBTYPES MUST BE MET<sup>14</sup>

### AGGRESSIVE SYSTEMIC MASTOCYTOSIS (ASM)

- $\geq 1$  "C" findings<sup>a</sup> and no evidence of mast cell leukemia

### SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGICAL NEOPLASM (SM-AHN)

- Also meets criteria for AHN as a distinct entity per the WHO classification

### MAST CELL LEUKEMIA (MCL)

- Bone marrow aspirate smears show  $\geq 20\%$  mast cells. In classic cases, mast cells account for  $\geq 10\%$  of peripheral blood white cells

**Subtyping may be complex and require expert consultation<sup>15</sup>**

<sup>a</sup>C-findings: Bone marrow dysfunction manifested by  $\geq 1$  cytopenia(s) [absolute neutrophil count  $<1.0 \times 10^9/L$ , hemoglobin  $<10$  g/dL, or platelets  $<100 \times 10^9/L$ ]; palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension; palpable splenomegaly with hypersplenism; malabsorption with weight loss from gastrointestinal tract mast cell infiltrates; skeletal involvement with large osteolytic lesions and/or pathologic fractures.

## IMPORTANT SAFETY INFORMATION

There are no contraindications for AYVAKIT.

Serious intracranial hemorrhage (ICH) may occur with AYVAKIT treatment; fatal events occurred in <1% of patients. Overall, ICH (eg, subdural hematoma, ICH, and cerebral hemorrhage) occurred in 2.9% of 749 patients who received AYVAKIT. In AdvSM patients who received AYVAKIT at 200 mg daily, ICH occurred in 2 of 75 patients (2.7%) who had platelet counts  $\geq 50 \times 10^9/L$  prior to initiation of therapy and in 3 of 80 patients (3.8%) regardless of platelet counts. Monitor patients closely for risk of ICH including those with thrombocytopenia, vascular aneurysm or a history of ICH or cerebrovascular accident within the prior year. Permanently discontinue AYVAKIT if ICH of any grade occurs. A platelet count must be performed prior to initiating therapy. AYVAKIT is not recommended in AdvSM patients with platelet counts  $< 50 \times 10^9/L$ . Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks. After 8 weeks of treatment, monitor platelet counts every 2 weeks or as clinically indicated based on platelet counts. Manage platelet counts of  $< 50 \times 10^9/L$  by treatment interruption or dose reduction.

Cognitive adverse reactions can occur in patients receiving AYVAKIT. Cognitive adverse reactions occurred in 39% of 749 patients and in 28% of 148 SM patients (3% were Grade >3). Memory impairment occurred in 16% of patients; all events were Grade 1 or 2. Cognitive disorder occurred in 10% of patients; <1% of these events were Grade 3. Confusional state occurred in 6% of patients; <1% of these events were Grade 3. Other events occurred in <2% of patients. Depending on the severity, withhold AYVAKIT and then resume at same dose or at a reduced dose upon improvement, or permanently discontinue.

AYVAKIT can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use an effective method of contraception during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT.

## IMPORTANT SAFETY INFORMATION (CONT.)

Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks after the final dose.

The most common adverse reactions ( $\geq 20\%$ ) were edema, diarrhea, nausea, and fatigue/asthenia.

Avoid coadministration of AYVAKIT with strong and moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce dose of AYVAKIT. Avoid coadministration of AYVAKIT with strong and moderate CYP3A inducers.

To report suspected adverse reactions, contact Blueprint Medicines Corporation at 1-888-258-7768 or the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**Please [click here](#) to see full Prescribing Information for AYVAKIT.**

**References:** 1. Gilreath JA, et al. *Clin Pharmacol*. 2019;11:77-92. 2. Verstovsek S. *Eur J Haematol*. 2013;90(2):89-98. 3. Garcia-Montero AC, et al. *Blood*. 2006;108(7):2366-2372. 4. Valent P, Akin C, Metcalfe DD. *Blood*. 2017;129(11):1420-1427. 5. Gotlib J, et al. *Blood*. 2013;121(13):2393-2401. 6. Jennings SV, et al. *Immunol Allergy Clin North Am*. 2018;38(3):505-525. 7. Theoharides TC, et al. *N Engl J Med*. 2015;373(2):163-172. 8. Schwaab J, et al. *J Allergy Clin Immunol Pract*. 2020;8(9):3121-3127. 9. Hartmann K, et al. *J Allergy Clin Immunol*. 2016;137(1):35-45. 10. Gülen T, et al. *J Intern Med*. 2016;279(3):211-228. 11. Arock M, et al. *Leukemia*. 2015;29(6):1223-1232. 12. Craig JW, et al. *Mod Pathol*. 2020;133(6):1135-1145. 13. Shomali W, Gotlib J. *Hematology*. 2018;2018(1):127-136. 14. Pardanani A. *Am J Hematol*. 2019;94(3):363-377. 15. Pardanani A. *Am J Hematol*. 2021;96(4):508-525.

FOR MORE INFORMATION ON TREATING PATIENTS WITH ADVANCED SM WITH AYVAKIT, GO TO [AYVAKIT.COM/HCP](http://AYVAKIT.COM/HCP) AND REVIEW THE [PRESCRIBING INFORMATION](#)



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