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| CLINICAL Utility of Molecular Testing in  Systemic Mastocytosis  Diagnostic Utility  Genomic profiling is a valuable tool to use alongside morphology and clinical characteristics for subtyping of systemic mastocytosis (SM)1.  Activating point mutations at codon 816 of *KIT* are observed in the majority (>90%) of patients with SM and constitute one of the minor diagnostic criteria for this disease2,3.  The most common activating mutation is *KIT* Asp816Val, however other activating *KIT* mutations have also been reported at the same codon (*e.g.* Asp816His/Tyr) and more rarely other codons2.  *KIT* mutation testing on a bone marrow sample should be considered in cases with high suspicion of SM even when no *KIT* mutation is detectable in the peripheral blood4.  A higher *KIT* Asp816Valallele burden in the peripheral blood suggests multilineage involvement and systemic mastocytosis with an associated haematological neoplasm (SM-AHN) should be considered4.  Cases of advanced SM (particularly SM-AHN) frequently have one or more mutations in addition to *KIT*, including *TET2*, *SRSF2*, *ASXL1*, *RUNX1*, *JAK2*, *NRAS*/*KRAS*, *CBL*, *IDH1/IDH2*, *SF3B1* and *EZH2*5,6.  Prognostic utility  Mutations in *ASXL1* and *RUNX1* have been associated with inferior outcomes in both indolent and advanced SM5,7,8.  Additionally mutations in *NRAS*8 and *SRSF2*5 have been associated with inferior outcomes in some but not all studies.  BIOMARKERS OF RESPONSE TO THERAPY  The *KIT* Asp816Val mutation is resistant to imatinib. Nilotinib and dasatinib also lack significant clinical activity.  SM presenting with rare *KIT* mutations outside the phosphotransferase domain are generally imatinib-sensitive.  *KIT* Asp816Valis the target of avapritinib (specific inhibitor) which has been FDA approved for advanced SM.  Midostaurin (multikinase inhibitor) is effective in advanced SM regardless regardless of *KIT* Asp816Val status9.  Serial monitoring of *KIT* Asp816Valto assess residual disease during or after cytoreductive and targeted therapy or following allogeneic stem cell transplantation may be of value1,4,10.  References  **1.** Reiter A, et al. New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. *Blood* 2020; **135**(16): 1365-76. **2.** Garcia-Montero AC, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood* 2006; **108**(7): 2366-72. **3.** Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, editor. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised 4th edition). Lyon: IARC; 2017. **4.** Arock M, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. *Leukemia* 2015; **29**(6): 1223-32. **5.** Jawhar M, et al. MARS: Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis. *J Clin Oncol* 2019; **37**(31): 2846-56. **6.** Pardanani A, et al. Next-generation sequencing in systemic mastocytosis: Derivation of a mutation-augmented clinical prognostic model for survival. *Am J Hematol* 2016; **91**(9): 888-93. **7.** Muñoz-González JI, et al. Frequency and prognostic impact of KIT and other genetic variants in indolent systemic mastocytosis. *Blood* 2019; **134**(5): 456-68. **8.** Pardanani A, et al. Mayo alliance prognostic system for mastocytosis: clinical and hybrid clinical-molecular models. *Blood Advances* 2018; **2**(21): 2964-72. **9.** Gotlib J, et al. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. *N Engl J Med* 2016; **374**(26): 2530-41. **10.** Jawhar M, et al. Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers. *Blood* 2017; **130**(2): 137-45. |