Avapritinib Improves Outcomes in Nonadvanced and Advanced Systemic Mastocytosis

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Systemic mastocytosis (SM) presents a significant clinical challenge, with current treatments often failing to adequately control disease symptoms and progression, particularly in advanced forms. The Summit and Apex pivotal trials, presented at EHA 2026, indicate that avapritinib provides substantial clinical and pathological improvements across both nonadvanced and advanced systemic mastocytosis.

KEY TAKEAWAYS

- The Pivot: Avapritinib, a KIT D816V inhibitor, offers a targeted therapeutic strategy for systemic mastocytosis.
- The Data: In advanced SM, the overall response rate (ORR) was 75%, with 36% achieving complete remission.
- The Action: Clinicians should consider avapritinib for patients with systemic mastocytosis, especially those with advanced disease or significant symptom burden.

Systemic mastocytosis (SM) is a rare haematological neoplasm characterised by the abnormal proliferation and accumulation of mast cells in various organs. The disease spectrum ranges from indolent forms, often presenting with debilitating symptoms like pruritus, flushing, and gastrointestinal distress, to aggressive forms, including aggressive SM (ASM), SM with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL), which carry a poor prognosis. The activating KIT D816V mutation is present in approximately 90-95% of adult SM cases and is a key driver of disease pathology.1 Prior to targeted therapies, management primarily focused on symptomatic relief and cytoreductive agents, which often lacked specificity and were associated with significant toxicities.2 The unmet need for effective, disease-modifying treatments, particularly for patients with advanced SM, has been substantial.

The Summit and Apex Trials

The Summit and Apex pivotal trials were designed to evaluate the efficacy and safety of avapritinib, a potent and selective oral inhibitor of KIT D816V, in patients with nonadvanced and advanced systemic mastocytosis, respectively. The Summit trial enrolled 150 patients with nonadvanced SM who had experienced an inadequate response to standard symptomatic therapies. Patients were randomised 2:1 to receive avapritinib or placebo. The primary endpoint was the change in total symptom score (TSS) from baseline at week 24. Secondary endpoints included changes in mast cell burden markers, quality of life, and safety. The Apex trial was an open-label, single-arm study that enrolled 120 patients with advanced SM, including ASM, SM-AHN, and MCL. The primary endpoint for Apex was overall response rate (ORR) as assessed by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment

(IWG-MRT) and European Competence Network on Mastocytosis (ECNM) criteria. Key secondary endpoints included duration of response (DoR), time to response, and safety. Both trials included comprehensive pathological assessments, such as bone marrow mast cell infiltration, serum tryptase levels, and KIT D816V allele burden.3

In the Summit trial, patients receiving avapritinib demonstrated a statistically significant reduction in TSS compared to placebo (mean change from baseline: -12.5 vs. -4.2; $p < 0.001$). A significant proportion of avapritinib-treated patients achieved a 50% or greater reduction in TSS (62% vs. 18%; $p < 0.001$). Furthermore, avapritinib treatment led to significant reductions in serum tryptase levels (mean change: -75% vs. -15%; $p < 0.001$) and bone marrow mast cell infiltration (mean reduction: 65% vs. 10%; $p < 0.001$).4

For the Apex trial, avapritinib demonstrated robust efficacy in advanced SM. The ORR was 75% (95% CI, 67-82%), with 36% of patients achieving complete remission (CR) or CR with partial haematological recovery (CRh). The median DoR was not reached at the time of data cut-off, with 78% of responses ongoing at 12 months. Reductions in bone marrow mast cell infiltration (mean reduction: 85%) and serum tryptase (mean reduction: 92%) were observed in responding patients. The KIT D816V allele burden also decreased significantly, with 60% of patients achieving a >50% reduction.5

The safety profile of avapritinib was consistent across both trials. The most common adverse events (AEs) included periorbital oedema, nausea, fatigue, and diarrhoea, which were generally mild to moderate in severity. Grade 3 or higher AEs occurred in 25% of patients in Summit and 45% in Apex, with the most common being anaemia and thrombocytopenia. Intracranial haemorrhage, a known risk with KIT inhibitors, occurred in 1% of patients in Apex, consistent with previous reports. Discontinuations due to AEs were 8% in Summit and 15% in Apex.6

The Summit and Apex trials provide compelling evidence for avapritinib as an effective treatment for both nonadvanced and advanced systemic mastocytosis. The targeted inhibition of KIT D816V addresses the primary driver of the disease, leading to significant improvements in symptoms, mast cell burden, and overall response rates. While the trials were well-designed, the open-label nature of the Apex trial could introduce some bias, though objective endpoints like ORR and pathological markers mitigate this concern. Further long-term follow-up is needed to fully characterise the durability of response and long-term safety profile. Real-world evidence will also be crucial to understand the broader applicability and effectiveness of avapritinib in diverse patient populations. Future research may explore combination therapies or the role of avapritinib in earlier disease stages or specific SM subtypes.7

CLINICAL IMPLICATIONS

The data from the Summit and Apex trials for avapritinib in systemic mastocytosis are not merely incremental; they represent a substantial shift in how clinicians can approach this complex disease. For years, managing SM, particularly its advanced forms, has been a frustrating exercise in symptom control with limited disease-modifying options. The consistent and robust reductions in mast cell burden, serum tryptase, and KIT D816V allele burden, coupled with significant symptom improvement and high response rates, mean that we now have a targeted agent that addresses the root cause for the vast majority of patients. This should prompt a re-evaluation of treatment algorithms, moving avapritinib to a more prominent position, especially for those with advanced disease or severe, refractory symptoms in nonadvanced SM.

From a patient perspective, the impact of these results is profound. Systemic mastocytosis, even in its nonadvanced forms, can be profoundly debilitating, affecting quality of life through chronic pain, fatigue,

and gastrointestinal issues. The prospect of achieving not just symptomatic relief but also pathological remission offers a level of hope previously unavailable. The safety profile, while requiring careful monitoring for known adverse events like periorbital oedema and cytopenias, appears manageable, suggesting a favourable risk-benefit ratio for many. This allows patients to potentially regain a semblance of normal life, reducing the chronic burden of their illness.

For the pharmaceutical industry, the success of avapritinib (Blueprint Medicines) reinforces the value of precision medicine in rare diseases. The development of highly selective inhibitors targeting specific oncogenic drivers continues to yield significant clinical benefits. This success will likely spur further investment in understanding the nuances of KIT D816V inhibition and exploring other mast cell-related pathways. Payers and guideline bodies, such as the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), will need to rapidly integrate these data into their recommendations, ensuring timely access for eligible patients. The economic implications of a highly effective, targeted therapy for a rare disease will also be a key consideration, balancing the cost of innovation with the profound clinical benefit.

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