KIT D816V-SELECTIVE TYROSINE KINASE INHIBITORS FOR THE TREATMENT OF ADVANCED SYSTEMIC MASTOCYTOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF EFFICACY AND SAFETY OUTCOMES

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INTRODUCTION AND AIM

Advanced systemic mastocytosis (AdvSM) is a rare clonal disorder defined by extracutaneous accumulation of mast cells. Despite the success of recent targeted therapies, AdvSM remains incurable. KIT D816V-selective tyrosine kinase inhibitors (TKIs) are first-line treatments, but comparative data on their long-term safety and efficacy remain scarce.[1–5]

Aim: To evaluate the comparative efficacy and safety of KIT D816V-selective tyrosine kinase inhibitors—avapritinib, midostaurin, and bezuclastinib—in patients with advanced systemic mastocytosis (AdvSM) through a systematic review and meta-analysis.

METHOD

Search Strategy & Analysis

- PubMed, Embase, Cochrane CENTRAL, and Google Scholar searched through February 2026.
- Five trials comprising 305 patients evaluating avapritinib, midostaurin, and bezuclastinib were included.[1–5]
- Efficacy outcomes: objective response rate (ORR), ≥50% reduction in serum tryptase, 12-month overall survival (OS) and progression-free survival (PFS).
- Safety outcomes: incidence of severe (Grade ≥3) neutropenia, thrombocytopenia, anemia, and non-hematologic toxicities.
- Analyzed in RevMan 5.4 using a generic inverse-variance random-effects model to calculate proportional fractions (Pf).[6]

CONCLUSIONS

Avapritinib delivers the highest response rates and deepest remissions in AdvSM, reinforcing its role as a preferred frontline therapy—though its association with severe neutropenia demands strict baseline patient selection and continuous hematologic monitoring.

Midostaurin and the investigational TKI bezuclastinib offer more favorable safety profiles and may be preferable for patients at high baseline risk of hematologic toxicity.

Indirect comparisons in the absence of head-to-head trials, substantial cross-study heterogeneity and small sample sizes typical of this rare disease, collectively limit the precision and generalizability of these pooled efficacy and safety estimates. Additionally, survival data for newer agents like bezuclastinib remain immature. This warrants a need for more direct comparative clinical trials to more definitively establish relative efficacy and safety.

RESULTS

Key Findings

- Five trials comprising 305 patients evaluated avapritinib, midostaurin, and bezuclastinib.[1–5]
- Avapritinib had the highest ORR (Pf=75.2%; 95% CI 64.9–83.2; p<0.001) and highest proportion achieving ≥50% tryptase reduction (Pf=94.8%; 95% CI 80.6–98.8; p<0.001).[3,4]
- Avapritinib also showed the highest 12-month OS (Pf=85.5%; p<0.001) and PFS (Pf=82.1%; p=0.005), but carried the highest risk of neutropenia (Pf=21.3%; 95% CI 15.3–29.6; p<0.001).[3,4]
- Midostaurin was associated with the highest risk of severe non-hematologic adverse events (Pf=66.8%; 95% CI 54.3–77.2; p=0.009).[1,2]
- Bezuclastinib demonstrated the lowest risk of severe thrombocytopenia (Pf=6.5%; 95% CI 2.0–21.9; p=0.0002).[5]

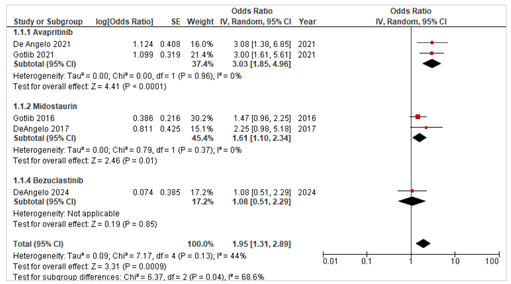

Figure 1. Forest plot of objective response rate (ORR) across avapritinib, midostaurin, and bezuclastinib trials (overall OR 1.95, 95% CI 1.31–2.89; Z=3.31, p=0.0009).

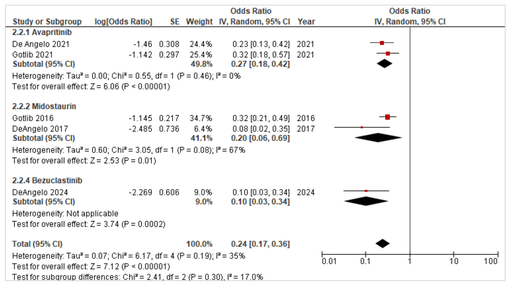

Figure 2. Forest plot of severe (Grade ≥3) neutropenia across avapritinib, midostaurin, and bezuclastinib trials (overall OR 0.24, 95% CI 0.17–0.36; Z=7.12, p<0.00001).

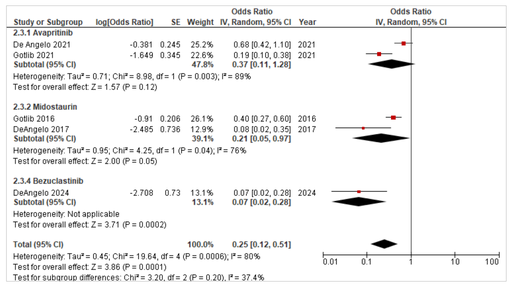

Figure 3. Forest plot of severe (Grade ≥3) thrombocytopenia across avapritinib, midostaurin, and bezuclastinib trials (overall OR 0.25, 95% CI 0.12–0.51; Z=3.86, p=0.0001).

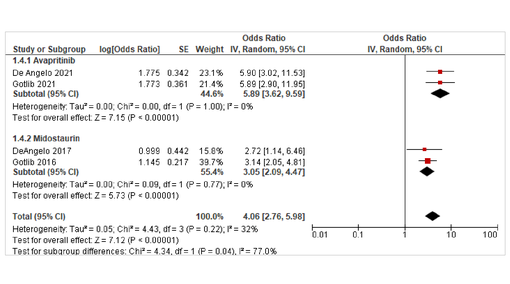

Figure 4. Forest plot of 12-month overall survival (OS) across avapritinib and midostaurin trials (overall OR 4.06, 95% CI 2.76–5.98; Z=7.12, p<0.00001).

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