blood® Blood Spotlight

Avapritinib for advanced systemic mastocytosis

Jason Gotlib,[1] Andreas Reiter,[2] and Daniel J. DeAngelo[3]

[1]Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA; [2]Department of Hematology and Oncology, University Hospital Mannheim, Mannheim, Germany; and [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Avapritinib, a highly selective inhibitor of KIT D816V, was approved by the Food and Drug Administration in 2021 for treatment of advanced systemic mastocytosis (AdvSM) and by the European Medicines Agency in 2022 for AdvSM after prior systemic therapy. The phase 1 EXPLORER and phase 2 PATHFINDER trials demonstrated that avapritinib can elicit complete and durable clinical responses and molecular remission of *KIT* D816V. Key management challenges relate to the complex mutational landscape of AdvSM, often found with an associated hematologic neoplasm.

Introduction

Advanced systemic mastocytosis (AdvSM) comprises 3 subtypes: aggressive systemic mastocytosis (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).[1-4] SM-AHN is the most frequently occurring (60% to 70%) AdvSM subtype. It is defined by the presence of both SM and an associated (almost always) myeloid neoplasm, the most common being a myelodysplastic/myeloproliferative neoplasm (eg, chronic myelomonocytic leukemia).[5-9] Historically, the overall survival (OS) of AdvSM has ranged up to 3 to 4 years, with MCL exhibiting the worst survival (<6 months to 2 years).[5,10-16]

Using highly sensitive polymerase chain reaction assays, the *KIT* D816V driver mutation is detected in 90% to 95% of patients with AdvSM.[17-20] The biologic and clinical heterogeneity of these neoplasms in part relates to the multilineage involvement of *KIT* D816V and the presence of a multimutated clonal landscape involving high-risk gene mutations (eg, *SRSF2*, *ASXL1*, and/or *RUNX1* [*S/A/R* panel]), as well as other pathogenic somatic variants commonly found in SM-AHN.[7,21-25] The high frequency of *KIT* D816V in mast cells (MCs) and AHN-derived cells (eg, monocytes in chronic myelomonocytic leukemia) make it an attractive therapeutic target.[26,27] However, the complex molecular profile of most AdvSM cases and the presence of an AHN may contribute to resistance and progression in the setting of KIT inhibitor monotherapy.[28]

KIT inhibition in AdvSM was first evaluated with the multikinase/KIT inhibitor midostaurin. The overall response rates (ORRs) in an investigator-initiated trial[29] and a single-arm, phase 2, non-randomized registrational trial (89 evaluable patients with ≥1 C findings)[30] were 69% and 60% (45% major responses), respectively, by modified criteria of Valent et al[31] and Cheson et al.[32] The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) performed post hoc analyses using response criteria of the International Working Group (IWG)-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis,[33] resulting in ORRs of 28% and 17%, respectively, the difference reflecting the FDA's decision not to include the category of clinical improvement (CI). Midostaurin elicited significant reductions of bone marrow (BM) MC burden, serum tryptase levels, and splenomegaly. It improved quality of life and reduced symptoms, except for nausea and vomiting, which are common midostaurin-related adverse events (AEs). The median progression-free survival (PFS) was 14.1 months and the OS was 28.7 months. These data led to FDA and EMA approval of midostaurin for AdvSM in 2017,[34,35] and established benchmarks for response and survival using KIT inhibition in these diseases.

Avapritinib

Avapritinib (Blueprint Medicines; Cambridge, MA) exhibits increased selectivity for D816V-mutated KIT compared with midostaurin, as well as 10-fold greater potency in vitro (50% inhibitory concentration for KIT D816V kinase activity, 0.27 nM vs 2.9 nM).[36] The centrally adjudicated phase 1 EXPLORER study (registered on https://www.clinicaltrials.gov as #NCT02561988) of patients with AdvSM-evaluated avapritinib at doses ranging from 30 to 400 mg orally daily, followed by a dose-expansion phase (n = 47), which evaluated 2 dose cohorts of 200 and 300 mg daily.[37] The primary end points were the maximum tolerated dose, recommended phase 2 dose, and safety. Secondary end points included ORR and changes in measures of MC burden. Although a maximum tolerated dose was not reached, 200 mg was ultimately chosen as the recommended phase 2 dose based on a composite of safety/tolerability, pharmacokinetics, efficacy, and reductions in measures of MC burden.

Among the 69 evaluable patients, the ORR was 75% according to modified IWG (mIWG) criteria, including a 36% overall complete remission (CR) rate (21% CR and 15% CR with partial hematologic recovery [CRh]).[37] Serial BM biopsies demonstrated reduction or elimination of MC aggregates, loss of MC CD25 expression, reversion of spindled MC morphology, and improvement of fibrosis.[38] A molecular CR was achieved in 30% of patients. The ORR and CR+CRh rates in midostaurin-naive vs midostaurin-treated patients were 83% vs 59% and 44% vs

18%, respectively. Similar ORRs were observed in patients with or without *S/A/R* mutations (74% vs 77%).[37] The estimated PFS rates in the response-evaluable population (n = 53) were 84% at 12 months and 63% at 24 months. During a median follow-up of 23 months, 14 patients (20%) exhibited disease progression, including 6 (9%) with transformation to secondary acute myeloid leukemia (AML). Molecular analyses of clinical progressors vs nonprogressors showed no consistent pattern of baseline or on-treatment myeloid mutations, changes in the variant allele frequency (VAF) of certain genes, or resistance mutations in *KIT*.[39]

The phase 2 PATHFINDER study (#NCT03580655) reported interim results in 32 response-evaluable patients treated with a starting dose of 200 mg daily.[40] The ORR was 75%, including 19% with a CR/CRh. An AdvSM Symptom Assessment Form showed that the mean total symptom scores (TSSs) improved rapidly after treatment initiation, decreasing by 7.1 points at cycle 3 from a baseline score of 18.3 and by 9.8 points by cycle 11 (P < .001).[40] Decreases in TSS mirrored improvements in quality of life assessed by the EORTC-QLQ-C30.

Pooled analysis of efficacy and safety for EXPLORER and PATHFINDER

Efficacy

A pooled analysis of 53 response-evaluable patients from EXPLORER and PATHFINDER initiated at an avapritinib dose of ≤200 mg daily was conducted.[41] Figure 1 displays the marked improvements of BM MC burden, serum tryptase level, spleen volume, and *KIT* D816V VAF. The pooled ORR response rate was 72% (CR/CRh [28%]+PR [28%]+CI [15%]) and deepening mIWG responses were observed over time (Figure 2). Median duration of response and treatment and time to overall response and CR/CRh are also shown.

Sixty percent of patients had dose interruptions, 68% had dose reductions, and 10% permanently discontinued the drug because of AEs (5% were treatment-related events).[41] There were 2 (3%) AE-related deaths, but neither was considered treatment related. Median time to first dose reduction caused by AEs was 6.9 weeks and the median dose at 6 months in the AdvSM population was 100 mg daily.[41]

Thirty-one of the 53 patients in the pooled population had been previously treated. The ORR in this subgroup was 71%, including a CR/CRh rate of 19%.[42] At a median follow-up of 17.7 months, OS at 12 and 24 months was 80% and 65%, respectively; the median OS was not reached in this previously treated population.

Safety

In the overall safety population of 131 patients who started avapritinib at doses of 30 to 400 mg daily (median follow-up, 12.7 months),[41] the most common nonhematologic AE (all grades %/grade ≥3%) were peripheral/periorbital edema (81%/4%), diarrhea (34%/<1%), nausea (31%/3%), fatigue/asthenia (28%/7%), and cognitive effects (25%/2%) (eg, memory impairment, confusional state, and encephalopathy).[41] Hematologic AEs included neutropenia (17%/16%), anemia (44%/27%), and the grouped terms thrombocytopenia/platelet count decreased (50%/30%). Progressive cytopenias may not only reflect avapritinib-related myelosuppression, but also persistence of the AHN.[43]

In the EXPLORER study, intracranial bleeding (ICB) occurred in 9 (13%) patients; 5 cases were asymptomatic (grade 1 and detected by prespecified protocol MRI brain imaging; 2 events were grade 2, and 1 each was grades 3 and 5 [the latter associated with head trauma]).[37] Seven of the 9 cases occurred in the setting of antecedent thrombocytopenia (platelet count, <50 × 10^9/L). No other consistent risk factors for ICB (eg, coagulopathy, use of antiplatelet or anticoagulant agents) were identified. Mitigation procedures were undertaken, including exclusion of patients with a platelet count <50 × 10^9/L, dose hold and reduction for emergent thrombocytopenia below this level, and increased platelet monitoring and transfusion support. These measures resulted in a decrease in ICBs in PATHFINDER[40]: 1 patient (1.6%) experienced a grade 2 subdural hematoma in the setting of progressive severe thrombocytopenia and before exclusion criteria were implemented. The FDA approved avapritinib in June 2021 for adults with all subtypes of AdvSM, but it is not recommended for patients with a platelet count of <50 × 10^9/L.[44] In March 2022, the EMA granted approval of avapritinib for patients with AdvSM after at least 1 systemic therapy.[45]

Long-term outcomes

In the EXPLORER overall AdvSM safety population, the median OS was not reached with a median follow-up duration of 23 months.[37] Patients without *S/A/R* mutations had longer OS compared with those with *S/A/R* mutations, and a baseline mutation-adjusted risk score ≥2 was associated with worse OS. Estimated 24-month OS rates were 76% for all patients with AdvSM, and 100%, 67%, and 92% for ASM, SM-AHN, and MCL subtypes, respectively.[37] The comparative estimated 24-month OS rates from the midostaurin registrational trial were 53% for all patients with AdvSM, and 86%, 49%, and 26% for ASM, SM-AHN, and MCL, respectively.[30] In the pooled analysis of 53 response-evaluable patients with AdvSM from EXPLORER and PATHFINDER with treatment initiated at an avapritinib of ≤200 mg daily, the estimated median OS for all patients with AdvSM was 46.9 months.[41]

A recent study compared pooled outcomes from EXPLORER and PATHFINDER vs patients treated with best available therapy collected through a multicenter, observational, retrospective chart review study conducted at 6 sites.[46] Avapritinib-treated patients exhibited significantly improved survival (adjusted hazard ratio, 0.48; 95% confidence interval, 0.29, 0.79; P = .004), significantly longer duration of treatment (23.8 vs 5.4 months; P < .001), and a 60% greater mean difference in the percentage of maximum reduction of serum tryptase levels. In the absence of prospective randomized trials, these real-world data provide a useful appraisal of the comparative activity and long-term outcomes of these treatments. A matching-adjusted, indirect treatment comparison between the patients enrolled in the trials of midostaurin and avapritinib also corroborated statistically significant improved ORR/CR rates and survival for avapritinib vs midostaurin.[47]

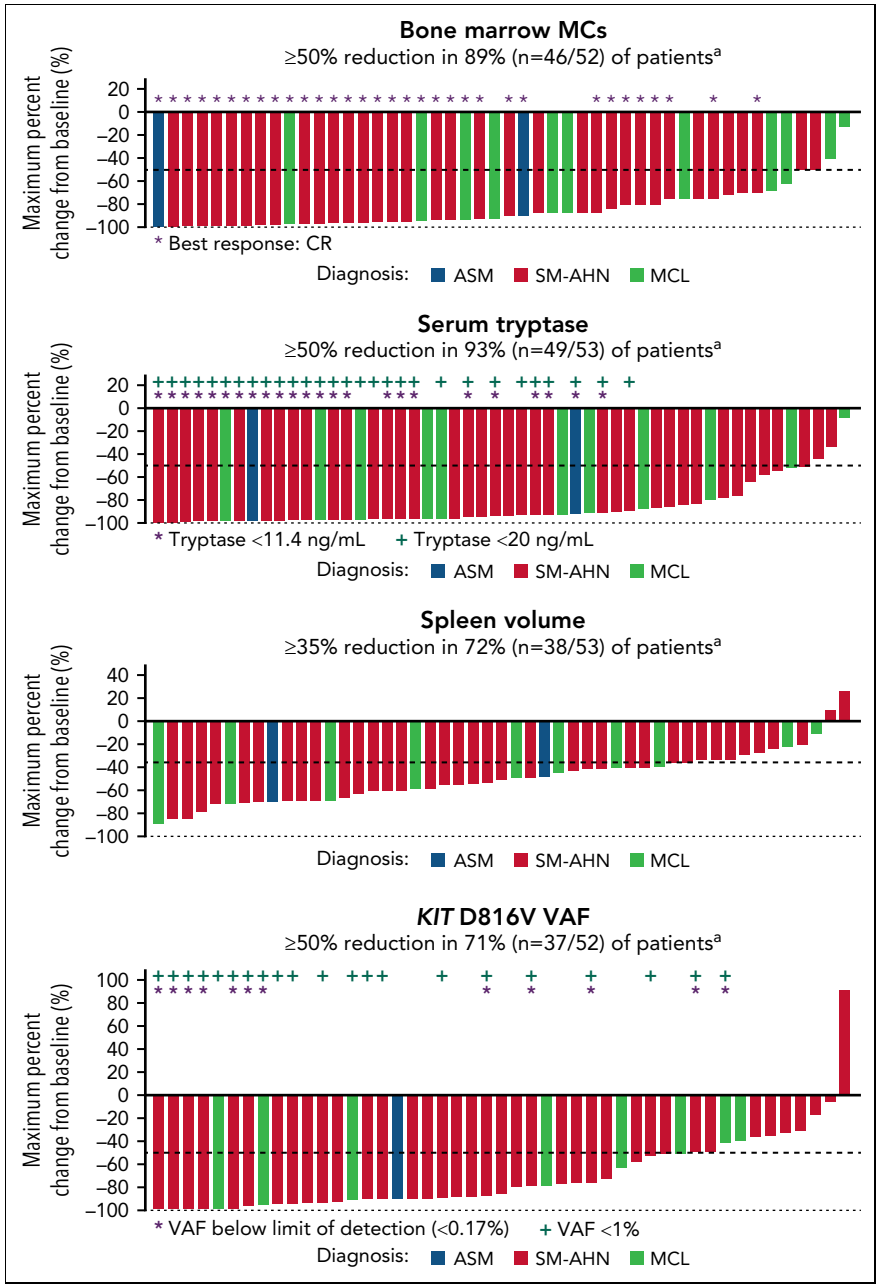


Figure 1. Reduction in measures of mast cell burden: pooled results from the phase 1 EXPLORER and interim phase 2 PATHFINDER studies. Waterfall plots demonstrating maximum percentage change from baseline in BM mast cell burden, serum tryptase level, spleen volume, and *KIT* D816V VAF. Data cutoff dates were 27 May 2020 for EXPLORER and 23 June 2020 for PATHFINDER. [a]Calculation includes patients without postbaseline assessments who were excluded from the waterfall plot.

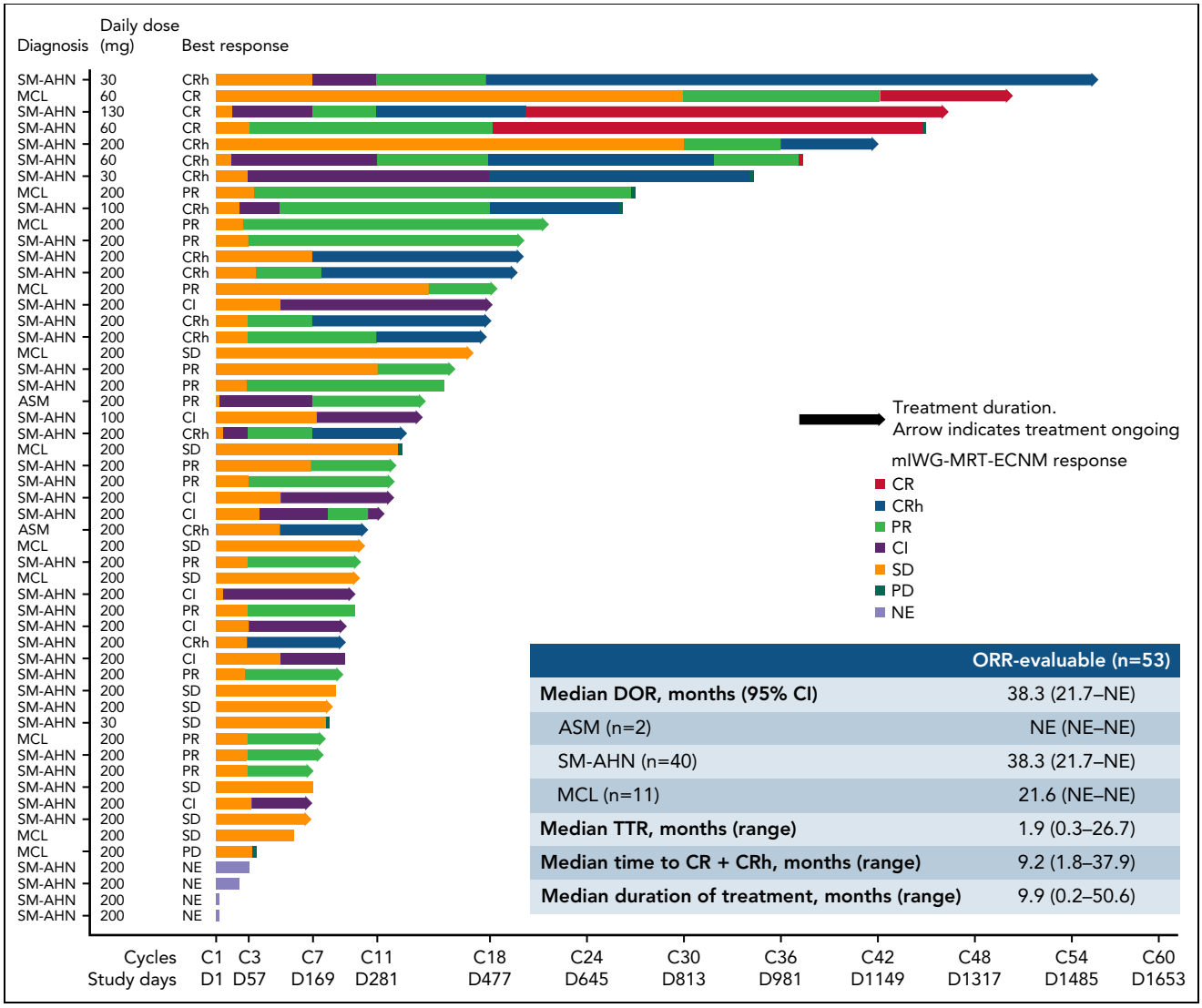
Future questions and challenges

Molecular remission of *KIT* D816V

Molecular remission of *KIT* D816V with avapritinib reflects a new response benchmark and should be a treatment goal in clinical practice.[37] *KIT* D816V VAF reflects all involved lineages: SM and, if present in the PB, the AHN.[7,17,24,25] Standards for molecular monitoring of *KIT* D816V and the concept of minimal residual disease (MRD) in AdvSM should be established, including optimal polymerase chain reaction assays and their sensitivities, preferred tissue compartment, and consensus definitions for levels of remission. Open questions relevant to MRD in AdvSM include (1) whether achievement of a molecular remission translates into prolonged PFS and OS; (2) whether the benefits of MRD negativity apply only to AdvSM subtypes without an AHN or the presence of a multimutated landscape beyond *KIT* D816V; and (3) whether molecular remissions permit time-limited treatment and the possibility of durable treatment-free remission.

SM-AHN

In clinical trials and daily practice, the major unmet therapeutic needs of SM-AHN include clinical progression and frank transformation to secondary AML. These needs have sparked interest in combining avapritinib with AHN-directed therapy. Although



	ORR-evaluable (n=53)
Median DOR, months (95% CI)	38.3 (21.7–NE)
ASM (n=2)	NE (NE–NE)
SM-AHN (n=40)	38.3 (21.7–NE)
MCL (n=11)	21.6 (NE–NE)
Median TTR, months (range)	1.9 (0.3–26.7)
Median time to CR + CRh, months (range)	9.2 (1.8–37.9)
Median duration of treatment, months (range)	9.9 (0.2–50.6)

Figure 2. mIWG-MRT-ECNM responses over time: pooled results from the phase 1 EXPLORER and interim phase 2 PATHFINDER studies. Swimmer plots demonstrate deepening mIWG-MRT-ECNM responses over time in 53 overall response-evaluable patients from the pooled population of patients treated with avapritinib at a dose of ≤200 mg daily. CI, clinical improvement; DOR, duration of response; mIWG-MRT-ENM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis; NE, not evaluable; PD, progressive disease; SD, stable disease; TTR, time to response.

both avapritinib and midostaurin can elicit marked reductions in PB monocytosis and eosinophilia,[29,30,37,40] the impact of AHN remission on PFS and OS needs more comprehensive study. Because EXPLORER and PATHFINDER excluded patients with ≥10% BM blasts, any conclusions about avapritinib's effects on these AHNs currently extend only to lower-grade disease.

Most AHNs are overlap myelodysplastic syndrome (MDS)/myeloproliferative neoplasms (MPNs), and to a lesser extent MDS or MPNs.[5,6,48] Future study designs will evaluate the feasibility of combining avapritinib with hypomethylating agents (HMAs). Because of the concern for ICBs with higher-grade thrombocytopenia, concurrent avapritinib plus HMA treatment is unlikely to be a tractable approach. A preferable strategy may consist of alternating sequential treatment based on clinical presentation and dynamic clinicopathologic changes in each compartment.

BLU-263 (Blueprint Medicines) is a KIT D816V inhibitor which is equipotent to avapritinib in vitro.[49] It exhibits minimal central nervous system penetration, and therefore is anticipated to produce fewer central nervous system side effects, including cognitive changes and ICB. Similar to the PIONEER trial of avapritinib in ISM, the phase 2/3 HARBOR study (#NCT04910685) is evaluating BLU-263 at doses of 25 to 100 mg daily vs placebo in patients with nonadvanced SM. If ICBs are not identified as a safety signal with doses of BLU-263 required for treatment of AdvSM, it provides a therapeutic window to evaluate concurrent and sequential combination strategies with AHN-directed therapies. It may also open the door to triplet regimens, such as the addition of venetoclax to KIT inhibitor/HMA combinations in high-risk SM-AHN.

Transplant considerations

The role of allogeneic hematopoietic stem cell transplantation (HSCT) is not well defined. In the retrospective series of allogenic HSCT in 57 patients, conducted in the pre-KIT inhibitor era, the ORR was 57%.[50] A diagnosis of MCL and reduced

intensity vs myeloablative conditioning were adverse prognostic factors for OS. Currently, possible considerations for HSCT include (1) patients with higher-risk disease according to mutation-adjusted risk score or other AdvSM prognostic scoring systems; (2) patients without adequate response (eg, primary refractory disease or progression while treated with KIT inhibitors who demonstrate chemoresponsive disease with cladribine or multiagent chemotherapy); or (3) patients on second-line avapritinib at the time of best response. In SM-AHN, HSCT remains a reasonable option, especially in patients with high-risk features within the AHN component. In these individuals, debulking of the SM component with avapritinib may be a useful (but untested) pretransplant strategy. Currently, there is no clinical experience with avapritinib in the pretransplant setting; however, because many patients undergo transplantation without being in CR, they are at a high risk of relapse, and KIT inhibitors should therefore be considered (based on clinical and molecular monitoring). The experience with KIT inhibition after transplant to prevent or treat relapse is similarly limited. In a recently published case, avapritinib elicited a CR of relapsed pediatric AML harboring *RUNX1-RUNX1T1* and the *KIT* D816V mutation.[51]

Conclusion

The hybrid nature of SM-AHN makes it particularly amenable to the study of its clonal architecture under the pressure of KIT inhibition, with or without AHN-directed therapy. Single cell sequencing[52] may provide insights into the molecular ontogeny of the SM and AHN disease compartments and how they co-evolve during response and progression on avapritinib or other KIT D816V inhibitors, including BLU-263 and bezuclastinib (CGT9486; Cogent Biosciences, Inc, Cambridge, MA).[53]

Acknowledgments

This work was supported by the Charles and Ann Johnson Foundation, the Stanford Cancer Institute Clinical Innovation Fund, and the Hematology Clinical Research Group, which supports mastocytosis research at Stanford (J.G.), and the "Deutsche José Carreras Leukämie-Stiftung" (grant DJCLS 08R/2020) (A.R.).

Authorship

Contribution: All authors contributed to the writing and review of the manuscript.

Conflict-of-interest disclosure: J.G. has received research grants (funds for administration of clinical trials) from Novartis, Blueprint Medicines, Deciphera, and Cogent Biosciences; has served on the advisory boards and received honoraria from Blueprint Medicines, Novartis, Deciphera, and Cogent Biosciences; and has received reimbursement of travel expenses from Novartis, and Blueprint Medicines. J.G. has served as Chair of the Central Review Committee for the registrational trial of midostaurin; currently serves as chair of the phase 1 EXPLORER and phase 2 PATHFINDER Response Adjudication Committees and as Chair of the Eligibility Committee and Central Response Review Committee or the APEX trial of bezuclastinib in AdvSM. A.R. has received research grants (funds for administration of clinical trials) from Novartis, Blueprint Medicines, and Deciphera; has served on the advisory boards of and received honoraria from Blueprint Medicines, Novartis, and Deciphera; and has received reimbursement of travel expenses from Novartis and Blueprint Medicines. A.R. has served as a member of the Central Review Committee for the registrational trial of midostaurin and currently serves as a member of the Response Adjudication Committee of the phase 2 PATHFINDER study. D.J.D. has received research funding from AbbVie, Glycomimetics, Novartis, Blueprint Medicines, and Cogent Biosciences; has served on the advisory board and received honoraria from Amgen, Autolos, Agios, Blueprint Medicines, Forty-Seven, Gilead, Incyte, Jazz, Novartis, Pfizer, Servier, and Takeda; is a member of the Data Safety and Monitoring Management Board for Daiichi-Sankyo and Fibrogen and on the Mount Sinai Myeloproliferative Neoplasms (MPN) Research Consortium; serves as a member of the phase 1 EXPLORER and phase 2 PATHFINDER Response Adjudication Committee; is a member of the Eligibility Committee and Central Response Review Committee for the APEX trial of bezuclastinib in AdvSM; and is the Co-Chair of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Leukemia Steering Committee.

ORCID profiles: J.G., 0000-0001-8253-6156; A.R., 0000-0002-7718-6507; D.J.D., 0000-0001-7865-2306.

Correspondence: Jason Gotlib, Stanford Cancer Institute/Stanford University School of Medicine, 875 Blake Wilbur Dr, Room 2324, Stanford, CA. 94305-6555; email: jason.gotlib@stanford.edu.

Footnote

Submitted 23 June 2022; accepted 16 July 2022; prepublished online on *Blood* First Edition 25 July 2022. https://doi.org/10.1182/blood.2021014612.

REFERENCES

1. Valent P, Horny H-P, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res*. 2001;25(7):603-625.
2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
3. Horny HP, Akin C, Arber D, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2017:61-69.
4. Valent P, Akin C, Hartmann K, et al. Updated diagnostic criteria and classification of mast cell disorders: a consensus proposal. *HemaSphere*. 2021;5(11):e646.
5. Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood*. 2009;113(23):5727-5736.
6. Pardanani A, Lim KH, Lasho TL, et al. Prognostically relevant breakdown of 123 patients with systemic mastocytosis associated with other myeloid malignancies. *Blood*. 2009;114(18):3769-3772.
7. Reiter A, George TI, Gotlib J. New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. *Blood*. 2020;135(16):1365-1376.
8. Shomali W, Gotlib J. The new tool "*KIT*" in advanced systemic mastocytosis. *Hematology (Am Soc Hematol Educ Program)*. 2018;2018(1):127-136.
9. Pardanani A. Systemic mastocytosis in adults: 2021 Update on diagnosis, risk stratification and management. *Am J Hematol*. 2021;96(4):508-525.
10. Sperr WR, Kundi M, Alvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. *Lancet Haematol*. 2019;6(12):e638-e649.
11. Pardanani A, Shah S, Mannelli F, et al. Mayo alliance prognostic system for mastocytosis: clinical and hybrid clinical-molecular models. *Blood Adv*. 2018;2(21):2964-2972.
12. Jawhar M, Schwaab J, Álvarez-Twose I, et al. MARS: mutation-adjusted risk score for advanced systemic mastocytosis. *J Clin Oncol*. 2019;37(31):2846-2856.
13. Muñoz-González JI, Álvarez-Twose I, Jara-Acevedo M, et al. Proposed global prognostic score for systemic mastocytosis: a retrospective prognostic modelling study. *Lancet Haematol*. 2021;8(3):e194-e204.

14. Georgin-Lavialle S, Lhermitte L, Dubreuil P, Chandesris MO, Hermine O, Damaj G. Mast cell leukemia. *Blood*. 2013;121(8):1285-1295.

15. Jawhar M, Schwaab J, Meggendorfer M, et al. The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. *Haematologica*. 2017;102(6):1035-1043.

16. Jain P, Wang S, Patel KP, et al. Mast cell leukemia (MCL): clinico-pathologic and molecular features and survival outcome. *Leuk Res*. 2017;59:105-109.

17. Arock M, Sotlar K, Akin C, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. *Leukemia*. 2015;29(6):1223-1232.

18. Kristensen T, Vestergaard H, Bindslev-Jensen C, Møller MB, Broesby-Olsen S; Mastocytosis Centre, Odense University Hospital (MastOUH). Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol*. 2014;89(5):493-498.

19. Gotlib J, Gerds AT, Bose P, et al. Systemic mastocytosis, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2018;16(12):1500-1537.

20. Greiner G, Gurbisz M, Ratzinger F, et al. Digital PCR: a sensitive and precise method for KIT D816V quantification in mastocytosis. *Clin Chem*. 2018;64(3):547-555.

21. Schwaab J, Schnittger S, Sotlar K, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. *Blood*. 2013;122(14):2460-2466.

22. Jawhar M, Schwaab J, Schnittger S, et al. Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V(+) advanced systemic mastocytosis. *Leukemia*. 2016;30(1):136-143.

23. Jawhar M, Schwaab J, Hausmann D, et al. Splenomegaly, elevated alkaline phosphatase and mutations in the SRSF2/ASXL1/RUNX1 gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. *Leukemia*. 2016;30(12):2342-2350.

24. Garcia-Montero AC, Jara-Acevedo M, Teodosio C, 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):2366-2372.

25. Jawhar M, Schwaab J, Schnittger S, et al. Molecular profiling of myeloid progenitor cells in multi-mutated advanced systemic mastocytosis identifies KIT D816V as a distinct and late event. *Leukemia*. 2015;29(5):1115-1122.

26. Sotlar K, Marafioti T, Griesser H, et al. Detection of c-kit mutation Asp 816 to Val in microdissected bone marrow infiltrates in a case of systemic mastocytosis associated with chronic myelomonocytic leukaemia. *Mol Pathol*. 2000;53(4):188-193.

27. Sotlar K, Colak S, Bache A, et al. Variable presence of KITD816V in clonal haematological non-mast cell lineage diseases associated with systemic mastocytosis (SM-AHNMD). *J Pathol*. 2010;220(5):586-595.

28. Jawhar M, Schwaab J, Naumann N, et al. Response and progression on midostaurin in advanced systemic mastocytosis: *KIT* D816V and other molecular markers. *Blood*. 2017;130(2):137-145.

29. DeAngelo DJ, George TI, Linder A, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia*. 2018;32(2):470-478.

30. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med*. 2016;374(26):2530-2541.

31. Valent P, Akin C, Sperr WR, et al. Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. *Leuk Res*. 2003;27(7):635-641.

32. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108(2):419-425.

33. Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. *Blood*. 2013;121(13):2393-2401.

34. Center for Drug Evaluation and Research. Medical review. avapritinib. Accessed 19 June 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207997Orig1Orig2s000MedR.pdf

35. European Medicines Agency. Summary of Product Characteristics: Midostaurin. Accessed 19 June 2022. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/rydapt

36. Evans EK, Gardino AK, Kim JL, et al. A precision therapy against cancers driven by *KIT/PDGFRA* mutations. *Sci Transl Med*. 2017;9(414):eaao1690.

37. DeAngelo DJ, Radia DH, George TI, et al. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. *Nat Med*. 2021;27(12):2183-2191.

38. George TI, Karner KH, Moser KA, et al. Efficacy of avapritinib in patients with advanced systemic mastocytosis: hematologic and bone marrow responses from the phase 2 open-label, single-arm, pathfinder study [abstract]. *Blood*. 2021;138(suppl 1). Abstract 2565.

39. Deininger MW, DeAngelo DJ, Radia DH. Effective control of advanced systemic mastocytosis with avapritinib: mutational analysis from the EXPLORER clinical study [abstract]. *Blood*. 2021;138(suppl 1). Abstract 318.

40. Gotlib J, Reiter A, Radia DH, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. *Nat Med*. 2021;27(12):2192-2199.

41. Radia D, DeAngelo DJ, Deininger DW, et al. Efficacy and safety of ≤200 mg avapritinib in patients with advanced systemic mastocytosis: pooled results from the phase 1 EXPLORER and phase 2 PATHFINDER studies [abstract]. *Clin Lymphoma Myeloma Leukemia*. 2021;21(suppl 1):S367-S368.

42. Reiter A, Schwaab J, DeAngelo DJ, et al. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis [published online ahead of print 31 May 2022]. *Blood Adv*. https://doi.org/10.1182/bloodadvances.2022007539.

43. Shomali W, Gotlib J. Response criteria in advanced systemic mastocytosis: evolution in the era of KIT inhibitors. *Int J Mol Sci*. 2021;15(22):2983.

44. Food and Drug Administration. Medical review. Avapritinib: highlights of prescribing information. Accessed 19 June 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212608s007lbl.pdf

45. European Medicines Agency. Summary of Product Characteristics: Ayvakyt. Accessed 19 June 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf

46. Reiter A, Gotlib J, Álvarez-Twose I, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. *Leukemia*. 2022;36(8):2108-2120.

47. Pilkington H, Smith S, Roskell N, Iannazzo S. Indirect treatment comparisons of avapritinib versus midostaurin for patients with advanced systemic mastocytosis. *Future Oncol*. 2022;18(13):1583-1594.

48. Valent P, Oude Elberink JNG, Gorska A, et al; Study Group of the European Competence Network on Mastocytosis (ECNM). The data registry of the European Competence Network on Masotcytosis (ECNM): set up, projects, and perspectives. *J Allergy Clin Immunol Pract*. 2019;7(1):81-87.

49. Castells M, Bhavsar V, He K, Scherber R, Akin C. European Hematology Association Congress. HARBOR, a phase 2/3 study of BLU-263 in patients with indolent systemic mastocytosis and monoclonal mast cell activation syndrome [abstract]. *Hemasphere*. 2022;6(suppl):907-908.

50. Ustun C, Reiter A, Scott BL, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. *J Clin Oncol*. 2014;32(29):3264-3274.

51. Xue S, Huang W, Liu F, et al. Rapid response to avapritinib of acute myeloid leukemia with t(8;21) and *KIT* mutation relapse post allo-HSCT. *Leuk Lymphoma*. 2022;19:1-4.

52. Grootens J, Ungerstedt JS, Ekoff M, et al. Single-cell analysis reveals the KIT D816V mutation in haematopoietic stem and progenitor cells in systemic mastocytosis. *EBioMedicine*. 2019;43:150-158.

53. Gotlib J, George TI, Deininger MW, et al. A phase 2 study of bezuclastinib (CGT9486), an oral, selective, and potent KIT D816V inhibitor, in adult patients with advanced systemic mastocytosis [abstract]. *Blood*. 2021;138(suppl 1). Abstract 3636.