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Efficacy and safety of avapritinib in advanced systemic mastocytosis: 4-year follow-up of the PATHFINDER study

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Abstract:
Advanced systemic mastocytosis (AdvSM), a clonal hematologic neoplasm driven predominantly by D816V-mutant KIT, is often characterized by organ damage. Associated hematologic neoplasms (AHN; usually myeloid) are often present, leading to poor survival. We report on the oral, highly selective, potent KIT D816V inhibitor avapritinib (200-mg once-daily starting dose) with >4 years follow-up from the fully enrolled PATHFINDER (NCT03580655) study. Endpoints included overall response rate (ORR; primary), duration of response (DOR), progression-free survival (PFS), overall survival (OS), changes in objective biomarkers of disease, and safety (all secondary). Of 107 patients with AdvSM (including 71 [66%] with SM-AHN; overall population median follow-up: 49 months), 83 were response evaluable. ORR was 73% (95% confidence interval [95% CI], 63%-83%). Median DOR was 58 months, PFS 51 months, and OS 62 months. Disease progression occurred in 21/107 patients, predominantly in SM-AHN and largely driven by the AHN. Reductions in objective biomarkers of disease were observed. Most frequent (≥30% patients) treatment-emergent adverse events (TEAEs) (any grade; grade ≥3) were thrombocytopenia (58%; 31%); periorbital edema (57%; 6%), anemia (54%; 33%), peripheral edema (48%; 2%), and diarrhea (36%; 5%). Adverse events of special interest were cognitive effects (34%; 8%) and intracranial bleeds (4%, 2%). Eleven (10%) patients experienced TEAEs leading to death, of which 1 was deemed related to avapritinib by the principal investigator. With 4-year follow-up, avapritinib-treated patients with AdvSM experienced deep and durable responses and a favorable benefit-risk profile.

Conflict of interest: COI declared - see note

COI notes: J.G. is the chair of the Response Adjudication Committee, has received research funding, served on advisory boards, and received honoraria and funding to cover travel expenses from Blueprint Medicines Corporation. A.R. has received research funding, served on advisory boards, and received honoraria and funding to cover travel expenses from AbbVie, AOP, Blueprint Medicines Corporation, BMS, Cogent, GSK, Incyte, and Novartis. D.H.R. has been a clinical advisory board/study steering group member (EXPLORER/PATHFINDER) for Blueprint Medicines Corporation; a study steering committee member for Cogent Biosciences; involved in educational events and advisory boards for Novartis; and received author fees for Medscape cases. I.A.T. has received research funding from Blueprint Medicines Corporation and has received advisory board or speaker fees from Blueprint Medicines Corporation and Novartis. M.W.D. has received honoraria fees from Blueprint Medicines Corporation, Incyte, Medscape, Sangamo, and Takeda. Received consultancy fees from Blueprint Medicines Corporation, DisperSol, Fusion Pharma, Novartis, and Sangamo. Received research funding from Blueprint Medicines Corporation, Incyte, Leukemia & Lymphoma Society, Novartis, Pfizer, SPARC, and Takeda, is part of a study management committee for Blueprint Medicines Corporation and Takeda, and is a case author for Medscape. T.I.G. has received consulting fees and is a study steering committee member for Blueprint Medicines Corporation, BMS/Celgene, Cogent Biosciences, and Incyte. J.P. has received honorarium fees from Apellis, Alexion, AstraZeneca, Blueprint Medicines Corporation, BMS, Cogent, F. Hoffmann-La Roche, Grünenthal, MSD, Novartis, Omeros, Samsung Bioepis, and SOBI; and has served on the speaker's bureau of Alexion, Boehringer Ingelheim, Chugai, Novartis, Pfizer, and SOBI; and is a study steering committee member for Blueprint Medicines Corporation and Omeros. A.M. has received honorarium fees from Takeda, Pfizer, Novo Nordisk, Behring, AbbVie, Novartis, Cilag, Janssen, and Bayer. K.M.P. has participated in advisory boards for CTI Biopharma, AbbVie, Protagonist Therapeutics, PharmaEssentia, and Kura Oncology. A.M.V. serves on advisory boards for and received fees for lectures by Incyte, Novartis, GSK, AOP, and Blueprint Medicines Corporation. U.P. received research funding and honoraria from Amgen, Janssen, Jazz, and Novartis. O.H. received research funding from AB Science, BMS-Celgene, Alexion, Novartis, and Inatherys. O.H. has consulted for AB Science; and is a shareholder for AB Science. 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Agreement to Share Publication-Related Data and Data Sharing Statement: The anonymized derived data from this study that underlie the results reported in this article will be made available, beginning 12 months and ending 5 years after this article's publication, to any investigators who sign a data access agreement and provide a methodologically sound proposal to medinfo@blueprintmedicines.com. The study protocol will also be made available, as will a data fields dictionary.

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Efficacy and safety of avapritinib in advanced systemic mastocytosis: 4-year follow-up of the PATHFINDER study

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Running header: 4-year follow-up of AdvSM patients on avapritinib

Key points: 1 to 2 key point summaries (140 characters each)

- Avapritinib elicited a high rate of deep and durable responses (73% ORR; 30% CR/CRh). Median OS was 62 months after 4 years follow-up
- Disease progression rates were low during avapritinib treatment (20%) and manifested mostly as progression of the AHN

Explanation of novelty: (500 characters)

This manuscript provides the first report of the efficacy, overall survival, and safety of avapritinib, a selective inhibitor of *KIT* D816V, in AdvSM from the fully enrolled pivotal PATHFINDER study after median follow-up of 4 years. In addition, this manuscript provides insights into predictors of response and survival.

Data sharing

The anonymized derived data from this study that underlie the results reported in this article will be made available, beginning 12 months and ending 5 years after this article's publication, to any investigators who sign a data access agreement and provide a methodologically sound proposal to medinfo@blueprintmedicines.com. The study protocol will also be made available, as will a data fields dictionary.

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Abstract

Advanced systemic mastocytosis (AdvSM), a clonal hematologic neoplasm driven predominantly by D816V-mutant *KIT*, is often characterized by organ damage. Associated hematologic neoplasms (AHN; usually myeloid) are often present, leading to poor survival. We report on the oral, highly selective, potent KIT D816V inhibitor avapritinib (200-mg once-daily starting dose) with >4 years follow-up from the fully enrolled PATHFINDER (NCT03580655) study. Endpoints included overall response rate (ORR; primary), duration of response (DOR), progression-free survival (PFS), overall survival (OS), changes in objective biomarkers of disease, and safety (all secondary). Of 107 patients with AdvSM (including 71 [66%] with SM-AHN; overall population median follow-up: 49 months), 83 were response evaluable. ORR was 73% (95% confidence interval [95% CI], 63%-83%). Median DOR was 58 months, PFS 51 months, and OS 62 months. Disease progression occurred in 21/107 patients, predominantly in SM-AHN and largely driven by the AHN. Reductions in objective biomarkers of disease were observed. Most frequent (≥30% patients) treatment-emergent adverse events (TEAEs) (any grade; grade ≥3) were thrombocytopenia (58%; 31%); periorbital edema (57%; 6%), anemia (54%; 33%), peripheral edema (48%; 2%), and diarrhea (36%; 5%). Adverse events of special interest were cognitive effects (34%; 8%) and intracranial bleeds (4%, 2%). Eleven (10%) patients experienced TEAEs leading to death, of which 1 was deemed related to avapritinib by the principal investigator. With 4-year follow-up, avapritinib-treated patients with AdvSM experienced deep and durable responses and a favorable benefit-risk profile.

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Key words: Systemic mastocytosis; tyrosine kinase inhibitor; *KIT* D816V; avapritinib

Introduction

Systemic mastocytosis (SM), including advanced SM (AdvSM), is a rare clonal hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases.[1-4] The prevalence of SM has been estimated at up to 1 in 5,000 people.[5-8] AdvSM is characterized by the accumulation and infiltration of neoplastic *KIT* D816V-mutant mast cells and potentially by non-mast cell lineages, which may result in organ damage, historically referred to as C-findings. For example, World Health Organization-defined C-findings include: cytopenias, liver function abnormalities (e.g., elevated alkaline phosphatase) with or without portal hypertension and ascites, palpable splenomegaly with hypersplenism malabsorption which may be associated with hypoalbuminemia and weight loss), and large (≥2 cm) lytic bone lesions with or without pathologic factures and/or bone pain. Together with organ damage, mast cell mediator symptoms and cutaneous mast cell lesions (when present) often lead to diminished quality of life and poor survival[1,9-12]; indeed, median overall survival in AdvSM with midostaurin, an approved therapy, has been reported as less than 2.5 years.[13]

There are 3 recognized subtypes of advanced systemic mastocytosis (AdvSM): aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).[14-16] SM-AHN is the most prevalent and accounts for up to 70% of AdvSM diagnoses.[12,17] Cells derived from the AHN may also infiltrate various organs, making it a challenge to know the degree to which organ damage is related to the SM or AHN (or both). The most frequently reported AHN subtypes include chronic myelomonocytic leukemia and myelodysplastic/myeloproliferative neoplasms unclassifiable; however, myelodysplastic syndromes, myeloproliferative

neoplasms, chronic eosinophilic leukemia, and acute myeloid leukemia (AML) have also been reported.[18]

In AdvSM, gene mutations associated with myeloid malignancies are often observed alongside the *KIT* D816V mutation, resulting in a complex genetic landscape. Of these, *SRSF2*, *ASXL1*, and *RUNX1* (*S/A/R*) are high-risk mutations that have been shown to adversely affect survival.[19-22] The Mutation-Adjusted Risk Score (MARS) is a validated prognostic score that combines this mutational profile with clinical characteristics to estimate risk and improve treatment stratification.[23]

Avapritinib is a highly potent and selective KIT D816V inhibitor approved by the United States (US) Food and Drug Administration for the treatment of adults with AdvSM regardless of prior therapy and by the European Medicines Agency as monotherapy for the treatment of adult patients with ASM, SM-AHN, or MCL, after 1 or more prior systemic therapies. Avapritinib approval in AdvSM was based on the phase 1 open-label, single-arm dose escalation EXPLORER (NCT02561988) study and an interim analysis of 62 enrolled patients in the phase 2 open-label, single-arm PATHFINDER study (NCT03580655), [24-28] of whom 32 were response-evaluable (median follow-up of 10.4 months) by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis [mIWG-MRT-ECNM] criteria described previously[26,27] and shown in **supplemental Table 1**) In both studies, avapritinib demonstrated a 75% overall response rate (ORR) per mIWG-MRT-ECNM criteria.[26,27] Responses were rapid, durable, and observed across AdvSM subtypes regardless of prior therapy.[26,27,29]

Considering the promising results from prior reports, a deeper understanding of the long-term treatment with avapritinib in AdvSM is required. Here we report the efficacy and safety of avapritinib from the fully enrolled AdvSM patient population from the pivotal PATHFINDER study with a median follow-up of 4 years.

Methods

Study design

PATHFINDER (NCT03580655) is an international, multicenter, open-label, single-arm, phase 2 registrational study evaluating the efficacy and safety of avapritinib in adult patients with centrally-confirmed AdvSM conducted in US, Canada, and Europe (**supplemental Figure 1**). Eligible patients received a starting dose of avapritinib 200 mg once a day in 28-day cycles until confirmed progressive disease (PD) of SM (by mIWG-MRT-ECNM criteria), clinical progression of SM or AHN (decided by the investigator to require immediate initiation of cytoreductive therapy), avapritinib was no longer tolerated, patient withdrawal from the study, or death. Dose modification between 25 and 300 mg once a day was permitted according to prespecified criteria. This study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the Institutional Review Board or Independent Ethics Committee of each participating center. All patients provided written informed consent.

Full study design details, including eligibility, outcomes, assessments and statistical analysis methods have been previously reported.[26]

Eligibility

Eligible patients (≥18 years of age) had centrally confirmed diagnosis of AdvSM per World Health Organization criteria (2016)[30] and had an Eastern Cooperative Oncology Group (ECOG) Performance Status 0-3. Patients were excluded if they had: AML or high-risk myelodysplastic syndromes or Philadelphia chromosome–positive malignancies. To mitigate the risk of intracranial bleeds, as seen in earlier

studies,[27] patients with a platelet count of <50x10^9/L were excluded. The mIWG-MRT-ECNM response-evaluable population, as adjudicated by a central committee, included patients with a diagnosis of AdvSM who had: received at least 1 dose of avapritinib; at least 2 post-baseline bone marrow assessments and been on study for ≥24 weeks, or had an end of study visit; at least 1 evaluable C-finding (severe and quantifiable organ damage) or MCL regardless of C-findings. Patients with ASM or SM-AHN who did not have an evaluable C-finding were not considered response-evaluable. Evaluable C-findings per mIWG-MRT-ECNM criteria have been described previously.[26]

Outcomes and assessments

The primary endpoint was centrally adjudicated ORR by mIWG-MRT-ECNM criteria and included complete remission (CR), CR with partial hematologic recovery (CRh), partial remission (PR), and clinical improvement (CI). Other responses included stable disease (not meeting criteria for CR/CRh, PR, CI, or PD) and PD (as reported by the principal investigators or adjudicated by the study steering committee according to the mIWG- MRT-ECNM criteria) (**supplemental Table 1**).[26,27] Select prespecified secondary endpoints included: time to any response (time from first dose to the time of an initial evaluation of CI or better); duration of response (DOR; time from an initial documented CI or better to the time of an initial documented confirmed PD, loss of response, or death due to any cause, whichever occurs first); progression-free survival (PFS; time from first dose to the time of initial documented confirmed PD or death due to any cause, whichever occurs first); overall survival (OS; time from first dose to the time of death due to any cause); mean percentage change from baseline in measures of bone marrow mast cell burden, serum tryptase

level, blood *KIT* D816V variant allele frequency (VAF), and spleen volume; and safety. Responses according to pure pathologic response (PPR) were also assessed as a prespecified secondary endpoint and included morphologic CR (absence of bone marrow mast cell aggregates, serum tryptase <20 ng/mL), morphologic CRh with full or partial hematologic recovery, and morphologic PR (≥50% reduction in bone marrow mast cells and serum tryptase level). To be considered response evaluable according to PPR, patients had baseline bone marrow mast cell aggregates and/or serum tryptase ≥20 ng/mL.

For evaluation of bone marrow mast cell burden, formalin-fixed, paraffin-embedded bone marrow biopsies were sectioned at 3-4 μm thickness, and stained with hematoxylin and eosin, or underwent immunohistochemistry for CD117, tryptase, CD25, CD30, and CD34 using standard methods. Peripheral blood samples were drawn for serum tryptase and *KIT* D816V VAF analysis, the latter by droplet digital polymerase chain reaction assay with a limit of detection of 0.02%. MARS was conducted according to published criteria and included low (0-1), intermediate (2), and high (3-5) risk groups.[23]

In addition, post hoc logistic regression analyses on predictors of CR/CRh or PR, and Cox regression analyses on predictors of OS were conducted in the mIWG-MRT-ECNM response-evaluable population; these analyses were not pre-specified in the study protocol.

The safety population included all enrolled patients from the PATHFINDER study. Treatment-emergent AEs (TEAEs) were summarized by preferred term (according to the Medical Dictionary for Regulatory Activities version 18.1), severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse, Version 5.0),

seriousness, and relationship to study treatment. A treatment-related AE (TRAE) was defined as any AE likely or possibly related to avapritinib as assessed by the study investigator. Based on the incidence, medical importance, or potential clinical consequences, 2 grouped AEs of special interest were considered in the study: cognitive effects and intracranial bleeding (ICB). Grouped AE terms included AEs that describe similar medical concepts.

Statistical methods

Statistical methodology has been described previously.[26] The database lock was March 13, 2025. All safety analyses and secondary analyses were evaluated in the safety population, comprising patients who received at least 1 dose of avapritinib. Safety analyses were descriptive. For regression analyses, the following variables were assessed: age, diagnosis of ASM vs MCL, diagnosis of SM-AHN vs MCL, AHN presence (yes/no), prior antineoplastic therapy (yes/no), *S/A/R* mutational status, serum tryptase at baseline (as described above), bone marrow mast cell burden at baseline (as described above), and *KIT* D816V VAF at baseline. For OS regressions only, CR/CRh or PR (yes/no) and *KIT* D816V VAF best response status (positive/negative) were also assessed. All statistical analyses were conducted using SAS v.9.4 or higher.

Results

Patients

As of March 13, 2025, there were 107 patients with AdvSM who initiated avapritinib 200 mg (n = 105) or 100 mg (n = 2) once a day (**supplemental Figure 1)** and had median follow-up of 49.1 months (95% confidence interval [95% CI], 44.2-52.2 months). The median age was 68 (range, 31-88) years and 45 patients (42%) were female (**Table 1**). Thirty-eight patients (36%) had never received prior systemic therapy (henceforth termed treatment-naïve), and 69 patients (64%) had received at least 1 prior systemic therapy. The most common subtype was SM-AHN comprising 71 patients (66%). AHNs were also observed in 4 of the 15 patients with MCL.

At baseline, 103 patients (96%) were positive for the *KIT* D816V mutation, 101 patients (94%) carried at least 1 additional somatic mutation, and at least 1 *S/A/R* mutation was observed in 48 patients (45%). Additional patient demographics and baseline characteristics are summarized in **Table** 1. A breakdown of additional tier 1 and tier 2 mutations identified using next-generation sequencing is presented in **supplemental Table 2**. The most common (≥20% of patients) mIWG-MRT-ECNM C-findings at baseline were palpable splenomegaly of ≥5 cm (42%), transfusion-independent anemia (42%), and elevated (Grade ≥2) alkaline phosphatase (35%) (**supplemental Table 3).**

Responses

From the total population (N = 107), 24 patients did not have evaluable C-findings leaving 83 patients who were response-evaluable according to mIWG-MRT-ECNM criteria with a median follow-up of 51.8 months (95% CI, 48.0-55.0 months). As a

result of not being response-evaluable per mIWG-MRT-ECNM criteria, these patients were not included in these response analyses. The best confirmed ORR was 73% (n = 61/83; 95% CI, 63-83). Twenty-five patients (30%) achieved CR/CRh, 32 patients (39%) achieved PR, and 4 patients (5%) had CI (**Table 2**). Responses deepened over time and are shown in **supplemental Figure 2**. Responses were observed in patients regardless of AdvSM subtype or previous treatment history (**Table 2**). Best ORR by treatment history according to AdvSM subtype is presented in **supplemental Table 4**. In patients with a mIWG-MRT-ECNM response (n = 61), the median time to any response was 2.3 months (0.3-20.3) and median time to CR/CRh was 9.3 months (1.8-36.8). Median time to any response and CR/CRh by AdvSM subtype and treatment history is reported in **supplemental Table 4.** Resolution of C-findings from baseline in the mIWG-MRT-ECNM response-evaluable population with baseline C-findings is shown in **supplemental Table 3.**

Regression analyses of predictors of response are shown in the supplement.

Median DOR in all response-evaluable patients was 58 months (95% CI, 46 months–not evaluable) with DOR rates of 74% (95% CI, 63-86) at 36 months and 64% (95% CI, 50-78) at 48 months observed. In treatment-naïve patients, median DOR was not reached and was 58 (46-not evaluable) in patients with at least 1 prior systemic therapy. At 48 months, 62% (95% CI, 40-84) of treatment-naïve patients and 66% (95% CI, 48-84) of patients with at least 1 prior systemic therapy maintained a response to treatment. The DOR in these populations by subtype is shown in **supplemental Figure 3**.

In the PPR-evaluable population (N = 107), best confirmed ORR per PPR criteria was 74% (79/107; 95% CI, 64-82) and was consistent across AdvSM subtypes. In

total, 51 patients (55%) achieved a CR/CRh and 24 patients (22%) achieved a PR (**supplemental Table 5**).

Effect on markers of mast cell disease burden

In the safety population (N = 107), 92 of 105 (87%) patients with baseline and post-baseline assessments had a ≥50% reduction from baseline in bone marrow mast cells and 78/105 (74%) achieved a total clearance of bone marrow mast cell aggregates. Serum tryptase levels were decreased by ≥50% in 98/107 patients (92%), with 70/107 (65%) achieving a serum tryptase level of <20 ng/mL. In total, 88/107 patients (82%) achieved a ≥50% reduction of *KIT* D816V VAF, 68/107 patients (64%) achieved a VAF of <1%, and 15/107 patients (14%) achieved a VAF reduction under the limit of detection (<0.02%). Spleen volume was reduced by ≥35% in 76/105 patients (72%) and in 20/33 (61%) with baseline spleen palpation of ≥5 cm. In addition, a non-palpable spleen was the best response in 42/54 patients (78%) who had a palpable spleen at baseline.

Improvements in objective biomarkers of disease burden were durable and sustained through 4 years of follow-up. Box plots depicting reductions in biomarkers of disease burden over time in AdvSM can be seen in **Figure 1**. At 48 months, median percentage change from baseline was -90% in bone marrow mast cells, -94% in serum tryptase, -97% in *KIT* D816V VAF, and -56% for spleen volume.

Of the 27 patients with monocytosis at baseline, 26 patients (96%) had a ≥50% reduction in monocytes from baseline, and 23 (85%) achieved normalization of monocyte counts (<0.8 x 10^9/L). There were 23 patients with baseline eosinophilia

(absolute eosinophil count of >0.5 x 10^9/L) with 22 (96%) showing a ≥50% reduction from baseline of absolute eosinophil counts and all 23 achieved normalization (<0.5 x 10^9/L).

Survival measures

Median PFS in the response-evaluable population (n = 83) was 51 months (95% CI, 39 months-not evaluable), 45 months (95% CI, 31-62) in SM-AHN, and not reached in ASM or MCL subtypes (**Figure 2**). Median PFS was not reached in treatment-naïve patients and was 48 months (95% CI, 31-62) in patients with at least 1 prior systemic therapy (**supplemental Figure 4**).

Median OS in the safety population (N = 107) was 62 months (95% CI, 60 months-not evaluable), 60 months (95% CI, 50-not evaluable) in SM-AHN, and not reached in ASM or MCL subtypes (**Figures 2-3**). In the 4 patients with MCL-AHN, median OS was 9.2 months (95% CI, 1.4-not evaluable). In treatment-naïve patients, median OS was not reached and was 60 months (95% CI, 48 months-not evaluable) in patients with at least 1 prior systemic therapy (**supplemental Figure 5**). OS was not impacted by the number of C-findings at baseline and remained generally consistent in patients with AdvSM when stratified by number of C-findings at baseline (**supplemental Figure 6)**. Based on MARS risk category subgrouping, median OS in patients with low and intermediate scores was not reached regardless of history of previous systemic therapy. Patients with a high MARS score (n = 41) had a median OS of 48 months (95% CI, 23-NR; **supplemental Figure 7**).

Regression analyses of predictors of OS are shown in the supplement.

Disease progression

Disease progression was observed in 21 patients, including 6 with progression to AML; 19 of 21 had an initial diagnosis of SM-AHN or MCL-AHN. Patient characteristics for these 21 patients are presented in **supplemental Table 6.**

Safety

The median treatment duration (range) of the safety population (N = 107) was 32.7 months (0.2-63.5), with no patients still on treatment at the final database lock due to the end of the study (**supplemental Figure 1**); all 32 patients remaining on treatment prior to database lock continued avapritinib treatment outside of PATHFINDER. There were no new safety concerns identified with longer treatment.[26]

All patients experienced at least 1 TEAE. The most frequent (occurring in ≥25%) hematological TEAEs (any Grade; Grade ≥3) were thrombocytopenia (58%; 31%), anemia (54%; 33%), and neutropenia (34%; 30%). The most frequent non-hematological TEAEs (any Grade; Grade ≥3) were periorbital edema (57%; 6%), peripheral edema (48%; 2%), diarrhea (36%; 5%), nausea (27%; <1%), and arthralgia (26%; 2%). TEAEs and TRAEs (any Grade; Grade ≥3) occurring in ≥15% of patients are presented in **Table 3**.

Serious AEs (SAEs) occurred in 69 patients (64%) with treatment-related SAEs occurring in 15 patients (14%; **supplemental Table 7**). Eleven (10%) patients experienced AEs resulting in death (**Table 3**), with one assessed as related to avapritinib by the investigator—an 80-year-old male patient with a medical history of reduced kidney function and increased blood creatinine who died due to acute

kidney injury in the context of treatment with antibiotics for bilateral pneumonia complicated by diarrhea and vomiting.

Edema TEAEs were mostly Grade 1 or 2 and managed through dose modification with only 1 patient discontinuing treatment due to peripheral edema.

Cognitive effects and ICBs were events of special interest in the study. Cognitive effects occurred in 34% of patients and were considered treatment-related in 28% of patients. Most cognitive effects were Grade 1 or 2 with the most frequent (≥5% of patients; any Grade; Grade ≥3) being cognitive disorder (18%; 5%), memory impairment (8%; 0%), and confusional state (2%; <1%). Median time to onset for any Grade, and improvement and resolution for Grade ≥2 cognitive effects are presented in **supplemental Table 8**. Cognitive effects were generally managed through dose modification. As a result, treatment discontinuations due to cognitive effects were limited and occurred in 4 patients overall; 3 with cognitive disorder, age ranging 66 – 70 years old (2 Grade 3 and one Grade 2) assessed as related to treatment with avapritinib and one with Grade 3 dementia in a 71-year-old male patient, attributed to retrospectively confirmed Alzheimer's disease and not related to treatment with avapritinib.

Analyses of ICBs in patients from previous reports of the EXPLORER and PATHFINDER studies identified severe thrombocytopenia at baseline as a significant risk factor for ICBs.[26,27] Consequently, patients with baseline platelet counts of $<50\times10^9$/L were excluded from enrollment. In addition, increased platelet count monitoring with guidance for treatment interruption, dose reduction, and support for severe thrombocytopenia or treatment discontinuation were also implemented. These risk mitigation strategies substantially reduced the rate of ICBs

in PATHFINDER compared to EXPLORER.[27] ICBs occurred in 4 patients (4%) enrolled in PATHFINDER and included 2 patients with intracranial hemorrhages and 2 with subdural hematomas. All 4 patients had confounding factors such as medical history of hypertension (n = 3), use of antithrombotic treatment (n = 3), or head trauma around the time the bleeding occurred (n = 1). In addition, 3 of the 4 patients experienced severe thrombocytopenia over the course of the study treatment leading to avapritinib dose modification in all 3 patients, platelet transfusions in 2 patients, and treatment with thrombopoietin receptor agonists in 1 patient. All 4 patients discontinued avapritinib treatment and events were reported to have resolved; none of the patients died due to their ICBs. Treatment details for patients who had ICBs are presented in **supplemental Table 9**.

Overall, 38 patients (36%) discontinued treatment due to TEAEs, including 20 patients (19%) due to TRAEs. Dose modifications due to AEs (any cause; treatment-related) including reductions (79%; 78%), and interruptions (73%; 64%) are reported in **supplemental Tables 10 and 11**. Dose modifications due to TRAEs (interruptions; reductions) were mostly due to thrombocytopenia (25%; 30%), and neutropenia (22%; 22%).

The median time to first dose reduction and the median average daily dose (range) were 1.6 months (0.0-34.2) and 106 mg (27-240), respectively (**supplemental Table 12)**; of the 29 patients who reached 48 months of treatment, 3 were receiving >100 mg once a day, 12 were receiving avapritinib 100 mg once a day, and 14 <100 mg once a day at that time point. A breakdown of patient dosage over time is shown in **supplemental Table 13**.

Discussion

As the largest and longest prospective interventional study of any KIT inhibitor in AdvSM, results of the PATHFINDER study provide important guidance and support for the use of avapritinib in clinical practice. With 4 years of follow-up, median OS and PFS were 62 months and 51 months, respectively, reflecting a high rate of deep (73% median ORR; 30% CR/CRh) and durable (median DOR was 58 months) responses, as accompanied by persistent reductions in all disease burden biomarkers. A low rate of disease progressions was observed, primarily in patients with SM-AHN and manifested mostly as progression of the AHN. Avapritinib dose modifications were generally effective in the management of AEs including cytopenia, edema, and cognitive effects, allowing patients to remain on avapritinib therapy.

The deep and durable responses and OS in patients compare favorably to results observed with other AdvSM therapies. The multikinase/KIT inhibitor midostaurin demonstrated a median OS of 28.7 months and median DOR of 24.1 months in AdvSM.[13] In a retrospective external control study, avapritinib-treated patients from PATHFINDER and EXPLORER studies had significantly superior OS compared to patients receiving best available therapy (mainly midostaurin and cladribine).[31] In a more recent retrospective analysis comparing PATHFINDER and EXPLORER results specifically to those of midostaurin or cladribine, avapritinib treatment resulted in significantly improved OS, longer duration of treatment, and greater reduction in serum tryptase levels compared to midostaurin or cladribine in real-world clinical practice.[32] Furthermore, the effectiveness of avapritinib extended across all MARS-defined risk groups, and across all AdvSM subtypes, including

settings where other therapies can have diminished efficacy. While median OS with avapritinib was of shorter duration in the high MARS group vs low and intermediate MARS groups, outcomes were still improved in high MARS patients with avapritinib in PATHFINDER (median OS 4.2 years) compared to median OS of 1.2 years with midostaurin in a similar high MARS subgroup.[33] Similarly, in PATHFINDER, median OS was not reached in the MCL subtype, while OS reported for midostaurin in a pivotal clinical trial and a registry study were 9.4 months and 2.3 years, respectively.[13,34] It should be noted that, in the present study, median OS was numerically longer in patients with MCL only than in the small population of patients with MCL-AHN (n=4). Additionally, based on multivariate logistic regression analysis, treatment-naïve patients were significantly more likely to achieve CR/CRh with avapritinib than patients with a history of prior antineoplastic therapy. In the absence of a randomized controlled clinical trial, results of the PATHFINDER study, supported by published reports, favor avapritinib over other available therapies in adult patients with AdvSM.

The use of PPR criteria provides an option for objective evaluation of response to treatment in a broader patient population, which is not impacted by challenges and subjective evaluation errors associated with assessment of C-findings. Rates of CR/CRh were 51% and 30% with PPR and mIWG-MRT-ENCM criteria, respectively, with high ORRs in both 2 criteria (74% and 73%, respectively); PPR responses to avapritinib were similar to previous reports.[35] The practicality of evaluating only BM MC burden, tryptase, and complete blood counts—without the need for C-finding adjudication—makes PPR a useful tool for both community and academic physicians.

This 4-year follow-up of patients treated with avapritinib also provided important insights into the patterns of disease progression, with most progressions reported in patients with the SM-AHN subtype, 1 patient with MCL, and 1 patient with ASM. In addition, progressions were largely driven by the AHN. These observations may support the hypothesis that the AHN either represents a clonally distinct *KIT* D816V–negative neoplasm or a multi-mutated myeloid malignancy with other non *KIT* D81V mutations. Nonetheless, avapritinib treatment also resulted in marked decreases of baseline monocytosis and eosinophilia, suggesting its effects may in part be due to the presence of *KIT* D816V as a disease driver across different cell lineages of AdvSM and/or to indirect effects, such as reduced cytokine levels.[36] This highlights a need for the deeper understanding of the clonal dynamics during avapritinib therapy; indeed, in clonal architecture mapping in 4 avapritinib-treated patients with SM-AHN, avapritinib strongly impacted the mast cell component, but had varying impact on abnormal myeloid cells depending on the cellular distribution of *KIT* D816V and its relative role with co-mutations in the genomic landscape of such cases.[37] This also demonstrates the need to evaluate combination treatment strategies with selective KIT D816V–targeting agents.

Finally, the deep and durable responses, particularly the high rates of CR/CRh, reported here, provide an opportunity to re-evaluate the role of allogeneic hematopoietic stem cell transplantation (allo-HCT) in the modern KIT inhibitor era,[38-40] albeit, candidates for allo-HCT for SM treatment were excluded from this study. For example, patients with ASM or MCL without an AHN demonstrated the highest rates of durable OS on avapritinib and may not require allo-HSCT; in contrast, patients with SM-AHN wherein the AHN component would otherwise be transplanted should be evaluated for allo-HCT. Further data are needed to understand the

potential cytoreductive role of avapritinib before allo-HCT as well as its potential for preventing or treating post-transplant relapse.

After 4 years of follow-up, no new safety concerns were identified. Patients benefited from a starting dose at 200 mg once a day to enable disease control, although the average daily dose was 106 mg due to dose reductions over time, leading to 3 important conclusions: a flexible avapritinib dosing approach provided treatment benefit to patients with AdvSM, with higher doses used early in treatment to achieve rapid responses; responses were durable and maintained even at lower doses; and dose reductions, when needed, were an effective way to mitigate toxicities, maintaining the favorable safety profile and response to treatment. Indeed, cognitive effects were well managed with dose reductions, with very few leading to discontinuation.

This 4-year follow-up demonstrated that the strategy for the mitigation of ICB risk was effective. Through limiting enrollment to patients with platelet counts of $\geq 50 \times 10^9$/L, holding treatment in patients with platelet counts $< 50 \times 10^9$/L, supporting severe thrombocytopenia with platelet transfusions and thrombopoietin receptor agonists (at investigator discretion), and avoiding anticoagulants, the rate of ICBs was substantially reduced compared to previous studies.[27] There were no fatal occurrences of ICBs reported in this study.

The main limitations of this study include the open-label, uncontrolled design, precluding direct comparison to other therapies, as well as the relatively small study size that, although large for AdvSM, complicates subgroup analyses in this very heterogenous disease.

In conclusion, in this analysis of the PATHFINDER study with a median follow-up of 4 years, patients treated with avapritinib exhibited high rates of CR/CRh which were similarly associated with high rates of PFS and OS, particularly in patients without an AHN. These outcomes were associated with substantial and sustained reductions in objective biomarkers of disease burden such as bone marrow mast cells, serum tryptase and *KIT* D816V VAF, as well as reversion of organ damage. Logistic regression analyses also showed that treatment-naïve patients were more likely to achieve complete disease remissions, while achievement of CR/CRh and PR was predictive of longer OS. With prolonged follow-up, the well-characterized safety profile of avapritinib remained consistent with prior reports, supporting that administration of avapritinib over an extended period maintains a favorable benefit-risk profile in patients with AdvSM.

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Author contributions

Term	CRediT (contributor roles taxonomy) definition	Author initials
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims	J.G., A.R., D.J.D, I.B., H.M.L., S.R., S.D., J.I.M.G.
Methodology	Development or design of methodology; creation of models	J.G., A.R., D.J.D, I.B., H.M.L., S.R., S.D., J.I.M.G.
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components	N/A
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs	H.M.L.
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data	H.M.L.

Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection	J.G., A.R., D.H.R., I.A.T., M.W.D., T.I.G., J.P., A.M., K.M.P., A.M.V., U.P., O.H., A.E., C.B.L., R.M., C.U., M.T., I.D., J.G.J., R.Z., S.T.O., A.Y., E.O.H., P.B., S.G.L., W.R.S., E.A.G., M.B., J.L., I.B., H.M.L., S.R., S.D., J.I.M.G., D.J.D.
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools	J.G., A.R., D.H.R., I.A.T., M.W.D., T.I.G., J.P., A.M., K.M.P., A.M.V., U.P., O.H., A.E., C.B.L., R.M., C.U., M.T., I.D., J.G.J., R.Z., S.T.O., A.Y., E.O.H., P.B., S.G.L., W.R.S., E.A.G., M.B., J.L., I.B., H.M.L., S.R., S.D., J.I.M.G., D.J.D.
Data curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse	J.G., A.R., D.H.R., I.A.T., M.W.D., T.I.G., J.P., A.M., K.M.P., A.M.V., U.P., O.H., A.E., C.B.L., R.M., C.U., M.T., I.D., J.G.J., R.Z., S.T.O., A.Y., E.O.H., P.B., S.G.L., W.R.S., E.A.G., M.B., J. L., I.B., H.M.L., S.R., S.D., J.I.M.G., D.J.D.
Writing – original draft	Preparation, creation, and/or presentation of the published work, specifically writing the initial draft (including substantive translation)	J.G., A.R., D.H.R., I.A.T., M.W.D., T.I.G., J.P., A.M., K.M.P., A.M.V., U.P., O.H., A.E., C.B.L., R.M., C.U., M.T., I.D., J.G.J., R.Z., S.T.O., A.Y., E.O.H., P.B., S.G.L., W.R.S., E.A.G., M.B., J.L., I.B., H.M.L., S.R., S.D., J.I.M.G., D.J.D.
Writing – review & editing	Preparation, creation, and/or presentation of the published work by those from the original research group, specifically critical review, commentary, or revision – including pre-or post-publication stages	J.G., A.R., D.H.R., I.A.T., M.W.D., T.I.G., J.P., A.M., K.M.P., A.M.V., U.P., O.H., A.E., C.B.L., R.M., C.U., M.T., I.D., J.G.J., R.Z., S.T.O., A.Y., E.O.H., P.B., S.G.L., W.R.S., E.A.G., M.B., J.L., I.B., H.M.L., S.R., S.D.,

		J.I.M.G., D.J.D.
Visualization	Preparation, creation, and/or presentation of the published work, specifically visualization/data presentation	J.G., A.R., D.H.R., I.A.T., M.W.D., T.I.G., J.P., A.M., K.M.P., A.M.V., U.P., O.H., A.E., C.B.L., R.M., C.U., M.T., I.D., J.G.J., R.Z., S.T.O., A.Y., E.O.H., P.B., S.G.L., W.R.S., E.A.G., M.B., J.L., I.B., H.M.L., S.R., S.D., J.I.M.G., D.J.D.
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team	J.G., A.R., D.J.D, I.B., H.M.L., S.R., S.D., J.I.M.G.
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Disclosures / Conflicts of interest

J.G. is the chair of the Response Adjudication Committee, has received research funding, served on advisory boards, and received honoraria and funding to cover travel expenses from Blueprint Medicines Corporation. A.R. has received research funding, served on advisory boards, and received honoraria and funding to cover travel expenses from AbbVie, AOP, Blueprint Medicines Corporation, BMS, Cogent, GSK, Incyte, and Novartis. D.H.R. has been a clinical advisory board/study steering group member (EXPLORER/PATHFINDER) for Blueprint Medicines Corporation; a study steering committee member for Cogent Biosciences; involved in educational events and advisory boards for Novartis; and received author fees for Medscape cases. I.A.T. has received research funding from Blueprint Medicines Corporation and has received advisory board or speaker fees from Blueprint Medicines Corporation and Novartis. M.W.D. has received honoraria fees from Blueprint Medicines Corporation, Incyte, Medscape, Sangamo, and Takeda. Received

consultancy fees from Blueprint Medicines Corporation, DisperSol, Fusion Pharma, Novartis, and Sangamo. Received research funding from Blueprint Medicines Corporation, Incyte, Leukemia & Lymphoma Society, Novartis, Pfizer, SPARC, and Takeda, is part of a study management committee for Blueprint Medicines Corporation and Takeda, and is a case author for Medscape. T.I.G. has received consulting fees and is a study steering committee member for Blueprint Medicines Corporation, BMS/Celgene, Cogent Biosciences, and Incyte. J.P. has received honorarium fees from Apellis, Alexion, AstraZeneca, Blueprint Medicines Corporation, BMS, Cogent, F. Hoffmann-La Roche, Grünenthal, MSD, Novartis, Omeros, Samsung Bioepis, and SOBI; and has served on the speaker's bureau of Alexion, Boehringer Ingelheim, Chugai, Novartis, Pfizer, and SOBI; and is a study steering committee member for Blueprint Medicines Corporation and Omeros. A.M. has received honorarium fees from Takeda, Pfizer, Novo Nordisk, Behring, AbbVie, Novartis, Cilag, Janssen, and Bayer. K.M.P. has participated in advisory boards for CTI Biopharma, AbbVie, Protagonist Therapeutics, PharmaEssentia, and Kura Oncology. A.M.V. serves on advisory boards for and received fees for lectures by Incyte, Novartis, GSK, AOP, and Blueprint Medicines Corporation. U.P. received research funding and honoraria from Amgen, Janssen, Jazz, and Novartis. O.H. received research funding from AB Science, BMS-Celgene, Alexion, Novartis, and Inatherys. O.H. has consulted for AB Science; and is a shareholder for AB Science. A.E. received compensation for his participation on the speaker's bureau of Blueprint Medicines Corporation. C.B.L. has received consultancy fees from Lilly, Novartis, UCB, and research support from Novartis. She is a non-paying member of the steering committee for an AB Science study. R.M. has been a consultant for Novartis, Sobi, GSK, BMS, Incyte, and PharmaEssentia. He has received research

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Tables

Table 1. Baseline patient demographics and characteristics of all patients

	All AdvSM (N = 107)	Patients with ≥1 prior therapy (n = 69)	Treatment-naïve patients (n = 38)	Response-evaluable AdvSM (n = 83)
Age, median years (range)	68 (31-88)	68 (31-86)	68 (39-88)	68 (31-88)
Female, n (%)	45 (42)	27 (39)	18 (47)	30 (36)
ECOG performance status, n (%)				
0-1	79 (74)	48 (70)	31 (82)	60 (72)
2-3	28 (26)	21 (30)	7 (18)	23 (28)
AdvSM subtype per central assessment, n (%)				
ASM	21 (20)	14 (20)	7 (18)	13 (16)
SM-AHN	71 (66)	43 (62)	28 (74)	55 (66)
CMML	31 (29)	20 (29)	11 (29)	27 (33)
MDS	12 (11)	6 (9)	6 (16)	6 (7)
MPN	3 (3)	3 (4)	0 (0)	2 (2)
MDS/MPN-U	15 (14)	8 (12)	7 (18)	12 (14)
CEL	6 (6)	3 (4)	3 (8)	5 (6)
Other	4 (4)	3 (4)	1 (3)	3 (4)
MCL*	15 (14)	12 (17)	3 (8)	15 (18)
KIT D816V mutation by central assay, n (%)	103 (96)	67 (97)	36 (95)	80 (96)
KIT D816V VAF,† median percent (range)	16 (ND-47)	20 (ND-47)	6 (ND-45)	19 (ND-47)
S/A/R mutation per central assay,‡ n (%)	48 (45)	25 (36)	23 (61)	40 (48)
MARS score, n (%)				
Low	40 (37)	26 (38)	14 (37)	26 (31)
Intermediate	26 (24)	18 (26)	8 (21)	21 (25)
High	41 (38)	25 (36)	16 (42)	36 (43)
BM mast cell burden, median percentage (range)	40 (1-95)	50 (1-95)	35 (3-90)	50 (1-95)
Serum tryptase level, median ng/mL (range)	262 (24-1600)	312 (24-1600)	178 (37-1336)	312 (24-1600)
Spleen volume, median mL (range)	839 (44-2897)	830 (44-2652)	863 (150-2897)	990 (44-2897)
One prior systemic therapy, n (%)	42 (39)	42 (61)	0	32 (39)
Prior antineoplastic therapy, n (%)				
Midostaurin	58 (54)	58 (84)	0	43 (52)
Cladribine	12 (11)	12 (17)	0	10 (12)
Imatinib	5 (5)	5 (7)	0	5 (6)
Interferon	11 (10)	11 (16)	0	7 (8)

AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; BM, bone marrow; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; ddPCR, droplet digital polymerase chain reaction; ECOG, Eastern Cooperative Oncology Group; MARS, Mutation-Adjusted Risk Score, MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MDS/MPN-U, myelodysplastic syndrome/myeloproliferative neoplasm-unclassifiable; MPN, myeloproliferative neoplasms; ND, not detected; NGS, next-generation sequencing; *S/A/R*, *SRSF2*, *ASXL*, and/or *RUNX1*; SM-AHN, systemic mastocytosis with an associated hematological neoplasm; VAF, variant allele frequency.

*In patients with the subtype MCL (n = 15), 4 patients had MCL-AHN and 11 patients had MCL with no AHN. †Assessed by ddPCR in both peripheral blood and bone marrow (majority were in peripheral blood; limit of detection 0.02%). ‡Assessed by NGS.

Table 2. Response rates in all response-evaluable patients (mIWG-MRT-ENCM criteria) by AdvSM subtype and treatment history

Best confirmed response, n (%)	All response-evaluable					
		AdvSM subtype				
	All (n = 83)	ASM (n = 13)	SM-AHN (n = 55)	MCL* (n = 15)	Patients with ≥1 prior systemic therapy (n = 53)	Treatment-naïve patients (n = 30)
ORR†	**61 (73)**	10 (77)	41 (75)	10 (67)	**35 (66)**	**26 (87)**
95% CI	**63-83**	46-95	61-85	38-88	**52-79**	**69-96**
Best response						
CR/CRh‡	**25 (30)**	4 (31)	18 (33)	3 (20)	**12 (23)**	**13 (43)**
CR	**14 (17)**	1 (8)	10 (18)	3 (20)	**6 (11)**	**8 (27)**
CRh	**11 (13)**	3 (23)	8 (15)	0	**6 (11)**	**5 (17)**
PR‖	**32 (39)**	6 (46)	19 (35)	7 (47)	**19 (36)**	**13 (43)**
CI	**4 (5)**	0	4 (7)	0	**4 (8)**	**0**
SD	**13 (16)**	3 (23)	7 (13)	3 (20)	**10 (19)**	**3 (10)**
PD¶	**2 (2)**	0	1 (2)	1 (7)	**2 (4)**	**0**
NE#	**7 (8)**	0	6 (11)	1 (7)	**6 (11)**	**1 (3)**

95% CI, 95% confidence interval; AdvSM, advanced systemic mastocytosis; BM, bone marrow; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; MCL, mast cell leukemia; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NE, not evaluable; ORR, overall response rate; PR, partial response; PD, progressive disease; SD, stable disease.
*The MCL subtype include patients with the subtypes MCL (n = 11) and MCL-AHN (n = 4). †CR + CRh + PR + CI. ‡CRh requires full resolution of all evaluable C-findings, elimination of BM mast cell aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as absolute neutrophil count >0.5×10^9/L with normal differential, platelet count >50×10^9/L, and Hgb level >8.0 g/dL). ‖PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both BM mast cells and serum tryptase. ¶Two patients had PD as best response. #Patients were considered NE if they did not have interpretable data for RE due to early treatment discontinuation.
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Table 3. TEAEs and TRAEs of safety population (N = 107)

	Any-cause TEAEs*		Treatment-related AEs	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any, n (%)	107 (100)	95 (89)	103 (96)	73 (68)
Non-hematological AEs in ≥15%, n (%)				
Periorbital edema†	61 (57)	6 (6)	59 (55)	6 (6)
Peripheral edema†	51 (48)	2 (2)	42 (39)	2 (2)
Diarrhea	38 (36)	5 (5)	16 (15)	1 (<1)
Nausea	29 (27)	1 (<1)	13 (12)	0
Arthralgia	28 (26)	2 (2)	7 (7)	0
Vomiting	25 (23)	2 (2)	9 (8)	1 (<1)
Face edema†	24 (22)	0	23 (21)	0
Fatigue	24 (22)	3 (3)	14 (13)	2 (2)
COVID-19	22 (21)	4 (4)	-	-
Epistaxis	20 (19)	0	6 (6)	0
Hair color changes	18 (17)	0	18 (17)	0
Pruritus	19 (18)	0	5 (5)	0
Rash	18 (17)	1 (<1)	7 (7)	1 (<1)
Abdominal pain	16 (15)	1 (<1)	2 (2)	0
Constipation	16 (15)	1 (<1)	4 (4)	0
Headache	16 (15)	0	8 (7)	0
Hematological AEs in ≥15%, n (%)				
Thrombocytopenia†	62 (58)	33 (31)	55 (51)	33 (29)
Anemia†	58 (54)	35 (33)	35 (33)	17 (16)
Neutropenia†	36 (34)	32 (30)	30 (28)	27 (25)
Blood alkaline phosphatase increased	17 (16)	3 (3)	9 (8)	2 (2)
Blood creatinine increased	16 (15)	1 (<1)	3 (3)	
AEs of special interest in ≥1%, n (%)				

Cognitive effects[†]	36 (34)	9 (8)	30 (28)	6 (6)
Cognitive disorder	21 (20)	5 (5)	19 (18)	5 (5)
Memory impairment	10 (9)	0	9 (8)	0
Confusional state	7 (7)	2 (2)	2 (2)	0
Delirium	3 (3)	2 (2)	0	0
Intracranial bleeding[†]	4 (4)	2 (2)	4 (4)	2 (2)
Subdural hematoma	2 (2)	2 (2)	2 (2)	2 (2)
Intracranial hemorrhage	2 (2)	0	2 (2)	0
AEs leading to death, n (%)	10 (9)[‡]		1 (<1)[¶]	

AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
*TEAEs were defined as any AE that occurred between the first dose of avapritinib through 30 days after the last dose of avapritinib. [†]Pooled terms. [‡]Ten deaths considered not related to treatment included Escherichia sepsis, Fournier's gangrene, pneumonia aspiration, septic endocarditis, septic shock, erosive gastritis, intra-abdominal hemorrhage, acute kidney injury, cardiac failure, and disease progression. [¶]One patient died due to acute kidney injury that was considered related to treatment, an 80-year-old male patient with a medical history of reduced kidney function and increased blood creatinine, who died due to acute kidney injury in the context of treatment with antibiotics due to bilateral pneumonia complicated with diarrhea and vomiting.

Figure Legends

Figure 1. Mean percentage change from baseline over time in biomarkers of disease. (A) Bone marrow mast cell.* (B) Serum tryptase.† (C) *KIT* D816V VAF. (D) Spleen volume.

VAF, variant allele frequency.
*Outliers above 150 percent change from baseline (n = 1) are not presented. †Outliers above 150 percent change from baseline (n = 4) are not presented.

Figure 2. Kaplan-Meier estimates for PFS and OS by AdvSM subtype. (A) PFS in all response-evaluable patients. (B) OS in safety population.

AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; NR, not reached; OS, overall survival; PFS, progression-free survival; SM-AHN, systemic mastocytosis with an associated hematological neoplasm.

Figure 3. OS in safety population by AdvSM subtype including MCL with no AHN.

AdvSM, advanced systemic mastocytosis; AHN, associated hematological neoplasm; ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; OS, overall survival; SM-AHN, systemic mastocytosis with an associated hematological neoplasm.

Figure 1

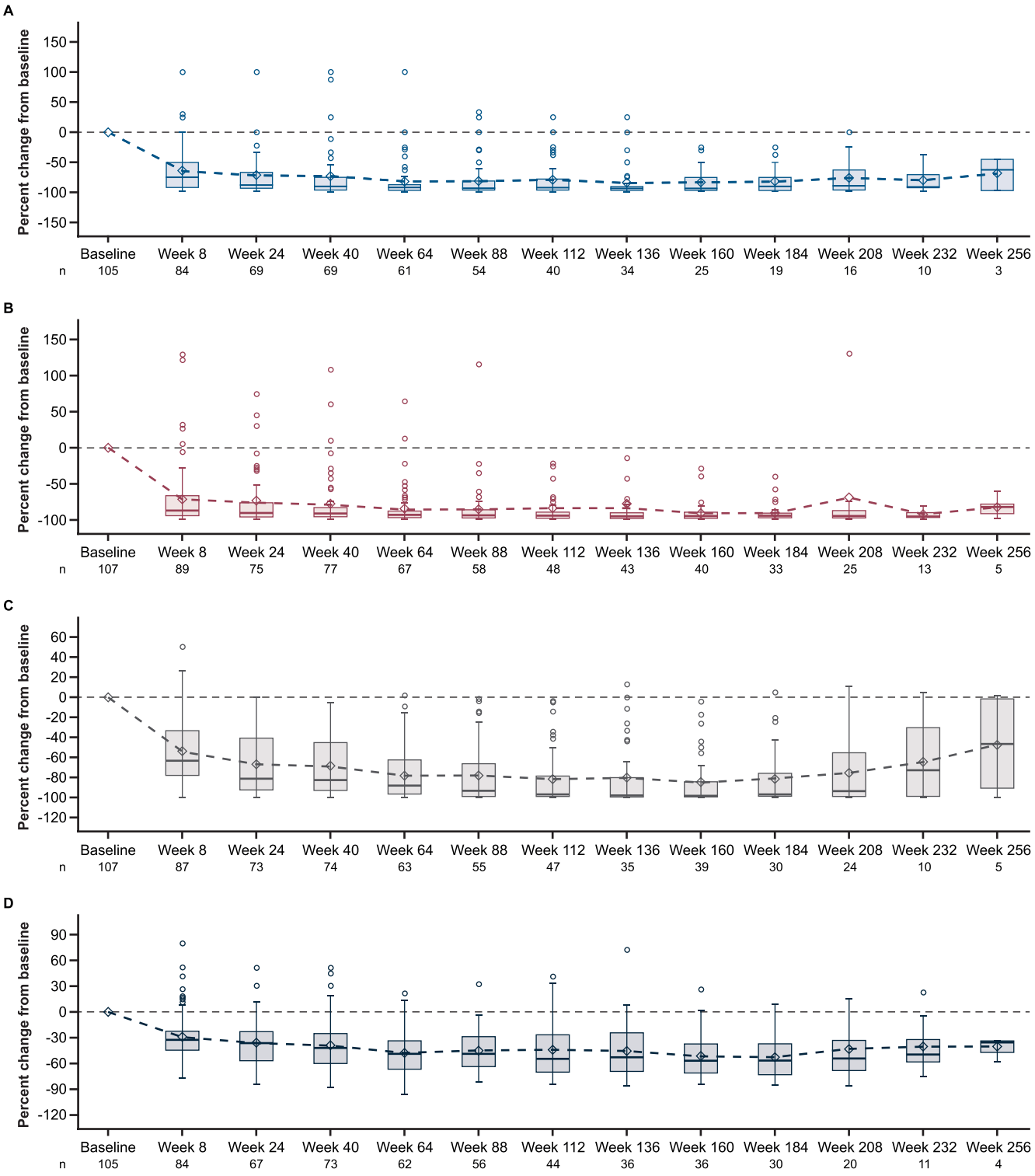

Figure 2

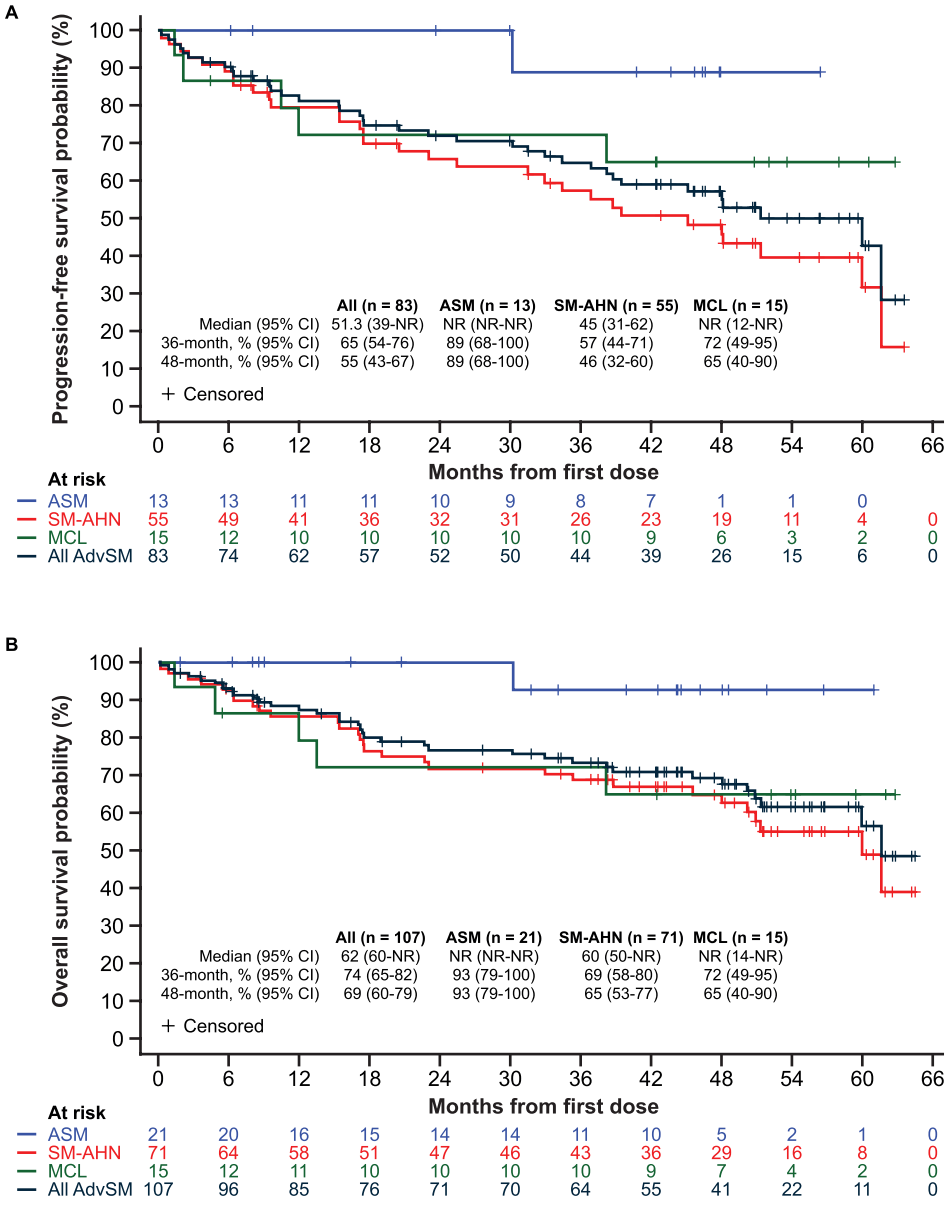

Figure 3