Leukemia Research 157 (2025) 107919

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Avapritinib versus midostaurin or cladribine in advanced systemic mastocytosis: A retrospective real-world external control study

Andreas Reiter [a,*], Jason Gotlib [b], Iván Álvarez-Twose [c], Deepti H. Radia [d], Johannes Lübke [a], Priyanka J. Bobbili [e], Aolin Wang [e], Saša Dimitrijević [f], Erin Sullivan [g], Juliana Schwaab [a], Ilene A. Galinsky [h], Cecelia Perkins [b], Wolfgang R. Sperr [i,j], Priya Sriskandarajah [d], Manasi Mohan [e], Teshawna Badu [e], Selvam R. Sendhil [e], Mei Sheng Duh [e], Peter Valent [i,j], Daniel J. DeAngelo [h]

[a] Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany
[b] Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, United States
[c] Institute of Mastocytosis Studies of Castilla La Mancha (CLMast) — Spanish Reference Center (CSUR) for Mastocytosis and CIBERONC, Virgen del Valle Hospital, Toledo, Spain
[d] Guy's & St Thomas' NHS Foundation Trust of Guy's Hospital, London, United Kingdom
[e] Analysis Group, Inc., Boston, MA, United States
[f] Blueprint Medicines GmbH, Zug, Switzerland
[g] Blueprint Medicines Corporation, Cambridge, MA, United States
[h] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, United States
[i] Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria
[j] Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria

ARTICLE INFO

Keywords:
Advanced systemic mastocytosis
Avapritinib
Midostaurin
Cladribine
Overall survival
Duration of treatment
Tryptase level

ABSTRACT

As there are no prospective randomized studies in patients with advanced systemic mastocytosis (AdvSM), we compared clinical outcomes between patients treated with avapritinib in the Phase I EXPLORER (NCT02561988) and Phase II PATHFINDER (NCT03580655) trials (N = 176) and patients treated with midostaurin (N = 99) or cladribine (N = 49) from a global, multi-center, retrospective, chart review study. Overall survival (OS) and duration of treatment (DOT) were compared between the cohorts using inverse probability of treatment weighting (IPTW)-adjusted Cox proportional hazards models, and maximum reduction in serum tryptase levels was compared using adjusted generalized linear models. Median OS was not reached (95% confidence interval [CI]: 46.9 months, not estimable) for avapritinib, 28.6 (18.2, 44.6) months for midostaurin, and 23.4 (14.8, 40.6) months for cladribine. The avapritinib cohort had significantly longer OS compared to midostaurin (hazard ratio [HR] [95% CI]: 0.59 [0.36, 0.97]) and cladribine (0.32 [0.15, 0.67]), longer DOT (vs. midostaurin: 0.63 [0.41, 0.96]; vs. cladribine: 0.14 [0.09, 0.23]), and greater reduction in serum tryptase levels with mean difference [95% CI] vs. midostaurin of −72.8 % [−101.1 %, −44.6 %] and vs. cladribine of −25.0 % [−32.4 %, −17.7 %] (all $p < 0.05$). Results were similar in treatment-naïve (1 L) and previously treated (2 L+) patients; there was improved OS in 1 L avapritinib vs. 1 L midostaurin patients (HR: 0.14 [0.05, 0.42]; $p < 0.001$) and in 2 L+ avapritinib vs. 2 L+ cladribine patients (0.34 [0.16, 0.71]; $p = 0.004$). Together, we show that avapritinib treatment resulted in significantly improved OS, longer DOT, and greater reduction in serum tryptase levels compared to midostaurin or cladribine in real-world clinical practice.

1. Introduction

Advanced systemic mastocytosis (AdvSM) is characterized by uncontrolled expansion and infiltration of neoplastic mast cells and other clonal, usually myeloid cells in various organs, leading to organ damage [1–5]. The three subtypes of AdvSM defined by the World Health Organization (WHO) include SM with an associated hematologic neoplasm (SM-AHN), mast cell leukemia (MCL), and aggressive systemic

* Correspondence to: Department of Hematology and Oncology, University Hospital Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.
E-mail address: andreas.reiter@medma.uni-heidelberg.de (A. Reiter).

https://doi.org/10.1016/j.leukres.2025.107919
Received 18 April 2025; Received in revised form 18 June 2025; Accepted 14 July 2025
Available online 15 July 2025

mastocytosis (ASM). All AdvSM subtypes are associated with a poor prognosis with a short overall survival (OS): 24 months for SM-AHN, 2—24 months for MCL, and 42 months for ASM when patients are treated with conventional antineoplastic therapies [6–10]. Major goals of treatment in AdvSM are to reduce or eliminate the mast cell burden, mitigate organ damage, improve the patients' quality of life, and extend survival. As the *KIT* D816V mutation was expressed in neoplastic mast cells in a majority (>90 %) of patients with SM in previous clinical studies (PATHFINDER and EXPLORER) and new KIT-targeting drugs are available, inhibition of KIT is considered an important therapeutic goal [11–15]..

Avapritinib, a potent inhibitor of D816V-mutated KIT, was evaluated in adults with centrally confirmed AdvSM in two prospective multicenter, single-arm, open-label clinical trials, the Phase I EXPLORER trial (ClinicalTrials.gov Identifier: NCT02561988) [16] and Phase II PATHFINDER trial (NCT03580655) [17]. Analysis of data from 69 patients with AdvSM in EXPLORER reported an estimated 24-month OS rate of 76 % (95 % confidence interval [CI], 64–87 %). Furthermore, 74 % of patients achieved normalization of serum tryptase levels (<20 ng/mL) [16]. Similarly, in a pre-specified interim analysis of 62 patients from PATHFINDER [17] who received avapritinib primarily at a starting dose of 200 mg daily, the estimated 12-month OS rate was 86 % and 43 % achieved normalization of serum tryptase levels. Based on these findings, avapritinib was approved for the treatment of adults with AdvSM by the US Food and Drug Administration (FDA) in 2021 and by the European Medicines Agency (EMA), after prior systemic therapy, in 2022 [18–20].

Prior to the availability of avapritinib, two of the most common therapies used to treat AdvSM were midostaurin and cladribine. Midostaurin was approved for treatment of AdvSM by the FDA and EMA in 2017 [21,22]. The efficacy and safety of midostaurin have been reported in several clinical trials and observational studies; an open-label study demonstrated that midostaurin treatment produced a response in 28.3 % of patients across all subtypes of AdvSM per International Working Group - Myeloproliferative Neoplasms Research and Treatment - European Competence Network on Mastocytosis (IWG-MRT-ECNM) consensus criteria, and median OS was 29.9 months [23]. Cladribine is often used in patients who have progressed on other therapies and has been shown to reduce the total mast cell burden [24–26], although few patients achieve a complete remission and nearly all responding patients will eventually relapse. A registry-based analysis comparing the efficacy of midostaurin (n = 63) and cladribine (n = 23) found that midostaurin was superior to cladribine in terms of significantly improved OS (median 4.2 vs. 1.9 years) and leukemia-free survival (2.7 vs. 1.3 years) [26]. In drug-resistant AdvSM, polychemotherapy and allogeneic hematopoietic stem cell transplantation are often recommended in transplant-eligible patients [3,4].

Although there are no randomized clinical trials comparing avapritinib to either midostaurin or cladribine in AdvSM, understanding the comparative effectiveness of avapritinib and the alternative best available therapies (BAT) for AdvSM is essential to inform clinical decision making. Previously, we compared outcomes of patients with AdvSM who received avapritinib in the EXPLORER and PATHFINDER trials to those of patients treated with BAT in a real-world setting. The results indicated that the avapritinib cohort had significantly better survival (hazard ratio [HR] [95% CI]: 0.48 [0.29, 0.79]; $p = 0.004$) compared to the BAT cohort [27], however that analysis did not separately evaluate and compare avapritinib outcomes to specific treatments in regular clinical practice. This study (NCT04695431) compared clinical outcomes of patients with AdvSM who were treated with avapritinib in EXPLORER and PATHFINDER with those of patients treated with midostaurin or cladribine in real-world clinical practice using data from retrospective chart review [28].

2. Materials and methods

2.1. Study population

2.1.1. Clinical trial data

This study used pooled individual patient data from the Phase I EXPLORER [16] and Phase II PATHFINDER [17] trials with a data cut-off date of April 20, 2021 (data on file, Blueprint Medicines Corporation). In EXPLORER, patients were treated at different avapritinib starting doses ranging from 30 to 400 mg daily while in PATHFINDER, all patients received an avapritinib starting dose of 200 mg daily. The primary analysis included patients who initiated avapritinib at any dose. In the pooled sample, median follow-up time for OS was 17.1 months.

Subgroup analyses were conducted using pooled patient-level data from the Phase I EXPLORER trial with data cutoff date of January 19, 2023, and the Phase II PATHFINDER trial with data cut-off date of September 15, 2023. The subgroup analyses were limited to EXPLORER and PATHFINDER trial patients who received an avapritinib starting dose of 200 mg daily, which is the recommended starting dosage for patients with AdvSM. In the pooled sample for the subgroup analyses, median follow-up time for OS was 36.2 months.

2.1.2. Real-world data

To generate real-world data on midostaurin and cladribine for AdvSM, a global, observational, retrospective chart review study was conducted at the following six Centers of Excellence for the treatment of AdvSM: Dana-Farber Cancer Institute (US), Guy's and St Thomas' NHS Foundation Trust (United Kingdom), Virgen del Valle Hospital of Toledo (Spain), Medical University of Vienna (Austria), University Hospital Mannheim (Germany), and the Stanford Cancer Institute (US). De-identified, longitudinal, individual-level data of eligible patients with AdvSM who received any systemic treatment were collected via medical chart abstraction into a standardized, structured, electronic case report form from March 26 to October 4, 2021 [27]. Institutional Review Board or Ethics committee approvals were issued at each site.

2.2. Sample selection

Patients receiving treatment with any systemic therapy for AdvSM were identified based on inclusion and exclusion criteria similar to those of EXPLORER and PATHFINDER [16,17,27]. The real-world study population included adults (aged ≥18 years) with an AdvSM diagnosis and documented subtype in their chart (ASM, SM-AHN, or MCL), and who had received ≥1 line(s) of systemic therapy (not necessarily as first line [1 L]) for AdvSM at a participating site on or after January 1, 2009. If a patient received multiple lines of therapy at a participating site, data on all available lines of therapy were collected and analyzed. Patients who received treatment with midostaurin or cladribine at any dose were included in this analysis. The index date was defined as the initiation of each line of midostaurin or cladribine therapy at a participating site.

Patients were excluded if they had a history of another primary malignancy that was diagnosed or required therapy within 3 years before the index date, except for completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma *in situ* at any site.

2.3. Study endpoints

The primary endpoint was OS, defined for all cohorts as the time between the index date and death due to any cause. Patients who were alive at the end of data collection were censored at the date of last contact (midostaurin and cladribine cohorts) or at the last known date alive (avapritinib cohort). Additionally, patients in the midostaurin and cladribine cohorts were censored at avapritinib initiation, if applicable.

Secondary endpoints included duration of treatment (DOT), defined as the time between the index date and treatment discontinuation for

any reason, and maximum reduction in serum tryptase levels within a line of therapy (hereafter referred to as 'reduction in serum tryptase'). For the DOT analyses, lines of therapy with unknown discontinuation date and unknown last known prescription date were excluded. Other response endpoints, such as complete and partial response and safety endpoints were not included due to the lack of uniform assessment criteria or uniform definitions in non-protocol clinical practice.

Time to next treatment line (TtNTL) was defined as time from index date to initiation of next line of therapy and was described for the cladribine cohort. While DOT can be considered a proxy measure for time to disease progression, TtNTL may be a more informative proxy measure in the context of treatment with cladribine. This is because cladribine is typically administered with a fixed number of treatment cycles (though patients may discontinue treatment if their disease is in remission or progresses). TtNTL was not captured in the EXPLORER and PATHFINDER trials.

2.4. Baseline covariates

Key adjustment covariates used in this analysis were selected *a priori* and informed by clinical input and prognostic scores (Mutation-Adjusted Risk Score and the International Prognostic Scoring System in Mastocytosis) [26,29–32]. These covariates included: age; sex; region (North America or Europe); European Cooperative Oncology Group (ECOG) score; AdvSM subtype; presence of skin involvement; number and types of prior lines received (tyrosine kinase inhibitor [TKI], cytoreductive therapy, or biologic/other systemic therapy); presence of anemia (hemoglobin <10 g/dL), thrombocytopenia (platelet count $<100 \times 10^9$/L), or leukocyte count $\geq 16 \times 10^9$/L; serum tryptase level ≥125 ng/mL; and presence and number of mutations within the *SRSF2/ASXL1/RUNX1* gene panel [29,33].

2.5. Statistical analyses

2.5.1. Cohort characteristics and covariates

Descriptive statistics were used to summarize key covariates in all cohorts. Comparisons between cohorts were conducted using the Wilcoxon rank-sum test for continuous variables and chi-squared test for categorical variables (for categorical variables with expected counts <5, the Fisher's exact test was used).

2.5.2. Outcome analyses

For OS and DOT, the median time-to-event was estimated for each cohort individually using the Kaplan-Meier method. Corresponding 95% CIs and log-rank test *p* values were reported across all lines of therapy, along with survival and on-treatment rates at specific time points.

Comparative analyses of endpoints employed a two-step process to obtain an adjusted effect estimate that was doubly robust against confounding [27,34]. First, stabilized, and truncated (at the 1st and 99th percentiles), inverse-probability-of-treatment-weights (IPTW) were created using logistic regression models conditional on the pre-specified key covariates [35].

Next, IPTW-weighted multivariable Cox proportional hazards models were used to compare survival/DOT and IPTW-weighted multivariable generalized estimating equation linear models were used to compare reduction in serum tryptase between the avapritinib and midostaurin or cladribine cohorts, with robust variance estimation and further adjustment for key covariates that remained unbalanced (i.e., standardized difference >10 %) after weighting. A two-sided $p < 0.05$ was considered statistically significant without multiplicity adjustment.

2.5.3. Subgroup analyses

The subgroup analyses were conducted using pooled data from the EXPLORER and PATHFINDER 2023 data cuts, limited to patients who received an avapritinib starting dose of 200 mg daily. The primary endpoint of OS and the secondary endpoint of DOT were compared in the following subgroups: patients who received 1 L avapritinib in EXPLORER and PATHFINDER vs. 1 L midostaurin patients and patients who received at least one prior line of systemic therapy (2 L+ patients) prior to initiating avapritinib in EXPLORER and PATHFINDER vs. 2 L+ cladribine patients. Subgroup analyses among 1 L avapritinib patients vs. 1 L cladribine patients were not performed due to inadequate sample size of patients receiving 1 L cladribine. In addition, subgroup analyses among 2 L+ avapritinib patients vs. 2 L+ midostaurin patients were not conducted due to the lack of direct comparability between the two cohorts (over half of the 2 L+ avapritinib patients had previously been treated with midostaurin).

2.6. Software

All data cleaning and analyses were conducted using SAS® Enterprise Guide® (version 7.1) and R (version 3.6.3).

3. Results

3.1. Study sample

The avapritinib cohort was composed of 176 patients (contributing data on 176 therapeutic lines) included in the EXPLORER (n = 69) and PATHFINDER (n = 107) trials (Table 1). The midostaurin and cladribine cohorts were composed of 94 patients (99 therapeutic lines) and 44 patients (49 therapeutic lines), respectively. A patient could contribute data on more than one therapeutic line. For example, a patient could contribute data on two lines of therapy with midostaurin if they had received treatment with another agent between them, with no overlap in dates of initiation and discontinuation.

3.1.1. Baseline characteristics and IPTW weighting

The mean (standard deviation [SD]) ages of the avapritinib (66.3 [10.7] years), midostaurin (67.1 [11.6] years), and cladribine (64.6 [10.1] years) cohorts were similar, as were the proportions of female patients (41.5 %, 32.3 %, and 40.8 %, respectively) (Table 1). The *KIT* D816V mutation was present in 91.8 %, 89.3 %, and 90.7 % of the avapritinib, midostaurin, and cladribine cohorts, respectively. The mean (SD) ECOG scores were 1.2 (0.8), 1.1 (0.8) and 0.9 (0.5) for the avapritinib, midostaurin, and cladribine cohorts, respectively. Prior to IPTW-weighting, and compared with patients in the midostaurin cohort, patients in the avapritinib cohort were more likely to be from North America, less likely to have thrombocytopenia, and more likely to have zero mutated genes in the *SRSF2/ASXL1/RUNX1* panel. Prior to IPTW-weighting, and compared with patients in the cladribine cohort, patients in the avapritinib cohort were more likely to be from North America, more likely to have SM-AHN, and less likely to have thrombocytopenia. After weighting by truncated, stabilized IPTW weights, the standardized differences between avapritinib and the comparators decreased to ≤10 % for most covariates, indicating the cohorts were comparable with regard to key covariates (Tables A.1 and A.2).

3.1.2. Prior lines of therapy

A total of 41.4 % of the midostaurin cohort and 59.2 % of the cladribine cohort had prior lines of systemic therapy, compared with 62.5 % of the avapritinib cohort (Table A.3). The most common prior treatments in the midostaurin cohort were cladribine (23.2 %), interferon-alfa (7.1 %), and hydroxyurea (7.1 %); for the cladribine cohort, they were midostaurin (40.8 %), interferon-alfa (16.3 %), and hydroxyurea (12.2 %). For the avapritinib cohort, the most common prior treatments were midostaurin (46.0 %), cladribine (12.5 %), and interferon-alfa (8.0 %).

Table 1
Summary of baseline characteristics.

Baseline characteristics, unweighted sample[a]	Avapritinib cohort	Midostaurin cohort	*p* value (avapritinib vs. midostaurin)	Cladribine cohort	*p* value (avapritinib vs. cladribine)
Number of unique patients	N = 176	N = 94		N = 44	
Number of lines of therapy	N = 176	N = 99		N = 49	
Demographic characteristics					
Age (years)			0.359		0.250
Mean (SD)	66.3 (10.7)	67.1 (11.6)	–	64.6 (10.1)	–
Median (min, max)	68.0 (31.0, 88.0)	69.1 (25.8, 87.3)	–	66.1 (45.1, 87.5)	–
Sex, n (%)					
Female	73 (41.5 %)	32 (32.3 %)	0.171	20 (40.8 %)	1.000
Male	103 (58.5 %)	67 (67.7 %)	0.171	29 (59.2 %)	1.000
Region, n (%)					
North America	102 (58.0 %)	19 (19.2 %)	< 0.001*	3 (6.1 %)	< 0.001*
Europe	74 (42.0 %)	80 (80.8 %)	< 0.001*	46 (93.9 %)	< 0.001*
Medical history					
Performance status					
ECOG			0.878		0.124
n (%)	176 (100.0 %)	99 (100.0 %)	–	49 (100.0 %)	–
Mean (SD)	1.2 (0.8)	1.1 (0.8)	–	0.9 (0.5)	–
Median (min, max)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	–	1.0 (0.0, 2.0)	–
ECOG category, n (%)					
0	36 (20.5 %)	19 (19.2 %)	0.925	9 (18.4 %)	0.904
1	92 (52.3 %)	54 (54.5 %)	0.813	35 (71.4 %)	0.026*
≥2	48 (27.3 %)	26 (26.3 %)	0.968	5 (10.2 %)	0.022*
Anemia,[b] n (%)	104 (59.1 %)	57 (57.6 %)	0.907	32 (65.3 %)	0.534
Thrombocytopenia,[c] n (%)	67 (38.1 %)	56 (56.5 %)	0.005*	28 (57.1 %)	0.026*
Disease characteristics					
AdvSM subtype diagnosis, n (%)					
SM-AHN	119 (67.6 %)	65 (65.7 %)	0.843	25 (51.0 %)	0.049*
ASM	29 (16.5 %)	21 (21.2 %)	0.416	17 (34.7 %)	0.009*
MCL	28 (15.9 %)	13 (13.1 %)	0.657	7 (14.3 %)	0.957
Any skin involvement, n (%)	58 (33.0 %)	30 (30.3 %)	0.751	16 (32.7 %)	1.000
Leukocyte count ≥16 × 10^9/L, n (%)	33 (18.8 %)	23 (23.2 %)	0.465	13 (26.5 %)	0.320
Serum tryptase (ng/mL)			0.463		0.151
n (%)	176 (100.0 %)	93 (93.9 %)		42 (85.7 %)	
Mean (SD)	308.9 (277.2)	299.6 (296.6)	–	410.4 (351.0)	–
Median (min, max)	216.4 (12.4, 1600.0)	211.0 (15.7, 1690.0)	–	302.0 (63.9, 1298.0)	–
≥125 ng/mL, n (%)	132 (75.0 %)	68 (68.7 %)	0.323	32 (65.3 %)	0.243
KIT mutation					
Patients tested, n (%)	170 (96.6 %)	93 (98.9 %)	0.428	43 (97.7 %)	1.000
KIT D816V positive, n (%)	156 (91.8 %)	83 (89.3 %)	0.650	39 (90.7 %)	0.765
SRSF2/ASXL1/RUNX1 gene panel, n (%)					
Patients tested for ≥ 1 mutation	176 (100.0 %)	78 (83.0 %)	< 0.001*	40 (90.9 %)	0.001*
Number of mutated genes in panel					
0	92 (52.3 %)	27 (34.6 %)	0.014*	15 (37.5 %)	0.131
1	54 (30.7 %)	34 (43.6 %)	0.064	15 (37.5 %)	0.518
≥2	30 (17.1 %)	17 (21.8 %)	0.469	10 (25.0 %)	0.345

Abbreviations: ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; max, maximum; MCL, mast cell leukemia; min, minimum; SD, standard deviation; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.
Notes:
* denotes $p < 0.05$.
[a] The baseline period was defined as 8 weeks leading up to the index date for the avapritinib cohort and the 12 weeks leading up to the index date for the midostaurin and cladribine cohorts. Descriptive statistics are reported at the line of therapy level for all variables except *KIT* and *SRSF2/ASXL1/RUNX1* mutations, which are reported at the patient level, because each patient in the midostaurin or cladribine cohorts could contribute more than one line of therapy to the analysis.
[b] For both the avapritinib cohort and the midostaurin and cladribine cohorts, anemia included reported anemia and hemoglobin less than 10 g/dL.
[c] For both the avapritinib cohort and the midostaurin and cladribine cohorts, thrombocytopenia included reported thrombocytopenia and platelet count less than 100 × 10^9/L.

3.2. Primary analysis

3.2.1. Overall survival

In the unweighted sample, there were 34 (19.3 %) deaths among 176 avapritinib patients, 56 (59.6 %) among 94 midostaurin patients, and 29 (65.9 %) among 44 cladribine patients, with a mean follow-up of 17.9, 27.9, and 24.2 months, respectively (Table 2). Across all lines of therapy, median OS was not reached (NR, 95% CI: 46.9, not estimable [NE]) for the avapritinib cohort, 28.6 (18.2, 44.6) months for the midostaurin cohort, and 23.4 (14.8, 40.6) months for the cladribine cohort (both log-rank $p < 0.001$; Fig. 1). After IPTW-weighting, the median OS in the avapritinib cohort was 49.0 months (95% CI: 46.9, NE), while it was 42.0 months (95% CI: 26.8, NE) in the midostaurin cohort and 23.4 months (95% CI: 14.0, 42.8) in the cladribine cohort (Tables A.4 and A.5). In the adjusted analysis after IPTW-weighting, with further adjustment for variables with standardized difference >10 % after weighting, avapritinib was associated with significantly improved OS compared with midostaurin (HR [95% CI]: 0.59 [0.36, 0.97]; $p = 0.037$) and cladribine (HR [95% CI]: 0.32 [0.15, 0.67]; $p = 0.003$) (Table 2).

3.2.2. Duration of treatment

The DOT analyses included 176 patients in the avapritinib cohort, 94 in the midostaurin cohort, and 42 in the cladribine cohort (Table 3). Across all lines of therapy, discontinuation occurred in 38.1 % and 84.8 % of therapeutic lines in the avapritinib and midostaurin cohorts, respectively. In the unweighted sample, the median DOT was 30.6 (95%

Table 2
Summary of overall survival.

Overall survival	Avapritinib cohort	Midostaurin cohort	Cladribine cohort
Number of unique patients	**N = 176**	**N = 94**	**N = 44**
Number of lines of therapy	**N = 176**	**N = 99**	**N = 49**
Deaths from unique patients, n (%)	34 (19.3 %)	56 (59.6 %)	29 (65.9 %)
Unique patients censored due to avapritinib initiation, n (%)	–	12 (12.8 %)	6 (13.6 %)
Unique patients censored due to new primary malignancy after index date, n (%)	–	5 (5.3 %)	2 (4.5 %)
Mean follow-up (months)	17.9	27.9	24.2
Median OS, unweighted sample (months) (95% CI)	NR (46.9, NE)	28.6 (18.2, 44.6)	23.4 (14.8, 40.6)
Avapritinib vs. midostaurin: HR, IPTW-weighted sample (95% CI); *p* value[a]	0.59 (0.36, 0.97); 0.037*		
Avapritinib vs. cladribine: HR, IPTW-weighted sample (95% CI); *p* value[b]	0.32 (0.15, 0.67); 0.003*		

Abbreviations: AdvSM, advanced systemic mastocytosis; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability treatment weighting; NE, not estimable; NR, not reached; OS, overall survival.
Notes:
* denotes $p < 0.05$.
[a] The IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference >10 % after weighting, including sex, region, AdvSM subtype, number of prior lines of therapy, and prior use of tyrosine kinase inhibitors.
[b] The IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference >10 % after weighting, including age, region, anemia (hemoglobin less than 10 g/dL), and number of mutated genes within the *SRSF2/ASXL1/RUNX1* gene panel.

CI: 21.4, NE) months in the avapritinib cohort, and 9.0 (6.8, 14.0) months in the midostaurin cohort. In the adjusted analysis, DOT was significantly longer in the avapritinib cohort than the midostaurin cohort (IPTW-weighted median [95% CI]: 23.8 [21.4, 40.9] vs. 13.3 [8.1, 22.4] months; HR [95% CI]: 0.63 [0.41, 0.96]; $p = 0.032$).

In the unweighted cladribine cohort, the median TtNTL was 8.5 (95% CI: 7.2, 17.7) months, and median DOT was 4.7 (95% CI: 3.8, 5.8) months. TtNTL was not available for the avapritinib cohort, as patient

Table 3
Summary of duration of treatment.

Duration of treatment	Avapritinib cohort	Midostaurin cohort	Cladribine cohort
Number of unique patients	**N = 176**	**N = 94**	**N = 42**
Number of lines of therapy	**N = 176**	**N = 99**	**N = 45**
Number of discontinued lines of therapy, n (%)	67 (38.1 %)	84 (84.8 %)	42 (93.3 %)
Number of censored lines of therapy, n (%)	109 (61.9 %)	15 (15.2 %)	3 (6.7 %)
Median DOT (months) (95% CI)	30.6 (21.4, NE)	9.0 (6.8, 14.0)	4.7 (3.8, 5.8)
Avapritinib vs. midostaurin: HR, IPTW-weighted sample (95% CI); *p* value[a]	0.63 (0.41, 0.96); 0.032*		
Avapritinib vs. cladribine: HR, IPTW-weighted sample (95% CI); *p* value[b]	0.14 (0.09, 0.23); < 0.001*		

Abbreviations: AdvSM, advanced systemic mastocytosis; CI, confidence interval; DOT, duration of treatment; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NE, not estimable.
Notes:
* denotes $p < 0.05$.
[a] The IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference >10 % after weighting, including sex, region, AdvSM subtype, number of prior lines of therapy, and prior use of tyrosine kinase inhibitors.
[b] The IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference >10 % after weighting, including age, region, anemia (hemoglobin <10 g/dL), and number of mutated genes within the *SRSF2/ASXL1/RUNX1* panel.

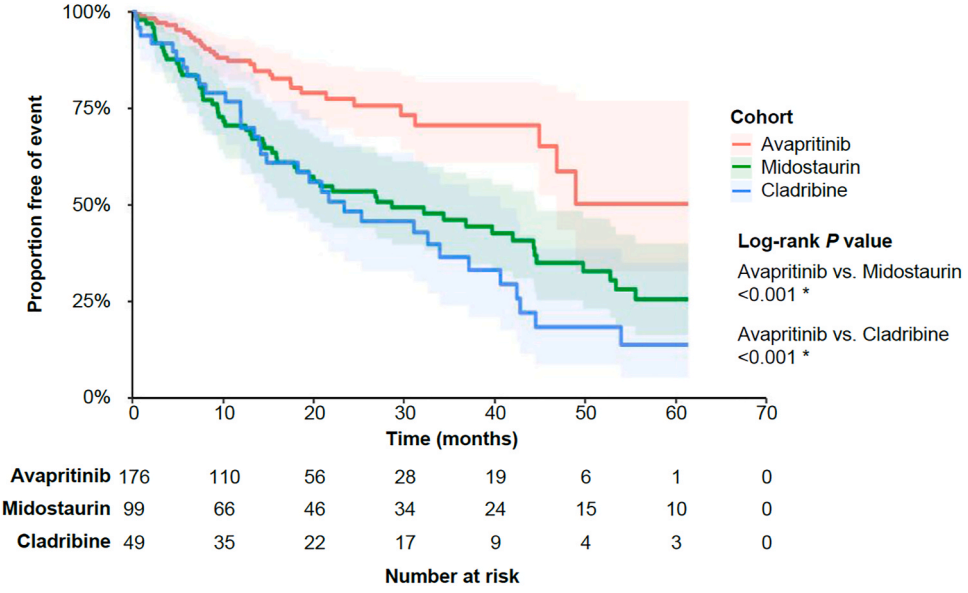

Fig. 1. Unweighted overall survival for avapritinib versus midostaurin or cladribine[a,b,c]. Abbreviations: AdvSM, advanced systemic mastocytosis; OS, overall survival. Notes: [a] Patients from the midostaurin and cladribine cohorts could contribute multiple lines of therapy. A total of 99 lines of therapy were contributed by 94 patients in the midostaurin cohort, and 49 lines of therapy were contributed by 44 patients in the cladribine cohort. [b] The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort. [c] Lines of therapy with unknown discontinuation date and unknown last known prescription date were excluded from the analysis.

follow-up in the EXPLORER and PATHFINDER trials ended prior to initiation of the next treatment line. However, an adjusted comparison of DOT between the avapritinib and cladribine cohorts indicates that DOT was significantly longer in the avapritinib cohort (IPTW-weighted median DOT [95% CI]: 26.4 [22.9, NE] vs. 5.0 [4.0, 5.4] months; HR [95% CI]: 0.14 [0.09, 0.23]; $p < 0.001$).

3.2.3. Reduction in serum tryptase levels

The analysis of reduction in serum tryptase level included 175 patients in the avapritinib cohort, 79 in the midostaurin cohort, and 28 in the cladribine cohort (Fig. 2A, Tables A.6 and A.7). After weighting, across all lines of therapy, the maximum percentage reduction in serum tryptase levels was greater in the avapritinib cohort relative to both comparators, with a mean difference of −72.8 % (95 % CI: −101.1 %, −44.6 %) vs. midostaurin and −25.0 % (−32.4 %, −17.7 %) vs. cladribine (both $p < 0.001$).

3.3. Subgroup analyses

The subgroup analyses were conducted using pooled data from the EXPLORER and PATHFINDER 2023 data cuts, with median follow-up of 36.2 months, limited to patients who received an avapritinib starting dose of 200 mg daily.

3.3.1. Overall survival in subgroups

In previously untreated patients, before weighting, the median OS was significantly improved among patients who received 1 L avapritinib (n = 46 patients/therapeutic lines) vs. 1 L midostaurin (n = 58 patients/therapeutic lines) (NR [95% CI: NE, NE] vs. 28.6 [18.2, 49.8] months, respectively; HR [95% CI]: 0.24 [0.11, 0.53]; $p < 0.001$) (Table 4, Figure A.1). After weighting, the median OS associated with 1 L avapritinib remained significantly improved relative to 1 L midostaurin (NR [95% CI: NE, NE] vs. 32.2 [22.1, 44.3] months; HR [95% CI]: 0.14 [0.05, 0.42]; $p < 0.001$).

Among patients with prior treatment, before weighting, the median OS was significantly improved among patients who received 2 L+ avapritinib (n = 79 patients/therapeutic lines) vs. 2 L+ cladribine (n = 27 patients, 29 therapeutic lines) (52.4 [95% CI: 50.2, NE] vs. 21.7 [14.0, 42.4] months, respectively; HR [95% CI]: 0.35 [0.20, 0.63]; $p < 0.001$) (Table 4, Figure A.2). After weighting, the median OS associated with 2 L+ avapritinib remained significantly improved compared with 2 L+ cladribine (52.4 [95% CI: 50.2, NE] vs. 21.7 [14.0, 42.8] months; HR [95% CI]: 0.34 [0.16, 0.71]; $p = 0.004$).

3.3.2. Duration of treatment in subgroups

In previously untreated patients, before weighting, the median DOT was significantly longer among patients who received 1 L avapritinib (n = 46 patients/therapeutic lines) vs. 1 L midostaurin (n = 58 patients/therapeutic lines) (37.6 [95% CI: 24.9, NE] vs. 11.6 [7.5, 22.1] months, respectively; HR [95% CI]: 0.45 [0.28, 0.72]; $p < 0.001$). After weighting, the DOT associated with 1 L avapritinib remained significantly longer than 1 L midostaurin (37.6 [23.8, 51.4] vs. 13.3 [7.5, 42.2] months; HR [95% CI]: 0.42 [0.24, 0.74]; $p = 0.003$) (Supplemental Table A.8).

Among previously treated patients, before weighting, the median DOT was significantly longer among patients who received 2 L+ avapritinib (n = 79 patients/therapeutic lines) vs. 2 L+ cladribine (n = 24 patients, 25 therapeutic lines) (25.1 [95% CI: 18.3, 34.8] vs. 4.7 [2.7, 8.1] months, respectively; HR [95% CI]: 0.21 [0.12, 0.33]; $p < 0.001$). After weighting, 2 L+ avapritinib was associated with significantly longer DOT compared with 2 L+ cladribine (24.0 [18.0, 34.4] vs. 4.7 [2.1, 5.4] months; HR [95% CI]: 0.20 [0.11, 0.37]; $p < 0.001$) (Supplemental Table A.8).

4. Discussion

We previously compared efficacy outcomes of patients with AdvSM who received avapritinib in the EXPLORER and PATHFINDER trials to those of patients treated with best available therapies in a real-world setting (N = 141, contributing data on 222 lines of therapy) [27]. The present study compared OS, DOT, and maximum reduction in serum tryptase levels between patients with AdvSM treated with avapritinib in the EXPLORER and PATHFINDER trials and a subset of patients from the real-world cohort who were treated with midostaurin (N = 99 lines of therapy) or cladribine (N = 49 lines of therapy). Additionally, this study included comparisons of OS and DOT between patients treated with 1 L and 2 L+ avapritinib 200 mg daily starting dose, using updated data from the Phase II EXPLORER and PATHFINDER trials (median follow-up

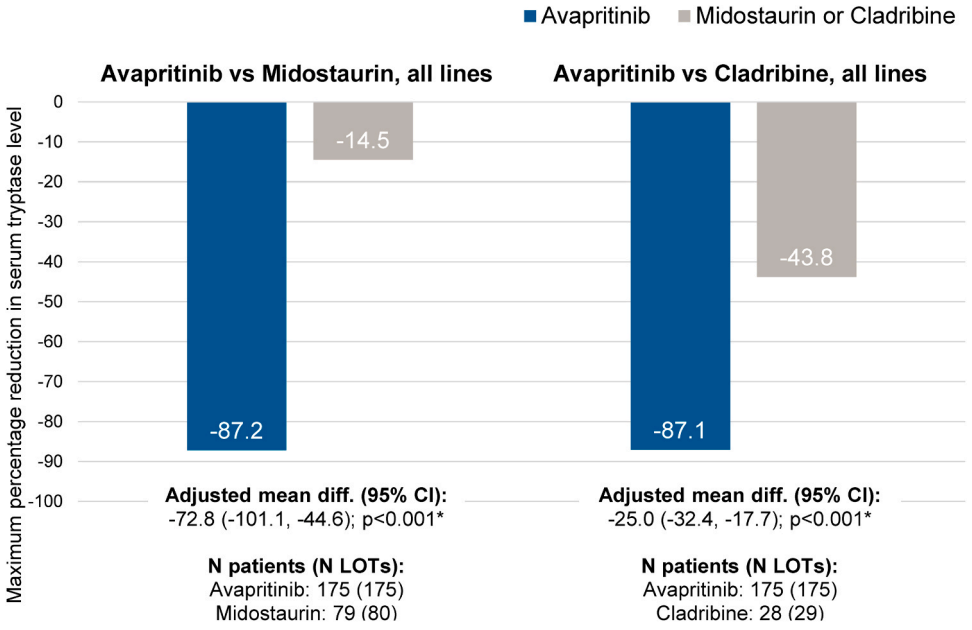

Fig. 2. Comparison of maximum percentage reduction in serum tryptase levels for avapritinib versus midostaurin or cladribine[a]. * denotes $p < 0.05$. Abbreviations: CI, confidence interval; diff, difference; LOT, line of therapy. Note: [a] Lines of therapy without a tryptase measurement at baseline and lines of therapy with unknown discontinuation and last prescription date were excluded from the analyses.

Table 4
Summary of overall survival in patient subgroups.

1 L avapritinib 200 mg (EXPLORER and PATHFINDER pooled population, 2023) vs. 1 L midostaurin[a,b]								
	Unweighted sample				IPTW-weighted sample			
	Avapritinib cohort	Midostaurin cohort	Estimate (95% CI)	*p* value	Avapritinib cohort	Midostaurin cohort	Estimate (95% CI)	*p* value
Number of lines of therapy (number of unique patients)	46 (46)	58 (58)			43 (43)	58 (58)		
Mean follow-up (months)	32.2	26.1			32.2	26.1		
Median OS (months) (95% CI)[c]	NR (NE, NE)	28.6 (18.2, 49.8)	–	–	NR (NE, NE)	32.2 (22.1, 44.3)	–	–
HR (95% CI)	–	–	0.24 (0.11, 0.53)	<0.001 *	–	–	0.14 (0.05, 0.42)	<0.001 *

2L+ Lavapritinib 200 mg (EXPLORER and PATHFINDER pooled population, 2023) vs. 2L+ cladribine[a,d]								
	Unweighted sample				IPTW-weighted sample			
	Avapritinib cohort	Cladribine cohort	Estimate (95% CI)	*p* value	Avapritinib cohort	Cladribine cohort	Estimate (95% CI)	*p* value
Number of lines of therapy (number of unique patients)	79 (79)	29 (27)			79 (79)	24 (22)		
Mean follow-up (months)	28.5	25.1			28.5	25.1		
Median OS (months) (95% CI)[c]	52.4 (50.2, NE)	21.7 (14.0, 42.4)	–	–	52.4 (50.2, NE)	21.7 (14.0, 42.8)	–	–
HR (95% CI)	–	–	0.35 (0.20, 0.63)	<0.001 *	–	–	0.34 (0.16, 0.71)	0.004*

Abbreviations: 1 L, first line of therapy; 2 L+ , second or later line of therapy; AdvSM, advanced systemic mastocytosis; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NE, not estimable; NR, not reached; OS, overall survival.
Notes:
* denotes $p < 0.05$.
[a] Data from EXPLORER (data cut-off date of January 19, 2023) and PATHFINDER (data cut-off date of September 15, 2023) were used.
[b] The IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference >10 % after weighting, including sex, region, ECOG score, AdvSM subtype, leukocyte count of 16×10^9 per L or higher, and number of mutated genes within the *SRSF2/ASXL1/RUNX1* gene panel.
[c] Median overall survival was estimated using the Kaplan-Meier method.
[d] The IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference >10 % after weighting, including age, ECOG score, anemia (hemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100×10^9/L), serum tryptase level of 125 ng/mL or higher, and number of mutated genes within the *SRSF2/ASXL1/RUNX1* gene panel.

time of 36.2 months), to patients receiving 1 L midostaurin and 2 L+ cladribine in real-world clinical practice, respectively. Patients who received midostaurin in second line or later had often previously received cladribine or hydroxyurea, whereas a substantial portion of patients who received avapritinib in second line or later were previously treated with midostaurin, a superior front-line therapy for AdvSM compared with cladribine or hydroxyurea. Because such systematic differences affecting OS are difficult to fully address via statistical methods alone, comparisons of outcomes among patients treated with avapritinib vs. midostaurin in the 2 L+ setting were not conducted.

After adjusting for differences in key prognostic factors and confounders between the two treatment cohorts, avapritinib was associated with significantly improved OS compared to midostaurin across all therapeutic lines. Midostaurin was administered as 1 L treatment in over half (58.6 %) of the therapeutic lines included in this analysis, and subgroup analyses comparing survival among patients treated with 1 L avapritinib in pooled EXPLORER and PATHFINDER data vs. 1 L midostaurin suggested that patients receiving 1 L avapritinib (in the recommended label dose of 200 mg) experienced significantly improved survival. These results provide valuable insights on the comparative effectiveness of these treatments in the absence of randomized controlled clinical trials.

The median OS observed in the midostaurin cohort for all therapeutic lines and for the 1 L subgroup was 28.6 months, which is somewhat shorter than the OS reported for midostaurin in existing literature. For example, a large open-label study of 116 AdvSM patients by Gotlib et al. [8] reported a median OS of 34 months for midostaurin-treated patients in the intention-to-treat population, while a median OS of 28.7 months was reported in the primary efficacy population. The German retrospective registry analysis by Lübke et al. [26] reported that the OS for midostaurin-treated patients was 37.2 months among both 1 L and 2 L patients and 42.0 months among 1 L patients. The different findings on observed OS may be attributed to differences in the sample sizes, patients' disease characteristics, and baseline prognostic factors. The median DOT observed for the midostaurin cohort was 9.0 months, which is generally consistent with prior studies of midostaurin administered in all lines (i.e., 7.9 months in Singh et al. [36] and 8.4 months in Rossignol et al. [37]). The median maximum percentage change in tryptase in the IPTW-weighted midostaurin cohort was −36.9 %, which is also generally consistent with prior studies of midostaurin (i.e., −58 % in Gotlib et al. [8] and −47 % in DeAngelo et al. [38]).

Avapritinib was associated with significantly improved OS and DOT compared to cladribine across all therapeutic lines, as well as in the 2 L+ setting. The median OS observed in the cladribine cohort was 23.4 months for all therapeutic lines, and 21.7 months in the 2 L+ setting. These findings are slightly longer than the median OS reported for patients treated with cladribine in existing literature; for example, a recent registry study by Lübke et al. reported a median OS of 18.0 months among both 1 L and 2 L patients and 14.4 months among 2 L patients [39]. The difference in OS findings may likely be attributed to differences in disease severity; 65.3 % of patients in the cladribine cohort (all lines) had SM-AHN or MCL subtypes of AdvSM, as compared to 88.6 % of cladribine patients in the registry study. The median DOT observed for the cladribine cohort (all lines) was 4.7 months, which is comparable to that reported in the same registry study (3.6 months among both 1 L and 2 L patients).

This study employed several strategies to maximize the comparability of the avapritinib and comparator cohorts. These included selecting patients in the midostaurin and cladribine cohorts based on similar eligibility criteria to those used in the EXPLORER and PATHFINDER trials, using a standardized procedure for data collection across study sites, and harmonization of definitions for the outcomes and key baseline characteristics between treatment cohorts. As a result, the baseline risk profiles of the trial and real-world cohorts were quite

comparable, as evidenced by the minimal differences between unadjusted and adjusted results for OS and DOT. Additionally, the reasonably large sample size permitted the use of rigorous statistical methods such as IPTW-weighting and doubly robust estimation, which were used to account for the potential differences in the comprehensive list of *a priori* specified key adjustment covariates between the avapritinib and midostaurin or cladribine cohorts. IPTW is preferable to methods such as propensity score matching because it allows for the efficient use of data from all trial and external control patients, thereby enhancing power and the generalizability of findings.

There are also several limitations that should be considered when interpreting the results of this study. First, due to the retrospective nature of data collection for the midostaurin and cladribine cohorts, there may be incomplete reporting for characteristics such as performance status and *KIT* D816V variant allele fraction. Similarly, in the non-protocol clinical setting, serum tryptase levels may be measured less frequently or consistently than in a trial, which could lead to underestimation of the maximum reduction of serum tryptase level for the midostaurin or cladribine cohorts. However, these limitations are partially mitigated as all participating sites are centers with expertise in the treatment of AdvSM that offered high-quality real-world data. This study did not include outcomes such as response rate or progression-free survival, as assessments of disease response per IWG-MRT-ECNM criteria were not available in the real-world cohort of patients receiving treatment with midostaurin or cladribine.

Second, to ensure adequate sample size, real-world patients were eligible for the midostaurin/cladribine cohorts if treatment began in 2009 or later, whereas patients from the EXPLORER and PATHFINDER trials began recruitment in 2016. Thus, results may have been impacted by unmeasured confounders related to changes in clinical practice for treating and monitoring these patients. Sensitivity analysis of further adjustment of index year in the IPTW-weighted Cox models did not change the conclusion.

Third, AdvSM diagnosis information collected for the midostaurin and cladribine cohorts was based on local clinician-assessed evaluation using the 2016 revision to the WHO diagnostic criteria, and the correct diagnosis might not have been made prior to the substantial increases in disease awareness and knowledge occurring over the past decade. AdvSM diagnoses for the avapritinib cohort were based on the same criteria but were confirmed by the trials' Response Assessment Committees. Thus, misclassification of the clinician-assessed AdvSM diagnosis of patients with indolent systemic mastocytosis (SM) and smoldering SM in the midostaurin and cladribine cohorts was possible. This may have resulted in an underestimation of the difference in OS since OS for patients with indolent SM and smoldering SM is typically better than for patients with AdvSM.

4.1. Conclusions

The results from this study suggest that patients with AdvSM treated with avapritinib experienced significantly improved survival and longer DOT, as well as greater reductions in serum tryptase levels compared to real-world patients treated with midostaurin or cladribine across all lines of therapy. Furthermore, the findings from subgroup analyses indicate significant treatment benefit in terms of improved OS and DOT for patients treated with first-line avapritinib compared to those treated with first-line midostaurin. Similarly, when comparing patients in the 2 L+ setting, treatment with avapritinib resulted in a superior OS and DOT. These data offer important insights for healthcare providers that may help inform treatment decisions for patients with AdvSM.

Author contributions

A. Reiter, J. Gotlib, I. Álvarez-Twose, D. H. Radia, J. Lübke, J. Schwaab, I. A. Galinsky, C. Perkins, W. R. Sperr, P. Sriskandarajah, P. Valent, and D. J. DeAngelo were responsible for reviewing the study protocol, performing medical chart screening and abstraction, assisting with result interpretation, and providing comments on the manuscript drafts. P. J. Bobbili, A. Wang, M. Mohan, T. Badu, S. R. Sendhil, and M. Duh were responsible for designing the study protocol, coordinating data collection, cleaning and analyzing data, interpreting results, preparing tables and figures for the manuscript, and reviewing the manuscript drafts. S. Dimitrijević and E. Sullivan were responsible for securing funding for the study, designing the study protocol, assisting with result interpretation, and providing comments on the manuscript drafts. All authors reviewed and approved the final version of the manuscript.

CRediT authorship contribution statement

Andreas Reiter: Writing – review & editing, Methodology, Data curation. **Jason Gotlib**: Writing – review & editing, Methodology, Data curation. **Iván Álvarez-Twose**: Writing – review & editing, Methodology, Data curation. **Deepti H. Radia**: Writing – review & editing, Methodology, Data curation. **Johannes Lübke**: Writing – review & editing, Methodology, Data curation. **Priyanka J. Bobbili**: Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Aolin Wang**: Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Saša Dimitrijević**: Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Erin Sullivan**: Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Juliana Schwaab**: Writing – review & editing, Methodology, Data curation. **Ilene A. Galinsky:** Writing – review & editing, Methodology, Data curation. **Cecelia Perkins**: Writing – review & editing, Methodology, Data curation. **Wolfgang R. Sperr:** Writing – review & editing, Methodology, Data curation. **Priya Sriskandarajah**: Writing – review & editing, Methodology, Data curation. **Manasi Mohan**: Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Teshawna Badu**: Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Selvam R. Sendhil**: Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Mei Sheng Duh**: Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Peter Valent**: Writing – review & editing, Methodology, Data curation. **Daniel J. DeAngelo**: Writing – review & editing, Methodology, Data curation.

Ethics approval, informed consent, and consent to participate

This study was conducted in accordance with the protocol, compliance to General Data Protection Regulation (GDPR), compliance to Health Insurance Portability and Accountability Act (HIPAA), and applicable laws and regulations in corresponding countries. The protocol, protocol amendments, and other relevant documents were submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study was initiated.

Informed consent was obtained from patients for enrollment in the EXPLORER and PATHFINDER trials. Existing patient level data from EXPLORER and PATHFINDER patients was used to construct the trial cohorts and no further site involvement was required. The requirement for informed consent from patients still alive who were enrolled in the external control group was determined by the IRB used by the institution where the records are held.

This study received ethics approval from all participating study sites including Ethics Committee of the Medical Faculty Mannheim of Heidelberg University (Germany), Ethics Committee of the Medical University of Vienna (Austria), Ethics Committee for Clinical Drug Research of the Toledo University Hospital Complex (Spain), National Institute for Health Research Clinical Research Network (United Kingdom), Dana-

Farber Cancer Institute (United States), and Stanford University (United States).

Funding

This study was supported by Blueprint Medicines Corporation.

Declaration of Competing Interest

A. Reiter, J. Gotlib, I. Álvarez-Twose, D. H. Radia, J. Lübke, J. Schwaab, I. A. Galinsky, C. Perkins, W. R. Sperr, P. Sriskandarajah, P. Valent, and D. J. DeAngelo are affiliated with institutions that have received consulting fees for this study from Blueprint Medicines Corporation. S. Dimitrijević and E. Sullivan are employees of Blueprint Medicines Corporation and hold stock/options. P. J. Bobbili, A. Wang, M. Mohan, T. Badu, and M. Duh are current employees of Analysis Group, Inc., which has received consulting fees from Blueprint Medicines Corporation for the conduct of this research.

A. Reiter was a member of the Study Steering Committee for the global trial of midostaurin (Novartis), the Response Assessment Committee (RAC) for studies of avapritinib in AdvSM (Blueprint Medicines Corporation), and the Study Steering Committee for the phase II trial of ripretinib in AdvSM (Deciphera Pharmaceuticals); has received research funding for the conduct of these trials; and has received honoraria and reimbursement of travel expenses from Novartis and Deciphera Pharmaceuticals. J. Gotlib has received consulting fees and research funding from Blueprint Medicines Corporation, Deciphera, Incyte and Kartos Therapeutics, and has served as chair of the RAC for Blueprint Medicines Corporation' EXPLORER study, and for the PATHFINDER study, and as co-chair for the Deciphera Study Steering Committee for ripretinib in AdvSM, and chair of the Central Response Review Committee for the phase 2 study of bezuclastinib in AdvSM. I. Álvarez-Twose is the principal investigator of the PATHFINDER study in Spain and has received advisory board fees and research funding from Blueprint Medicines Corporation as well as advisory board fees and honoraria for educational events from Novartis. D. H. Radia has received consulting fees and research funding from Blueprint Medicines Corporation, is a member of the RACs for the EXPLORER and PATHFINDER studies and has received honoraria from Novartis for educational events and consultancy. J. Schwaab has received advisory board fees and research funding from Blueprint Medicines Corporation, research funding from Cogent, and honoraria from Novartis. W. R. Sperr has received honoraria from AbbVie, BMS-Celgene, Jazz, Novartis, Pfizer, and Thermo Fisher. P. Valent has received honoraria from AOP Orphan, Blueprint Medicines Corporation, Novartis, Pfizer, Stemline, Servier, and Cogent. D.J. DeAngelo has served as a consultant for Amgen, Agios, Autolus, Blueprint Medicines Corporation, Forty-Seven, Incyte Corporation, Jazz, Novartis, Pfizer, Shire and Takeda, and received research funding from AbbVie, Blueprint Medicines Corporation, GlycoMimetics and Novartis. J. Lübke, I. A. Galinsky, C. Perkins, and P. Sriskandarajah have no further competing interests to report.

Acknowledgements

The 'Deutsche José-Carreras Leukämie-Stiftung' (grant no. DJCLS 08 R/2020) supported data collection at the University Hospital Mannheim, Germany. Morgan Johnson and Victoria Allen assisted with data collection for Dana-Farber Cancer Institute. Javier Muñoz-González, PhD, a former employee of Sofpromed Investigación Clínica, assisted with data collection for Hospital Virgen del Valle. Susanne Herndlhofer and Karoline V. Gleixner assisted with data collection for the Medical University of Vienna. Monika Ciesieslka and Rebecca Todd assisted with data collection for Guy's & St Thomas' NHS Foundation Trust. Assistance with data collection and statistical analysis was provided by Nisha Hazra, PhD and Louise Yu, employees of Analysis Group, Inc. Andi Chin, Sonia Cheung, Anamika Khanal, and Estella Dong, former employees of Analysis Group, Inc., also aided with data collection and statistical analysis. Shelley Batts, PhD, a former employee of Analysis Group, Inc., provided drafts and editorial assistance to the authors during preparation of this manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.leukres.2025.107919.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

[1] P. Valent, H.P. Horny, L. Escribano, et al., Diagnostic criteria and classification of mastocytosis: a consensus proposal, Leuk. Res 25 (7) (Jul 2001) 603–625, https://doi.org/10.1016/s0145-2126(01)00038-8.
[2] P. Valent, C. Akin, L. Escribano, et al., Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria, Eur. J. Clin. Invest 37 (6) (Jun 2007) 435–453, https://doi.org/10.1111/j.1365-2362.2007.01807.x.
[3] P. Valent, C. Akin, D.D. Metcalfe, Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts, Blood 129 (11) (Mar 16 2017) 1420–1427, https://doi.org/10.1182/blood-2016-09-731893.
[4] P. Valent, C. Akin, K. Hartmann, et al., Updated diagnostic criteria and classification of mast cell disorders: a consensus proposal, HemaSphere 5 (11) (2021) e646.
[5] J. Schwaab, O.H.N. Cabral do, N. Naumann, et al., Importance of adequate diagnostic workup for correct diagnosis of advanced systemic mastocytosis, J. Allergy Clin. Immunol. Pr. 8 (9) (Oct 2020) 3121–3127, https://doi.org/10.1016/j.jaip.2020.05.005.
[6] K.-H. Lim, A. Tefferi, T.L. Lasho, et al., Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors, Blood 113 (23) (2009) 5727–5736, https://doi.org/10.1182/blood-2009-02-205237.
[7] S. Georgin-Lavialle, L. Lhermitte, P. Dubreuil, M.-O. Chandesris, O. Hermine, G. Damaj, Mast cell leukemia, Blood 121 (8) (2013) 1285–1295, https://doi.org/10.1182/blood-2012-07-442400.
[8] J. Gotlib, H.C. Kluin-Nelemans, T.I. George, et al., Efficacy and safety of midostaurin in advanced systemic mastocytosis, N. Engl. J. Med 374 (26) (2016) 2530–2541, https://doi.org/10.1056/NEJMoa1513098.
[9] M. Jawhar, J. Schwaab, M. Meggendorfer, et al., The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm, Haematologica 102 (6) (2017) 1035–1043.
[10] J.D. Khoury, E. Solary, O. Abla, et al., The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms, Leukemia 36 (7) (Jul 2022) 1703–1719, https://doi.org/10.1038/s41375-022-01613-1.
[11] P. Erben, J. Schwaab, G. Metzgeroth, et al., The KIT D816V expressed allele burden for diagnosis and disease monitoring of systemic mastocytosis, Ann. Hematol. 93 (1) (Jan 2014) 81–88, https://doi.org/10.1007/s00277-013-1964-1.
[12] N. Naumann, J. Lubke, S. Baumann, et al., Adverse prognostic impact of the KIT D816V transcriptional activity in advanced systemic mastocytosis, Int J. Mol. Sci. 22 (5) (Mar 4 2021), https://doi.org/10.3390/ijms22052562.
[13] J. Lubke, N. Naumann, S. Kluger, et al., Inhibitory effects of midostaurin and avapritinib on myeloid progenitors derived from patients with KIT D816V positive advanced systemic mastocytosis, Leukemia 33 (5) (May 2019) 1195–1205, https://doi.org/10.1038/s41375-019-0450-8.
[14] P. Navarro-Navarro, I. Alvarez-Twose, A. Perez-Pons, et al., KITD816V mutation in blood for the diagnostic screening of systemic mastocytosis and mast cell activation syndromes, Allergy 78 (5) (May 2023) 1347–1359, https://doi.org/10.1111/all.15584.
[15] T. Kristensen, H. Vestergaard, C. Bindslev-Jensen, M.B. Moller, S. Broesby-Olsen, Centre O.U.H. Mastocytosis, Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis, Am. J. Hematol. 89 (5) (May 2014) 493–498, https://doi.org/10.1002/ajh.23672.
[16] D.J. DeAngelo, D.H. Radia, T.I. George, et al., Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial, Nat. Med 27 (2021) 2183–2191, https://doi.org/10.1038/s41591-021-01538-9.
[17] J. Gotlib, A. Reiter, D.H. Radia, et al., Efficacy and safety of avapritinib in advanced systemic mastocytosis: Interim analysis of the phase 2 PATHFINDER trial, Nat. Med 27 (2021) 2192–2199.
[18] United States Food and Drug Administration. FDA approves avapritinib for advanced systemic mastocytosis. Accessed July 30, 2021, ⟨https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-avapritinib-advanced-systemic-mastocytosis⟩.
[19] United States Food and Drug Administration. Highlights of prescribing information: AYVAKIT (avapritinib). Accessed October 15, 2021, ⟨https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212608s007lbl.pdf⟩.

[20] European Medicines Agency. Ayvakyt (avapritinib). Accessed June 15, 2022, ⟨https://www.ema.europa.eu/en/medicines/human/EPAR/ayvakyt⟩.
[21] K. Tzogani, Y. Yu, D. Meulendijks, et al., European Medicines Agency review of midostaurin (Rydapt) for the treatment of adult patients with acute myeloid leukaemia and systemic mastocytosis, ESMO Open 4 (6) (Nov 2019), https://doi.org/10.1136/esmoopen-2019-000606.
[22] United States Food and Drug Administration. Highlights of prescribing information: RYDAPT (midostaurin). Accessed October 15, 2021, ⟨https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf⟩.
[23] Rydapt: EPAR - Product Information. October 25, 2017. ⟨https://www.ema.europa.eu/en/documents/product-information/rydapt-epar-product-information_en.pdf⟩.
[24] K.H. Lim, A. Pardanani, J.H. Butterfield, C.Y. Li, A. Tefferi, Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine, Am. J. Hematol. 84 (12) (2009) 790–794.
[25] A. Tefferi, C.Y. Li, J.H. Butterfield, H.C. Hoagland, Treatment of systemic mast-cell disease with cladribine, N. Engl. J. Med 344 (4) (Jan 25 2001) 307–309, https://doi.org/10.1056/NEJM200101253440415.
[26] J. Lübke, J. Schwaab, N. Naumann, et al., Superior efficacy of midostaurin over cladribine in advanced systemic mastocytosis: a registry-based analysis, J. Clin. Oncol. (2022) JCO2101849, https://doi.org/10.1200/JCO.21.01849.
[27] A. Reiter, J. Gotlib, I. Alvarez-Twose, et al., Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis, Leukemia (Jul 5 2022), https://doi.org/10.1038/s41375-022-01615-z.
[28] Retrospective study assessing the effect of avapritinib versus best available therapy in patients with AdvSM. ClinicalTrials.gov identifier: NCT04695431. Updated January 10, 2022. ⟨https://www.clinicaltrials.gov/study/NCT04695431⟩.
[29] M. Jawhar, J. Schwaab, I. Álvarez-Twose, et al., MARS: mutation-adjusted risk score for advanced systemic mastocytosis, J. Clin. Oncol. 37 (31) (2019) 2846–2856.
[30] A. Reiter, T.I. George, J. Gotlib, New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis, Blood 135 (16) (2020) 1365–1376.
[31] M. Jawhar, J. Schwaab, N. Naumann, et al., Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers, Blood 130 (2) (Jul 13 2017) 137–145, https://doi.org/10.1182/blood-2017-01-764423.
[32] M. Jawhar, J. Schwaab, S. Schnittger, et al., Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V+ advanced systemic mastocytosis, Leukemia 30 (1) (2016) 136–143.
[33] W.R. Sperr, M. Kundi, I. Alvarez-Twose, et al., International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study, Lancet Haematol. 6 (12) (2019) e638–e649.
[34] M.J. Funk, D. Westreich, C. Wiesen, T. Sturmer, M.A. Brookhart, M. Davidian, Doubly robust estimation of causal effects, Am. J. Epidemiol. 173 (7) (Apr 1 2011) 761–767, https://doi.org/10.1093/aje/kwq439.
[35] P.C. Austin, E.A. Stuart, Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies, Stat. Med 34 (28) (Dec 10 2015) 3661–3679, https://doi.org/10.1002/sim.6607.
[36] A. Singh, A. Al-Kali, K.H. Begna, et al., Midostaurin therapy for advanced systemic mastocytosis: mayo clinic experience in 33 consecutive cases, Am. J. Hematol. (2022), https://doi.org/10.1002/ajh.26498.
[37] J. Rossignol, L. Polivka, L. Maouche-Chrétien, L. Frenzel, P. Dubreuil, O. Hermine, Recent advances in the understanding and therapeutic management of mastocytosis, F1000Res 8 (2019), https://doi.org/10.12688/f1000research.19463.1.
[38] D.J. DeAngelo, T.I. George, A. Linder, et al., Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial, Leukemia 32 (2) (Feb 2018) 470–478, https://doi.org/10.1038/leu.2017.234.
[39] J. Lubke, N. Naumann, G. Metzgeroth, et al., Response and resistance to cladribine in patients with advanced systemic mastocytosis: a registry-based analysis, Ann. Hematol. 102 (8) (Aug 2023) 2077–2085, https://doi.org/10.1007/s00277-023-05180-y.