Overall Survival and Duration of Treatment in Patients with Advanced Systemic Mastocytosis Receiving Avapritinib Versus Midostaurin or Best Available Therapy in a Real-World Setting

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Background

- Advanced systemic mastocytosis (AdvSM) is characterized by the accumulation of neoplastic mast cells in various organs and tissues.[1] The World Health Organization (WHO) delineates three subtypes of AdvSM: aggressive systemic mastocytosis (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).
- As the majority (~95%) of patients with systemic mastocytosis carry a *KIT* D816V mutation, recent therapeutic advances have focused on *KIT* inhibitors.[2-4]
- Avapritinib is a selective inhibitor of D816V-mutated *KIT* approved for AdvSM patients in the United States (US)[5] and Europe (after prior systemic therapy)[6] based on findings from two single-arm trials: EXPLORER (Phase 1; NCT02561988)[7] and PATHFINDER (Phase 2; NCT03580655).[8]
- No randomized controlled trial (RCT) has yet been conducted to compare the efficacy of avapritinib against best available therapies (BAT) for AdvSM, such as the multi-kinase/*KIT* inhibitor midostaurin or the purine analog cladribine.

Objective

- This study builds on prior work[9] and compared overall survival (OS) and duration of treatment (DOT) between patients with AdvSM treated with avapritinib 200mg QD starting dose in the PATHFINDER study and patients treated with BAT in a real-world retrospective chart review study conducted at six global sites (NCT04695431).

Study design

Data sources

- Clinical trial data (avapritinib patients)
  - Data from patients treated with 200mg QD avapritinib starting dose in the safety population of the PATHFINDER trial was used (data cut-off: September 9, 2022; median follow-up of 26.3 months; data on file, Blueprint Medicines Corporation).
- Real-world data (BAT patients)
  - An observational, retrospective chart review study was conducted at 6 global sites (4 European, 2 US) to identify and collect data from AdvSM patients receiving BAT.
  - De-identified data from eligible patients were collected via medical chart abstraction into a standardized electronic case report form from March 26 to October 4, 2021.

Real-world patient selection

- Real-world patients treated with BAT were identified based on inclusion and exclusion criteria similar to those from PATHFINDER:
- **Inclusion criteria:**
  - Adults (aged ≥18 years) with an AdvSM diagnosis documented in their chart
  - Received ≥1 line of systemic therapy (not necessarily as first line [1L]) at a participating study site on or after January 1, 2009
  - For patients receiving multiple lines of therapy (LOTs) at a participating site, data on all available therapies were collected and analyzed
  - The date of initiation of each LOT at the participating site was defined as the index date
- **Exclusion criteria:**
  - 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* in any site
  - Received avapritinib as the first therapy for AdvSM at a participating site

Methods

Comparisons

- In the 1L setting, avapritinib was compared to midostaurin.
- In second or later lines (2L+), avapritinib was compared to all 2L+ BAT used in real-world clinical practice, including midostaurin and cladribine.

Study endpoints

- OS was defined as time from treatment initiation to death from any cause. Patients still alive at the end of the study were censored at the last known alive date (avapritinib patients) or the earliest of avapritinib initiation, new primary malignancy, or date of last contact (BAT patients).
- DOT was defined as time from treatment initiation to last dose date (avapritinib patients) or discontinuation for any reason (BAT patients).

Statistical analysis

- Inverse probability of treatment weighting (IPTW) was used to adjust for differences in *a priori* identified key prognostic covariates between treatment cohorts; e.g., age, sex, ECOG score, presence of thrombocytopenia or anemia at baseline, elevated serum tryptase levels, number and types of prior lines of therapy, among others.
- Median OS and DOT in the IPTW-weighted sample were assessed using the Kaplan-Meier method.
- IPTW-weighted Cox proportional hazards regression models, adjusting for variables that remained unbalanced after weighting (standardized mean difference >10%), were used to compare OS and DOT between cohorts.

Results

Baseline characteristics

- **1L analysis vs. midostaurin**
  - This analysis included 38 patients treated with avapritinib and 58 patients treated with midostaurin (**Table 1**).
  - Mean age at treatment initiation and mean duration of follow-up (**Table 3**) were similar between the avapritinib and midostaurin cohorts.
  - A higher proportion of avapritinib vs. midostaurin patients had ≥1 mutated gene in the *SRSF2/ASXL1/RUNX1 (S/A/R)* panel (**Table 1**).
  - Elevated (>125ng/mL)[10] serum tryptase at baseline was similar between cohorts.
- **2L+ analysis vs. BAT**
  - This analysis included 67 patients treated with avapritinib and 73 patients treated with BAT, contributing 104 LOTs (**Table 1**).
  - Mean age at treatment initiation and mean duration of follow-up (**Table 3**) were similar between the avapritinib and BAT cohorts.
  - Agent-level information was available for 89 LOTs in the BAT cohort, and common 2L+ agents received were midostaurin (46.1%), cladribine (32.6%), and hydroxyurea (7.9%) (**Table 2**).
  - A higher proportion of avapritinib vs. BAT LOTs had elevated serum tryptase at baseline and received prior treatment with tyrosine kinase inhibitors (**Table 1**).
  - Fewer avapritinib vs. BAT LOTs had ≥1 *S/A/R* mutation.

Table 1. Baseline demographics and clinical characteristics

Baseline characteristics, unweighted sample[1]	1L avapritinib	1L midostaurin	2L+ avapritinib	2L+ BAT
Number of unique patients	N = 38	N = 58	N = 67	N = 73
Number of lines of therapy	N = 38	N = 58	N = 67	N = 104
Age (years), mean (SD)	68.3 (8.9)	67.4 (11.6)	66.6 (11.2)	65.5 (11.7)
Female, n (%)	18 (47.4%)	16 (27.6%)	26 (38.8%)	36 (34.6%)
Region, n (%)				
North America	19 (50.0%)	13 (22.4%)	27 (40.3%)	9 (8.7%)
Europe	19 (50.0%)	45 (77.6%)	40 (59.7%)	95 (91.3%)
ECOG				
0	6 (15.8%)	12 (20.7%)	16 (23.9%)	21 (20.2%)
1	25 (65.8%)	28 (48.3%)	31 (46.3%)	67 (64.4%)
≥2	7 (18.4%)	18 (31.0%)	20 (29.9%)	16 (15.4%)
Anemia, n (%)	22 (57.9%)	29 (50.0%)	40 (59.7%)	71 (68.3%)
Thrombocytopenia, n (%)	8 (21.1%)	29 (50.0%)	25 (37.3%)	66 (63.5%)
AdvSM subtype diagnosis, n (%)				
SM-AHN	28 (73.7%)	40 (69.0%)	41 (61.2%)	53 (51.0%)
ASM	7 (18.4%)	14 (24.1%)	14 (20.9%)	26 (25.0%)
MCL	3 (7.9%)	4 (6.9%)	12 (17.9%)	25 (24.0%)
Any skin involvement, n (%)	10 (26.3%)	18 (31.0%)	23 (34.3%)	37 (35.6%)
Leukocyte count ≥16 x 10^9/L, n (%)	5 (13.2%)	15 (25.9%)	9 (13.4%)	25 (24.0%)
Serum tryptase ≥125 ng/mL, n (%)	27 (71.1%)	40 (69.0%)	54 (80.6%)	68 (65.4%)
***SRSF2/ASXL1/RUNX1 (S/A/R)* mutation panel**				
Patients that were tested for at least one mutation, n (%)	38 (100.0%)	46 (79.3%)	67 (100.0%)	79 (76.0%)
Number of mutated genes within *S/A/R* panel, n (%)				
0	15 (39.5%)	15 (25.9%)	43 (64.2%)	31 (29.8%)
1	17 (44.7%)	22 (37.9%)	14 (20.9%)	30 (28.8%)
≥2	6 (15.8%)	9 (15.5%)	10 (14.9%)	18 (17.3%)
Number of prior lines of systemic therapy received, n (%)				
0	38 (100.0%)	58 (100.0%)	-	-
1	-	-	44 (65.7%)	69 (66.3%)
2	-	-	15 (22.4%)	24 (23.1%)
≥3	-	-	8 (11.9%)	11 (10.6%)
Prior treatments received, n (%)				
Tyrosine kinase inhibitor therapy	-	-	60 (89.6%)	50 (48.1%)
Cytotoxic therapy	-	-	17 (25.4%)	61 (58.7%)
Biologic or other systemic therapy[2]	-	-	15 (22.4%)	30 (28.8%)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; max: maximum; min: minimum; SD: standard deviation.
Notes:
[1] 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/BAT cohorts.
[2] Other systemic therapy included steroids and thalidomide or derivatives.

Table 2. Summary of treatments received by the 2L+ BAT cohort

	2L+ BAT
Number of unique patients	N = 73
Total number of lines of therapy included	N = 104
Agents used in each included line of therapy, n (%)	
Tyrosine kinase inhibitor therapy	49 (47.1%)
Cytotoxic therapy	52 (50.0%)
Biologic therapy	11 (10.6%)
Agent-level information available[1]	**N = 89**
Tyrosine kinase inhibitor	
Midostaurin	41 (46.1%)
Ripretinib	2 (2.2%)
Dasatinib	1 (1.1%)
Imatinib	1 (1.1%)
Cytotoxic therapy	
Cladribine	29 (32.6%)
Hydroxyurea	7 (7.9%)
Azacitidine	3 (3.4%)
Biologic	
Pegylated interferon	5 (5.6%)
Brentuximab vedotin	2 (2.2%)
Interferon-alpha	2 (2.2%)
Gemtuzumab ozogamicin	1 (1.1%)

Note:
[1] Agent-level information for 2L+ treatments was reported among patients from all study sites except Medizinische Universität Wien (Vienna, Austria) (N=15 lines of therapy), where only treatment class information was collected per local regulations.

Overall survival

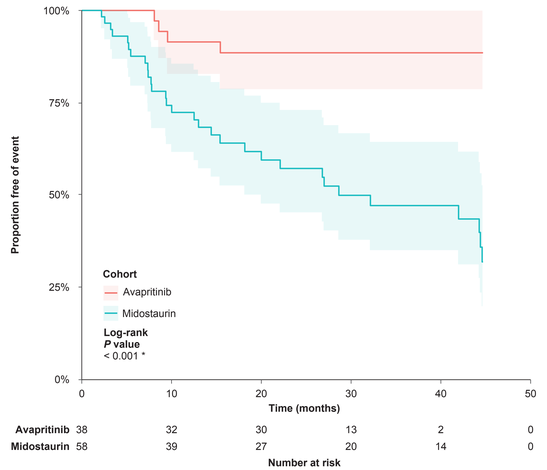
- **1L analysis vs. midostaurin**
  - During the follow-up period, deaths occurred in 4 (10.5%) avapritinib patients and 33 (56.9%) midostaurin patients (**Table 3**).
  - Unweighted median OS was not reached (NR) (95% confidence interval [CI]: not estimable [NE], NE) in the avapritinib cohort, and 28.6 months (95% CI: 18.2, 49.8) in the midostaurin cohort (**Figure 1**).
  - OS was significantly longer among avapritinib vs. midostaurin patients in IPTW-weighted Cox analysis (hazard ratio [HR] [95% CI]: 0.19 [0.06, 0.57]; *P*=0.003).
- **2L+ analysis vs. BAT**
  - During the follow-up period, deaths occurred in 17 (25.4%) avapritinib patients and 50 (68.5%) BAT patients.
  - Unweighted median (95% CI) OS was NR (NE, NE) in the avapritinib cohort, and 20.3 months (14.9, 33.9) in the BAT cohort (**Figure 2**).
  - OS was significantly longer among avapritinib vs. BAT patients in IPTW-weighted Cox analysis (HR [95% CI]: 0.34 [0.16, 0.75]; *P*=0.008).

Table 3. Summary of overall survival

	1L avapritinib	1L midostaurin	*P* value	2L+ avapritinib	2L+ BAT	*P* value
Number of unique patients	N = 38	N = 58		N = 67	N = 73	
Number of lines of therapy	N = 38	N = 58		N = 67	N = 104	
Deaths from unique patients, n (%)	4 (10.5%)	33 (56.9%)	-	17 (25.4%)	50 (68.5%)	-
Unique patients censored due to avapritinib initiation, n (%)	-	8 (13.8%)	-	-	9 (12.3%)	-
Unique patients censored due to new primary malignancy after index date, n (%)	-	4 (6.9%)	-	-	2 (2.7%)	-
Mean follow-up (months)	24.7	26.1	-	22.1	25.2	-
Median OS (months), unweighted sample (95% CI)	NR (NE, NE)	28.6 (18.2, 49.8)	-	NR (NE, NE)	20.3 (14.9, 33.9)	-
Median OS (months), IPTW-weighted sample (95% CI)[1]	NR (NE, NE)	32.2 (20.0, 44.6)	-	NR (30.2, NE)	17.9 (14.8, 36.5)	-
HR, IPTW-weighted sample (95% CI)[1,2]	0.19 (0.06, 0.57)		0.003*	0.34 (0.16, 0.75)		0.008*

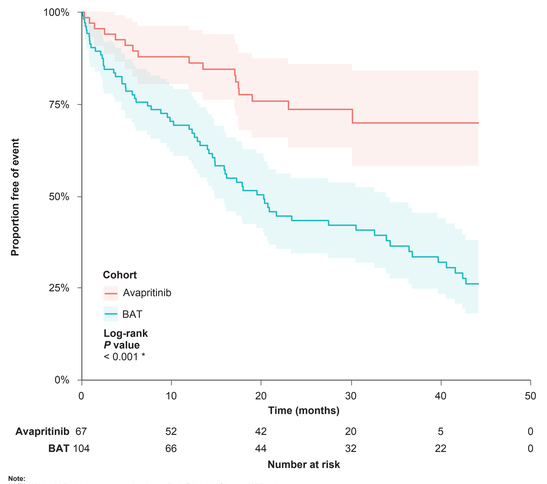
*P value less than 0.05.
Abbreviations: ECOG: Eastern Cooperative Oncology Group.
Notes:
[1] Stabilized weights were generated using the following baseline characteristics: age, sex, ECOG score, anemia (hemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100 x 10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16 × 10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, and number of mutated genes within the *S/A/R* panel. In the 2L+ analysis, weights also accounted for region, number of prior lines of therapy, and prior use of tyrosine kinase inhibitor, cytotoxic, biologic or other systemic therapy. To reduce variability, stabilized weights were capped at the 1st and 99th percentiles.
[2] IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model OS and further adjusted for covariates with a standardized difference >10% after weighting. HR and the corresponding 95% CI and *P* value were presented. Two-sided *P* value < 0.05 was considered statistically significant without multiplicity adjustment.

Figure 1. Unweighted Kaplan-Meier curves of overall survival among 1L avapritinib vs. midostaurin[1]



Note:
[1] The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort.

Figure 2. Unweighted Kaplan-Meier curves of overall survival among 2L+ avapritinib vs. BAT[1]



Note:
[1] The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort.

Duration of treatment

- **1L analysis vs. midostaurin**
  - Unweighted median (95% CI) DOT was 41.3 months (33.9, NE) in the avapritinib cohort, and 11.6 months (7.5, 22.1) in the midostaurin cohort (**Table 4**).
  - DOT was significantly longer among avapritinib vs. midostaurin patients in IPTW-weighted Cox analysis (HR [95% CI]: 0.37 [0.19, 0.70]; *P*=0.002).
- **2L+ analysis vs. BAT**
  - The DOT analysis included 67 patients treated with BAT, contributing 97 LOTs; seven LOTs with unknown discontinuation date and unknown last known prescription date were excluded.
  - Unweighted median (95% CI) DOT was 24.0 months (20.8, NE) in the avapritinib cohort, and 5.2 months (3.1, 8.1) in the BAT cohort.
  - DOT was significantly longer among avapritinib vs. BAT LOTs in IPTW-weighted Cox analysis (HR [95% CI]: 0.35 [0.21, 0.58]; *P*<0.001).

Conclusions

- This study supports the use of avapritinib as 1L treatment for AdvSM, demonstrating significant OS and DOT benefits compared to patients treated with 1L midostaurin in standard clinical practice.
- This study also supports the use of avapritinib in 2L+, with significant improvement in OS and DOT as compared to BAT.
- In the absence of a RCT, these data offer important insights on the superior efficacy and suggest good tolerability of avapritinib as compared to midostaurin and other available therapies for patients with AdvSM, and may help inform treatment decisions.

Table 4. Summary of duration of treatment

	1L avapritinib	1L midostaurin	*P* value	2L+ avapritinib	2L+ BAT	*P* value
Number of unique patients	N = 38	N = 58		N = 67	N = 67	
Number of lines of therapy	N = 38	N = 58		N = 67	N = 97	
Number of discontinued lines of therapy	12 (31.6%)	49 (84.5%)	-	35 (52.2%)	86 (88.7%)	-
Number of censored lines of therapy	26 (68.4%)	9 (15.5%)	-	32 (47.8%)	11 (11.3%)	-
Median DOT (months), unweighted sample (95% CI)	41.3 (33.9, NE)	11.6 (7.5, 22.1)	-	24.0 (20.8, NE)	5.2 (3.1, 8.1)	-
Median DOT (months), IPTW-weighted sample (95% CI)[1]	41.3 (33.9, 41.3)	13.0 (7.5, 25.5)	-	21.3 (10.5, NE)	5.4 (3.5, 9.8)	-
HR, IPTW-weighted sample (95% CI)[1,2]	0.37 (0.19, 0.70)		0.002*	0.35 (0.21, 0.58)		<0.001*

*P value less than 0.05.
Abbreviations: ECOG: Eastern Cooperative Oncology Group.
Notes:
[1] Stabilized weights were generated using the following baseline characteristics: age, sex, ECOG score, anemia (hemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100 x 10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16 × 10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, and number of mutated genes within the *S/A/R* panel. In the 2L+ analysis, weights also accounted for region, number of prior lines of therapy, and prior use of tyrosine kinase inhibitor, cytotoxic, biologic or other systemic therapy. To reduce variability, stabilized weights were capped at the 1st and 99th percentiles.
[2] IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model DOT and further adjusted for covariates with a standardized difference >10% after weighting. HR and the corresponding 95% CI and *P* value were presented. Two-sided *P* value < 0.05 was considered statistically significant without multiplicity adjustment.

Limitations

- Despite the use of rigorous statistical methods to adjust for key measured variables, the results of this retrospective, non-randomized study may have been impacted by incomplete data and unmeasured confounding due to evolving disease management practices and baseline differences between cohorts.

Acknowledgements

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References

1. Valent P, Akin C, Hartmann K, et al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. *HemaSphere*. 2021;5(11):e646.
2. Garcia-Montero AC, Jara-Acevedo M, Teodosio C, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood*. Oct 1 2006;108(7):2366-72. doi:10.1182/blood-2006-04-015545
3. Kristensen T, Vestergaard H, Bindslev-Jensen C, Moller MB, Broesby-Olsen S, Mastocytosis Centre OUH. Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol*. May 2014;89(5):493-8. doi:10.1002/ajh.23672
4. Ungerstedt J, Ljung C, Klimkowska M, Gulen T. Clinical Outcomes of Adults with Systemic Mastocytosis: A 15-Year Multidisciplinary Experience. *Cancers (Basel)*. Aug 16 2022;14(16)doi:10.3390/cancers14163942
5. 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
6. European Medicines Agency. Ayvakyt (avapritinib). Accessed June 15, 2022, https://www.ema.europa.eu/en/medicines/human/EPAR/ayvakyt
7. DeAngelo DJ, Radia DH, George TI, et al. Safety and efficacy of avapritinib in advanced systemic mastocytosis: The phase 1 EXPLORER trial. *Nat Med*. 2021;27:2183-2191. doi:https://doi.org/10.1038/s41591-021-01538-9
8. Gotlib J, Reiter A, Radia DH, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: Interim analysis of the phase 2 PATHFINDER trial. *Nat Med*. 2021;27:2192-2199.
9. Reiter A, Gotlib J, Álvarez-Twose I, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. *Leukemia*. 2022;in press
10. Sperr WR, Kundi M, Alvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): A retrospective cohort study. *Lancet Haematol*. 2019;6(12):e638-e649.