Improved Overall Survival in Patients with Advanced Systemic Mastocytosis Treated with Avapritinib versus Real-World Therapy based on Mutation-Adjusted Risk Score (MARS) Stratification

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Background

- Advanced systemic mastocytosis (AdvSM) is a rare hematologic neoplasm, characterized by the accumulation of neoplastic mast cells in various organs and tissues resulting in organ damage and shortened survival.[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]
- MARS is a prognostic tool classifying AdvSM patients into low-, intermediate-, and high-risk survival groups based on age (>60 years), anemia (hemoglobin <10 g/dL), thrombocytopenia (platelet count <100x10^9/L), and the presence and number of *SRSF2*, *ASXL1*, or *RUNX1 (S/A/R)* mutations.
- Prior retrospective analyses of overall survival (OS) showed improved OS for patients treated with avapritinib vs. midostaurin or best available therapy (BAT).[9,10] A recent analysis showed a hazard ratio (HR) of 0.19 for avapritinib vs. midostaurin in frontline (1L) therapy and 0.34 for avapritinib vs. BAT in second or later-lines (2L+) of treatment in AdvSM, regardless of MARS.[11]
- MARS-defined intermediate- and high-risk patients face poor prognoses,[12,13] making it essential to evaluate treatment outcomes in this underserved population.

Objective

- The objective of this analysis was to compare OS between MARS-defined intermediate- and high-risk patients treated with avapritinib (200 mg/day starting dose) in the PATHFINDER trial and those treated with BAT in a real-world clinical setting. Analyses were stratified by line of therapy (LOT). Subgroup analyses were performed among patients with SM-AHN.

Study design

Data sources

- Clinical trial data (patients treated with avapritinib)
  - Data from patients treated with 200mg daily avapritinib starting dose in the safety population of the PATHFINDER trial was used (NCT03580655; data cut-off: September 15, 2023; median follow-up of 38.0 months; data on file, Blueprint Medicines Corporation).
- Real-world data (patients treated with BAT)
  - Data from AdvSM patients receiving BAT included in an observational, retrospective chart review study (NCT04695431) conducted at 6 global sites (4 European, 2 US).
  - De-identified data from eligible patients were collected via medical chart abstraction into a standardized electronic case report form (CRF) 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 1L) at a participating study site on or after January 1, 2009
  - For patients receiving multiple 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

Analyses were restricted to LOTs in the combined cohorts of MARS-defined intermediate- or high-risk (score >1) patients. Analyses were conducted separately among patients receiving 1L and 2L+ treatment.

- In the 1L setting, avapritinib was compared to midostaurin.
- In the 2L+ setting, avapritinib was compared to all 2L+ BAT used in real-world clinical practice, including midostaurin and cladribine.
- Subgroup analyses were conducted in both the 1L and 2L+ settings among patients with SM-AHN disease subtype.

Study endpoint

- 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).

Statistical analysis

- Inverse probability of treatment weighting (IPTW) was used to adjust for differences in *a priori* identified key prognostic covariates between treatment cohorts; i.e., age, sex, region, ECOG score, skin involvement, elevated leukocyte counts (≥16 x 10^9/L), elevated serum tryptase levels (>125ng/mL),[14] and number and types of prior lines of therapy.
- Median OS in the IPTW-weighted sample was 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 between cohorts. Non-violation of the proportionality assumption for all Cox proportional hazards models was supported by Kolmogorov-type supremum tests.[15]

Results

Baseline characteristics

- **1L Analysis of Avapritinib vs. Midostaurin**
  - This analysis included 24 patients treated with avapritinib and 43 patients treated with midostaurin (**Table 1**).
  - Before weighting, more avapritinib patients had anemia and fewer had thrombocytopenia, elevated serum tryptase, and elevated leukocyte counts at baseline.
  - Distributions of AdvSM subtypes were similar between the cohorts, with ~79% of each cohort having SM-AHN.
- **2L+ Analysis of Avapritinib vs. BAT**
  - This analysis included 41 patients treated with avapritinib and 55 patients treated with BAT, contributing 71 LOTs (**Table 1**).
  - Agent-level information was available for 61 LOTs in the BAT cohort, and common 2L+ agents received were midostaurin (47.5%), cladribine (34.4%), and hydroxyurea (8.2%) (**Table 2**).
  - A higher proportion of avapritinib vs. BAT LOTs had elevated serum tryptase at baseline and received prior treatment with tyrosine kinase inhibitors. Fewer avapritinib vs. BAT LOTs had thrombocytopenia, elevated leukocyte counts, and ≥1 *S/A/R* mutation (**Table 1**).
  - Distributions of AdvSM subtypes were similar between the cohorts, with ~70% of each cohort having SM-AHN.

Table 1. Baseline demographic and clinical characteristics among MARS-defined intermediate- or high-risk patients

Baseline characteristics, unweighted sample[1]	1L Avapritinib	1L Midostaurin	2L+ Avapritinib	2L+ BAT
Number of unique patients	N = 24	N = 43	N = 41	N = 55
Number of lines of therapy	N = 24	N = 43	N = 41	N = 71
Age (years), mean (SD)	70.3 (7.5)	70.9 (8.3)	71.0 (9.1)	67.3 (10.6)
Female, n (%)	10 (41.7%)	11 (25.6%)	15 (36.6%)	16 (22.5%)
Region, n (%)				
North America	13 (54.2%)	7 (16.3%)	17 (41.5%)	5 (7.0%)
Europe	11 (45.8%)	36 (83.7%)	24 (58.5%)	66 (93.0%)
ECOG category, n (%)				
0	3 (12.5%)	5 (11.6%)	8 (19.5%)	12 (16.9%)
1	14 (58.3%)	24 (55.8%)	18 (43.9%)	47 (66.2%)
≥2	7 (29.2%)	14 (32.6%)	15 (36.6%)	12 (16.9%)
Anemia, n (%)	18 (75.0%)	26 (60.5%)	34 (82.9%)	57 (80.3%)
Thrombocytopenia, n (%)	8 (33.3%)	28 (65.1%)	25 (61.0%)	59 (83.1%)
AdvSM subtype diagnosis, n (%)				
SM-AHN	19 (79.2%)	34 (79.1%)	29 (70.7%)	50 (70.4%)
ASM	3 (12.5%)	6 (14.0%)	7 (17.1%)	10 (14.1%)
MCL	2 (8.3%)	3 (7.0%)	5 (12.2%)	11 (15.5%)
Any skin involvement, n (%)	6 (25.0%)	8 (18.6%)	12 (29.3%)	18 (25.4%)
Leukocyte count ≥16 x 10^9/L, n (%)	3 (12.5%)	12 (27.9%)	5 (12.2%)	19 (26.8%)
Serum tryptase ≥125 ng/mL, n (%)	15 (62.5%)	31 (72.1%)	32 (78.0%)	45 (63.4%)
***SRSF2/ASXL1/RUNX1 (S/A/R)* mutation panel**				
Patients that were tested for at least one mutation, n (%)	24 (100.0%)	35 (81.4%)	41 (100.0%)	61 (85.9%)
Number of mutated genes within S/A/R panel, n (%)				
0	4 (16.7%)	5 (11.6%)	18 (43.9%)	14 (19.7%)
1	14 (58.3%)	21 (48.8%)	13 (31.7%)	29 (40.8%)
≥2	6 (25.0%)	9 (20.9%)	10 (24.4%)	18 (25.4%)
Number of prior lines of systemic therapy received, n (%)				
0	24 (100.0%)	43 (100.0%)	0 (0.0%)	0 (0.0%)
1	0 (0.0%)	0 (0.0%)	29 (70.7%)	49 (69.0%)
2	0 (0.0%)	0 (0.0%)	8 (19.5%)	16 (22.5%)
≥3	0 (0.0%)	0 (0.0%)	4 (9.8%)	6 (8.5%)
Prior treatments received, n (%)				
TKI therapy	-	-	35 (85.4%)	33 (46.5%)
Cytotoxic therapy	-	-	11 (26.8%)	44 (62.0%)
Biologic or other systemic therapy[2]	-	-	7 (17.1%)	13 (18.3%)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; IPTW: inverse probability of treatment weighting; max: maximum; min: minimum; *S/A/R: SRSF2/ASXL1/RUNX1*; SD: standard deviation; TKI: tyrosine kinase inhibitor.
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.
[3] Agent-level information for prior treatments was reported among patients from all study sites except Medizinische Universität Wien (Vienna, Austria) (N=10 lines of therapy), where only treatment class information was collected per local regulations.

Table 2. Summary of treatments received by MARS-defined intermediate- or high-risk patients in the the 2L+ BAT cohort

	2L+ BAT
Number of unique patients	N = 55
Number of lines of therapy	N = 71
Agents used in each line of therapy, n (%)	
TKI therapy	33 (46.5%)
Cytotoxic therapy	39 (54.9%)
Biologic therapy	3 (4.2%)
Agent-level information available[1]	**N = 61**
TKI	
Midostaurin	29 (47.5%)
Dasatinib	1 (1.6%)
Imatinib	1 (1.6%)
Ripretinib	1 (1.6%)
Cytotoxic therapy	
Cladribine	21 (34.4%)
Hydroxyurea	5 (8.2%)
Azacitidine	3 (4.9%)
Biologic	
Interferon-alpha	1 (1.6%)
Pegylated interferon	1 (1.6%)

Abbreviation: TKI: tyrosine kinase inhibitor.
Note:
[1] Agent-level information for 2L+ treatments was reported among patients from all study sites except Medizinische Universität Wien (Vienna, Austria) (N=10 lines of therapy), where only treatment class information was collected per local regulations.

Overall survival

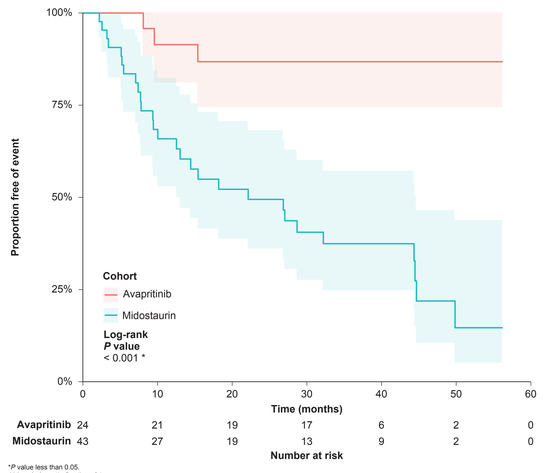
- **1L Analysis of Avapritinib vs. Midostaurin**
  - During the follow-up period, deaths occurred in 3 (12.5%) avapritinib patients and 30 (69.8%) midostaurin patients (**Table 3**).
  - Unweighted median OS was not reached (NR) (95% confidence interval [CI]: not estimable [NE], NE) in the avapritinib cohort, and was 22.1 months (95% CI: 12.5, 44.6) in the midostaurin cohort (**Figure 1**).
  - After adjustment, in IPTW-weighted Cox analysis, OS was significantly improved among avapritinib vs. midostaurin patients, with hazard ratio (HR) of 0.08 (95% CI: 0.02, 0.29) and *P*<0.001.
- **2L+ Analysis of Avapritinib vs. BAT**
  - During the follow-up period, deaths occurred in 17 (41.5%) avapritinib patients and 43 (78.2%) BAT patients (**Table 3**).
  - Unweighted median OS was 50.2 months (95% CI: 30.2, NE) in the avapritinib cohort, and was 14.2 months (95% CI: 9.5, 20.7) in the BAT cohort (**Figure 2**).
  - After adjustment, OS was significantly improved among avapritinib vs. BAT patients (HR [95% CI]: 0.28 [0.13, 0.61]; *P*=0.001).

Table 3. Summary of overall survival among MARS-defined intermediate- or high-risk patients

Overall survival	1L Avapritinib	1L Midostaurin	*P* value	2L+ Avapritinib	2L+ BAT	*P* value
Number of unique patients	N = 24	N = 43		N = 41	N = 55	
Number of lines of therapy	N = 24	N = 43		N = 41	N = 71	
Deaths from unique patients, n (%)	3 (12.5%)	30 (69.8%)	–	17 (41.5%)	43 (78.2%)	–
Unique patients censored due to avapritinib initiation, n (%)	–	4 (9.3%)	–	–	5 (9.1%)	–
Unique patients censored due to new primary malignancy after index date, n (%)	–	4 (9.3%)	–	–	2 (3.6%)	–
Mean follow-up (months)	33.1	22.5	–	28.4	17.6	–
Median OS, unweighted sample (months) (95% CI)	NR (NE, NE)	22.1 (12.5, 44.6)	–	50.2 (30.2, NE)	14.2 (9.5, 20.7)	–
Number of lines of therapy, IPTW-weighted sample[1]	Effective N = 24	Effective N = 42		Effective N = 36	Effective N = 66	
Median OS, IPTW-weighted sample (months) (95% CI)[1]	NR (NE, NE)	26.8 (14.4, 49.8)	–	50.2 (50.2, NE)	14.8 (13.2, 32.6)	–
HR, IPTW-weighted sample (95% CI)[1,2]	0.08 (0.02, 0.29)		<0.001*	0.28 (0.13, 0.61)		0.001*

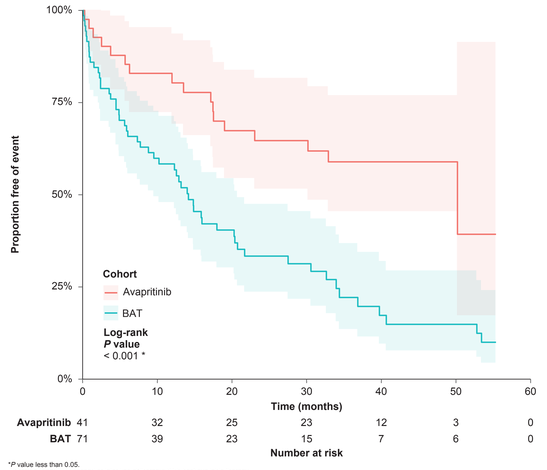
*P value less than 0.05.
Abbreviation: ECOG: Eastern Cooperative Oncology Group.
Notes:
[1] Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, AdvSM subtype, skin involvement, leukocyte count of 16 × 10^9 per L or higher, and serum tryptase concentration of 125 ng/mL or higher. In the 2L+ analysis, weights also accounted for 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 MARS-defined intermediate- or high-risk patients, 1L avapritinib vs. midostaurin[1]



*P value less than 0.05.
Abbreviation: 1L: first line of therapy.
Note:
[1] The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort. Comparison of avapritinib to midostaurin was conducted in the combined cohorts of MARS-defined intermediate- or high-risk patients.

Figure 2. Unweighted Kaplan-Meier curves of overall survival among MARS-defined intermediate- or high-risk patients, 2L+ avapritinib vs. BAT[1]



*P value less than 0.05.
Abbreviations: 2L+: second or later line of therapy; BAT: best available therapy.
Note:
[1] The Kaplan-Meier curve was truncated at the maximum follow-up of the avapritinib cohort. Comparison of avapritinib to BAT was conducted in the combined cohorts of MARS-defined intermediate- or high-risk patients.

- **1L SM-AHN Subgroup**
  - Deaths occurred in 3 (15.8%) avapritinib patients and 23 (67.6%) midostaurin patients (**Table 4**).
  - Unweighted median OS was NR (95% CI: NE, NE) in the avapritinib cohort, and was 18.2 months (95% CI: 12.5, NE) in the midostaurin cohort.
  - After adjustment, OS was significantly improved among avapritinib vs. midostaurin patients (HR [95% CI]: 0.09 [0.02, 0.36]; *P*<0.001).
- **2L+ SM-AHN Subgroup**
  - Deaths occurred in 13 (44.8%) avapritinib patients and 29 (76.3%) BAT patients (**Table 4**).
  - Unweighted median OS was 50.2 months (95% CI: 23.0, NE) in the avapritinib cohort, and was 13.2 months (95% CI: 7.7, 21.7) in the BAT cohort.
  - After adjustment, OS was significantly improved among avapritinib vs. midostaurin patients (HR [95% CI]: 0.31 [0.13, 0.74]; *P*=0.008).

Conclusions

- Avapritinib was associated with significantly improved OS for AdvSM patients with intermediate- or high-risk MARS compared to BAT, including in the SM-AHN disease subtype.
- The benefit of avapritinib was particularly pronounced in the 1L setting when compared to midostaurin, and benefits persist in the 2L+ setting.
- Overall, this analysis further characterizes the survival benefit of avapritinib among AdvSM patients with poor prognoses,[13] and offers valuable information to guide treatment decisions in this historically underserved patient population.

Table 4. Summary of overall survival among MARS-defined intermediate- or high-risk patients with SM-AHN

Overall survival	1L Avapritinib	1L Midostaurin	*P* value	2L+ Avapritinib	2L+ BAT	*P* value
Number of unique patients	N = 19	N = 34		N = 29	N = 38	
Number of lines of therapy	N = 19	N = 34		N = 29	N = 50	
Deaths from unique patients, n (%)	3 (15.8%)	23 (67.6%)	–	13 (44.8%)	29 (76.3%)	–
Unique patients censored due to avapritinib initiation, n (%)	–	3 (8.8%)	–	–	4 (10.5%)	–
Unique patients censored due to new primary malignancy after index date, n (%)	–	4 (11.8%)	–	–	2 (5.3%)	–
Mean follow-up (months)	32.2	20.0	–	29.4	14.6	–
Median OS, unweighted sample (months) (95% CI)	NR (NE, NE)	18.2 (12.5, NE)	–	50.2 (23.0, NE)	13.2 (7.7, 21.7)	–
Number of lines of therapy, IPTW-weighted sample[1]	Effective N = 19	Effective N = 33		Effective N = 27	Effective N = 51	
Median OS, IPTW-weighted sample (months) (95% CI)[1]	NR (NE, NE)	22.1 (13.0, 61.5)	–	50.2 (23.0, NE)	13.2 (7.7, 27.5)	–
HR, IPTW-weighted sample (95% CI)[1,2]	0.09 (0.02, 0.36)		<0.001*	0.31 (0.13, 0.74)		0.008*

*P value less than 0.05.
Abbreviation: ECOG: Eastern Cooperative Oncology Group.
Notes:
[1] Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, skin involvement, leukocyte count of 16 × 10^9 per L or higher, and serum tryptase concentration of 125 ng/mL or higher. In the 2L+ analysis, weights also accounted for number of prior lines of 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.

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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