Overall Survival in Patients with Advanced Systemic Mastocytosis Receiving Avapritinib Versus Midostaurin or Cladribine

Abstract P1014

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Background

- Advanced systemic mastocytosis (AdvSM) is a rare myeloproliferative neoplasm commonly distinguished by the accumulation of neoplastic mast cells in bone marrow and other tissues and organs[1,2]
- The World Health Organization (WHO) characterizes AdvSM in three subtypes: aggressive systemic mastocytosis (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL)[3]
- AdvSM patients typically have poor prognosis, with a median overall survival (OS) of approximately 3.5 years for ASM, 2 years for SM-AHN, and 0.5−2 years for MCL[4-7]
- The majority (>90%) of patients with AdvSM harbor the KIT D816V mutation,[8,9] which has been associated with poor survival[10]
- Avapritinib, a selective *KIT* D816V inhibitor, was approved for the treatment of adults with AdvSM in the US[11] and Europe (for AdvSM patients treated with prior systemic therapy)[12] based on results from two single-arm trials: Phase 1 EXPLORER (NCT02561988) and Phase 2 PATHFINDER (NCT03580655)[13,14]

Aim

- This study (NCT04695431) compared OS between patients with AdvSM who were treated with avapritinib in the EXPLORER and PATHFINDER trials and those treated with midostaurin or cladribine in real-world clinical practice[15]

Methods

Data sources

- Clinical trial data (*avapritinib cohort*)
  - Data from patients treated with avapritinib in the safety populations of the EXPLORER and PATHFINDER trials was used (data cut-off: April 20, 2021; data on file, Blueprint Medicines Corporation)
- Real-world data (*midostaurin and cladribine cohorts*)
  - A global, observational, retrospective chart review study was conducted at 6 study sites (4 European, 2 US) to identify and collect data from AdvSM patients who received treatment with midostaurin or cladribine
  - De-identified data from eligible patients were abstracted from medical records into a standardized electronic case report form from March 26, 2021 to October 4, 2021

Sample selection

- Real-world patients treated with midostaurin or cladribine were identified based on the following key inclusion and exclusion criteria, similar to those from the EXPLORER and PATHFINDER trials
- **Inclusion criteria:**
  - Adults (aged ≥18 years) with a diagnosis of AdvSM and documented subtype in their chart (ASM, SM-AHN, or MCL)
  - Received ≥1 line of systemic therapy (not necessarily as first line) consisting of midostaurin or cladribine 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 therapies were collected and analyzed
    - The date of initiation of each line of therapy 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

Study endpoint

- For all cohorts, OS was defined as the interval of time between initiation of therapy (i.e., of midostaurin, cladribine, or avapritinib) and death due to any cause
- If alive at the end of the study, patients were censored at the date of last contact (midostaurin and cladribine cohorts), or at the last known alive date (avapritinib cohort)
- Midostaurin and cladribine cohort patients later treated with avapritinib were censored at avapritinib initiation

Statistical analysis

- Unadjusted OS was assessed using the Kaplan-Meier method
- On-treatment survival rates at specific time points were obtained using the Nelson-Aalen Estimator[16,17]
- Inverse probability of treatment weighting (IPTW) was used to adjust for differences in key prognostic covariates between treatment cohorts
- IPTW-weighted Cox proportional hazards models adjusted for variables that remained unbalanced after weighting and were used to compare OS between the avapritinib cohort and the midostaurin and cladribine cohorts

Results

Baseline demographics

- This analysis included 176 patients treated with avapritinib, 94 treated with midostaurin (contributing 99 lines of therapy), and 44 treated with cladribine (contributing 49 lines of therapy) (**Table 1**)
- Median (range) age was 68.0 (31.0−88.0) for avapritinib, 69.1 (25.8−87.3) for midostaurin, and 66.1 (45.1−87.5) years for cladribine patients
- There were 58.5% male patients in the avapritinib cohort, versus 68.1% in the midostaurin cohort and 61.4% in the cladribine cohort

Table 1. Baseline demographics and clinical characteristics

Baseline characteristics, unweighted sample[1]	Avapritinib cohort	Midostaurin cohort	*P* value[2,3]	Cladribine cohort	*P* value[2,4]
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, n (%)	104 (59.1%)	57 (57.6%)	0.907	32 (65.3%)	0.534
Thrombocytopenia, n (%)	67 (38.1%)	56 (56.6%)	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
Skin involvement					
Any skin involvement, n (%)	58 (33.0%)	30 (30.3%)	0.751	16 (32.7%)	1.000
Leukocyte count					
≥16 x 10^9/L, n (%)	33 (18.8%)	23 (23.2%)	0.465	13 (26.5%)	0.320
Serum tryptase (ng/mL)					
≥125 ng/mL, n (%)	132 (75.0%)	68 (68.7%)	0.324	32 (65.3%)	0.243
KIT mutation					
Patients that were tested for at least one mutation, 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 (S/A/R) mutation panel					
Patients that were tested for at least one mutation, n (%)	176 (100.0%)	78 (83.0%)	<0.001*	40 (90.9%)	0.001*
Number of mutated genes in *S/A/R* panel, n (%)					
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

*P<0.05

Abbreviations: ASM: aggressive systemic mastocytosis; ECOG: Eastern Cooperative Oncology Group; max: maximum; MCL: mast cell leukemia; min: minimum; S/A/R: SRSF2/ASXL1/RUNX1; SD: standard deviation; SM-AHN: systemic mastocytosis with an associated hematologic neoplasm.

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 and cladribine cohorts. Descriptive statistics are reported at the line of therapy level for all variables except KIT and S/A/R mutations , which are reported at the patient level, since each patient in the midostaurin or cladribine cohorts could contribute more than one line of therapy to the analysis.

[2] 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, Fisher's exact tests were used instead of Chi-squared.

[3] Statistical comparisons were conducted between the avapritinib and midostaurin cohorts.

[4] Statistical comparisons were conducted between the avapritinib and cladribine cohorts.

Baseline clinical characteristics

- Fewer patients in the cladribine cohort (51.0%) had an SM-AHN subtype, compared to patients in the avapritinib (67.6%) and midostaurin (65.7%) cohorts, while more patients in the cladribine cohort had an ASM subtype (34.7%), compared to patients in the avapritinib (16.5%) and midostaurin (21.2%) cohorts (**Table 1**)
- Mean (SD) Eastern Cooperative Oncology Group (ECOG) score was 1.2 (0.8), 1.1 (0.8), and 0.9 (0.5) for the avapritinib, midostaurin, and cladribine cohorts, respectively
- Among patients who were tested for a KIT mutation, 91.8%, 89.3% and 90.7% of patients in the avapritinib, midostaurin, and cladribine cohorts tested positive for KIT D816V, respectively
- A greater proportion of patients in the midostaurin and cladribine cohorts (56.6% and 57.1%, respectively) had thrombocytopenia at baseline, compared to patients in the avapritinib cohort (38.1%)

Prior systemic therapy

- Avapritinib was received as first-line (1L) therapy in 66 (37.5%) patients, while 58 (58.6%) received midostaurin in 1L and 20 (40.8%) received cladribine in 1L (**Table 2**)
- There were 110 (62.5%) avapritinib patients treated with prior systemic therapy, versus 41 (41.4%) and 29 (59.2%) in the midostaurin and cladribine cohorts, respectively
- In the avapritinib and cladribine cohorts, patients were most frequently pretreated with TKIs (52.3% and 42.9%, respectively), and the agent most commonly used was midostaurin
- Patients in the midostaurin cohort were most frequently pretreated with cytoreductive therapies (30.3%), and the agent most commonly used was cladribine

Table 2. Prior systemic therapy used to treat AdvSM patients

Prior systemic therapy	Avapritinib cohort	Midostaurin cohort	*P* value[1,2]	Cladribine cohort	*P* value[1,3]
Number of unique patients	**N = 176**	**N = 94**		**N = 44**	
Number of lines of therapy	**N = 176**	**N = 99**		**N = 49**	
Number with prior systemic therapy, n (%)	110 (62.5%)	41 (41.4%)	0.001*	29 (59.2%)	0.798
Number of prior lines of systemic therapy received, n (%)			<0.001*		<0.001*
Mean (SD)	1.0 (1.1)	0.1 (0.4)	--	0.1 (0.3)	--
Median (min, max)	1.0 (0.0, 6.0)	0.0 (0.0, 1.0)	--	0.0 (0.0, 1.0)	--
0	66 (37.5%)	58 (58.6%)	0.001*	20 (40.8%)	0.798
1	68 (38.6%)	29 (29.3%)	0.154	18 (36.7%)	0.939
2	28 (15.9%)	9 (9.1%)	0.160	7 (14.3%)	0.957
≥3	14 (8.0%)	3 (3.0%)	0.123	4 (8.2%)	1.000
Prior treatments received, n (%)[4]					
TKI	92 (52.3%)	12 (12.1%)	<0.001*	21 (42.9%)	0.315
Midostaurin	81 (46.0%)	5 (5.1%)	<0.001*	20 (40.8%)	0.627
Dasatinib	6 (3.4%)	4 (4.0%)	0.750	2 (4.1%)	0.686
Imatinib	10 (5.7%)	5 (5.1%)	1.000	2 (4.1%)	1.000
Other[5]	10 (5.7%)	0 (0.0%)	--	0 (0.0%)	--
Cytoreductive therapy	33 (18.8%)	30 (30.3%)	0.042*	11 (22.4%)	0.709
Cladribine	22 (12.5%)	23 (23.2%)	0.032*	5 (10.2%)	0.850
Hydroxyurea	9 (5.1%)	7 (7.1%)	0.691	6 (12.2%)	0.148
Other[5]	7 (4.0%)	2 (2.0%)	0.496	1 (2.0%)	1.000
Biologic therapy	23 (13.1%)	13 (13.1%)	1.000	10 (20.4%)	0.291
Interferon-alpha	14 (8.0%)	7 (7.1%)	0.977	8 (16.3%)	0.141
Pegylated interferon	3 (1.7%)	4 (4.0%)	0.256	2 (4.1%)	0.299
Other[5]	4 (2.3%)	2 (2.0%)	1.000	0 (0.0%)	--

*P<0.05

Abbreviations: AdvSM: advanced systemic mastocytosis; max: maximum; min: minimum; SD: standard deviation; TKI: tyrosine kinase inhibitor.

Notes:

[1] 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, Fisher's exact tests were used instead of Chi-squared.

[2] Statistical comparisons were conducted between the avapritinib and midostaurin cohorts.

[3] Statistical comparisons were conducted between the avapritinib and cladribine cohorts.

[4] Individual treatments that were observed in ≥4.0% of lines of therapy in any cohort are reported.

[5] Other TKIs included ibrutinib, nilotinib, ripretinib, and ruxolitinib. Other cytoreductive therapies included azacitinide, decitabine, and chlorambucil. Other biologic therapies included brentuximab vedotin, obinituzumab, and rituximab.

OS: Avapritinib versus midostaurin

- In unweighted analysis of avapritinib versus midostaurin, mean follow-up durations were 17.9 and 27.9 months, respectively
- Deaths occurred in 34 (19.3%) avapritinib patients and 56 (59.6%) midostaurin patients
- In the unweighted analysis, median OS was not reached (95% CI: 46.9, not estimable) in the avapritinib cohort and was 28.6 months (95% CI: 18.2, 44.6) in the midostaurin cohort (**Figure 1**)
- In the weighted Cox analysis, OS was significantly improved in the avapritinib versus midostaurin cohort (hazard ratio [HR] [95% CI]: 0.59 [0.36, 0.97]; P<0.001), even with further adjustment for unbalanced variables (**Table 3**)

OS: Avapritinib versus cladribine

- In the unweighted analysis, the mean follow-up durations for the avapritinib and cladribine cohorts were 17.9 and 24.2 months, respectively
- Deaths occurred in 29 (65.9%) cladribine patients
- In the unweighted analysis, median OS in the cladribine cohort was 23.4 months (95% CI: 14.8, 40.6) (**Figure 1**)
- Weighted Cox analysis showed that OS was significantly improved in the avapritinib versus cladribine cohort (HR [95% CI]: 0.32 [0.15, 0.67]; P=0.003), even with further adjustment for unbalanced variables (**Table 3**)

Table 3. Summary of OS for avapritinib versus midostaurin and avapritinib versus cladribine

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[1,2]	0.59 (0.36, 0.97); <0.001*		
Avapritinib vs. Cladribine: HR, IPTW-weighted sample (95% CI); *P* value[1,2]	0.32 (0.15, 0.67); 0.003*		

*P<0.05

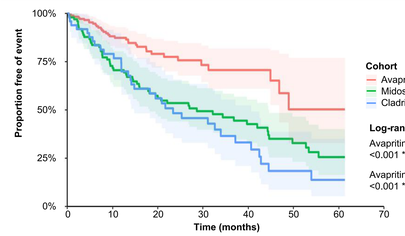
Abbreviations: AdvSM: advanced systemic mastocytosis; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IPTW: inverse probability of treatment weighting; OS: overall survival; NE: not estimable; NR: not reached; S/A/R: SRSF2/ASXL1/RUNX1.

Notes:

[1] The IPTW-weighted Cox proportional hazards model with a robust sandwich variance estimator was used to model overall survival 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.

[2] Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anemia (hemoglobin <10 g/dL), thrombocytopenia (platelet count <100 x 10^9/L), AdvSM subtype, skin involvement, leukocyte count ≥16 × 10^9/L, serum tryptase level ≥125 ng/mL, number of mutated genes within the S/A/R panel, number of prior lines of therapy, and prior use of TKI, cytoreductive, and biologic therapy.

Figure 1. KM curve for OS of patients with AdvSM treated with avapritinib versus midostaurin or cladribine



*P<0.05

Abbreviations: AdvSM: advanced systemic mastocytosis; KM: Kaplan-Meier; OS: overall survival.

Note: The follow-up times for the midostaurin and cladribine cohorts were truncated to match the maximum follow-up time of the avapritinib cohort. In the midostaurin cohort, 94 patients contributed 99 lines of therapy to the analysis. In the cladribine cohort, 44 patients contributed 49 lines of therapy to the analysis.

Limitations

- Due to the retrospective nature of data collection for patients treated with midostaurin or cladribine, results may have been impacted by incomplete reporting for key prognostic characteristics, such as performance status
  - A sensitivity analysis assessing the impact of missing performance status indicated that this is not expected to impact results
- A few patients from the midostaurin or cladribine cohorts went on to receive avapritinib as part of the EXPLORER or PATHFINDER trials. Since no identifiable information was collected for real-world patients, these patients may have been included in the avapritinib trial cohort
  - These patients were included in the analysis, but were censored at avapritinib initiation to ensure their time on treatment was not counted in both the real-world and trial cohorts

Conclusions

- The results of this observational, retrospective, study indicate that patients with AdvSM who were treated with avapritinib in EXPLORER and PATHFINDER experienced significantly improved survival compared with patients treated with midostaurin or cladribine in real world clinical practice
- Given the lack of randomized controlled trials, these data offer essential insights into the improved survival of patients treated with avapritinib compared to commonly used alternative therapies for AdvSM

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