

S201

EFFICACY AND SAFETY OF AVAPRITINIB IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS: INTERIM RESULTS FROM THE OPEN-LABEL, SINGLE-ARM, PHASE 2 PATHFINDER STUDY

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Background:

Systemic mastocytosis (SM) is a rare, clonal, hematologic neoplasm which is driven by the *KIT*D816V mutation in ~95% of cases. Treatment outcomes remain poor for patients (pts) with advanced systemic mastocytosis (AdvSM), which includes aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). In the Phase 1 EXPLORER study (NCT02561988), avapritinib, a potent KIT D816V inhibitor, induced rapid, durable responses which deepened over time in pts with AdvSM regardless of prior therapy or subtype.

Aims:

PATHFINDER (NCT03580655) is a pivotal open-label, single-arm Phase 2 study evaluating avapritinib in pts with AdvSM.

Methods:

Pts aged ≥ 18 years with centrally confirmed diagnosis of an AdvSM subtype. Primary endpoint was overall response rate (ORR) by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (miWG-MRT-ECNM) criteria. This pre-specified interim analysis (null hypothesis ORR 28% based on midostaurin) included 32 ORR-evaluable pts. Mean baseline change in AdvSM-Symptom Assessment Form Total Symptom Score (TSS) and safety were secondary endpoints. All pts gave informed consent.

Results:

As of June 23, 2020, 62 pts with AdvSM received avapritinib primarily at 200 mg orally once daily (QD); 52/62 (84%) pts remained on treatment. Median age was 69 years (range 31–88), 45% were female, 31% had ECOG PS 2–3, and 68% had prior systemic therapy (55% with midostaurin). The primary endpoint was met with an ORR of 75% (95% CI 57–89) in 32 ORR-evaluable pts as per the pre-specified interim analysis ($P=1.6 \times 10^{-9}$; median follow-up 10.4 months) (Table). Complete remission with full or partial hematologic recovery occurred in 6 (19%) pts. Median time to response was 2 (range 0.3–12) months; responses deepened over time. Median overall survival (OS) in the ORR-evaluable population was not reached; estimated 12-month OS was 87%. In the safety population (N=62), there were $\geq 50\%$ reductions from baseline for serum tryptase (87%; n=54), marrow mast cells (71%; n=44), and *KIT* D816V variant allele fraction (53%; n=33). Mean TSS at baseline (n=56) was 18.3; fatigue, spots, itching, flushing, and abdominal pain were the most severe symptoms; TSS improved rapidly and was sustained through cycle 11 with mean 36% improvement ($P < 0.001$), corresponding to a mean decrease of 9.8 points from baseline (n=22). Common ($\geq 25\%$) adverse events (AEs; any grade, Grade ≥ 3) were peripheral (50%, 3%) and periorbital (35%, 3%) edema, thrombocytopenia (32%, 8%), and anemia (29%, 16%). Overall, 3 (5%) pts discontinued due to a treatment-related AE and 3 (5%) pts discontinued due to disease progression, including 1 pt with transformation to acute myeloid leukemia. There were 3 (5%) deaths, all considered unrelated to treatment. Seven (11%) pts had cognitive AEs (all Grade 1–2). Grade 4 subdural hematoma occurred in 1 (2%) pt with severe thrombocytopenia (platelets $< 50 \times 10^9/L$) at baseline and prior to the event. Subsequent pts with pre-treatment severe thrombocytopenia were excluded, platelet monitoring increased, and dose interruption for severe thrombocytopenia recommended.

Image:

Table. Confirmed ORR and best response by miWG-MRT-ECNM criteria in pts with AdvSM*

Outcome, n (%)	All (n=32)							
	All (n=32)	ASM (n=2)	SM-AHN (n=26)	MCL (n=4)	Prior therapy (n=23)	No prior therapy (n=9)	Prior Midostaurin (n=17)	No Prior Midostaurin (n=15)
ORR ^b	24 (75)	2 (100)	21 (81)	1 (25)	17 (74)	7 (78)	14 (82)	10 (67)
95%CI	57–89	16–100	61–93	1–81	52–90	40–97	57–96	38–88
CR	0	0	0	0	0	0	0	0
CRh	6 (19) ^f	1 (50)	5 (19)	0	3 (13)	3 (33)	3 (18)	3 (20)
PR	10 (31)	1 (50)	8 (31)	1 (25)	7 (30)	3 (33)	5 (29)	5 (33)
CI	8 (25)	0	8 (31)	0	7 (30)	1 (11)	6 (35)	2 (13)
SD	4 (13)	0	2 (8)	2 (50)	2 (9)	2 (22)	0	4 (27)
PD	1 (3)	0	0	1 (25)	1 (4)	0	0	1 (7)
NE	3 (9)	0	3 (12)	0	3 (13)	0	3 (18)	0

*The PATHFINDER pre-specified interim occurred in 32 ORR-evaluable pts with a diagnosis of AdvSM, who received at least 1 dose of avapritinib and were evaluable per miWG-MRT-ECNM criteria at baseline and had ≥ 2 complete postbaseline response assessments and ≥ 6 cycles of therapy (or came off study).

^bCR + CRh + PI + CI, all lasting ≥ 12 weeks.

^fMedian time to CRh: 5.6 months (range 1.8–6.1).

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; MCL, mast cell leukemia; miWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NE, not evaluable for response; ORR, overall response rate; PD, progressive disease; PR, partial remission; pts, patients; SD, stable disease; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.

Summary/Conclusion:

The PATHFINDER registrational study interim analysis showed avapritinib 200 mg QD starting dose induced rapid, durable responses which deepened over treatment regardless of AdvSM subtype or prior therapy and improved symptoms in pts with AdvSM. Avapritinib was generally well tolerated with few pts discontinuing treatment due to AEs.

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