Avapritinib improves symptoms and quality of life in indolent systemic mastocytosis: 12-month outcome of the real-world AVATAR study

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Objective

Indolent systemic mastocytosis (ISM) is a clonal disorder characterized by the accumulation of neoplastic mast cells (MCs) in various organs, mostly driven by KIT D816V mutation.

Avapritinib is the first targeted therapy approved for the treatment of moderate to severe ISM. In a randomized, placebo-controlled phase 2 study (PIONEER, NCT03731260), avapritinib demonstrated significant improvements compared to placebo in the primary endpoint of total symptom score and key secondary endpoints, including objective measures of mast cell burden. Treatment was generally well tolerated at the 25 mg dose, with adverse event rates similar to placebo.

While the PIONEER trial showed efficacy and safety of avapritinib under controlled settings, the experience of patients treated in real-world practice remains less characterized.

The objective of this study was to characterize ISM patients treated with avapritinib in routine practice and to evaluate clinical, laboratory and patient-reported outcomes. Specifically, we aimed to assess the impact of treatment on the quality of life, symptom severity, and mast cell burden.

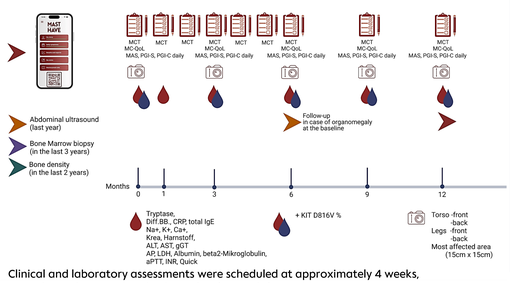
Methods

The AVATAR study is a single-center, real-world observational study at the Interdisciplinary Mastocytosis Center, Institute of Allergology, Charité - Universitätsmedizin Berlin. Patients were eligible if they fulfilled the 2022 WHO/ICC diagnostic criteria for ISM and qualified for avapritinib therapy despite symptomatic treatment. Patients who had been treated with avapritinib for at least 3 months were included in the current report.

Clinical data were extracted from medical records, while patient-reported outcome measures (PROMs) were administered digitally via the MASTHAVE® app or on paper.

Patients were treated in accordance to the standards of care. Prior to treatment initiation, all patients underwent laboratory screening to assess safety and eligibility, including blood count, liver and renal function tests, electrolytes, and coagulation parameters. For women of childbearing potential, a negative pregnancy test was required, and all patients were counseled on the need for reliable contraception due to the potential teratogenic risk of avapritinib.

Figure 1. AVATAR study design



Clinical and laboratory assessments were scheduled at approximately 4 weeks, 12 weeks, and every 12 weeks thereafter (±4 weeks).

Table 1. Baseline disease features

Parameter	Analyzed cohort
Total, n	20
Age, years **	54 ± 11 (29 - 69)
Gender, female, n/total (%)	12/20 (60.0)
Anaphylaxis, n/total (%)	6/20 (30.0)
Osteoporosis, n/total (%)	8/20 (40.0)
Spontaneous fractures, n/total (%)	5/20 (25.0)
Disease Duration, years **	17 ± 12 (3 - 44)
Skin lesions (i.e. MIS), n/total (%)	20/20 (100.0)
Hepato-/Splenomegaly, n/total (%)	4/20 (20.0)
MC infiltrates in BM, n/total (%)	17/19 (89.5)
MC % in BM **	15 ± 12 (0 - 40), n=16
Serum tryptase, ng/ml *	33.5 (23.8 – 95.5), n=20
KIT D816V burden in PB, % *	1.37 (0.23 – 3.81), n=20
KIT D816V burden in PB ≥4.00%, n/total (%)	5/20 (25.0)
KIT D816V burden in PB ≥2.00%, n/total (%)	7/20 (35.0)
MCT Score *	8 (5 - 11), n=20
MC-QoL Total Score *	56 (42 - 68), n=19

Results

Figure 2. Mastocytosis-associated QoL impairment during treatment

*indicate statistically significant reductions compared to baseline (p < 0.05).
[$] the number of patients for Domain scores is different for this time point (Table 2)

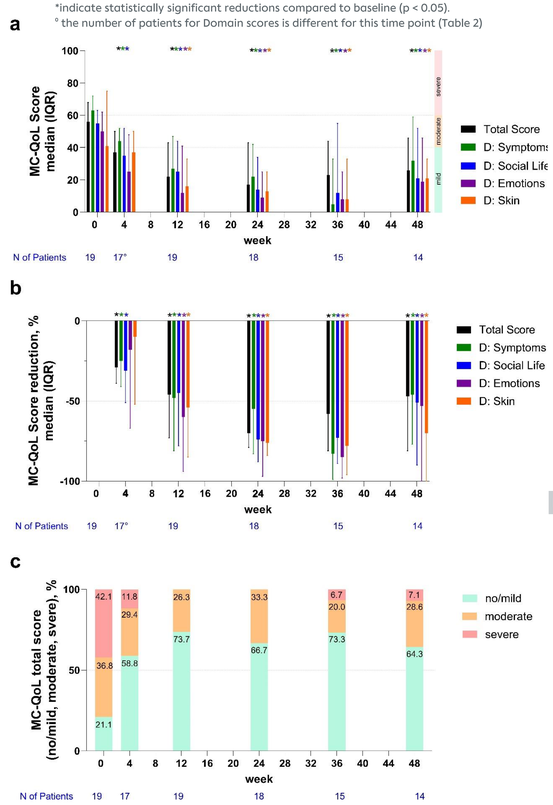


Figure 3. Disease control during treatment

*indicate statistically significant reductions compared to baseline (p < 0.05)

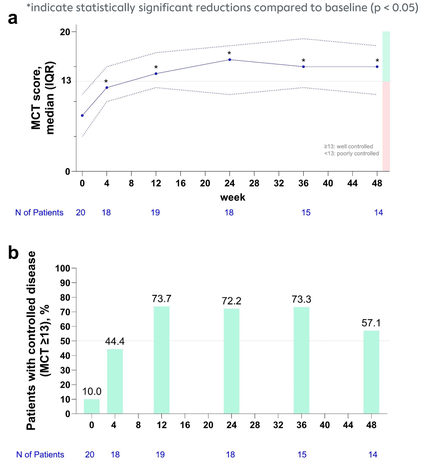


Figure 4. Serum tryptase levels during treatment

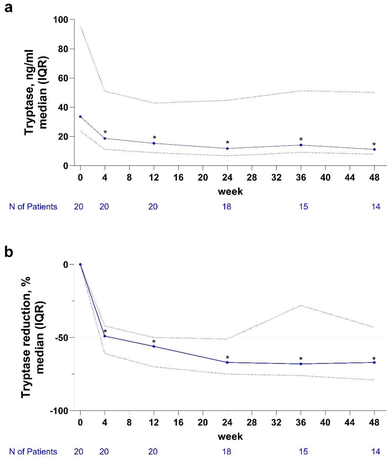
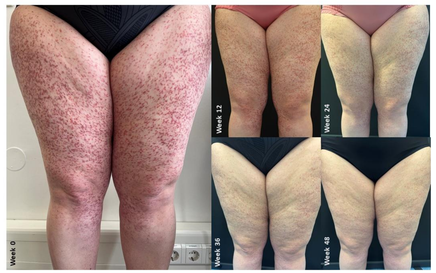


Figure 5. Clinical improvement of cutaneous manifestations during treatment

(a) A 36-year-old female patient; Frontal view of the thighs.



(b) A 48-year-old male patient Frontal view of the trunk.

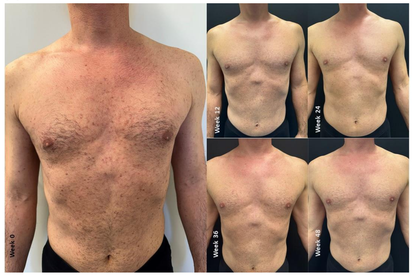


Table 2. Patient-reported outcome measures and laboratory values over 48 weeks of treatment

Parameter	Week 0	Week 4	Week 12	Week 24	Week 36	Week 48
Number	20	20	20	18	15	14
MCT baseline	n=20	n=18	n=19	n=18	n=15	n=14
- Score *	8 (5 - 11)	12 (10 - 15)	14 (12 - 17)	16 (11 - 18)	15 (12 - 19)	15 (11 - 18)
- ≥13, n (%)	2 (10.0)	8 (44.4)	14 (73.7)	13 (72.2)	11 (73.3)	8 (57.1)
MC-QoL Total	n=19	n=17	n=19	n=18	n=15	n=14
- Score *	56 (42 - 68)	37 (27 - 50)	22 (14 - 43)	17 (9 - 43)	23 (7 - 44)	26 (8 - 46)
- no/mild (score 0-39), n (%)	4 (21.1)	10 (58.8)	14 (73.7)	12 (66.7)	11 (73.3)	9 (64.3)
- moderate (score 40-59), n (%)	7 (36.8)	5 (29.4)	5 (26.3)	6 (33.3)	3 (20.0)	4 (28.6)
- severe (score ≥60), n (%)	8 (42.1)	2 (11.8)	0 (0.0)	0 (0.0)	1 (6.7)	1 (7.1)
- % change from baseline *	NA	-29 (-39; -4)	-46 (-73; -33)	-70 (-79; -34)	-58 (-81; -32)	-47 (-81; -17)
MC-QoL: "Symptoms"	n=19	n=16	n=19	n=18	n=15	n=14
- Score *	63 (47 - 72)	44 (30 - 52)	27 (14 - 47)	22 (5 - 42)	5 (1 - 33)	32 (9 - 59)
- % change from baseline *	NA	-25 (-41; -5)	-48 (-81; -17)	-55 (-83; -33)	-83 (-99; -32)	-46 (-77; -14)
MC-QoL: "Social Life"	n=19	n=16	n=19	n=18	n=15	n=14
- Score *	55 (38 - 63)	35 (28 - 52)	25 (11 - 44)	14 (5 - 34)	12 (5 - 55)	21 (6 - 52)
- % change from baseline *	NA	-31 (-51; -10)	-45 (-78; -26)	-74 (-88; -25)	-73 (-89; -17)	-51 (-90; -19)
MC-QoL: "Emotions"	n=19	n=16	n=19	n=18	n=15	n=14
- Score *	50 (25 - 62)	25 (13 - 48)	12 (2 - 41)	9 (3 - 25)	8 (0 - 25)	19 (0 - 46)
- % change from baseline *	NA	-18 (-67; 0)	-60 (-94; -25)	-75 (-97; -34)	-85 (-98; -38)	-53 (-100; -16)
MC-QoL: "Skin"	n=19	n=16	n=19	n=18	n=15	n=14
- Score *	41 (33 - 75)	37 (16 - 50)	16 (8 - 33)	13 (6 - 25)	8 (2 - 33)	21 (0 - 33)
- % change from baseline *	NA	-10 (-52; 0)	-54 (-85; -22)	-76 (-84; -39)	-78 (-96; -40)	-70 (-100; -26)
Tryptase	n=20	n=20	n=20	n=18	n=15	n=14
- ng/ml *	33.5 (23.8 – 95.5)	18.6 (11.1 – 51.0)	15.3 (8.9 – 42.8)	11.7 (6.7 - 44.7)	14.1 (9.1 – 51.2)	11.1 (7.8 - 50.1)
- % change from baseline *	NA	-49 (-61; -42)	-56 (-70; -50)	-67 (-75; -51)	-68 (-76; -28)	-67 (-79; -43)
- <20 ng/ml, n/total (%)	4/20 (20.0)	11/20 (55.0)	11/20 (55.0)	11/18 (61.1)	8/15 (53.3)	9/14 (64.3)
KIT D816V VAF in PB	n=20		n=17	n=12	n=13	
- % *	1.37 (0.23 – 3.81),	NA	0.88 (0.28 - 1.60)	1.08 (0.03 - 2.03)	1.16 (0.39 – 4.65)	1.40 (0.56 – 4.50)
- % change from baseline *	NA	NA	-50 (-65; 5)	-39 (-82; 2)	-29 (-74; 65)	-21 (-43; 54)
AP	n=20	n=18	n=20	n=18	n=15	n=14
- IU/L *	82.5 (62.0 – 89.8)	94.5 (78.5-119.3)	86.0 (74.0 – 94.8)	80.5 (65.0 - 92.3)	80.0 (63.0 - 86.0)	74.5 (66.5 -87.5)

* Values are presented as median (IQR)

Conclusions

Our findings demonstrate that the benefits of avapritinib observed under controlled trial conditions are reproducible in a real-world ISM population with a broad spectrum of symptoms, comorbidities, mast cell burden, and disease duration.
The absence of a predictive effect for most established risk factors suggests that treatment decisions should not be restricted based on these parameters in ISM patients with skin involvement.
The rapid onset and durability of improvement in both subjective and objective outcomes highlight the potential of avapritinib to rapidly achieve disease control as early as 4 weeks after treatment initiation and durably maintain that control through 48 weeks of therapy.
At the same time, the observed interindividual variability highlights the need for more refined, phenotype-driven approaches to better characterize treatment response and inform personalized management strategies in ISM.
These findings support the use of avapritinib in routine clinical practice and underscore the need for further multicenter real-world studies.

References

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✓ Pyatilova P, Akin C, Alvarez-Twose I, et al. Refined Treatment Response Criteria for Indolent Systemic Mastocytosis Proposed by the ECNM-AIM Consortium. J Allergy C Immunol Pract. 2022 Aug;10(8):2015-2024. doi: 10.1016/j.jaip.2022.05.037.

Abbreviations: AP, Alkaline Phosphatase, ISM, indolent systemic mastocytosis; QoL, quality of life; IQR, interquartile range; PB, peripheral blood; SD, standard deviation; MIS, mastocytosis in the skin; MCT, Mastocytosis Control Test; MC-QoL, Mastocytosis Quality of Life Questionnnaire; VAF, variant allele fraction

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