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VIRTUAL

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

Andreas Reiter[1], Daniel J. DeAngelo[2], Deepti Radia[3], Michael W. Deininger[4], Tracy I. George[5], Jens Panse[6], Alessandro M. Vannucchi[7], Madlen Jentzsch[8], Iván Alvarez-Twose[9], Andrzej Mital[10], Olivier Hermine[11], Ingunn Dybedal[12], Elizabeth O. Hexner[13], Lisa K. Hicks[14], Lambert Span[15], Ruben Mesa[16], Prithviraj Bose[17], Kristen M. Pettit[18], Mark L. Heaney[19], Stephen Oh[20], Jayita Sen[21], Hui-Min Lin[21], Brenton G. Mar[21], Jason Gotlib[22]

[1]Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; [3]Guy's & St Thomas' NHS Foundation Trust, London, UK; [4]Division of Hematology and Hematologic Malignancies, University of Utah, Huntsman Cancer Institute, Salt Lake City, USA; [5]ARUP Laboratories, University of Utah, Salt Lake City, USA; [6]Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Aachen, Germany; [7]Center for Research and Innovation of Myeloproliferative Neoplasms – CRIMM, Azienda Ospedaliera Universitaria Careggi, University of Florence, Florence, Italy; [8]Medical Clinic I – Hematology, Cellular Therapy and Hemostaseology, Leipzig University Hospital, Leipzig, Germany; [9]Institute of Mastocytosis Studies of Castilla-La Mancha, Spanish Reference Center of Mastocytosis, Toleda, Spain; [10]Department of Hematology and Transplantology, Medical University of Gdansk, Gdansk, Poland; [11]Necker–Enfants Malades Hospital and Imagine Institute, CEREMAST, Paris, France; [12]Department of Hematology, Oslo University Hospital, Oslo, Norway; [13]Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [14]Division of Hematology/Oncology, St. Michael's Hospital, University of Toronto, Toronto, Canada; [15]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [16]Mays Cancer Center at UT Health San Antonio MD Anderson, San Antonio, USA; [17]The University of Texas MD Anderson Cancer Center, Houston, USA; [18]University of Michigan, Ann Arbor, USA; [19]Columbia University Medical Center, New York, USA; [20]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, USA. [21]Blueprint Medicines Corporation, Cambridge, USA; [22]Division of Hematology, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, USA

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Novel therapies and targets in MPN

DISCLOSURES

Andreas Reiter, MD

I have the following financial relationships to disclose:

Steering committee member (PATHFINDER study): Blueprint Medicines Corporation

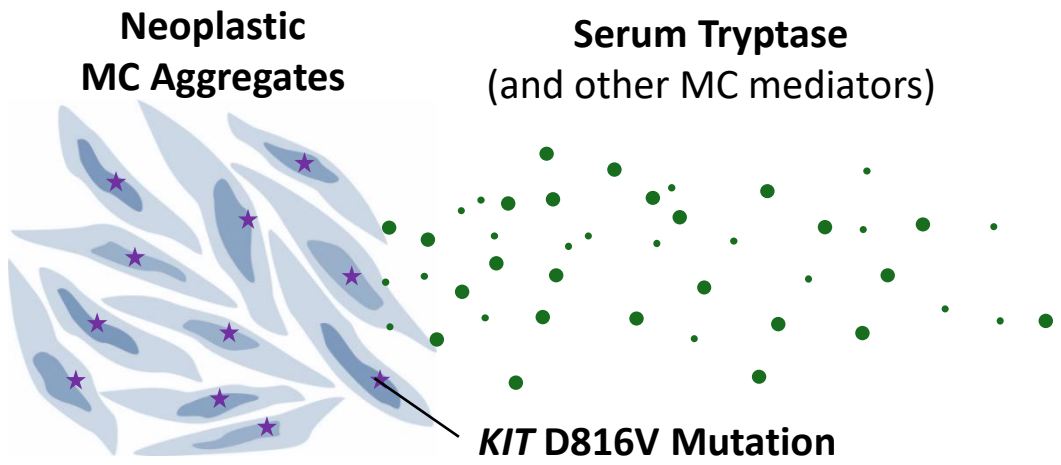
Advisory board fees/speaking fees/travel support: AbbVie, AOP Orphan, Blueprint Medicines Corporation, Celgene, Deciphera, Incyte, and Novartis

Research support: Novartis

Avapritinib is not approved as safe or effective for use in systemic mastocytosis by the FDA, EMA, or any healthcare authority in any jurisdiction.

ADVANCED SYSTEMIC MASTOCYTOSIS (AdvSM) IS A RARE HEMATOLOGIC NEOPLASM DRIVEN BY *KIT* D816V IN ~95% OF CASES

- Patients with AdvSM have elevated mast cell (MC) burden, organ damage and poor survival[1]
- MC hyperactivation leads to severe mediator symptoms and poor quality of life[1]
- Multikinase inhibitor midostaurin is the only approved therapy for all subtypes of AdvSM[a]
  - ORR[b] was 28% (CR+PR=15.9%) per IWG-MRT-ECNM criteria requiring resolution of organ damage[2,c]
  - Median overall survival was 2.5 years[3]
- Response in the AHN component of SM-AHN (a subcategory of AdvSM) has not previously been demonstrated



Organ Damage (C-findings)

- Cytopenias
- Liver dysfunction
- Ascites, pleural effusions
- Splenomegaly with hypersplenism
- Malabsorption with weight loss
- Large osteolytic lesions

[a]Imatinib is approved by the U.S. FDA for the treatment of ASM without or unknown *KIT* D816V mutation status. [b]Midostaurin ORR of 28.3% was comprised of 0.9% CR + 15% PR + 12.4% CI. ORR per Valent and Cheson criteria (MR+PR) was 59.6%. [c]Post hoc IWG-MRT-ECNM analysis in midostaurin SmPC requiring resolution of organ damage for ≥12 weeks;[2] per Valent criteria, which included lesser organ damage improvements for ≥8 weeks, ORR was 60%.[3]

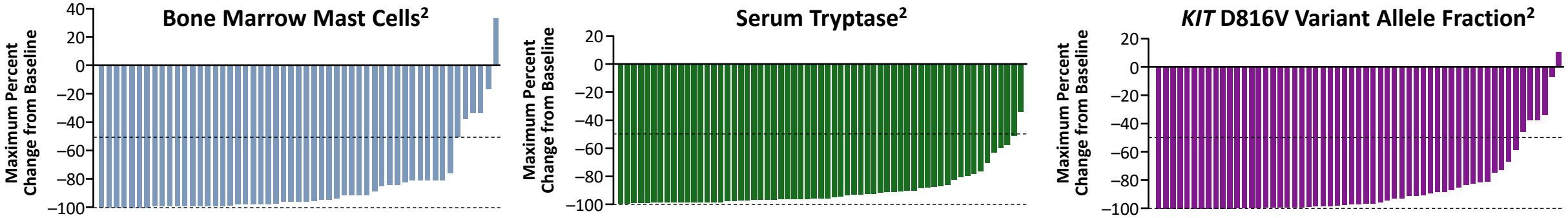
1. Pardanani A. *Am J Hematol*. 2019;94:363–377; 2. RYDAPT (midostaurin). Summary of Product Characteristics. 2017; 3. Gotlib J et al. *N Engl J Med*. 2016;374:2530–2541.
AHN, associated hematologic neoplasm; CI, clinical improvement; CR, complete remission; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MR, major response; ORR, overall response rate; PR, partial remission; SM, systemic mastocytosis; SmPC, Summary of Product Characteristics.

AVAPRITINIB, A POTENT AND SELECTIVE KIT D816V INHIBITOR, INDUCED DEEP REDUCTIONS IN MC BURDEN AND RESOLUTION OF ORGAN DAMAGE

- Highly potent on KIT D816V (biochemical IC_{50}=0.27 nM)[1]

Phase 1 Dose Escalation/Expansion EXPLORER Study (Secondary Endpoints)

- 75% ORR[a] per modified IWG-MRT-ECNM criteria[1]
- Responses were rapid, with complete remissions over time (median follow-up: 23 months)
- Improvements in mast cell burden, organ damage and patient symptoms and quality of life



Data cut-off: May 27, 2020.
[a]ORR is defined as CR + CRh + PR + CI.
1. Gotlib J et al. ASH 2020 [Oral 345]; 2. Gotlib J et al. EHA 2020 [Poster EP1079].
IC_{50}, half-maximal inhibitory concentration.

PATHFINDER PHASE 2 REGISTRATIONAL STUDY

Avapritinib 200[a] mg QD Starting Dose (Both Cohorts)

Enrolled (N=62) → **Central Review** → **Evaluable, Cohort 1 (n=52)**: AdvSM with ≥1 evaluable C-finding[b] → **Pre-specified Interim Analysis**

Central Review → **Non-Evaluable, Cohort 2 (n=10)**: AdvSM without evaluable C-finding[b]

- Central diagnosis of AdvSM
- ≥18 years of age
- ECOG PS 0–3
- **Excluded:** Platelets <50×10^9/L (added in 2019 to reduce risk of intracranial bleeding)

Once 32 patients have sufficient follow-up:

- On study ≥6 months (with ≥2 bone marrow assessments to allow for a confirmed response), or
- Off the study at any timepoint

Primary Endpoint (Cohort 1)

- Adjudicated ORR by modified IWG-MRT-ECNM criteria
- Interim analysis: Null hypothesis was 28% and a 1-sided type I error rate of 0.00625

Secondary Endpoints (Both Cohorts)

- Change in patient-reported symptoms (key secondary) and quality of life
- Change in disease burden
- Safety

[a]60 patients received 200 mg and 2 patients received 100 mg. [b]Per modified IWG-MRT-ECNM criteria, response assessment requires ≥1 evaluable C-finding at baseline. MCL without an evaluable C-finding may be assessed for response based on disease burden alone (Gotlib et al. *Blood*. 2013;21:2393–2401).
ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mast cell leukemia; QD, once-daily.

BASELINE CHARACTERISTICS

	Safety Population (N=62)	Interim Analysis Efficacy Population (n=32)
Median age, years (range)	69 (31–88)	68 (37–85)
Female, n (%)	28 (45)	14 (44)
ECOG Performance Status 2–3, n (%)	19 (31)	11 (34)
AdvSM subtype per central assessment, n (%)		
ASM	**9 (15)**	**2 (6)**
SM-AHN	**43 (69)**	**26 (81)**
CEL	**4 (6)**	**4 (13)**
CMML	**21 (34)**	**12 (38)**
MDS/MPN-U	**10 (16)**	**5 (16)**
MCL	**10 (16)**	**4 (13)**
KIT D816V positive in blood, n (%)	59 (95)	30 (94)
***SRSF2/ASXL1/RUNX1* mutation positive, n (%)**	**26 (42)**	**17 (53)**
Any prior anti-neoplastic therapy, n (%)	**42 (68)**	**23 (72)**
Midostaurin	**34 (55)**	**17 (53)**
Cladribine	**8 (13)**	**4 (13)**
BM biopsy MC burden, median percent (range)	45 (1–95)	50 (10–95)
Serum tryptase level, median ng/mL (range)	283 (24–1600)	293 (24–1600)

ASM, aggressive systemic mastocytosis; BM, bone marrow; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN-U, myeloproliferative neoplasms unclassifiable; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

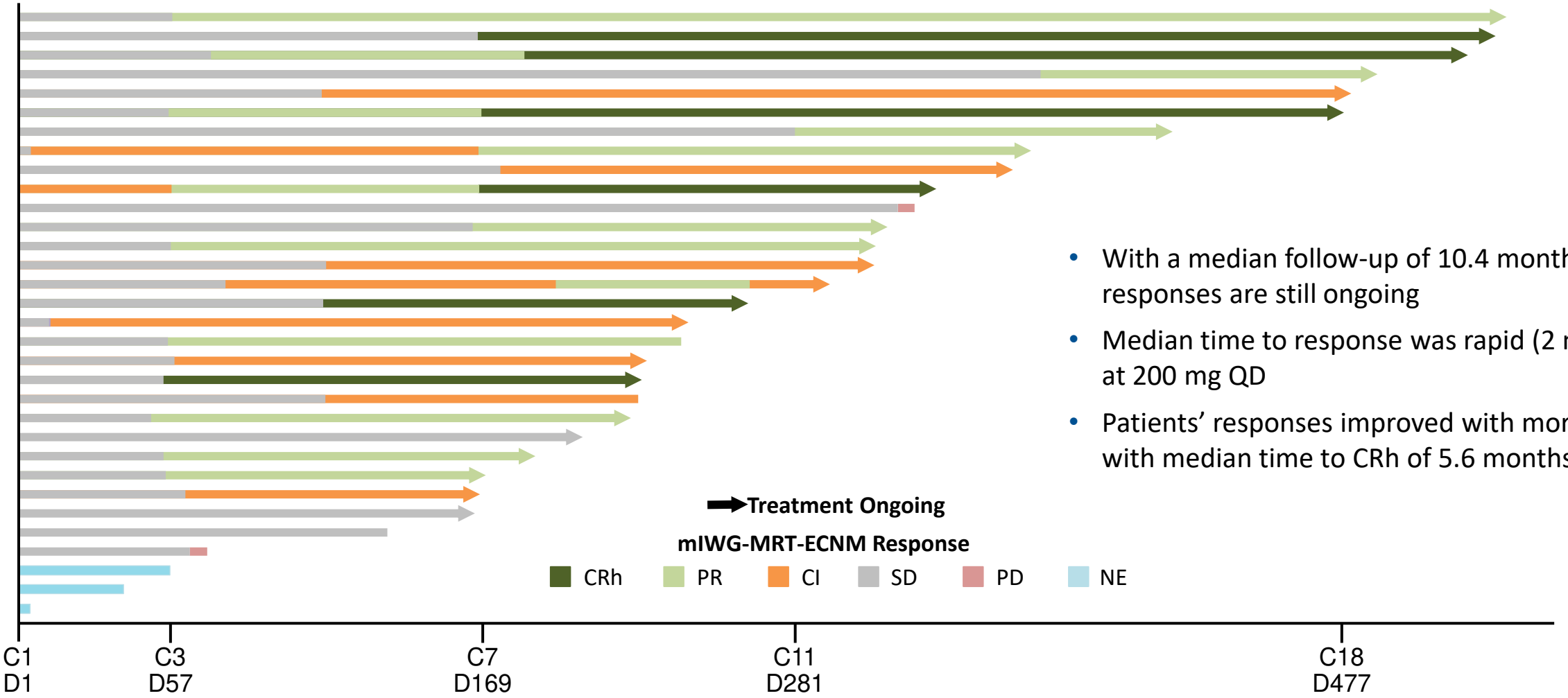
RESPONSES IN ALL SUBTYPES OF AdvSM, REGARDLESS OF PRIOR THERAPY

Best Confirmed Response, n (%)	All AdvSM (n=32)[c]	AdvSM Subtype			Any Prior Therapy	
		ASM (n=2)	SM-AHN (n=26)	MCL (n=4)	Yes (n=23)	No (n=9)
Overall Response Rate (CR + CRh + PR + CI)	**24 (75)**	2 (100)	21 (81)	1 (25)	17 (74)	7 (78)
CR + CRh[a] + PR	**16 (50)**	2 (100)	13 (50)	1 (25)	10 (43)	6 (67)
CR or CRh[a]	6 (19)	1 (50)	5 (19)	0	3 (13)	3 (33)
Complete Remission (CR)	0	0	0	0	0	0
CR with Partial Hematologic Recovery (CRh)[a]	6 (19)	1 (50)	5 (19)	0	3 (13)	3 (33)
Partial Remission (PR)[b]	10 (31)	1 (50)	8 (31)	1 (25)	7 (30)	3 (33)
Clinical Improvement (CI)	8 (25)	0	8 (31)	0	7 (30)	1 (11)
Stable Disease (SD)	4 (13)	0	2 (8)	2 (50)	2 (9)	2 (22)
Progressive Disease (PD)	1 (3)	0	0	1 (25)	1 (4)	0
Not Evaluable (NE)	3 (9)[d]	0	3 (12)	0	3 (13)	0

[a]CRh (mIWG-MRT-ECNM) requires full resolution of all evaluable C-findings, elimination of BM MC aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as ANC >0.5×10^9/L with normal differential, platelet count >50×10^9/L, and Hgb level >8.0 g/dL). [b]PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both BM MCs and serum tryptase. [c]One patient in the evaluable population started at 100 mg QD. [d]Three (9%) patients were in the interim analysis efficacy population but were assessed as "not evaluable" for response due to early withdrawal from study before a confirmed response could be determined (13 weeks).

ANC, absolute neutrophil count; Hgb, hemoglobin.

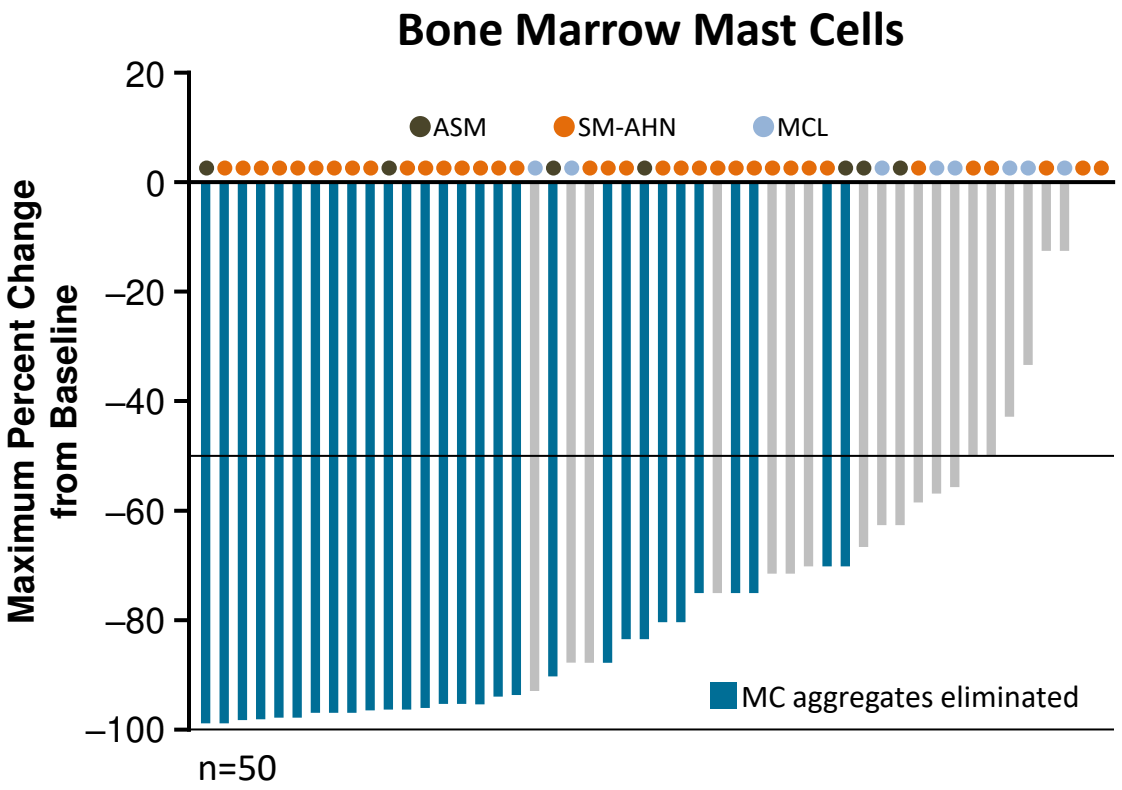
RESPONSES ON AVAPRITINIB IMPROVED WITH TIME

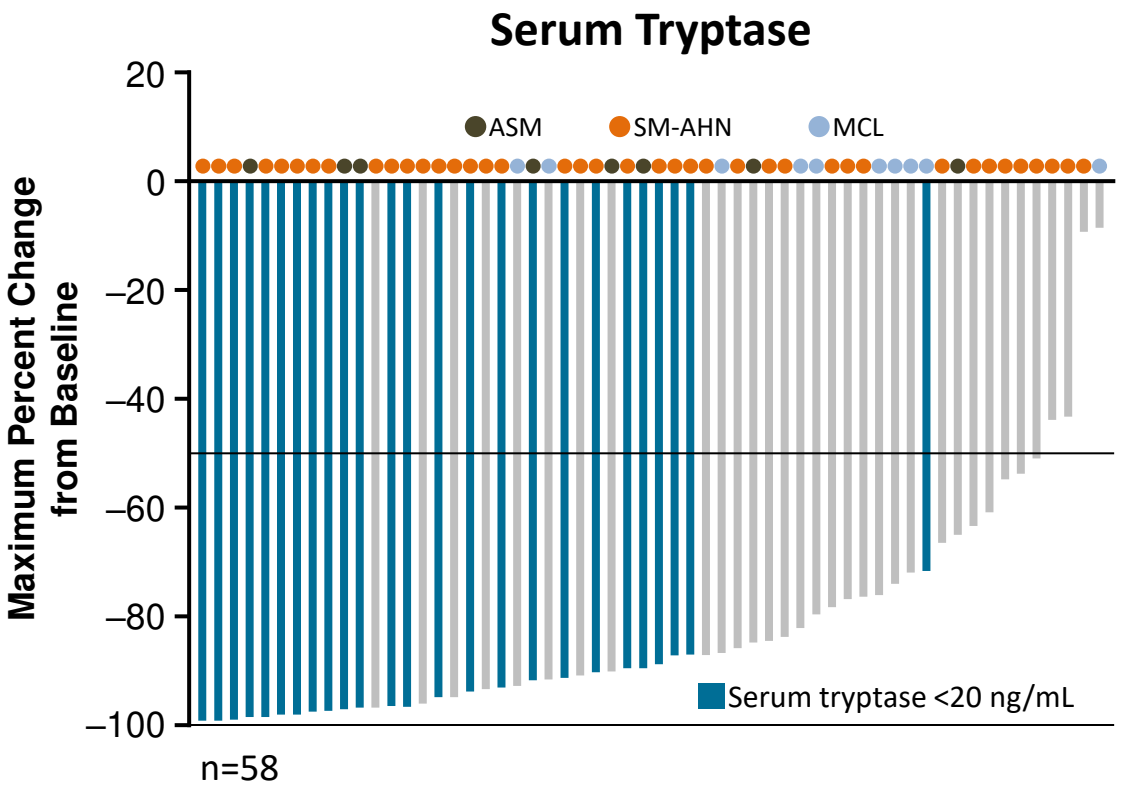


- With a median follow-up of 10.4 months all responses are still ongoing
- Median time to response was rapid (2 months) at 200 mg QD
- Patients' responses improved with more time with median time to CRh of 5.6 months

Each cycle is 28 days.
C, cycle; D, day.

AVAPRITINIB LED TO PROFOUND REDUCTIONS IN BONE MARROW MAST CELLS AND SERUM TRYPTASE IN PATHFINDER



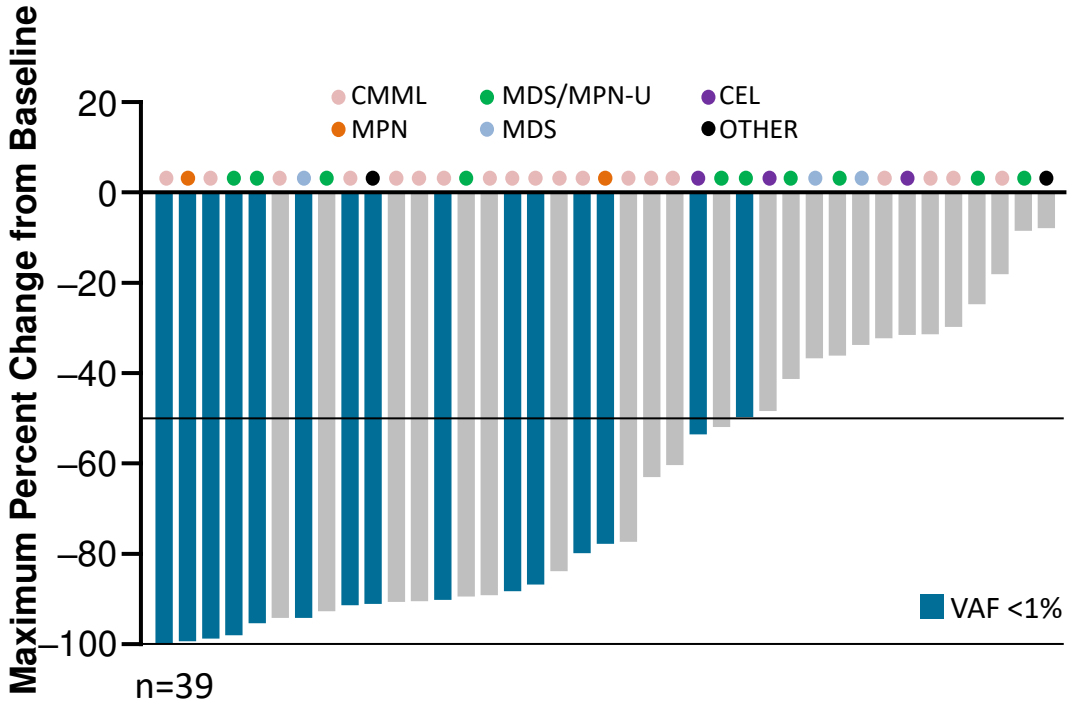


- 88% of patients achieved ≥50% reduction in marrow mast cells
- 60% of patients achieved elimination of marrow mast cell aggregates

- 93% of patients achieved ≥50% reduction in serum tryptase
- 43% of patients achieved reduction to <20 ng/mL

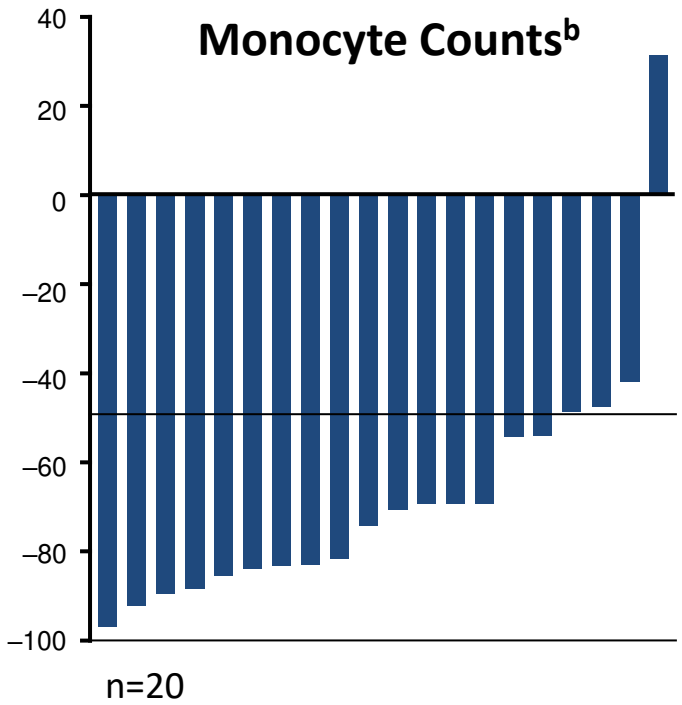
AVAPRITINIB LED TO PROFOUND REDUCTIONS IN MARKERS OF DISEASE BURDEN IN PATIENTS WITH SM-AHN

Reduction in Blood *KIT* D816V VAF[a]



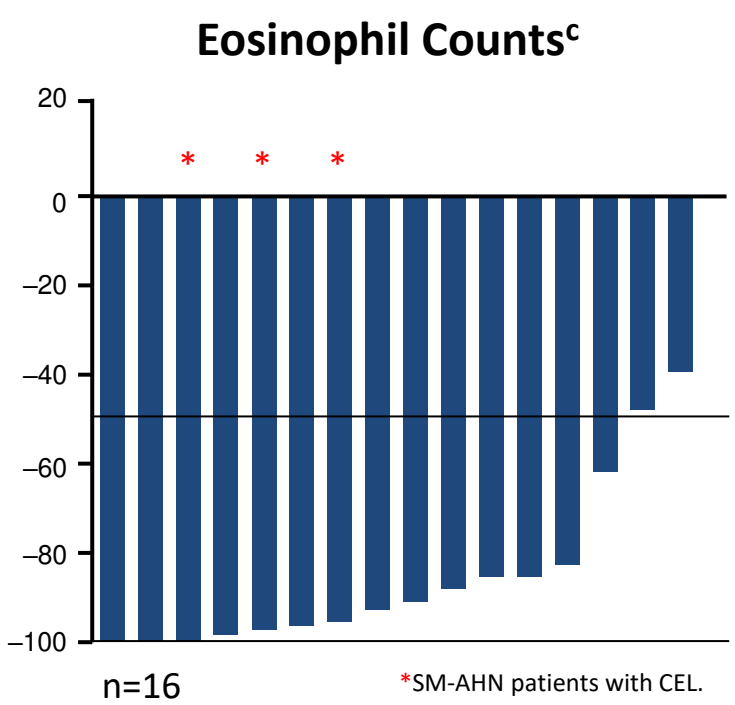
Significant blood *KIT* D816V allele burden is indicative of clonal *KIT* D816V involvement outside of mast cells, such as in the AHN component, as mast cells rarely circulate in blood

Reduction in Blood Absolute Monocyte Counts[b]



80% achieved ≥50% reduction in absolute monocyte count

Reductions in Blood Absolute Eosinophil Counts[c]



*SM-AHN patients with CEL.

88% achieved ≥50% reduction in absolute eosinophil count

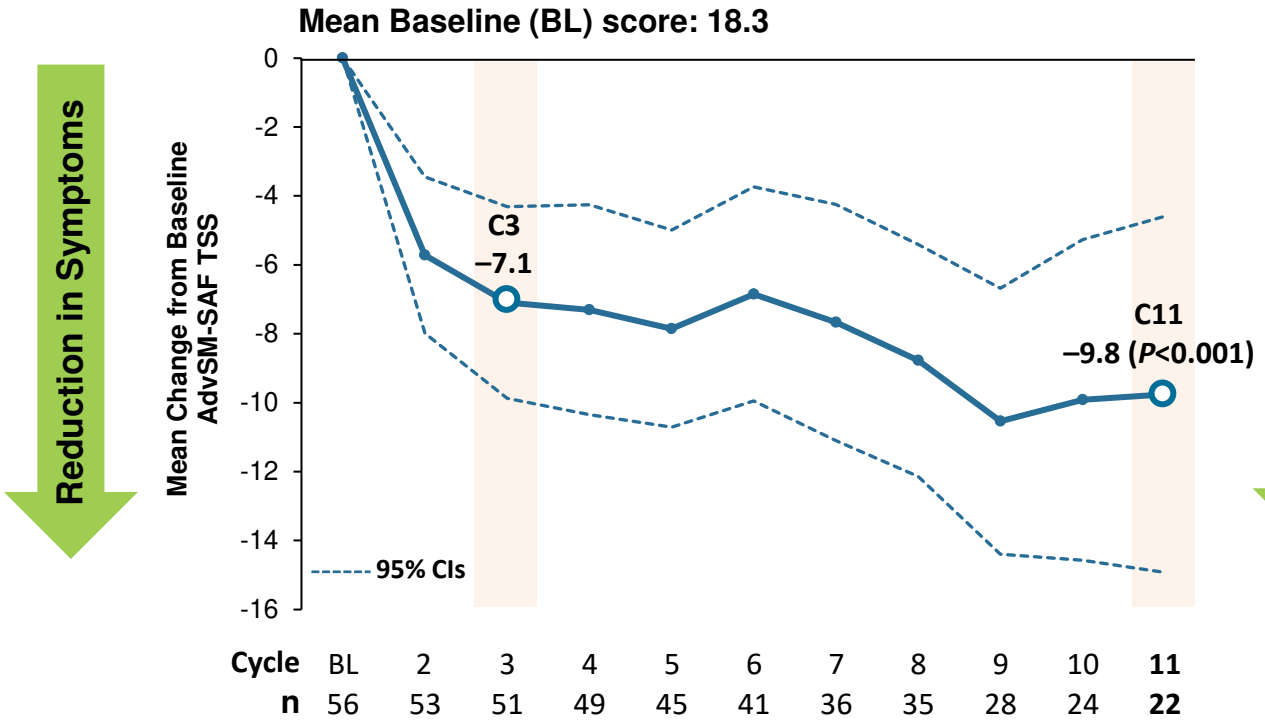
[a]Patients with SM-AHN. [b]Patients with SM-CMML. [c]Patients with eosinophilia and SM-CEL.

MPN, myeloproliferative neoplasms; SM-CEL, systemic mastocytosis with chronic eosinophilic leukemia; SM-CMML, systemic mastocytosis with chronic myelomonocytic leukemia; VAF, variant allele fraction.

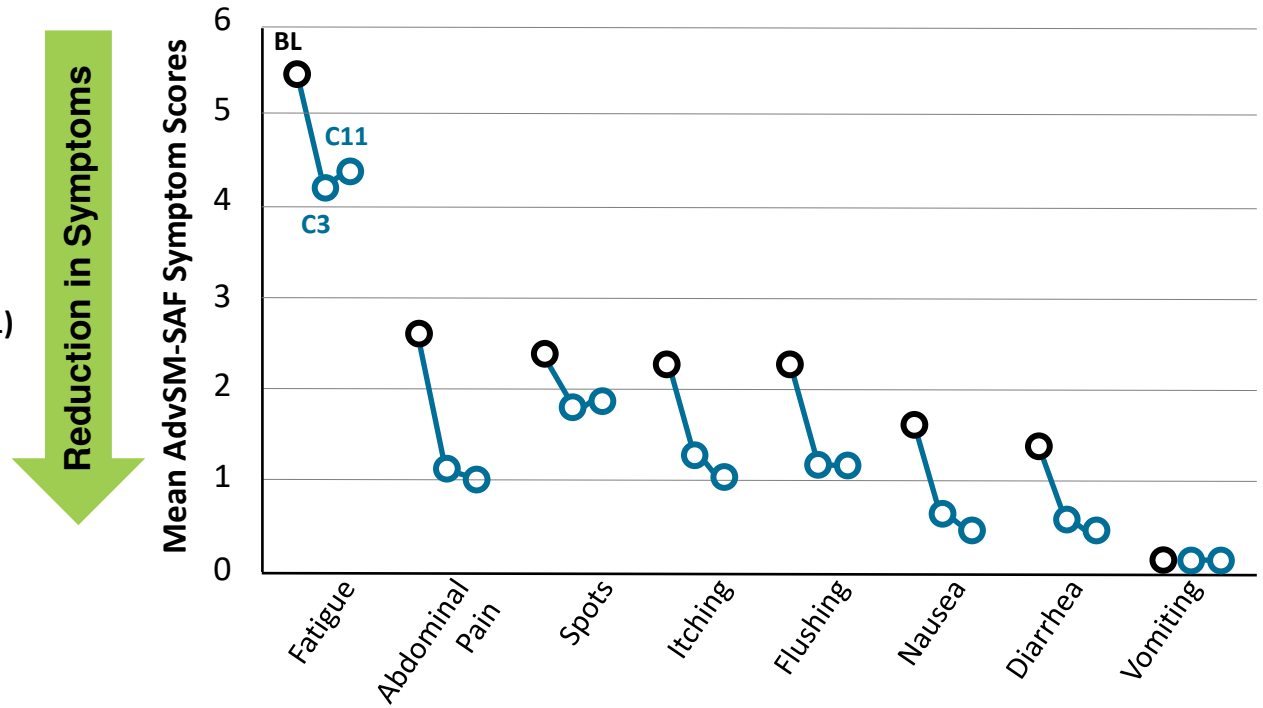
AVAPRITINIB LED TO RAPID AND DURABLE REDUCTION IN SM SYMPTOMS

Advanced Systemic Mastocytosis-Symptom Assessment Form (AdvSM-SAF): Validated patient-reported outcome tool in AdvSM[a]

Significant Reduction in Total Symptom Score



Reduction in Individual Symptom Scores



[a]Taylor F et al. 2019 ISPOR EU [Poster PRO143].
BL, baseline; C3, Cycle 3; C11, Cycle 11; TSS, total symptom score.

ADVERSE EVENTS (SAFETY POPULATION, N=62)

Adverse Events (AEs) in ≥15%	Any-cause AEs	
Non-hematologic, n (%)	Any Grade	Grade 3/4
Peripheral edema	31 (50)	2 (3)
Periorbital edema	30 (48)	2 (3)
Diarrhea	14 (23)	1 (2)
Nausea	11 (18)	1 (2)
Vomiting	11 (18)	1 (2)
Fatigue	9 (15)	2 (3)
Hematologic, n (%)		
Thrombocytopenia	28 (45)	10 (16)
Anemia	20 (32)	10 (16)
Neutropenia	15 (24)	15 (24)[a]

AE table includes pooled similar AE terms for periorbital edema, thrombocytopenia, anemia, and neutropenia.

- 52 (84%) remain on treatment
- 3 (5%) discontinued due to treatment-related AE
- 42 (68%) had a dose reduction due to an AE, most commonly due to neutropenia (19%) and thrombocytopenia (18%)
- No treatment-related deaths occurred
- Six patients had Gr 1 and one had Gr 2 cognitive AEs[b]
- One (1.6%) patient had a subdural hematoma (Gr 4), associated with pre-existing severe thrombocytopenia (<50×10^9/L), prior to exclusion of such patients
  - Protocol subsequently amended to exclude patients with baseline platelets <50,000/µL, increase CBC monitoring, and modify dose guidance[c]

[a]Five (8%) patients had Grade 4 neutropenia. [b]Confusional state (n=3), memory impairment (n=3), and cognitive disorder (n=1). [c]CBC monitored every 2 weeks for the first 4 weeks, then at least every 4 weeks, or every 2 weeks if platelets <75×10^9/L. If platelets <50×10^9/L, interrupt avapritinib and resume at lower dose when ≥50×10^9/L. Avapritinib treatment with platelet growth factor support or recurrent platelet transfusions was allowed with Sponsor approval.

CBC, complete blood count; Gr, Grade.

AVAPRITINIB REDUCED DISEASE BURDEN AND PATIENT SYMPTOMS

- Avapritinib with a starting dose of 200 mg QD induced rapid, durable, and improving responses, consistent with the phase 1 EXPLORER study
- ORR (CR + CRh + PR + CI) by mIWG-MRT-ECNM criteria was 75%, with all responses ongoing
- Profound reductions in mast cell burden (marrow mast cells and serum tryptase)
- Profound reductions in markers of disease burden (monocytosis, eosinophilia and blood *KIT* D816V VAF) in patients with SM-AHN
- Avapritinib was generally well tolerated with few discontinuations due to related AEs, and low incidence of intracranial bleeding

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