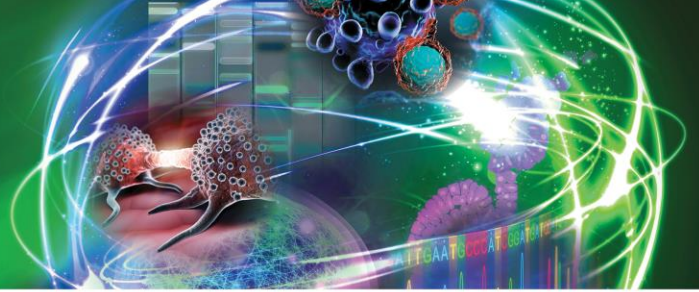
AACR American Association for Cancer Research
ANNUAL MEETING 2021
VIRTUAL #AACR21
APRIL 10-15, 2021 AND MAY 17-21, 2021 ★ AACR.ORG ★ AACR.ORG/AACR2021



PATHFINDER: Interim Analysis of Avapritinib in Patients with Advanced Systemic Mastocytosis (AdvSM)

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Disclosure Information

Daniel J. DeAngelo, MD, PhD

I have the following financial relationships to disclose:

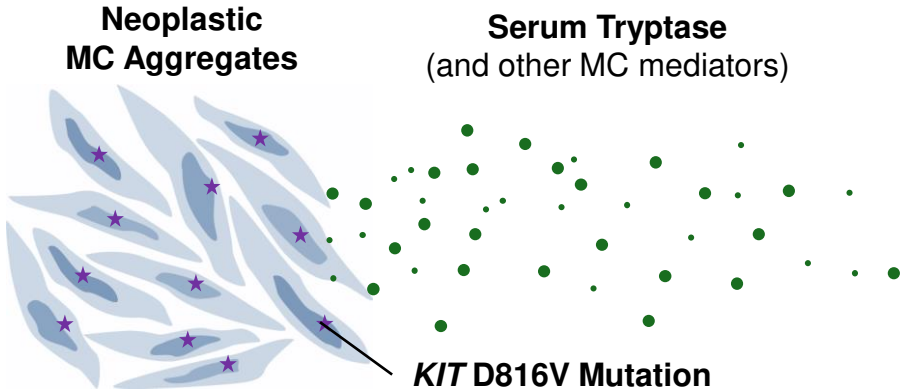
Consultant for:
Agios, Amgen, Autolus, Blueprint Medicines Corporation, Forty-Seven, Incyte Corporation, Jazz Pharmaceuticals, Novartis, Pfizer, Shire, and Takeda

Grant/Research support from:
AbbVie, Blueprint Medicines Corporation, GlycoMimetics, and 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% per IWG-MRT-ECNM criteria requiring resolution of organ damage[2,c]
  - Median overall survival was 2.5 years[3]



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]ORR is defined as CR + PR + CI. [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.

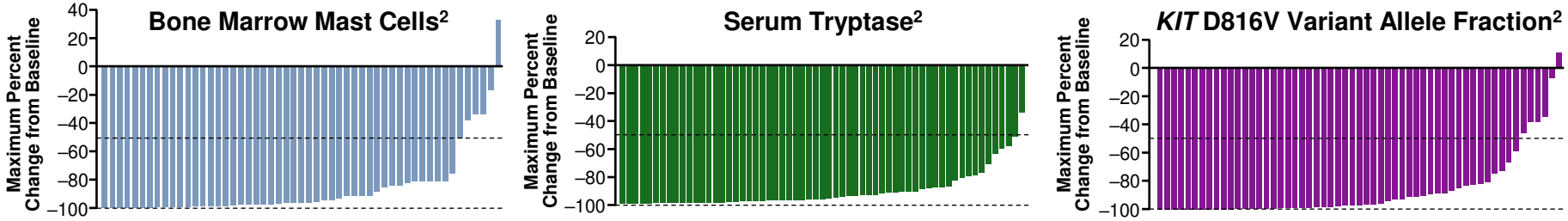
ASM, aggressive systemic mastocytosis; CI, clinical improvement; CR, complete remission; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; ORR, overall response rate; PR, partial remission; SmPC, Summary of Product 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)

Phase 1 Dose Escalation/Expansion EXPLORER Study[1]

- 75% ORR[a] per modified IWG-MRT-ECNM criteria
- 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**

Once 32 patients have sufficient follow-up[c]

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)

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). [c]Patients with sufficient follow-up for response assessment are on study ≥6 months (with ≥2 bone marrow assessments to allow for a confirmed response) or are off the study at any timepoint. 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)
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; SM-AHM, systemic mastocytosis with associated hematologic neoplasm; BM, bone marrow.

Efficacy of Avapritinib 200 mg QD in Interim Analysis

Best Confirmed Response, n (%)	All AdvSM (n=32)[a]
Overall Response Rate (CR + CRh + PR + CI)	**24 (75)**
CR or CRh	6 (19)
Complete Remission (CR)	0
CR with partial hematologic recovery	6 (19)
Partial Remission (PR)	10 (31)
Clinical Improvement (CI)	8 (25)
Stable Disease (SD)	4 (13)
Progressive Disease (PD)	1 (3)
Not Evaluable (NE)	3 (9)[b]

Interim analysis: passed (P=1.60×10^{-9})

CRh (mIWG-MRT-ECNM) requires

- **Full resolution of <u>all</u> evaluable C-findings**
- BM MC aggregates eliminated
- Serum tryptase <20 ng/mL
- Resolution of palpable hepatosplenomegaly

- **Partial hematologic recovery**
  - ANC >0.5×10^{9}/L with normal differential
  - Platelet count >50×10^{9}/L
  - Hgb level >8.0 g/dL

PR requires

- Full resolution of ≥1 evaluable C-findings
- ≥50% reduction in BM MCs, serum tryptase

[a]One patient in the evaluable population started at 100 mg QD. [b]Three (9%) of 32 patients in the interim analysis were assessed as not evaluable for response due to coming off study for AE before 13 weeks.
ANC, absolute neutrophil count; Hgb, hemoglobin.

Responses in All Subtypes of AdvSM, Regardless of Prior Therapy

Best Confirmed Response, n (%)	All AdvSM (n=32)[a]	AdvSM Subtype		
		ASM (n=2)	SM-AHN (n=26)	MCL (n=4)
Overall Response Rate (CR + CRh + PR + CI)	**24 (75)**	2 (100)	21 (81)	1 (25)
CR or CRh	6 (19)	1 (50)	5 (19)	0
Complete Remission (CR)	0	0	0	0
CR with partial hematologic recovery	6 (19)	1 (50)	5 (19)	0
Partial Remission (PR)	10 (31)	1 (50)	8 (31)	1 (25)
Clinical Improvement (CI)	8 (25)	0	8 (31)	0
Stable Disease (SD)	4 (13)	0	2 (8)	2 (50)
Progressive Disease (PD)	1 (3)	0	0	1 (25)
Not Evaluable (NE)	3 (9)[b]	0	3 (12)	0

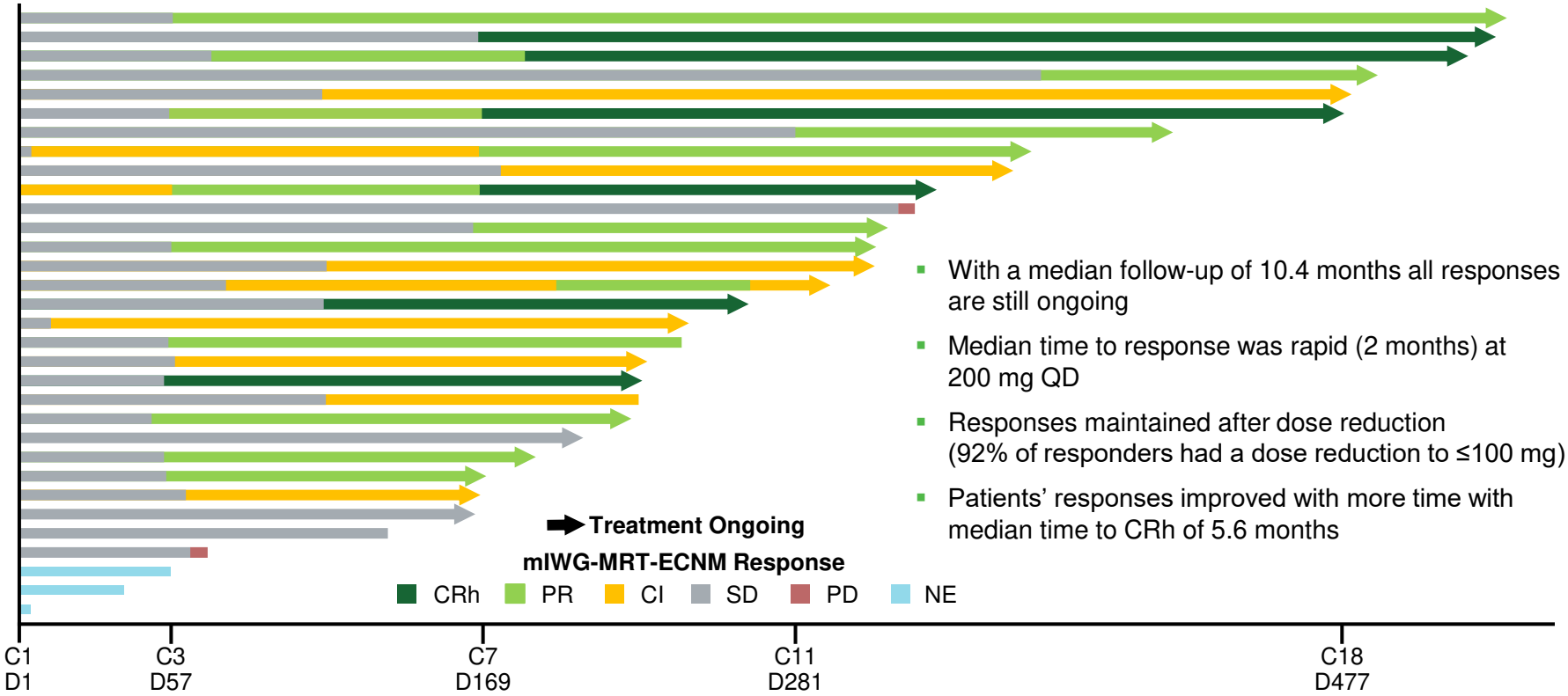
[a]One patient in the evaluable population started at 100 mg QD. [b]Three (9%) of 32 patients in the interim analysis were assessed as not evaluable for response due to coming off study for AE before 13 weeks.

Responses in All Subtypes of AdvSM, Regardless of Prior Therapy

Best Confirmed Response, n (%)	All AdvSM (n=32)[a]	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 or CRh	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	6 (19)	1 (50)	5 (19)	0	3 (13)	3 (33)
Partial Remission (PR)	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)[b]	0	3 (12)	0	3 (13)	0

[a]One patient in the evaluable population started at 100 mg QD. [b]Three (9%) of 32 patients in the interim analysis were assessed as not evaluable for response due to coming off study for AE before 13 weeks.

Responses on Avapritinib Improved with Time

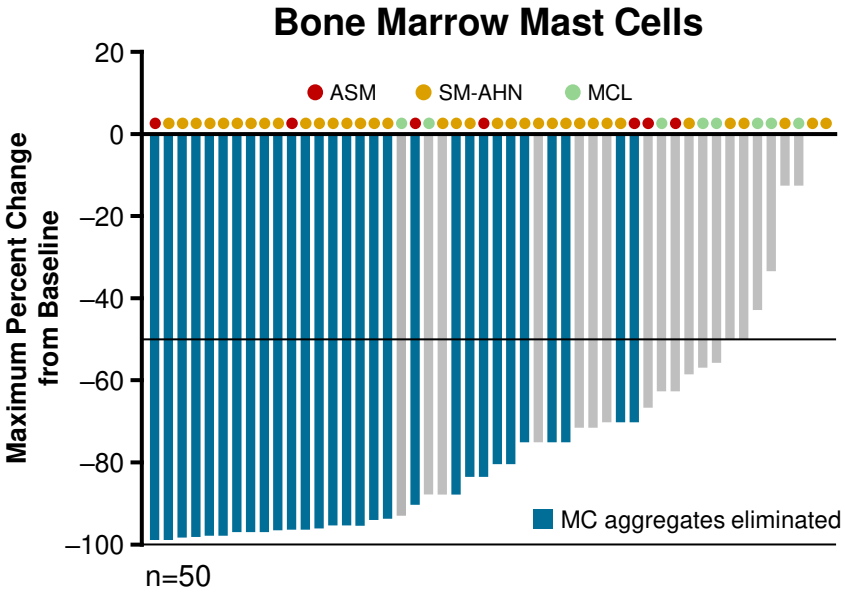


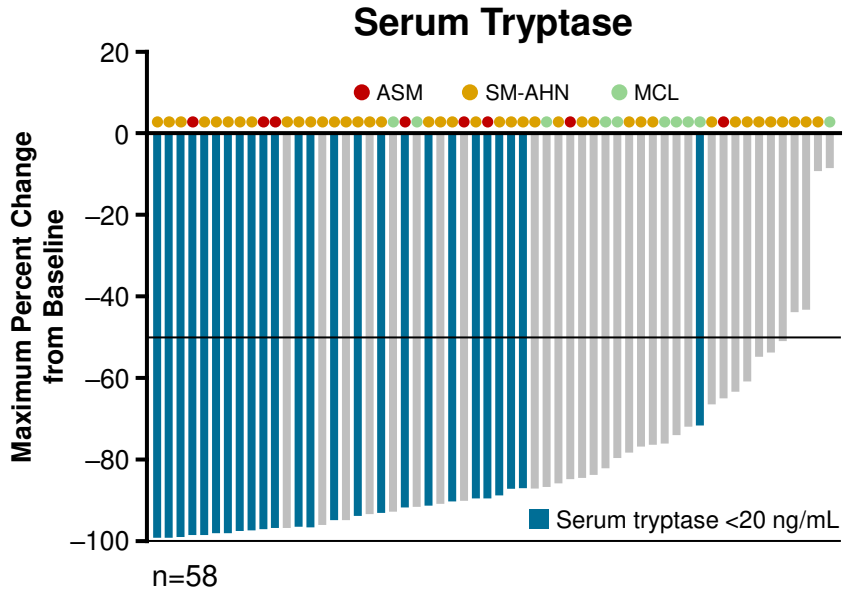
- With a median follow-up of 10.4 months all responses are still ongoing
- Median time to response was rapid (2 months) at 200 mg QD
- Responses maintained after dose reduction (92% of responders had a dose reduction to ≤100 mg)
- Patients' responses improved with more time with median time to CRh of 5.6 months

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

All data in presentation is as of June 23, 2020 data cut-off

Avapritinib Led to Profound Reductions in Bone Marrow Mast Cells and Serum Tryptase

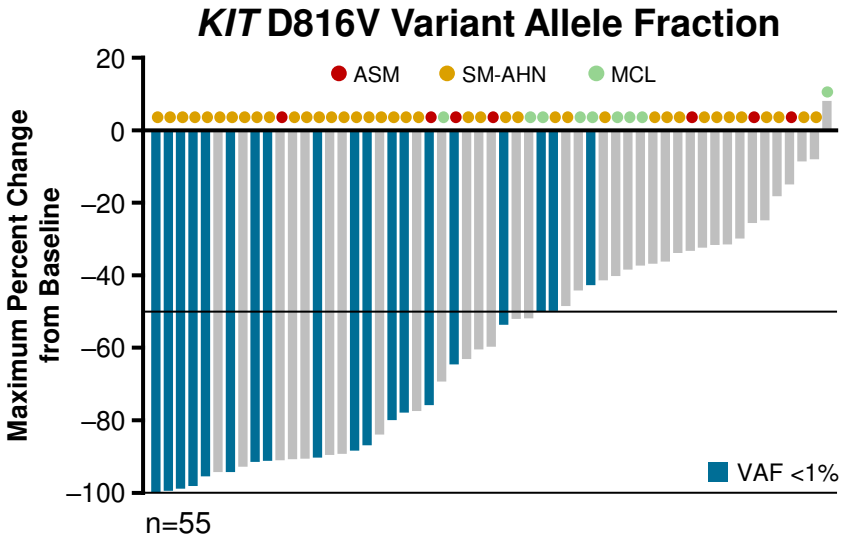




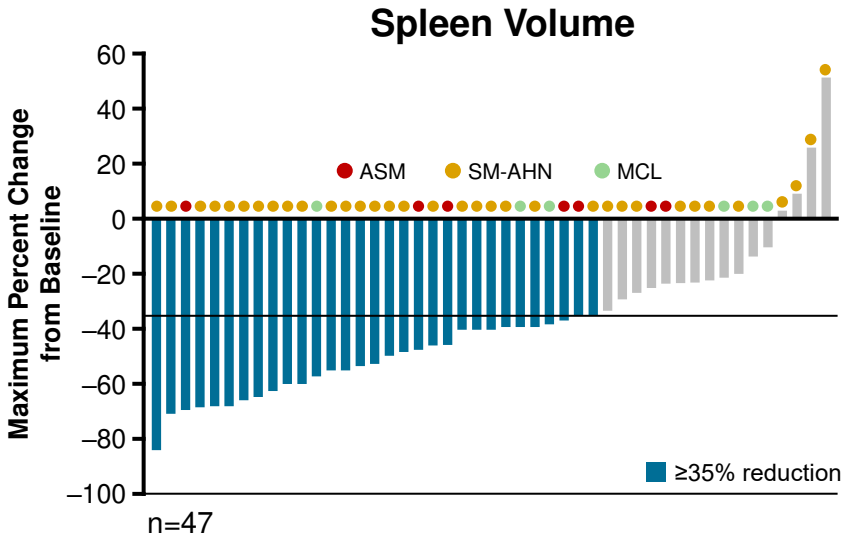
- 88% of patients achieved ≥50% reduction in marrow mast cells
- 60% of patients achieved elimination of marrow mast cell aggregates

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

Avapritinib Led to Profound Reductions in *KIT* D816V Allele Fraction and Spleen Volume



- 60% of patients achieved ≥50% reduction in VAF
- 35% of patients achieved VAF of <1%



- 66% of patients achieved a ≥35% reduction in spleen volume

VAF, variant allele fraction.

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.

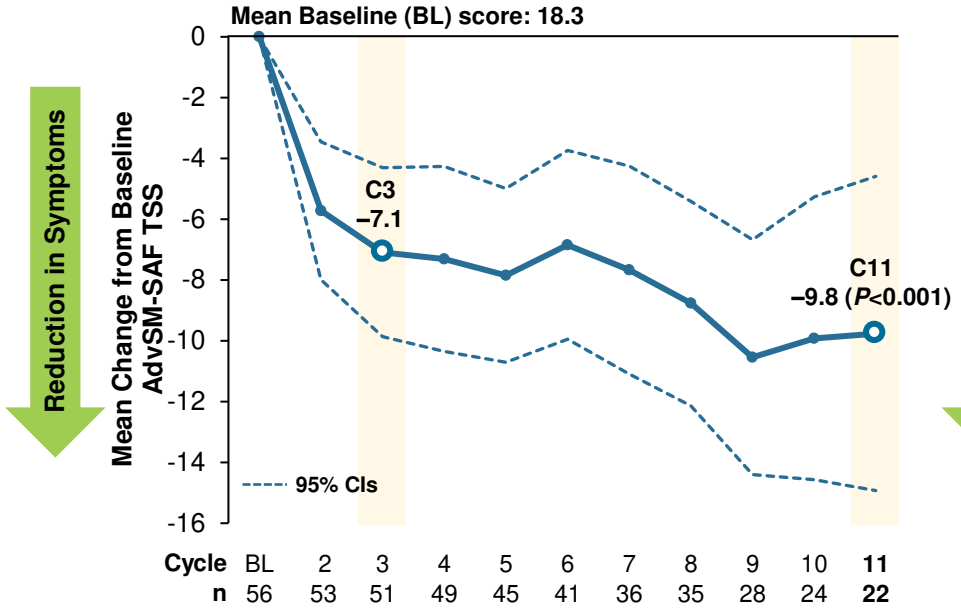
- 52 (84%) remain on treatment
- 3 (5%) discontinued due to treatment-related AE
- 42 (68%) had a dose reduction due to an AE, most commonly cytopenias
- No treatment-related deaths occurred
- Six patients had Gr 1 and one had Gr 2 cognitive AEs[b]
- One (1.6%) patient had a subdural hematoma (Gr 4), associated with pre-existing severe thrombocytopenia (<50×10^9/L), prior to exclusion of such patients
  - Subsequently excluded baseline severe thrombocytopenia, increased CBC monitoring, and modified 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.

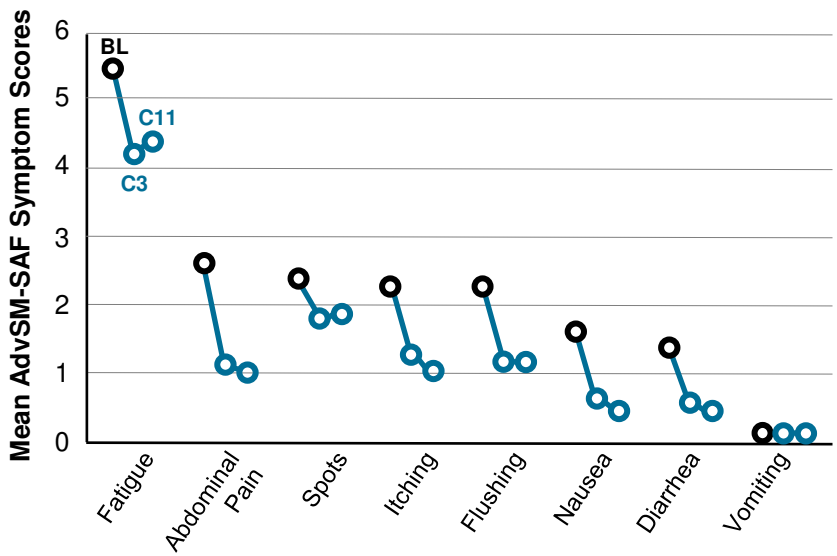
Avapritinib Led to Rapid and Durable Reduction in SM Symptoms

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

Significant Reduction in Total Symptom Score



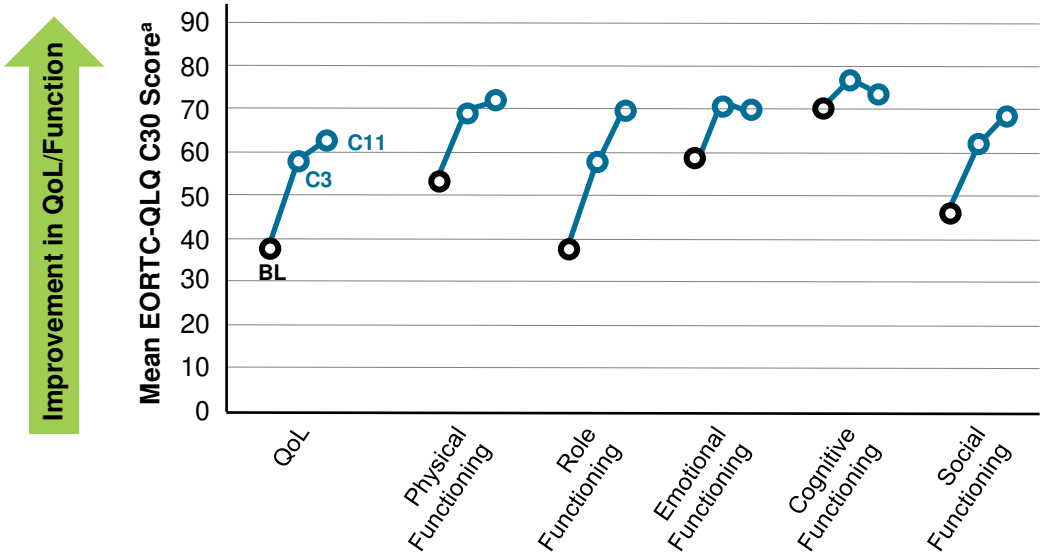
Reduction in Individual Symptom Scores



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

Avapritinib Led to Rapid and Durable Improvement in Quality of Life (QoL) and Functional Impairment

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C30)



- AdvSM patients have poor QoL and functional impairment at Baseline
- Improvements in QoL and Physical, Role, Emotional, Cognitive and Social Functioning

[a]BL (n=54); C3 (n=45); C11 (n=9).

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
- Reductions in disease burden (BM MCs, serum tryptase, *KIT* D816V VAF, and spleen volume)
- Significant reductions in symptom burden and improvements in quality of life
- Avapritinib was well tolerated with few patients discontinuing treatment due to related AEs

Acknowledgements

- Participating patients and families
- Avapritinib investigators and research coordinators
- Colleagues at Blueprint Medicines Corporation

- Medical writing and editorial support were provided by Kenny Tran, MSc and Michelle Seddon of Paragon, UK, supported by Blueprint Medicines Corporation, Cambridge, Massachusetts, USA