Avapritinib, a Potent and Selective Inhibitor of KIT D816V, Improves Symptoms of Advanced Systemic Mastocytosis (AdvSM)

Analyses of Patient Reported Outcomes (PROs) from the Phase 1 (EXPLORER) Study Using the AdvSM Symptom Assessment Form (AdvSM-SAF), a New PRO Questionnaire for AdvSM

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EXPLORER Advanced SM

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Systemic mastocytosis (SM) is a rare heterogenous clonal mast cell disorder driven by *KIT* D816V mutation

ADVANCED SM (AdvSM)

Mast cell leukemia (MCL)	SM with an associated hematological neoplasm (SM-AHN)	Aggressive SM (ASM)	Smoldering SM (SSM)	Indolent SM (ISM)

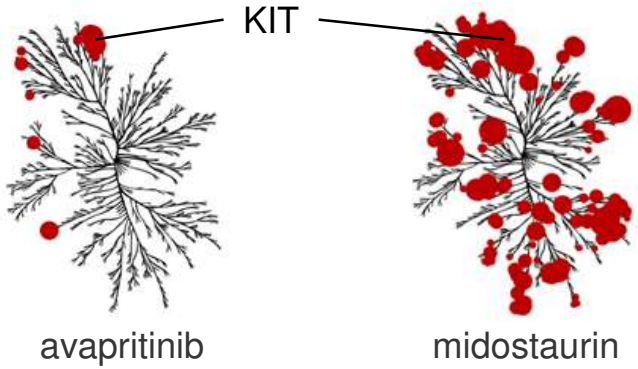
LIMITED TREATMENT OPTIONS

Multi-kinase inhibitor midostaurin	No approved therapies for ISM/SSM

Supportive care: anti-histamines, corticosteroids, cromolyn, leukotriene receptor antagonists

Avapritinib was designed to target KIT D816V

Potent and highly selective inhibitor of D816V mutant *KIT*



KIT D816V biochemical IC_{50}	
0.27 nM	2.9 nM

Evans EK et al. Sci Transl Med. 2017;9(414)

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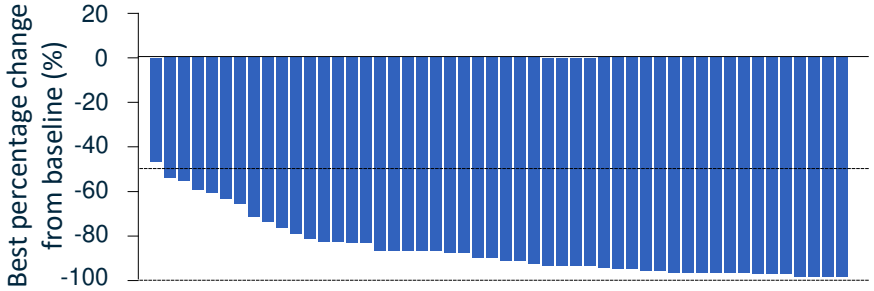
Clinical proof-of-concept in Phase 1 EXPLORER clinical trial[1-3]

m-IWG-MRT-ECNM ORR: 83%[2*]

Serum tryptase reduction in all patients[2]



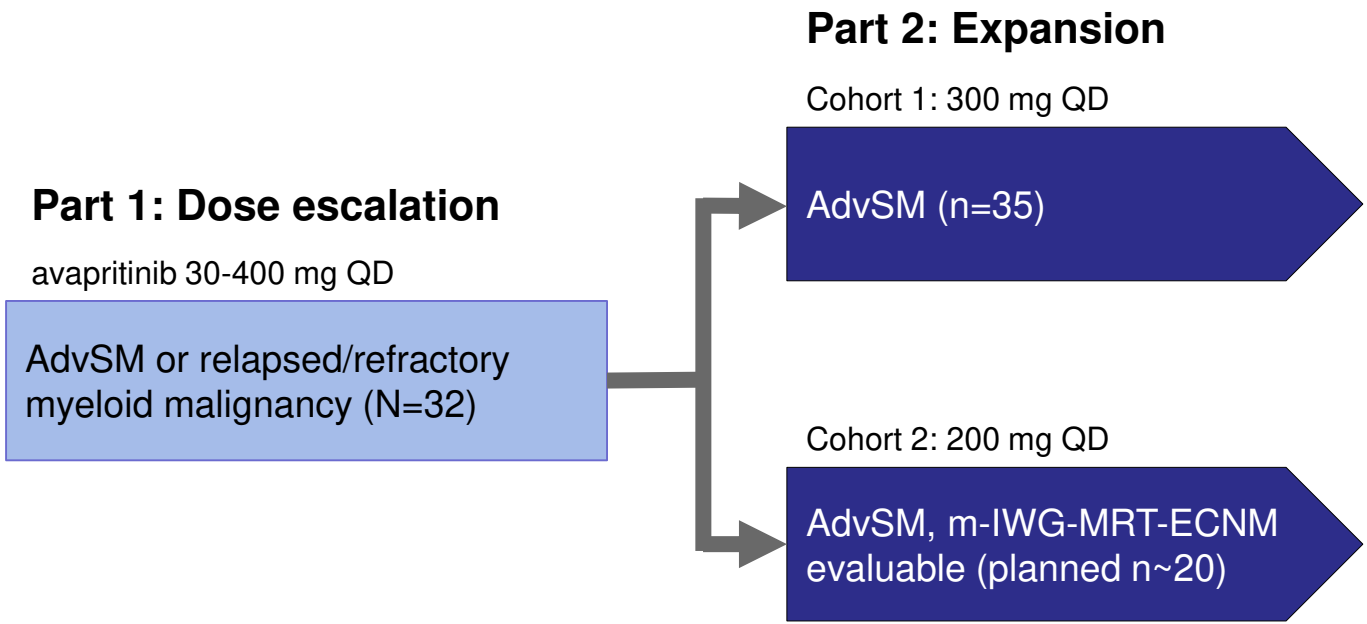
1. DeAngelo et al. ASH 2017 (Plenary Session)
2. Deininger et al. EHA 2018
3. Gotlib et al. ECNM 2018

Granted FDA Breakthrough Therapy Designation for AdvSM

m-IWG-MRT-ECNM, modified International Working Group Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis criteria; ORR, overall response rate

*Data previously reported at EHA 2018. Data cutoff date: April 30, 2018,

Phase 1 EXPLORER clinical trial design



Study objectives:
RP2D, safety, ORR per m-IWG-MRT-ECNM, patient-reported outcomes

All data in this presentation are based on a cut-off of September 30, 2018, unless otherwise noted; QD, once daily
RP2D, recommended Phase 2 dose

EXPLORER Advanced SM

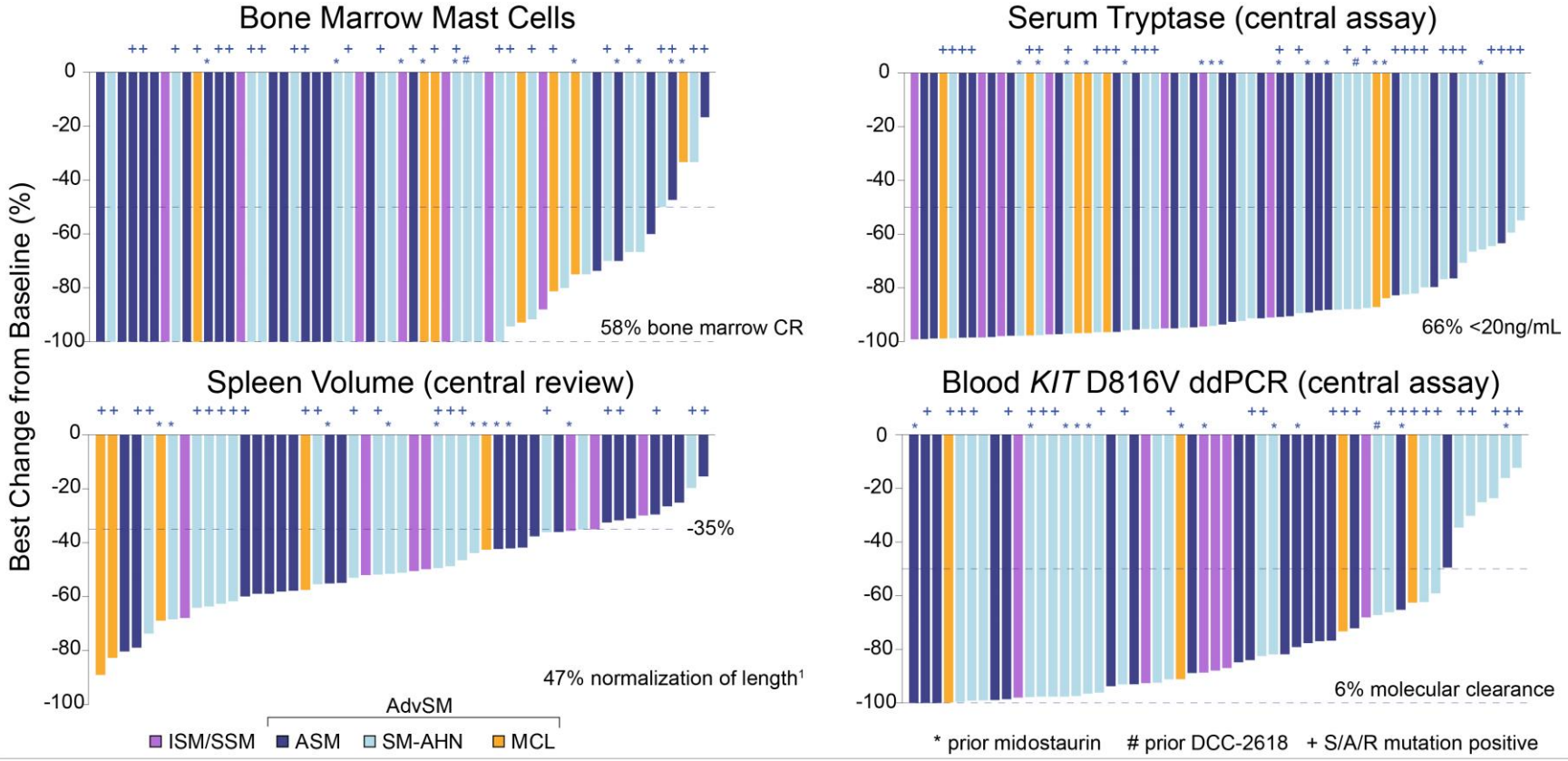
Baseline characteristics

Parameter		All patients (N=67)
Median age, years (range) / Female, n (%)		62 (34 – 83) / 33 (49)
SM subtype per central assessment, n (%)*	AdvSM ASM SM-AHN MCL ISM/SSM	60 (90) 23 (34) 30 (45) 7 (10) 7 (10)
ECOG performance status, n (%)	0-1 2-3	50 (75) 17 (25)
KIT mutation, n (%)	D816V D816Y Wild-type	56 (84) 1 (1) 10 (15)
SRSF2, *ASXL1* and/or *RUNX1* mutation positive, n (%), n=64		29 (45)
Prior anti-neoplastic therapy	Median # of therapies (range) Any, n (%) Midostaurin	1 (0 – 3) 40 (60) 14 (23)
Baseline steroid therapy for SM		22 (33)
Bone marrow mast cell (MC) burden (%), median (range), n=65		30 (2 – 95)
Serum tryptase (µg/L), median (range), n=64		161 (13 – 1414)
Evaluable* by mIWG-MRT-ECNM criteria, n (% of AdvSM)		29 (48)

*Central adjudication of AdvSM with mIWG-MRT-ECNM C-finding(s) and at least 25 weeks follow up

ECOG: Eastern Cooperative Oncology Group

Decline in mast cell burden across subtypes, regardless of prior therapy or co-mutation status



[1]by imaging or non-palpable

mIWG-MRT-ECNM responses are durable and deepen over time

Best response* n (%)	All doses (n=29)	≤200mg[1] QD (n=10)
ORR (CR + CRh + PR + CI)	**24 (83%)**	**9 (90%)**
Complete response (CR)	3 (10%)	3 (30%)
CR, partial hematologic recovery[2] (CRh)	4 (14%)	2 (20%)
Partial response (PR)	14 (48%)	3 (30%)
Clinical improvement (CI)	3 (10%)	1 (10%)
Stable disease (SD)	5 (17%)	1 (10%)
Progressive disease (PD)	0	0

- Ongoing treatment durations of up to 31 months (range 1+ to 31+)
- Median duration of response (DOR) not reached (median follow up 14 months)
- 12 month duration of response rate is 76%
- Median time to initial response is 2 months
- Median time to CR/CRh is 9 months

[1] started at ≤200mg QD. 90% have not dose escalated above 200mg as of the data cutoff date
[2] CRh: Requires all criteria for CR be met and response duration must be ≥12 weeks (to be confirmed); however, patient may have residual cytopenias. The following are required for CRh: ANC > 0.5 × 10^9/L with normal differential (absence of neoplastic MCs and blasts < 1%) *and* Platelet count > 50 × 10^9/L *and* Hgb level > 8.0 g/dL
*Pending confirmation: 3 transitioning from confirmed response to a deeper response, 3 transitioning from SD to first response

Treatment-emergent adverse events (AEs)

Adverse event, n (%)	Any Grade	Grade 3/4
NON-HEMATOLOGICAL AEs >15% (N=67)		
Periorbital edema	45 (67)	3 (4)
Fatigue	25 (37)	5 (7)
Nausea	24 (36)	3 (4)
Diarrhea	23 (34)	1 (1)
Peripheral Edema	23 (34)	0
Vomiting	19 (28)	2 (2)
Cognitive effects*	19 (28)	1 (1)
Hair color changes	17 (25)	1 (1)
Arthralgia	13 (19)	1 (1)
Dizziness	13 (19)	1 (1)
Abdominal pain	12 (18)	1 (1)
HEMATOLOGICAL AEs >10% (N=67)		
Anemia	35 (52)	18 (26)
Thrombocytopenia	21 (31)	12 (17)
Neutropenia	8 (12)	7 (10)

AEs of note: ascites (n=4 [6%]; n=1 [1%] at ≥ grade 3), pleural effusion (n=5 [7%], n=0 at ≥ grade 3),
*Cognitive effects include: cognitive disorder, confusional state, and memory impairment

- Most AEs were grade 1 or 2
- No treatment-related grade 5 AEs
- 4% (3/67) of patients discontinued due to treatment-related AEs
  - Refractory ascites, encephalopathy and intracranial bleed
- 66% (44/67) of patients had ≥ grade 3 treatment-related AEs and dose reduced
  - Most commonly hematologic AEs, typically in patients with prior cytopenias
  - Most dose reductions occurred at ≥300mg QD
- 78% (52/67) remain on treatment

AdvSM-SAF, first PRO tool designed specifically to assess AdvSM symptoms

Design and Validation

AdvSM-SAF was designed with input from disease experts, patients and regulatory authorities[1]

- Concept elicitation and questionnaire construction
- Questionnaire evaluation
- Validation and score interpretation (ongoing)

Symptom Assessment Form (SAF)

(all scores analyzed as last 7 days moving average)

Symptom	Domains	Score
Abdominal pain	GI domain	0-10 scored daily
Diarrhea		
Nausea		
Vomiting		
Spots	Skin domain	
Itching		
Flushing		
Fatigue		

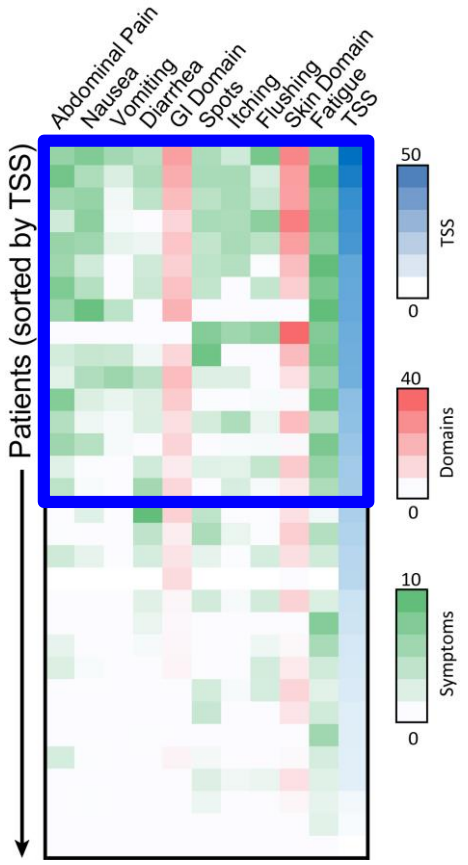
Total Symptom Score (TSS)

PRO: patient reported outcome

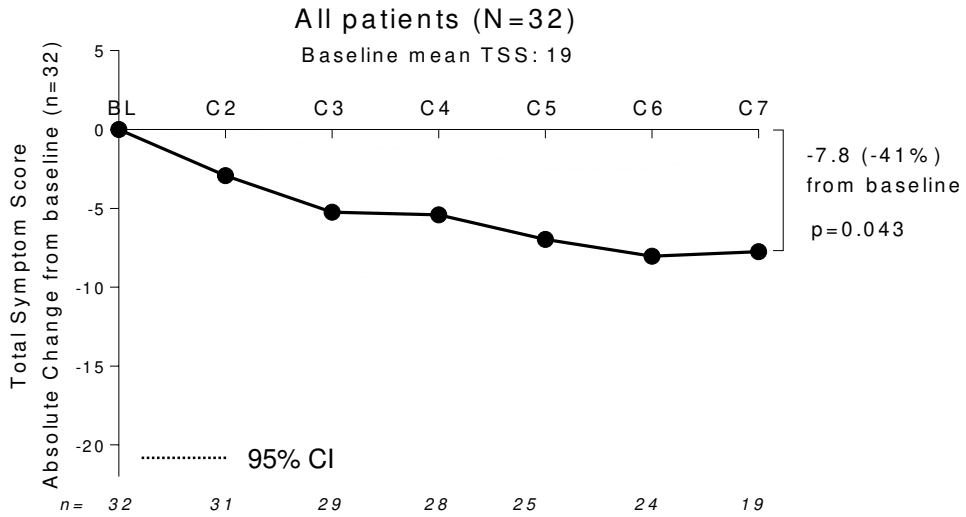
[1]Taylor et al. ISPOR 2017

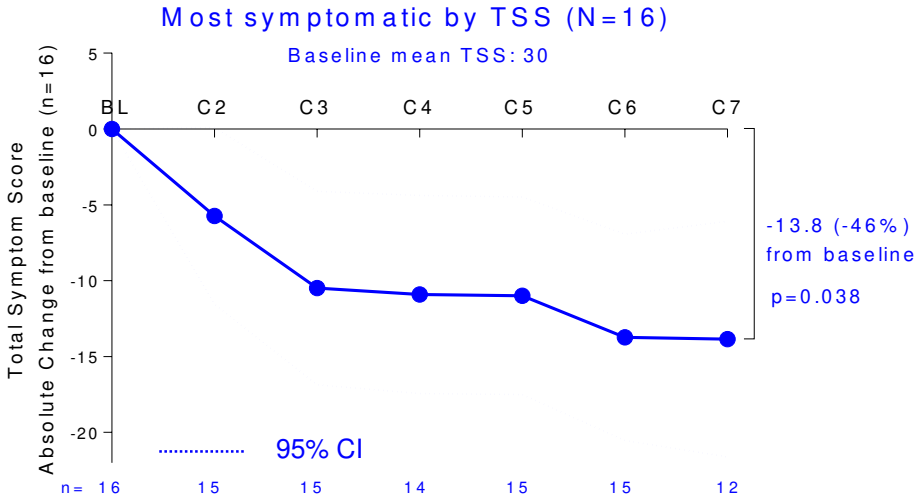
Baseline AdvSM-SAF scores are heterogeneous

Symptom	Domains	All patients (n=32) Mean (range)	Most symptomatic Top 50th percentile TSS (n=16) Mean (range)
Abdominal pain	GI domain	3 (0-9)	5 (0-9)
Diarrhea		2 (0-10)	3 (0-6)
Nausea		2 (0-10)	4 (0-10)
Vomiting		1 (0-6)	2 (0-6)
Spots	Skin domain	3 (0-9)	4 (0-9)
Itching		2 (0-6)	3 (0-6)
Flushing		2 (0-9)	3 (0-9)
Fatigue		6 (0-10)	8 (5-10)
Total symptom score (TSS)		19 (0-50)	30 (18-50)



Avapritinib improves overall mastocytosis symptoms





~40% mean reduction of symptoms from baseline TSS

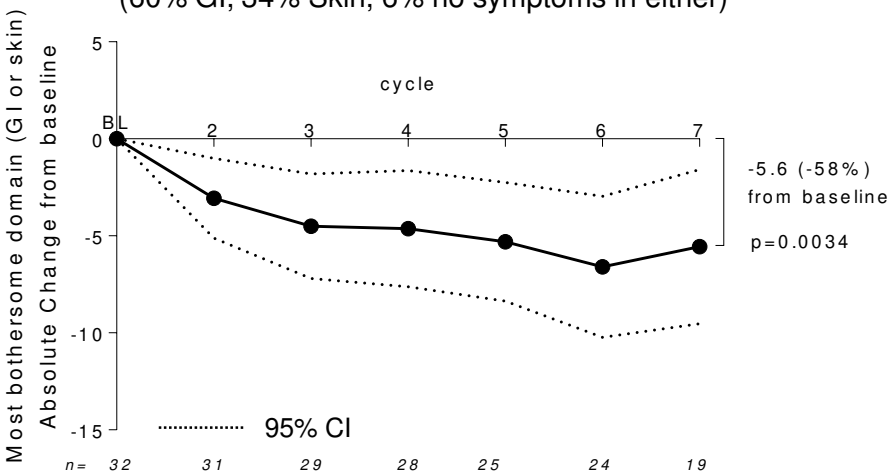
Of 22 patients with baseline steroids for mastocytosis (parts 1 and 2):

- *18/22 (80%) decreased their steroid dose on study*
- *9/22 (41%) discontinued their steroids entirely on study*

Avapritinib improves most bothersome symptom domain

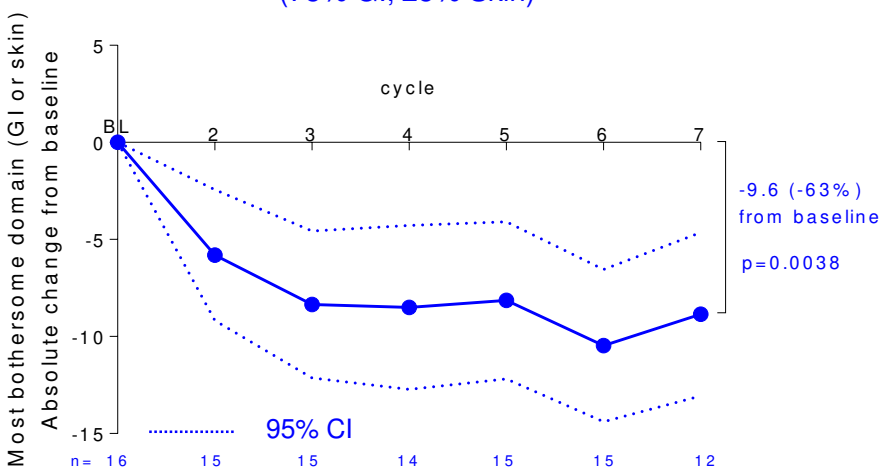
All patients (n=32)

Baseline mean most bothersome domain score: 9.7
(60% GI, 34% Skin, 6% no symptoms in either)



Most symptomatic by TSS (n=16)

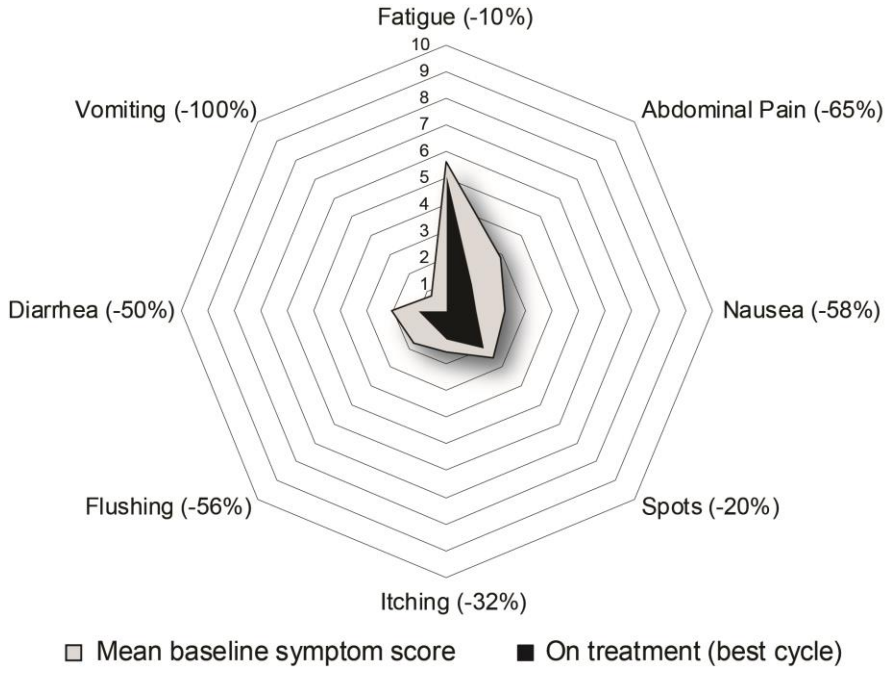
Baseline mean most bothersome domain score: 15.3
(75% GI, 25% Skin)



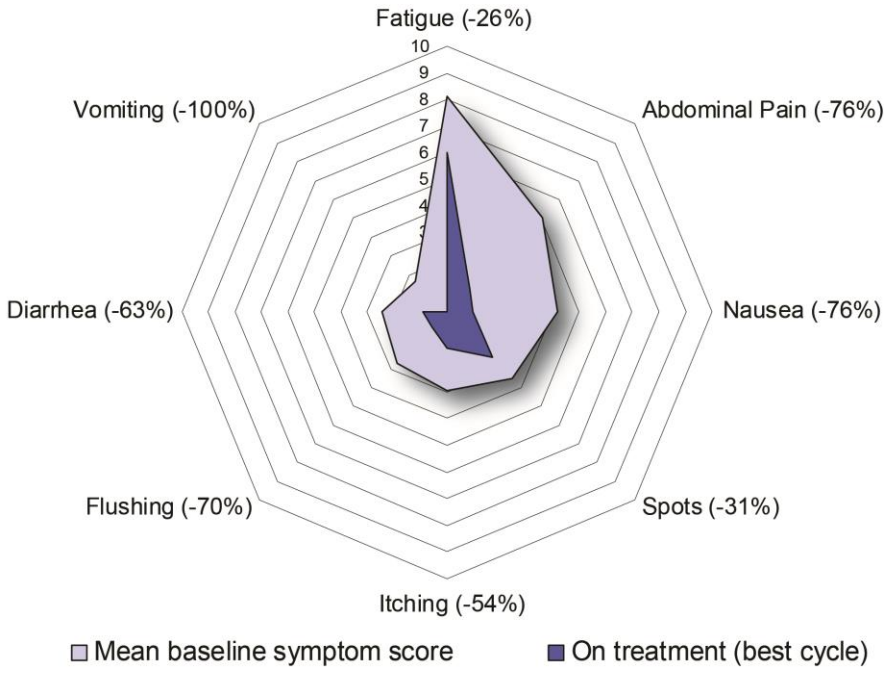
~60% mean reduction from baseline in most bothersome domain (GI or skin)

Avapritinib reduces individual mastocytosis symptoms

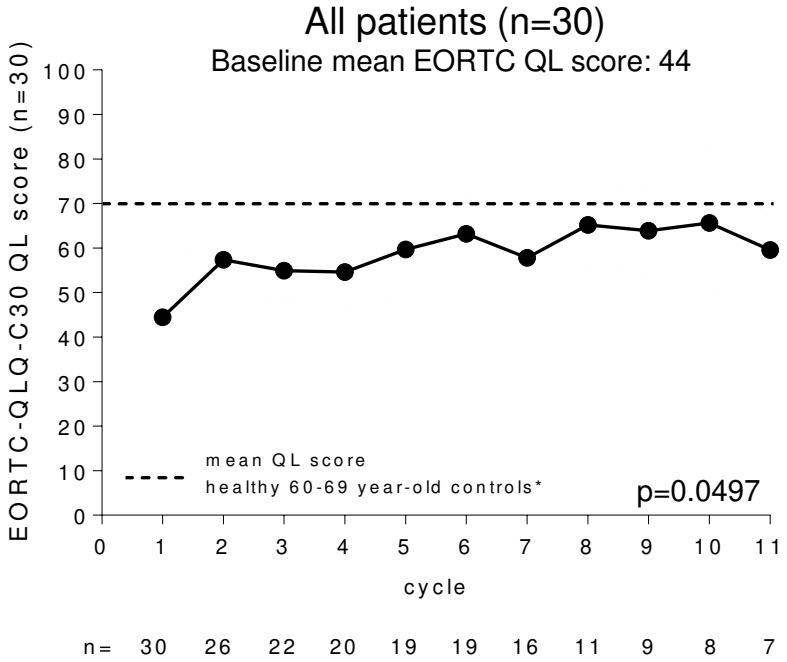
All patients (n=32)

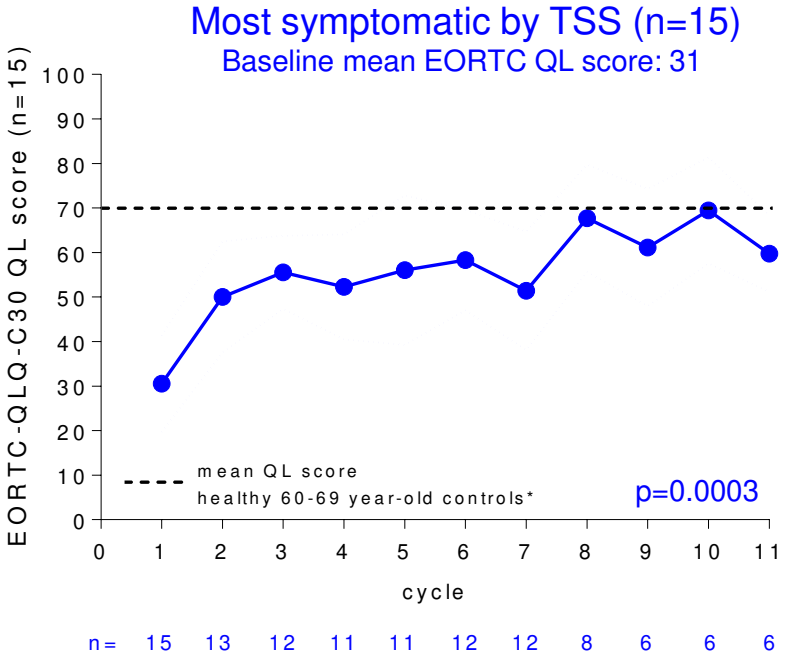


Most symptomatic by TSS (n=16)



Avapritinib improves quality of life of mastocytosis patients

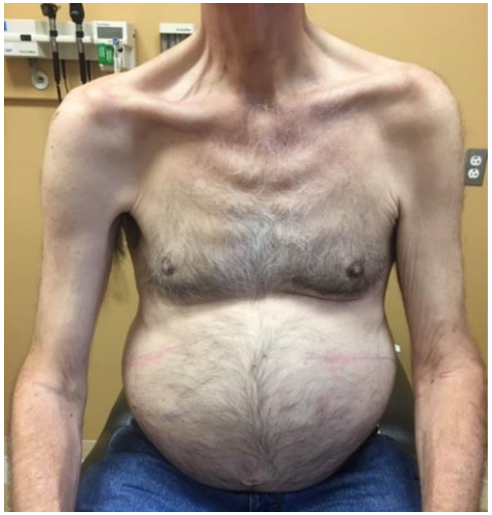




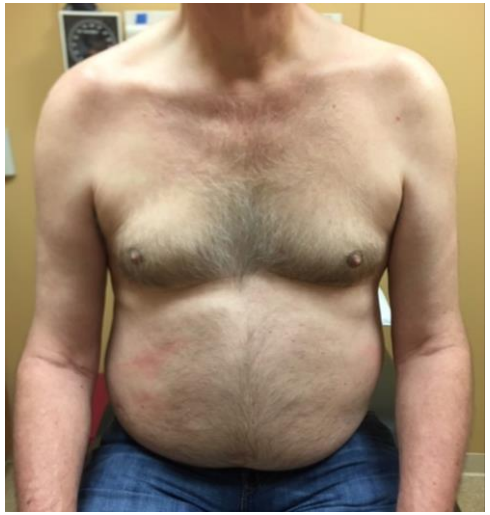
Significant improvement in EORTC quality of life (QL), approaching healthy age-matched controls

*Reference mean QL score from Hinz et al. Acta Oncologica. 2014

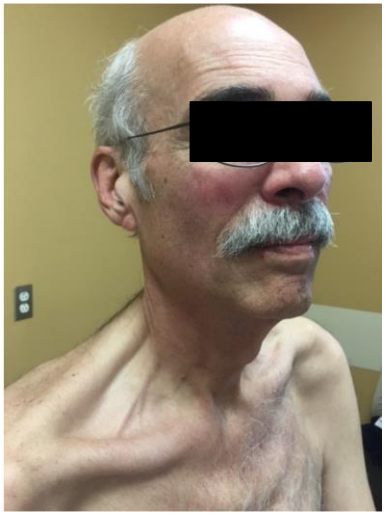
61 year old male with SM-AHN (CMML-1)



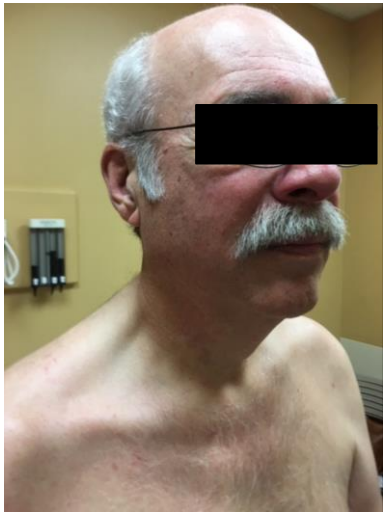
Baseline



Cycle 6 day 1



Baseline



Cycle 6 day 1

Prior therapy: DCC-2618

- Paracentesis-dependent ascites significantly improved on avapritinib 2 taps/week for 15L of fluid/week, now taps every 2-3 weeks and only 2-3L
- Albumin from 2.3 g/dL (G2) to 4 g/dL (normal)
- Gained 37 pounds of weight (not fluid) on study
- Tryptase from 416 ng/mL to 19.8 ng/mL
- Marrow mast cells from 30% to 5-10% after 2 cycles

Patient reported outcomes from AdvSM-SAF

Symptom improvement from baseline to cycle 6

- TSS -38% change (9.1 to 5.7)
- GI domain -69% change (1.9 to 0.6)
- Skin domain -47% change (2.1 to 1.1)

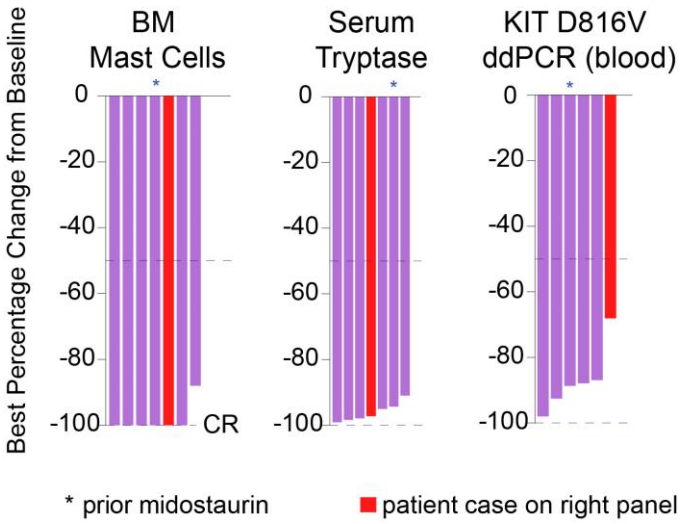
Data as of November 26, 2018

Patient permission granted for use of photos

ISM/SSM patient cohort from EXPLORER trial

All evaluable patients with ISM/SSM

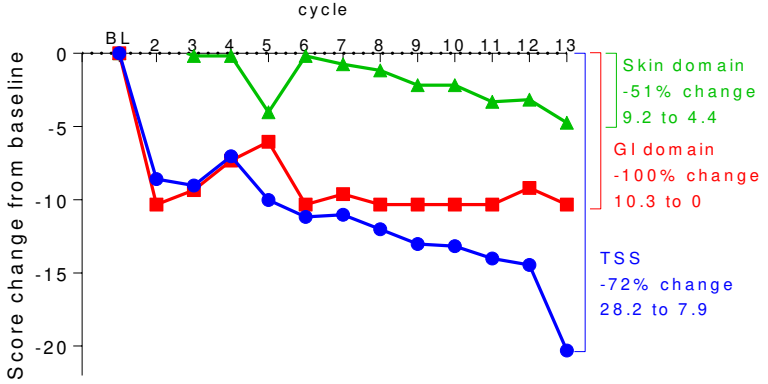
Objective measures of mast cell burden



All patients ongoing, median of 10 months

Case: 64-year-old woman with ISM

AdvSM-SAF total symptom score and domain scores



- Improvement in abdominal pain
- Confluent cutaneous lesions resolving
- Patient is continuing treatment on study

Avapritinib reduces objective signs and patient symptoms of SM Summary

- High response rate and durable clinical benefit in patients with AdvSM
  - 83% ORR by mIWG-MRT-ECNM (24% CR + CRh)
  - Median duration of response not reached
- Well tolerated with most AEs grade 1 or 2; 78% remain on study, up to 31 months ongoing
- First AdvSM specific PRO demonstrates significant improvement in total symptom score
- Significant improvement in EORTC quality of life, approaching healthy age-matched controls
- Clinical activity and initial PRO data support further evaluation in both AdvSM and ISM/SSM
  - PATHFINDER trial in AdvSM now enrolling
  - PIONEER trial in ISM/SSM planned to initiate by end of 2018

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