

PIONEER: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Avapritinib in Patients with Indolent or Smoldering Systemic Mastocytosis with Symptoms Inadequately Controlled with Standard Therapy

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PIONEER 
Indolent & Smoldering SM

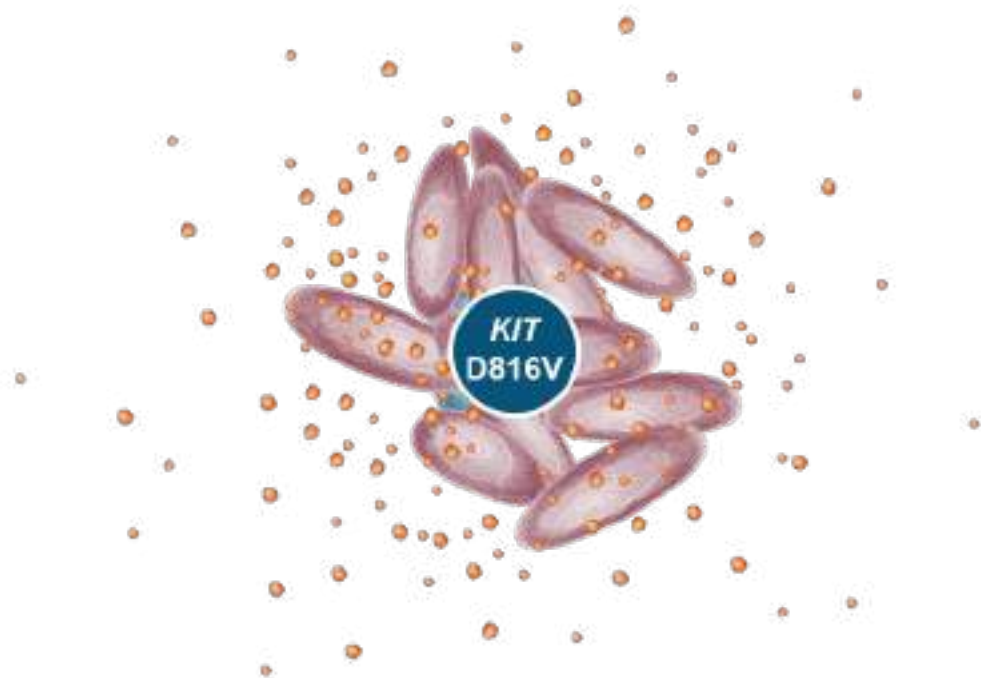


Disclosures

- Investigator: Blueprint Medicines' ongoing Phase 2 PIONEER trial in indolent and smoldering systemic mastocytosis
- Consultant: Blueprint Medicines, Novartis
- AYVAKIT™ (avapritinib) is approved by the FDA for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations, in the United States. Avapritinib has not been approved by the FDA or any other health authority for use in the United States for any other indication or in any other jurisdiction for any indication.
- All data in this presentation are based on a cut-off date of December 27, 2019 unless otherwise specified.



Systemic mastocytosis (SM) is a clonal mast cell (MC) neoplasm driven by *KIT* D816V

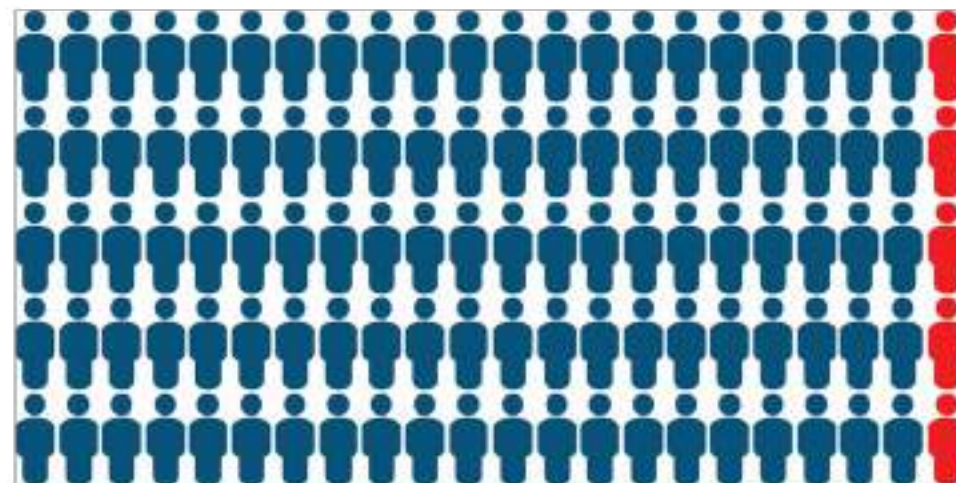


Hyperactivation and proliferation

Debilitating mediator symptoms in **skin**,
gastrointestinal and **neurocognitive** areas

Significant symptom directed polypharmacy

SM Prevalence of ~1:10,000
~32,000 estimated in US



~5% Advanced SM

Organ damage and decreased survival

~95% Non-advanced SM

Indolent and Smoldering SM

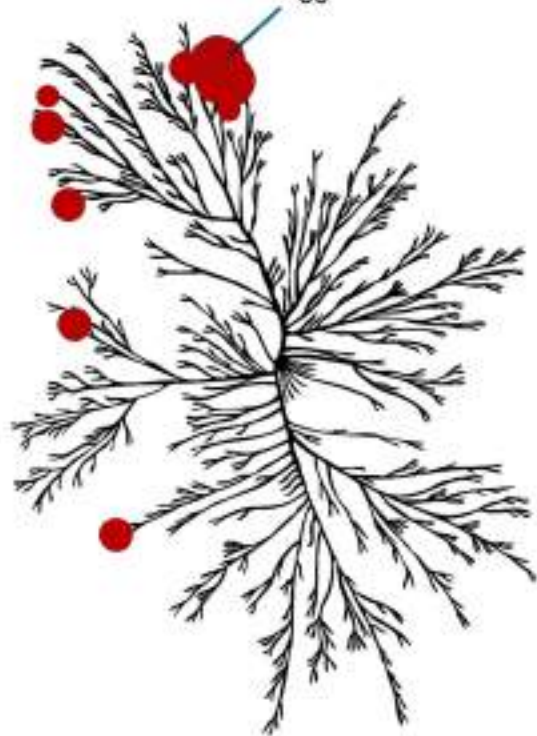
Suffer **long-term** with significant morbidity
and **poor quality of life**

No effective approved therapies to reduce
burden of disease

Avapritinib targets D816V with objective and symptomatic responses in SM

Highly potent on KIT D816V

Biochemical $IC_{50} = 0.27 \text{ nM}^1$



**Highly selective
kinome profile**

Objective responses in AdvSM

Phase 1 EXPLORER trial

77% confirmed ORR² in Advanced
SM at $\geq 200\text{mg}$ once daily

Responses deepen over time

FDA Breakthrough Designation for
AdvSM

Registration-enabling PATHFINDER
trial in AdvSM is currently enrolling

Efficacy on AdvSM symptoms

**Significant reduction in
AdvSM-SAF total symptom score³**
Potential for **resolution** of
mastocytosis in skin²



Baseline

On study

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)(CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content.

AdvSM, advanced systemic mastocytosis; IC_{50} , half-maximal inhibitory concentration; ORR, overall response rate; QD, once daily.

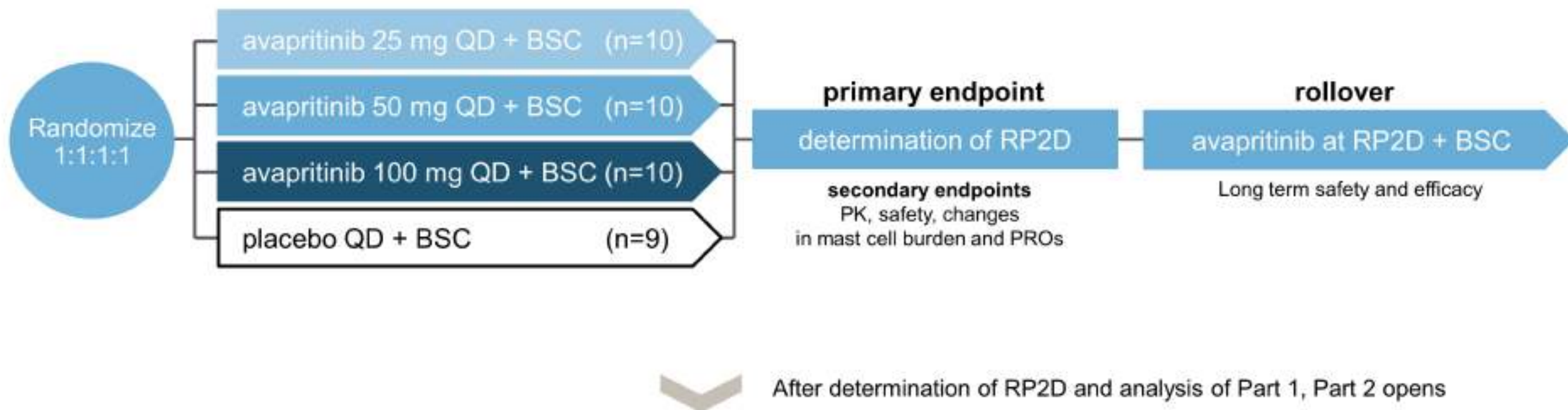
1. Evans EK et al. *Sci Transl Med*. 2017;9:eaa01690. 2. Radia D et al. Presented at the 24th European Hematology Association Congress, Amsterdam, the Netherlands, July 13-16, 2019. 3. Gotlib JR et al. *Blood*. 2018;132 (suppl 1):351.



Phase 2 PIONEER clinical trial in patients with non-advanced SM

Part 1: Dose Selection (fully enrolled)

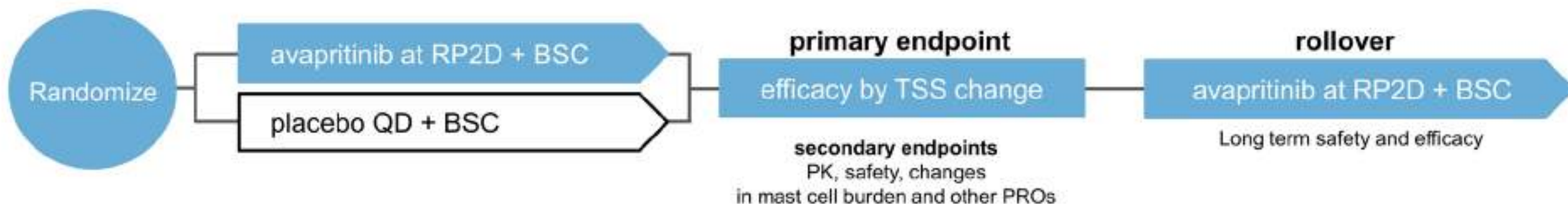
Selection of well tolerated long term chronic dose with appropriate benefit-risk for indolent SM



Phase 2 PIONEER clinical trial in patients with non-advanced SM

Part 2: Pivotal Efficacy (pending)

Registration-enabling portion powered to demonstrate efficacy over placebo



Key Eligibility Criteria

- Age ≥ 18 years, ECOG performance status 0–2
- Indolent SM confirmed by central pathology review of bone marrow biopsy, according to WHO criteria
- Moderate-to-severe symptoms based on minimum mean TSS over the 14-day eligibility screening period despite ≥ 2 classes of best supportive care (BSC) medications

Baseline patient and disease characteristics

All doses (N=39)

Patient Demographics			
Age (years), Median (range)		51 (21–75)	
Sex, n (%), Female		30 (77)	
ECOG PS, n (%), 0		12 (31)	
1		19 (49)	
2		8 (21)	
Mast Cell Burden			
Central diagnosis of indolent ISM, n (%)		39 (100)	
Tryptase (central), ng/mL, Mean (SD)		84 (101)	
Median (range)		45 (6–416)	
<11.4 ng/mL, n (%)		3 (8)	
11.4 to 20 ng/mL, n (%)		6 (15)	
>20 ng/mL, n (%)		30 (77)	
Bone marrow core biopsy MC (central), %			
Mean (SD)		16 (16)	
Median (range)		10 (1–60)	
MC aggregates present, %		90	
KIT D816V mutation	Local ^a	Central NGS ^b	Central ddPCR ^c
n (%) detected	31 (80)	11 (28)	37 (95)
Median MAF, % (range)	-	11 (1.9-31)	0.36 (0.0-30)

All doses (N=39)

SM Therapy, n (%)	
Prior cytoreductive therapy	6 (16)
Midostaurin, imatinib, dasatinib, masitinib	5 (13)
Interferon alfa	1 (3)
Baseline Supportive Care Meds, median (range)	4 (2-9)
H1 blockers	37 (95)
H2 blockers	30 (77)
Leukotriene receptor antagonists	23 (59)
Proton pump inhibitors	18 (46)
Cromolyn sodium	12 (31)
Corticosteroids	6 (15)
Omalizumab	9 (23)

Patient Disposition

Weeks on study, median (range)	18 (1–36)
Still on study, n (%)	37 (95)
Discontinued study, n (%)	2 (5)
Patient decision, n	1
Protocol non-compliance, n	1

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^aLocal quantitative and qualitative KIT testing of bone marrow and/or blood, various methods and sensitivities. ^bNGS=next generation sequencing targeted myeloid panel (central) in blood, algorithmic calling sensitivity to 1.9% MAF; ^cdigital droplet PCR in blood (central), sensitivity to 0.02% MAF, detected: positive at screening or C1D1, Median MAF and range at C1D1 in those with any detection. C1D1, cycle 1 day 1; ISM, indolent systemic mastocytosis; MAF, mutation allele fraction; MC, mast cells; PS, performance status; SD, standard deviation



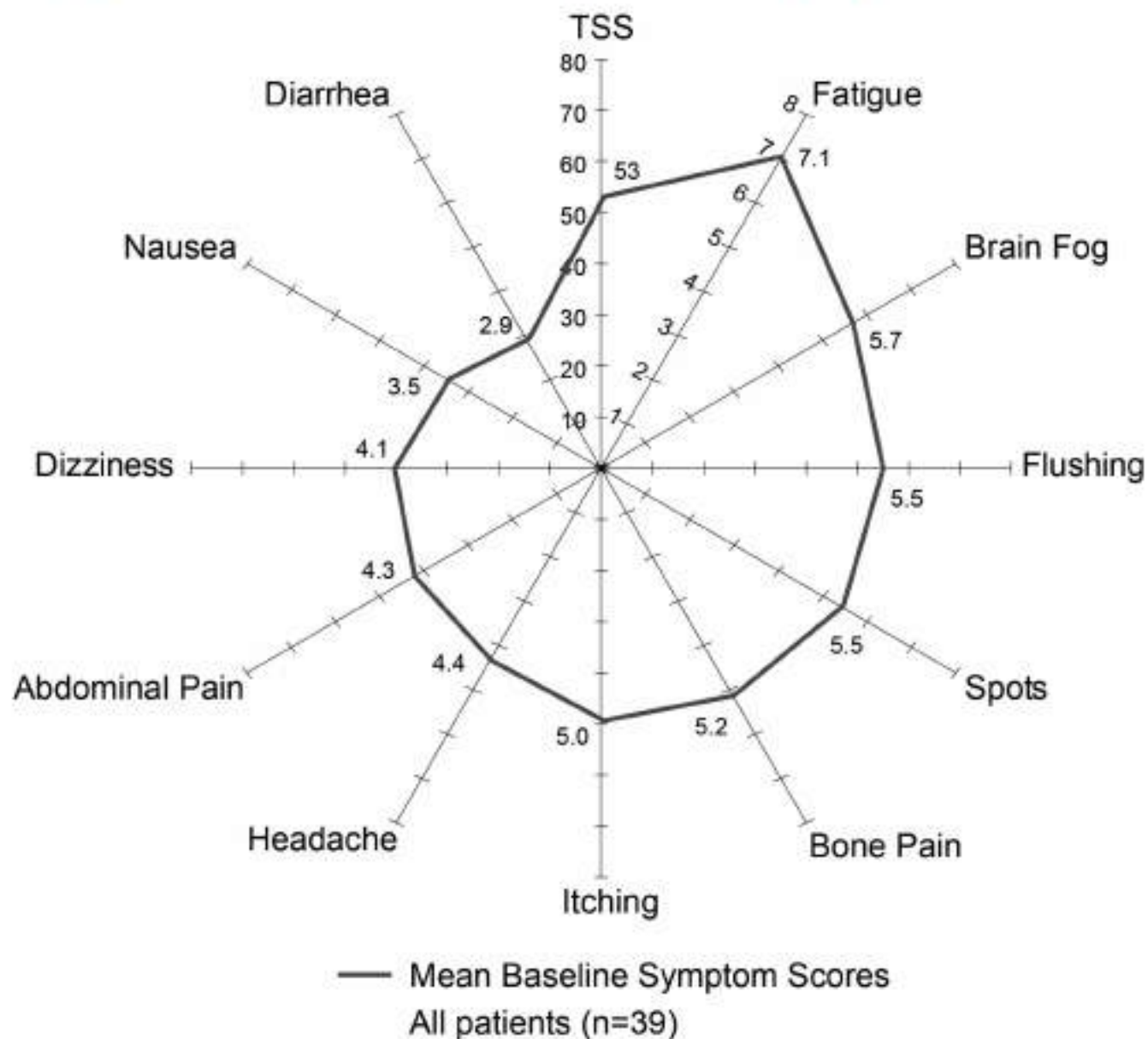
ISM-SAF, a reliable construct valid patient reported outcomes tools for ISM

ISM-Symptom Assessment Form (SAF)

- Clinical benefit measure and primary endpoint for PIONEER trial
- Designed with input from disease experts, patients and regulatory authorities to support regulatory approval

ISM-SAF		
Symptom	Score	Groups
Abdominal pain	Scored 0 – 10 daily (24 hour recall) on a handheld device	GI (0 – 30)
Diarrhea		
Nausea		
Spots		Skin (0 – 30)
Itching		
Flushing		
Brain Fog	0 is no symptoms 10 is worst	Neurocognitive (0 – 30)
Headache		
Dizziness		
Bone pain		
Fatigue		
Total Symptom Score (0-110)		

Significant baseline sign and symptom burden in patients enrolled on PIONEER



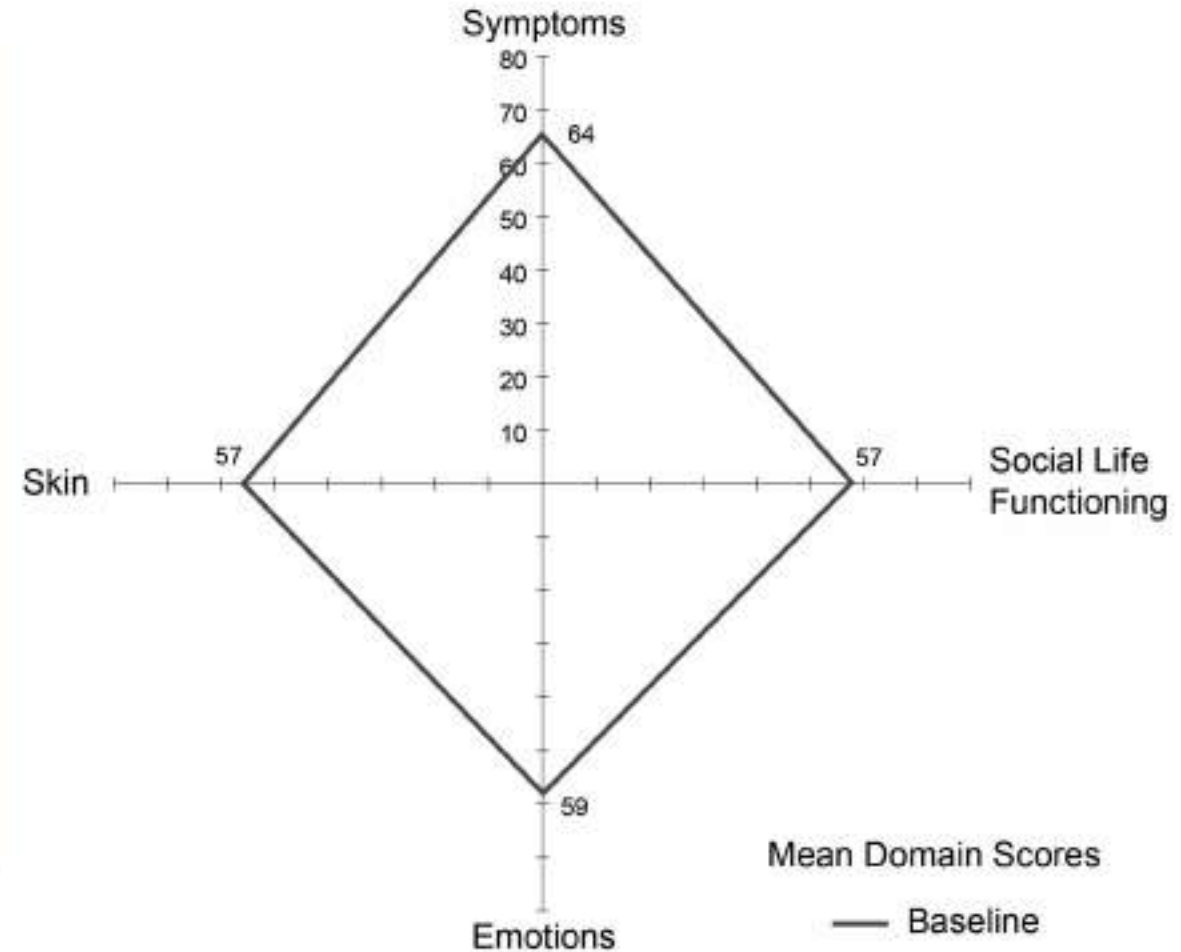
- Every patient with significant symptom burden at baseline
- Most severe symptoms in the 14 days prior to dosing were fatigue, brain fog, flushing and spots
- >99% daily adherence to ISM-SAF entry by patients
- Mean Total Symptom Score: 53



MC-QOL, a Quality of Life questionnaire for patients with ISM

Mastocytosis Quality of Life (MC-QoL) Questionnaire¹

- A quality of life tool developed for mastocytosis
- 27 questions across 4 domains: Skin, Symptoms, Social Life/Functioning and Emotions
- 2 week recall, performed at every study visit
- Each domain with 3 to 9 symptoms, each domain score and Mc-QoL total score scaled to 0-100



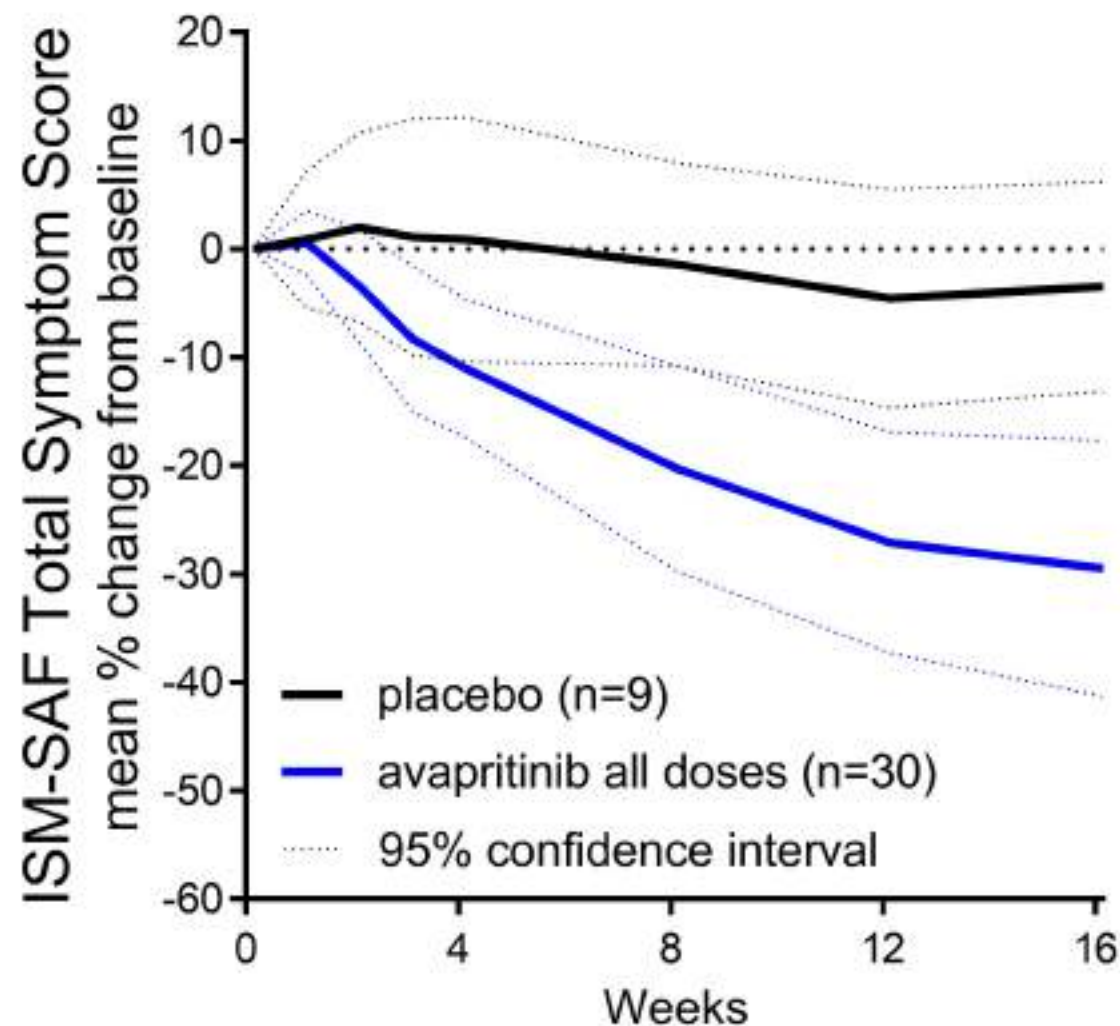
Mean MC-QoL Total Score: 60

Well tolerated safety profile across all doses with no grade 3 AEs at 25 mg

AE in >15% of placebo or combined avapritinib arms			avapritinib					
Preferred term	Placebo n=9		25 mg n=10		50 mg n=10		100 mg n=10	
% of subjects with ≥ 1 AE	any grade	grade 3	any grade	grade 3	any grade	grade 3	any grade	grade 3
	89	22	100	0	80	20	90	40
Nausea	22	0	10	0	60	10	40	0
Dizziness	22	0	30	0	30	0	40	0
Headache	11	0	30	0	30	10	30	10
Diarrhea	11	0	0	0	40	10	30	10
Fatigue	11	0	40	0	10	0	10	0
Face edema	0	0	10	0	0	0	40	0
Peripheral edema	0	0	10	0	20	0	20	0
Periorbital edema	0	0	0	0	20	0	30	0
Bone Pain	22	0	0	0	0	0	0	0

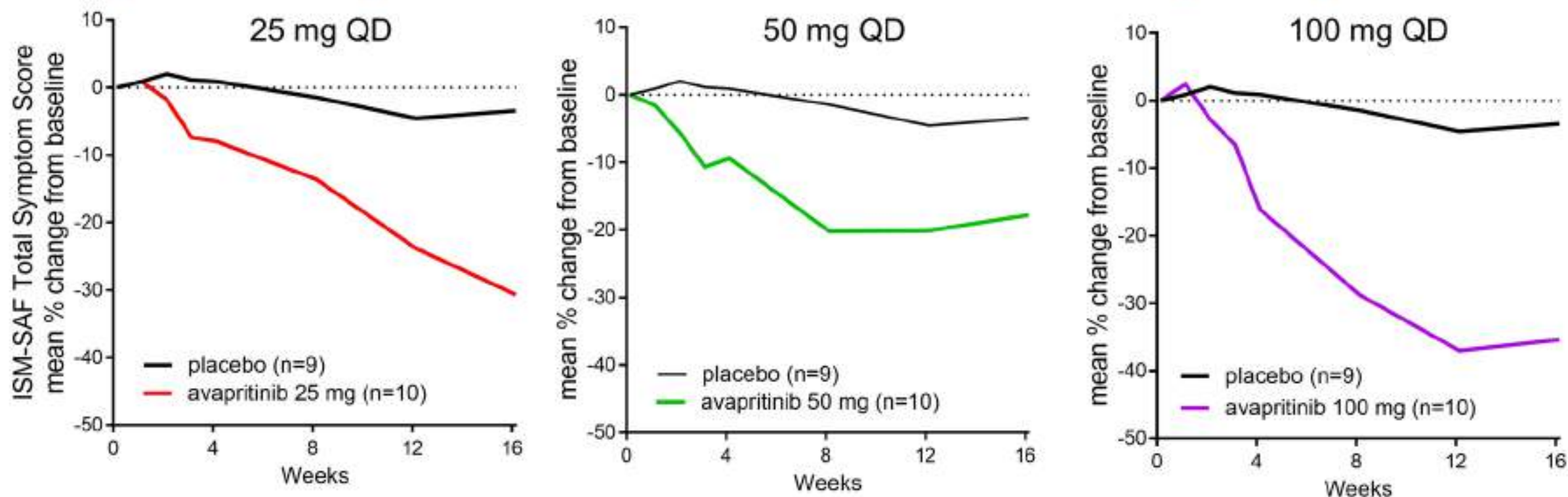
- No grade 4 or 5 AEs on study
- No patients discontinued treatment due to AE or progression to AdvSM
- No neutropenia, anemia, thrombocytopenia, or intracranial bleeding
- One grade 3 cognitive disorder in the 100 mg cohort resolved following dose modification; patient remains on treatment at 25 mg

Avapritinib significantly improves overall SM symptoms compared to placebo



- ~30% mean symptom reduction at 16 weeks in avapritinib treated patients measured by ISM-SAF TSS
- ~3% mean symptom reduction in placebo
- Difference is statistically significant ($p=0.001$) at 16 weeks of therapy

Avapritinib 25 mg QD achieves similar reduction to 100 mg QD by week 16

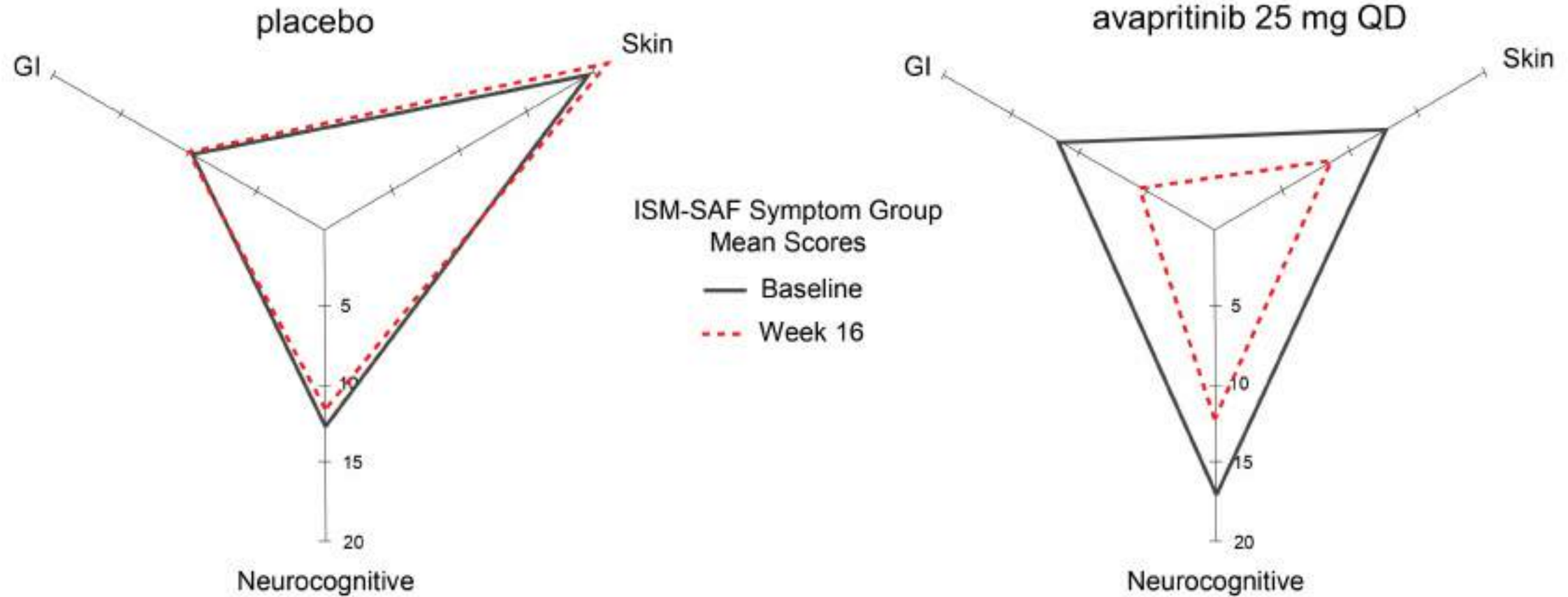


- 25 mg QD demonstrates similar % reduction in mean symptom burden to 100 mg dose at week 16

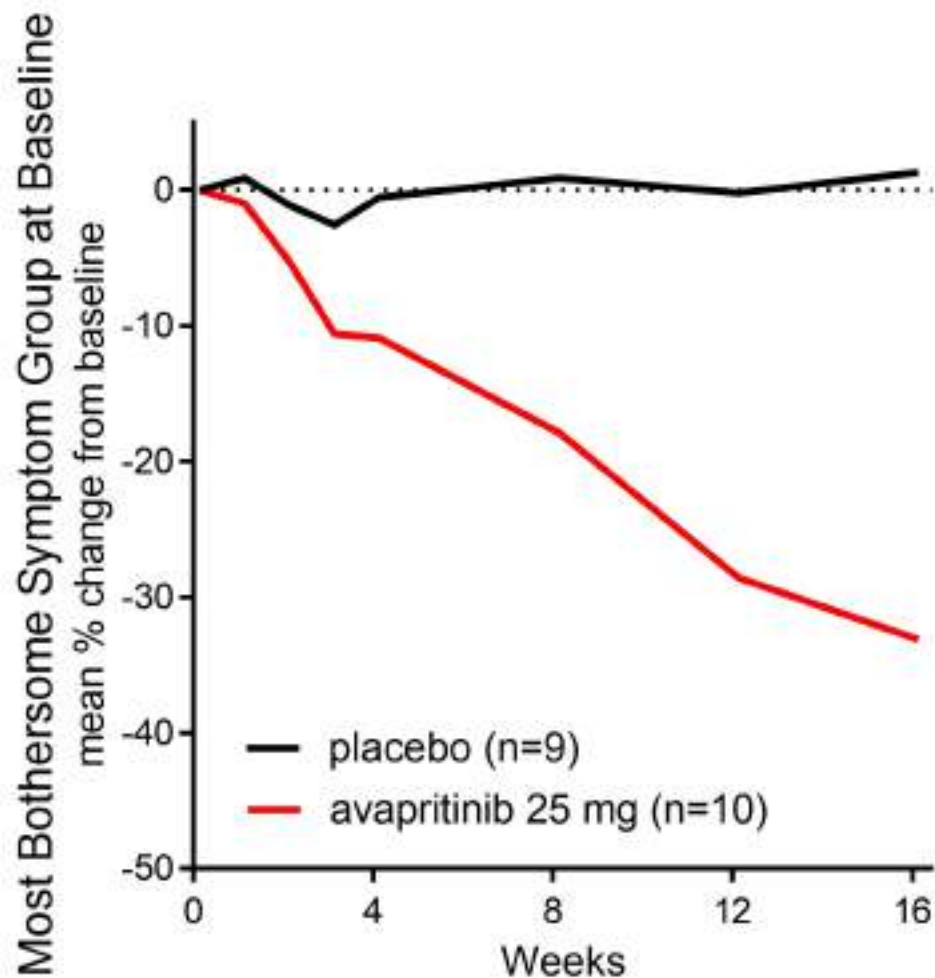
avapritinib 25 mg QD selected as the RP2D

25 mg dose provided similar mean improvements as higher doses with better tolerability

Avapritinib 25 mg QD achieves symptom reduction in GI, Skin and Neurocognitive symptom groups compared to placebo



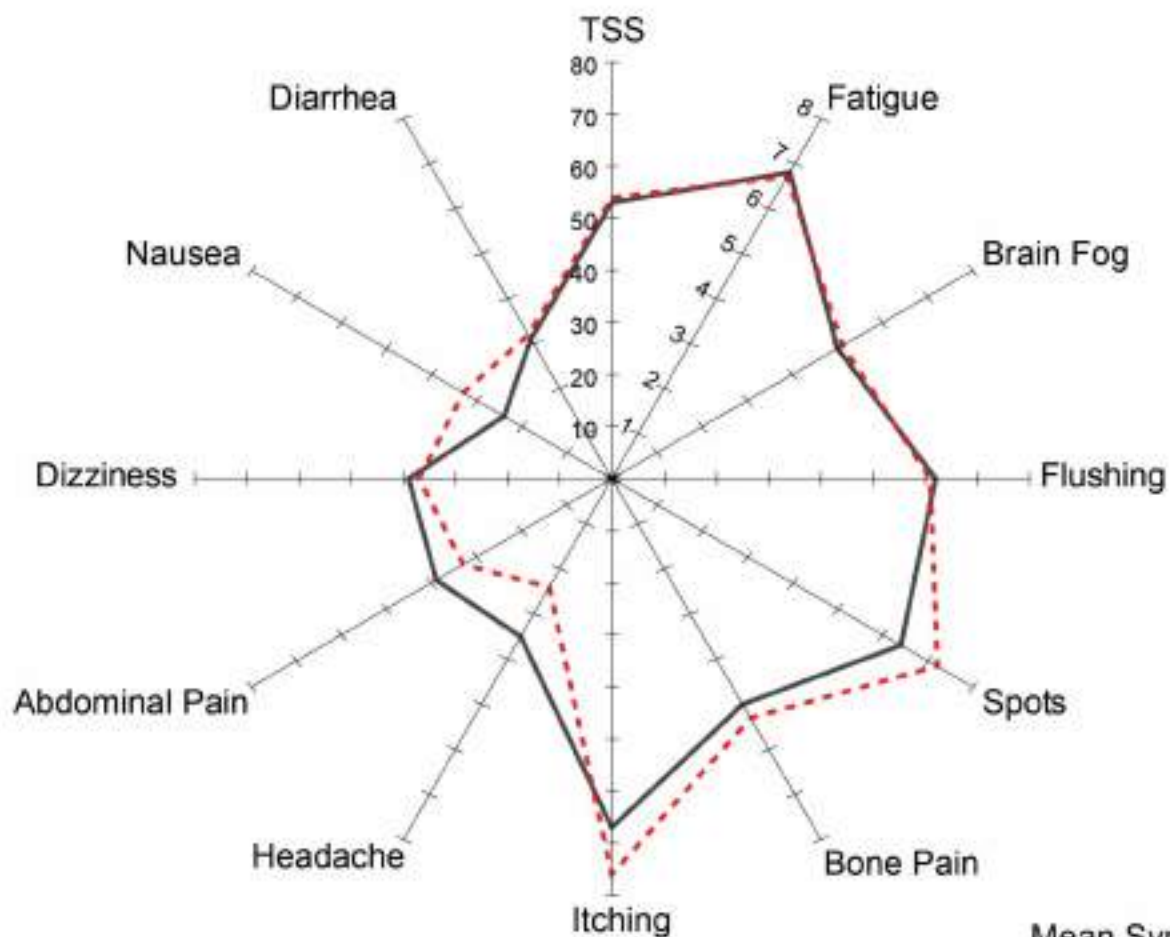
Avapritinib 25 mg QD improves most bothersome symptom group



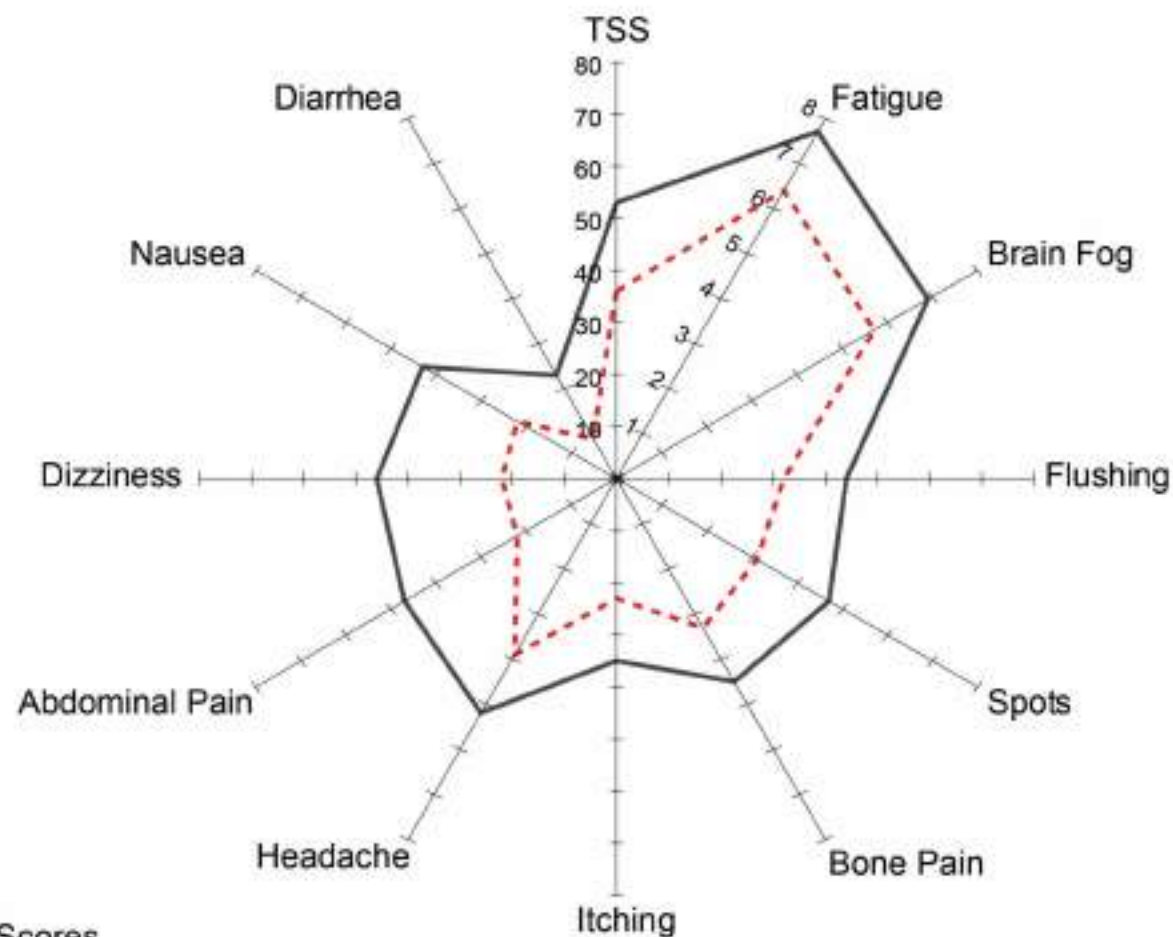
- Improvements in most bothersome symptom group at baseline for each patient
- The most bothersome symptom group for these patients were:
 - 47.4% Skin
 - 47.4% Neurocognitive
 - 5.2% GI

Avapritinib 25mg QD improves individual symptoms compared to placebo

placebo

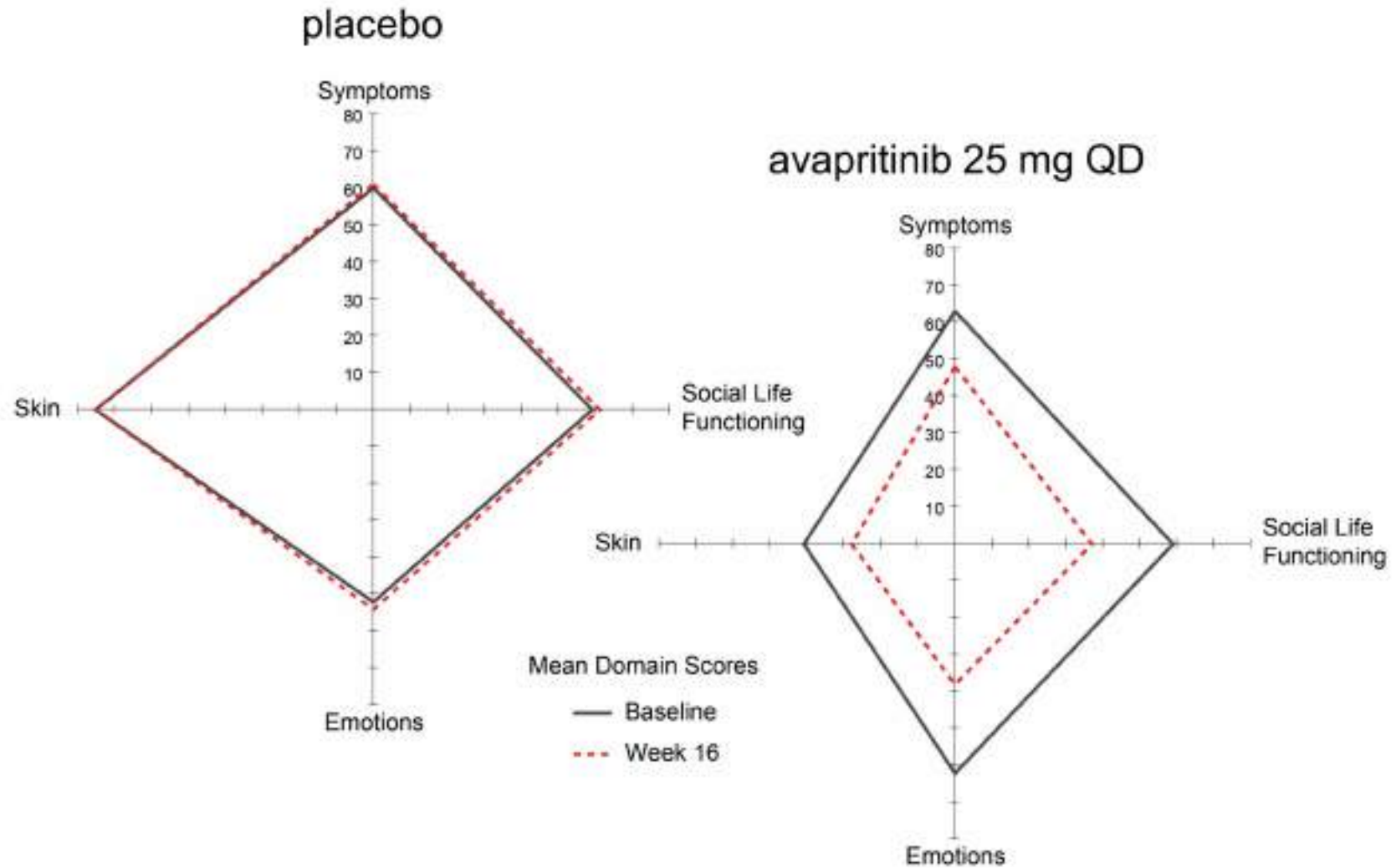
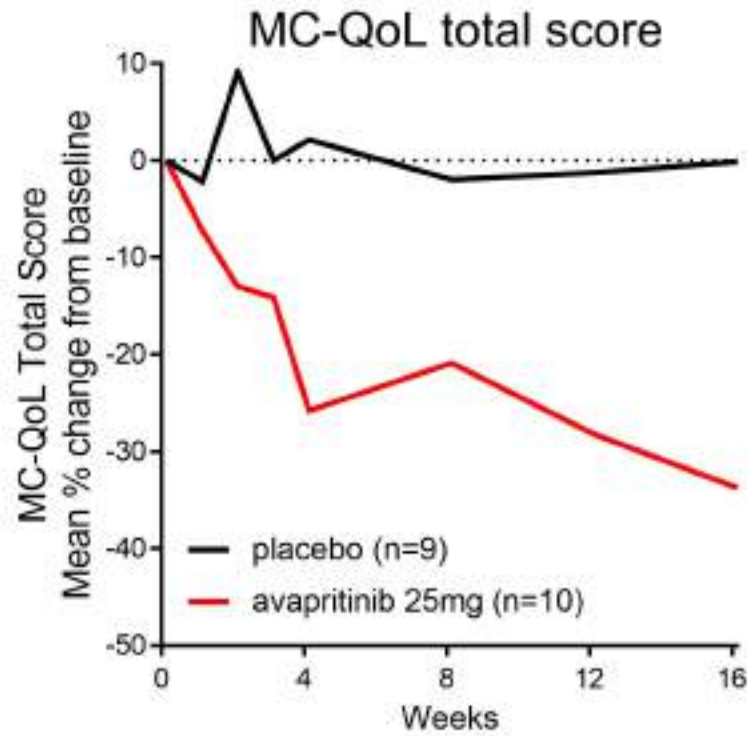


avapritinib 25 mg QD

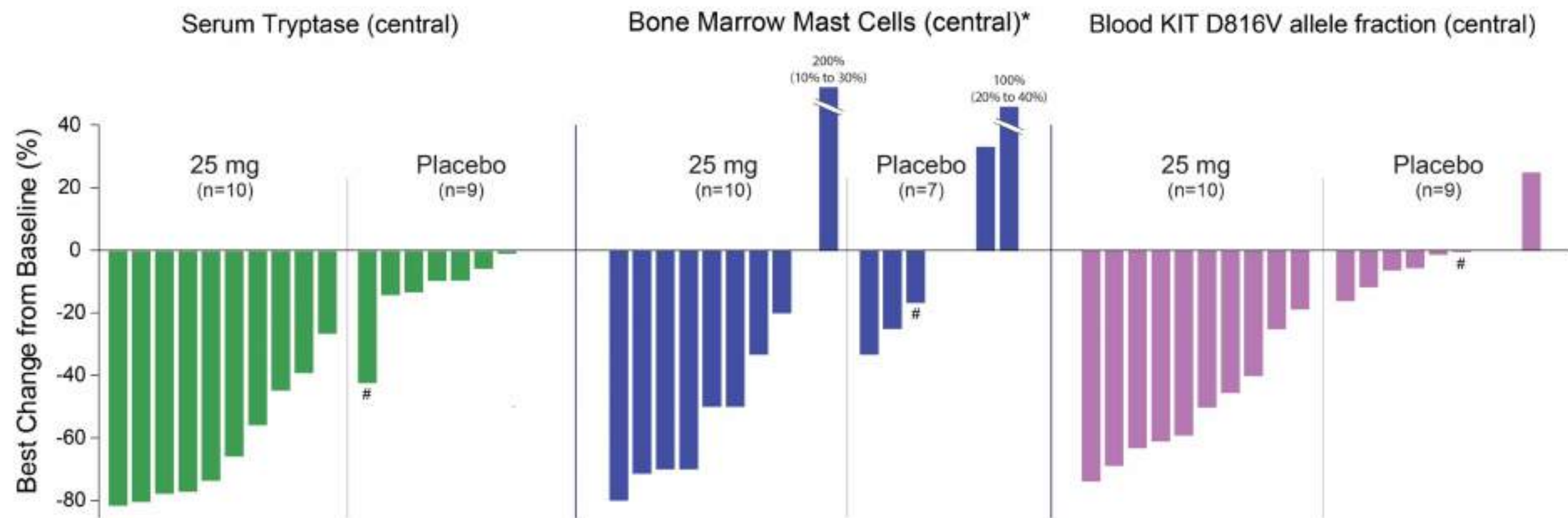


Mean Symptom Scores
— Baseline - - - Week 16

Improvements in Quality of Life with avapritinib 25mg QD by MC-QoL



Objective reductions in mast cell burden at 25 mg vs placebo



*Bone marrow MC assessment in SM may have variability in sampling due to patchy nature of disease. No patient on study has progressed to advanced disease. #patient received high dose IV steroids.

Conclusions

- Avapritinib treatment results in a statistically significant reduction in total symptom score at 16 weeks
- Avapritinib has a favorable safety profile in patients with indolent SM, supporting further evaluation of a chronic dosing regimen
 - 95% of patients remain on study, with no discontinuations for AEs
 - No grade ≥ 3 AEs occurred in the 25 mg QD cohort
- Avapritinib 25 mg QD achieves clinically meaningful improvements at 16 weeks and is the recommended part 2 dose
 - Reductions in bone marrow MC burden, serum tryptase and blood KIT D816V allele fraction
 - Improvements in clinical outcomes, as measured by ISM-SAF total symptom score and all symptom domain scores, at week 16
 - Improvements in quality of life, as measured by MC-QoL overall score and all domain scores, at week 16
- Part 2 of the registration-enabling PIONEER study is anticipated to initiate patient screening in June 2020