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

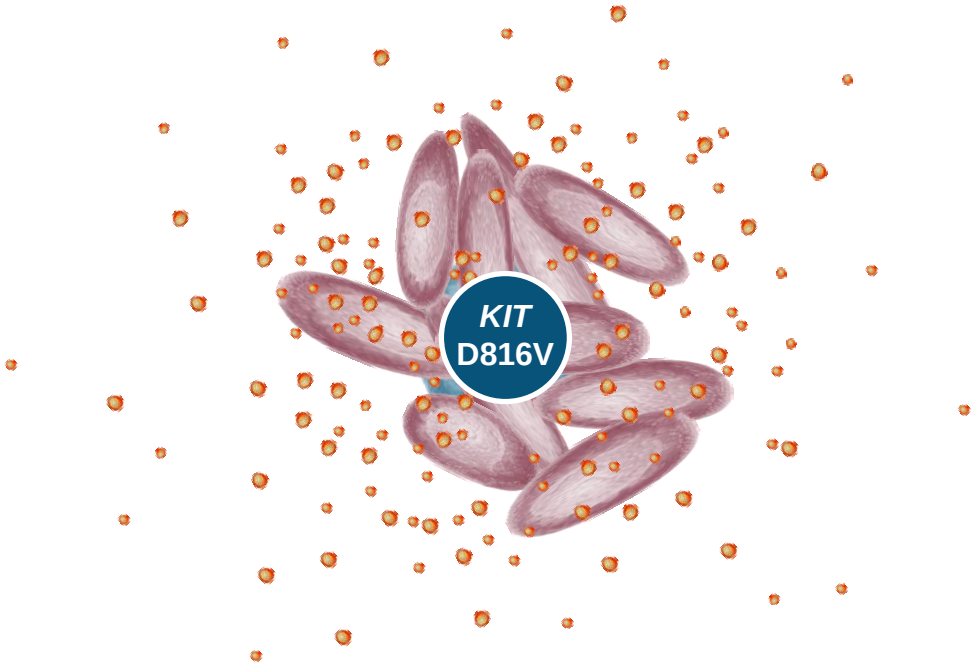
Disclosures

- 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

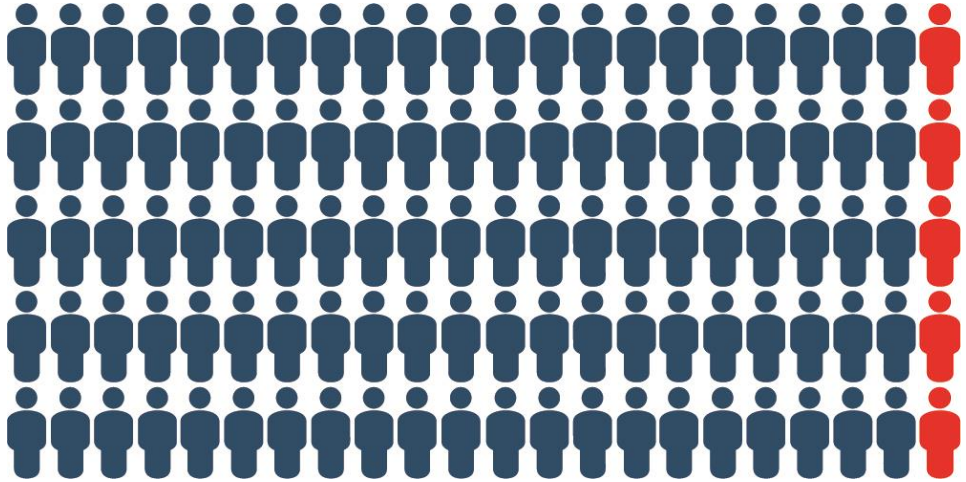


Hyperactivation and proliferation

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

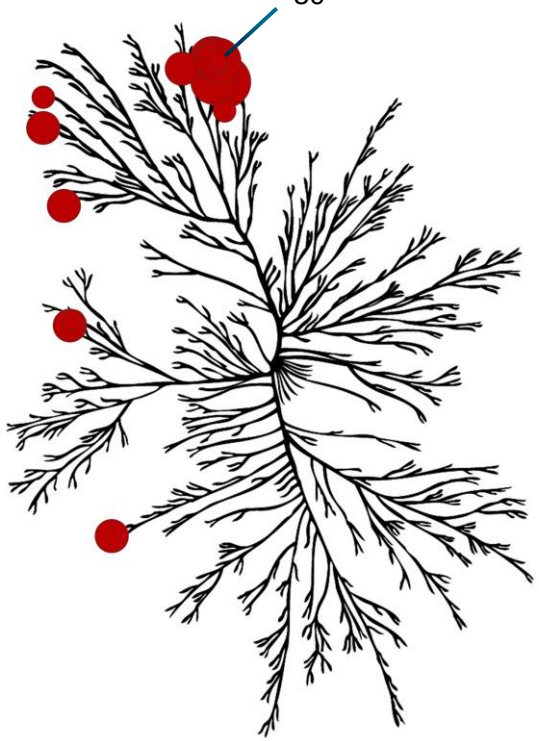
Suffer **long-term** with significant morbidity and **poor quality of life**

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 nM[1]



Highly selective
kinome profile

Objective responses in AdvSM

Phase 1 EXPLORER trial

77% confirmed ORR[2] in Advanced SM at ≥200mg once daily

Responses deepen over time

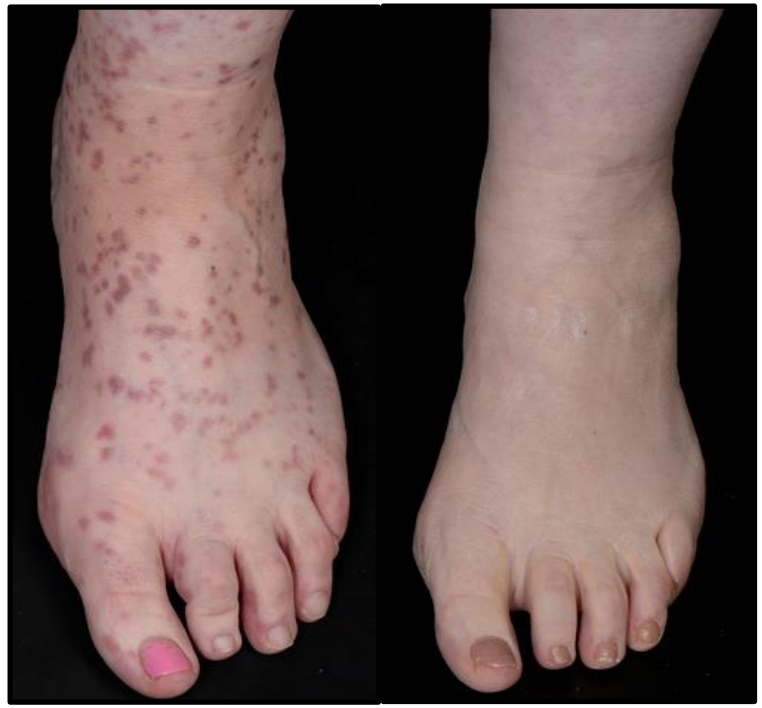
FDA Breakthrough Designation for AdvSM

Registration-enabling PATHFINDER trial in AdvSM is currently enrolling

Efficacy on AdvSM symptoms

Significant reduction in AdvSM-SAF total symptom score[3]

Potential for **resolution** of mastocytosis in skin[2]



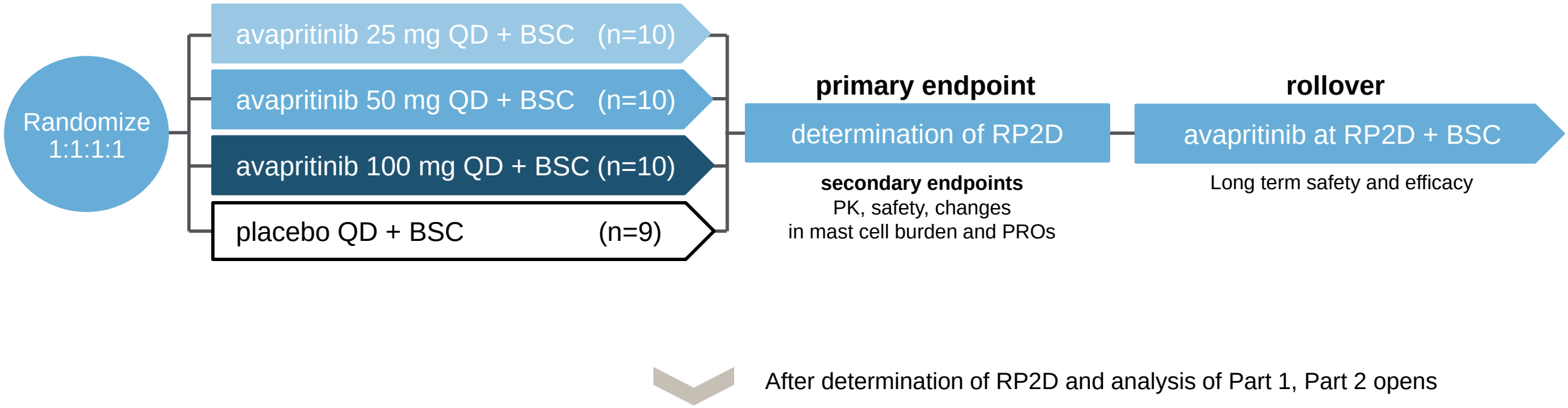
Baseline On study

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; IC50, half-maximal inhibitory concentration; ORR, overall response rate; QD, once daily.
1. Evans EK et al. *Sci Transl Med.* 2017;9:eaao1690. 2. Radia D et al. Presented at the 24th European Hematology Association Congress, Amsterdam, the Netherlands, July 1316, 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

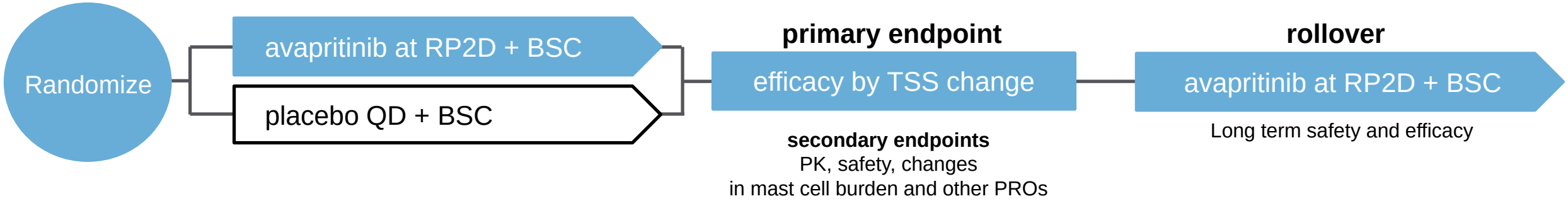


BSC, best supportive care; PK, pharmacokinetics; PRO, patient-reported outcome; RP2D, recommended part 2 dose.

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

ECOG, Eastern Cooperative Oncology Group TSS, total symptom score; WHO, World Health Organization.

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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[a]Local quantitative and qualitative KIT testing of bone marrow and/or blood, various methods and sensitivities. [b]NGS=next generation sequencing targeted myeloid panel (central) in blood, algorithmic calling sensitivity to 1.9% MAF; [c]digital 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 systematic 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

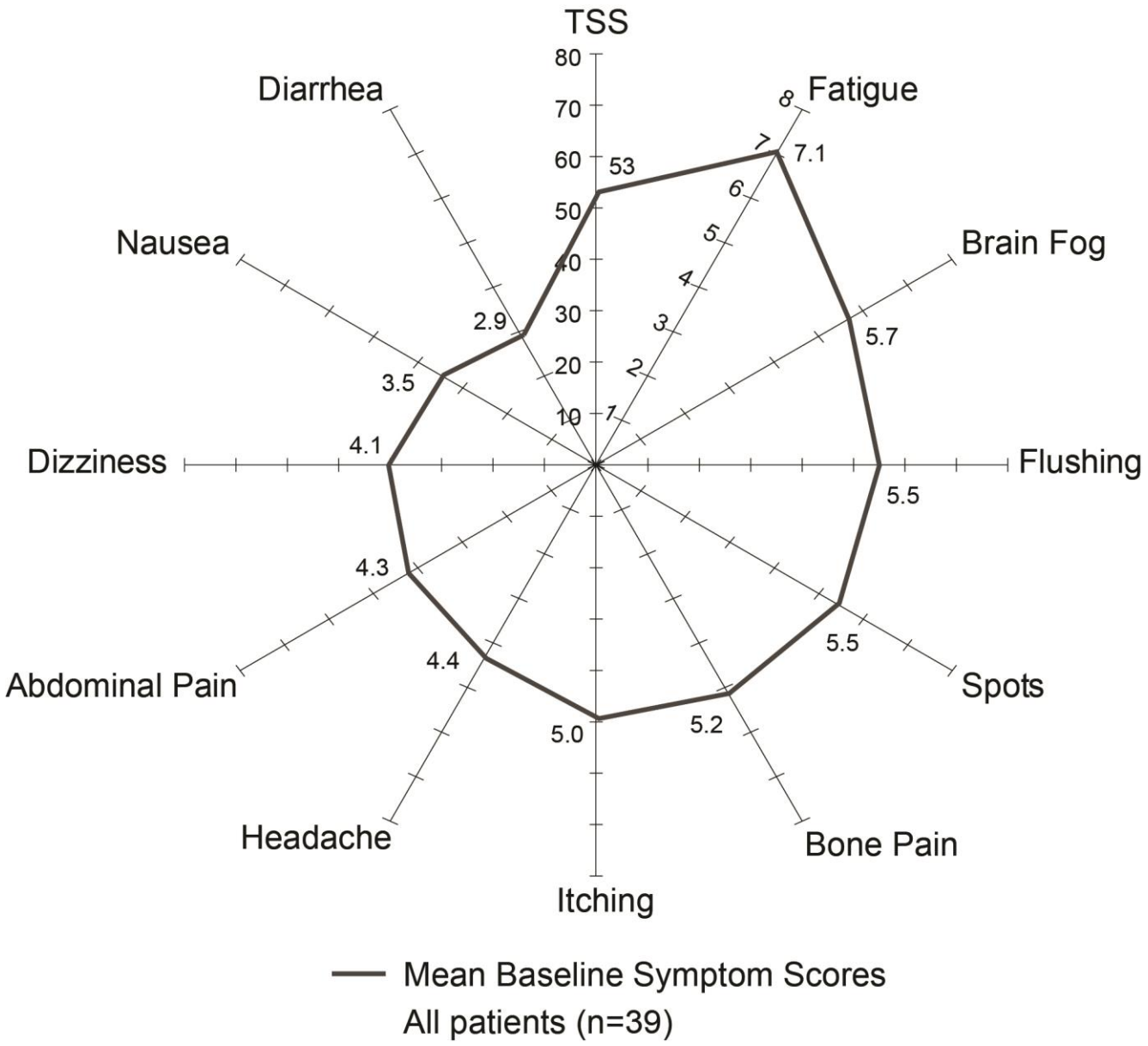
ISM-SAF		
Symptom	**Score**	**Groups**
Abdominal pain	Scored 0 – 10 daily (24 hour recall) on a handheld device 0 is no symptoms 10 is worst Analyzed as a 14-day moving average	GI (0 – 30)
Diarrhea		
Nausea		
Spots		Skin (0 – 30)
Itching		
Flushing		
Brain Fog		Neurocognitive (0 – 30)
Headache		
Dizziness		
Bone pain		
Fatigue		

Total Symptom Score (0-110)

GI, gastrointestinal; ISM, indolent SM.

1. Shields A et al. *Value Health.* 2019;22 (suppl 3):S867-868.

Significant baseline sign and symptom burden in patients enrolled on PIONEER

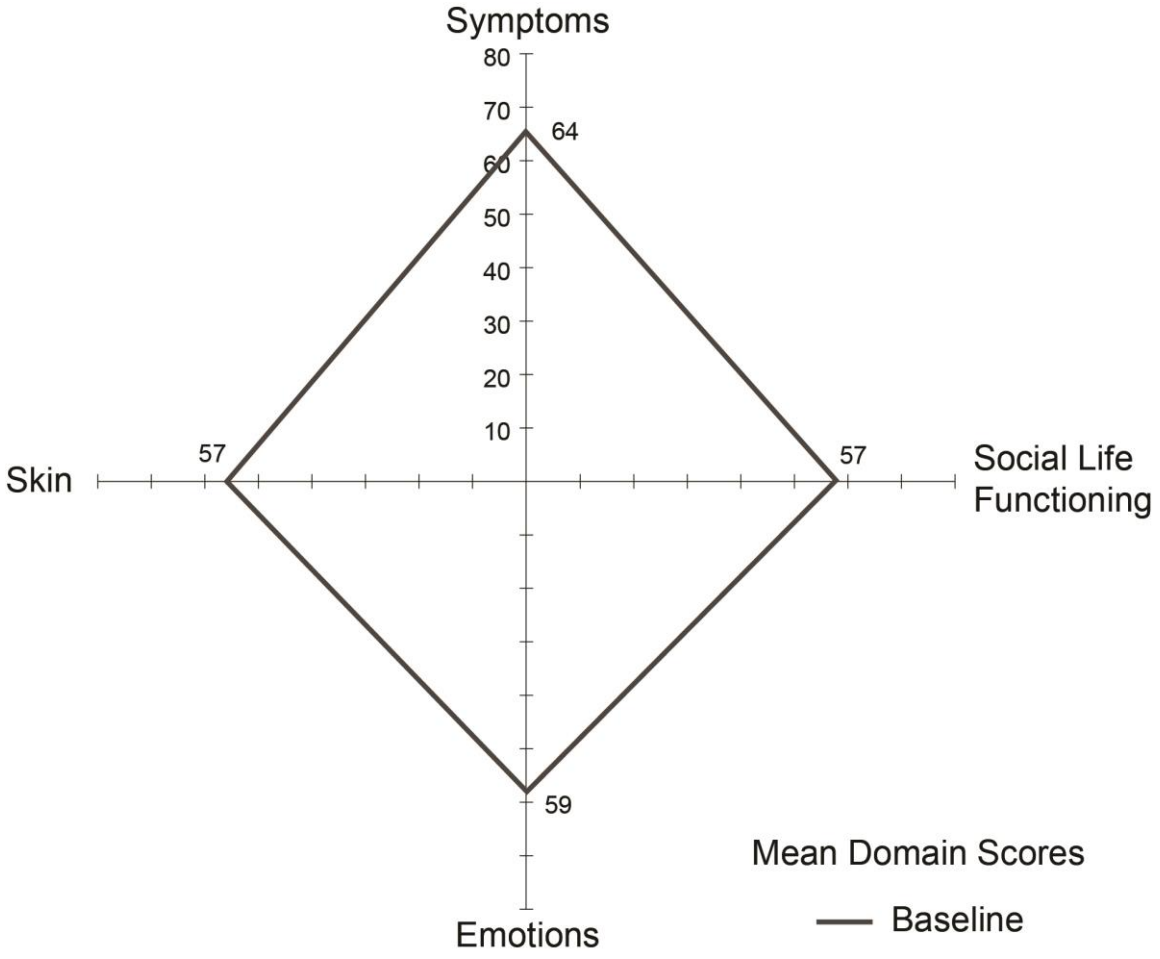


- Every patient with significant symptom burden at baseline
- Most severe symptoms in the 14 days prior to dosing were fatigue, brain fog, flushing and spots
- >99% daily adherence to ISM-SAF entry by patients
- Mean Total Symptom Score: 53

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

Mastocytosis Quality of Life (MC-QoL) Questionnaire[1]

- 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

1. Siebenhaar F et al. *Allergy*. 2016;71:869-87.

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

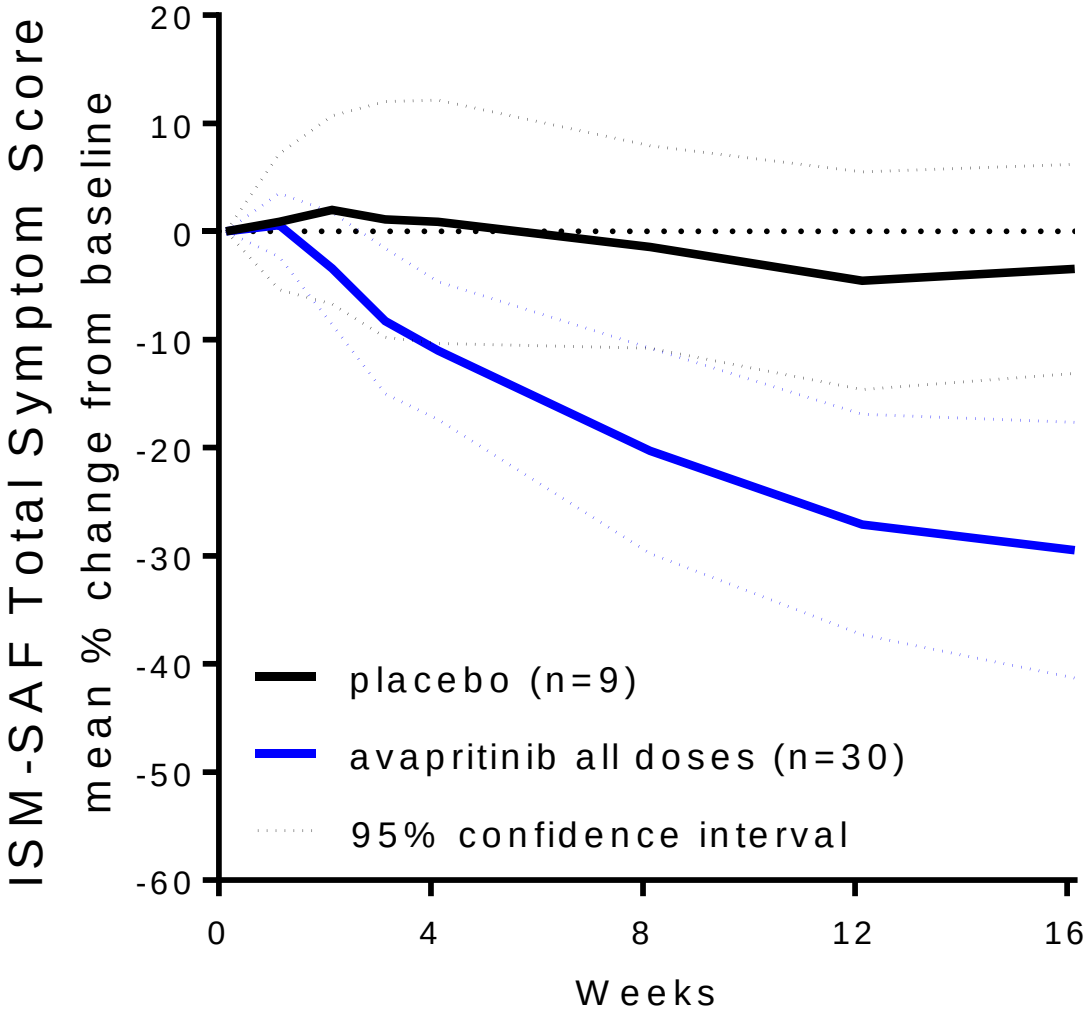
AE in >15% of placebo or avapritinib arms

Preferred term	Placebo n=9		avapritinib 25 mg n=10		avapritinib 50 mg n=10		avapritinib 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

AE, adverse event

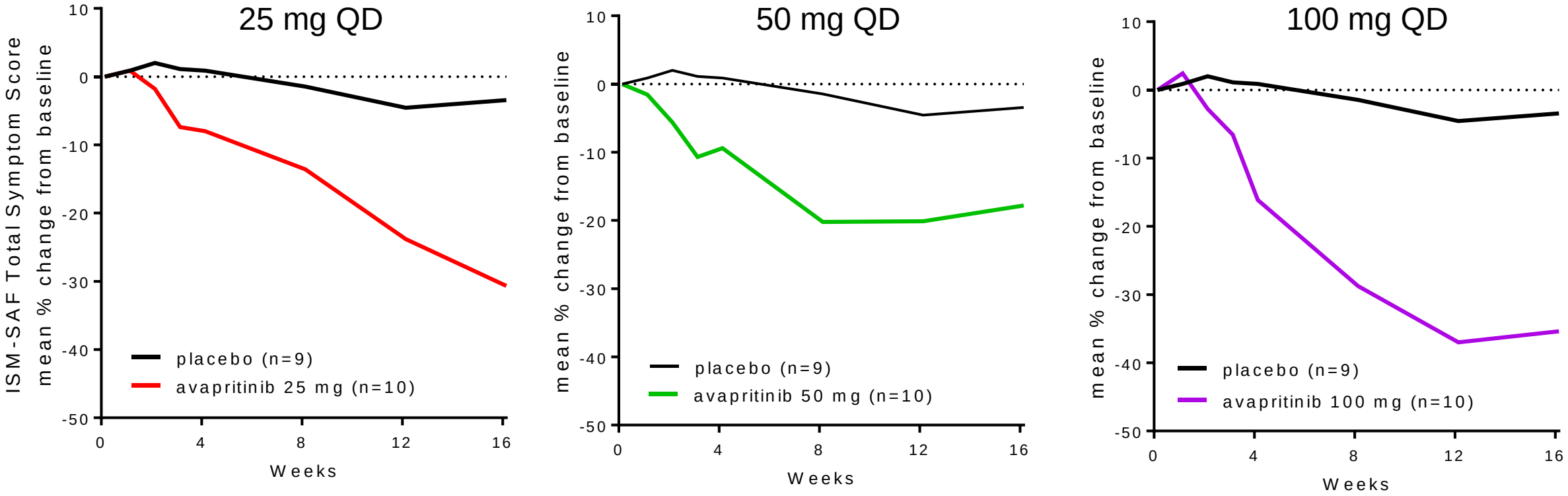
Avapritinib significantly improves overall SM symptoms compared to placebo



- ~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

n is number dosed in each cohort

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



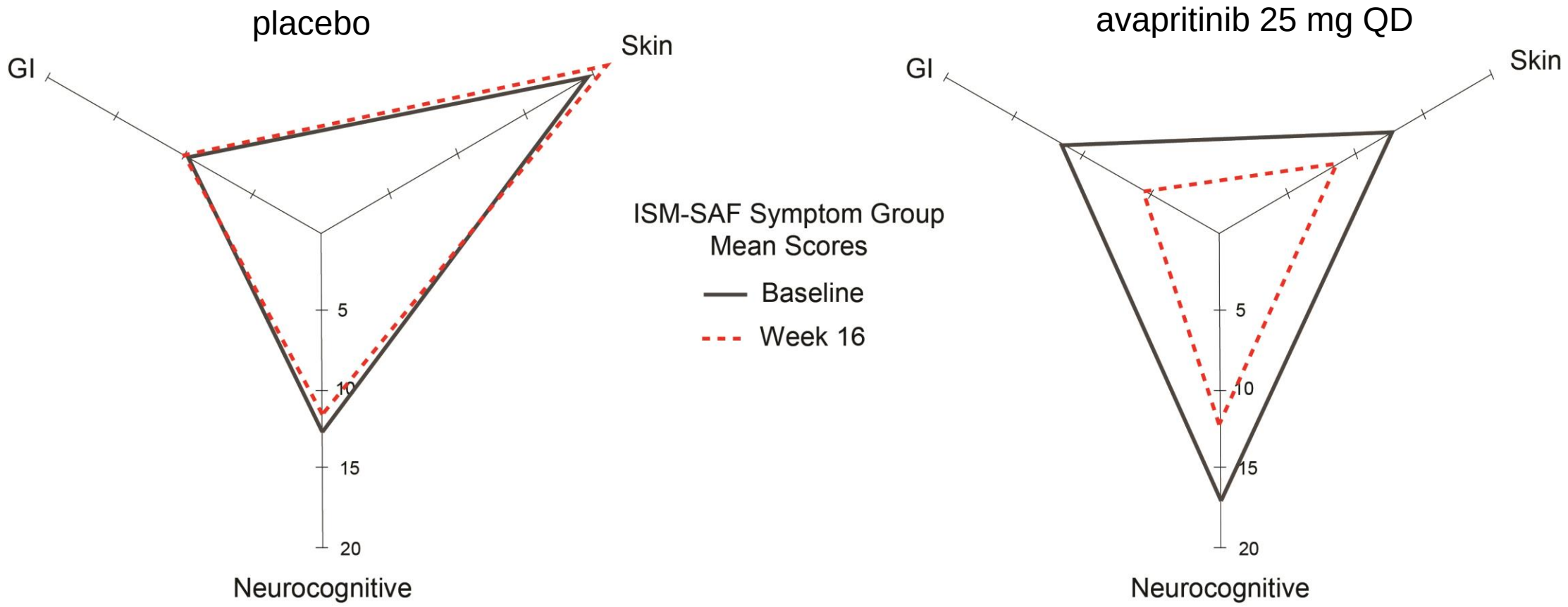
- 25 mg QD demonstrates similar % reduction in mean symptom burden to 100 mg dose at week 16

avapritinib 25 mg QD selected as the RP2D

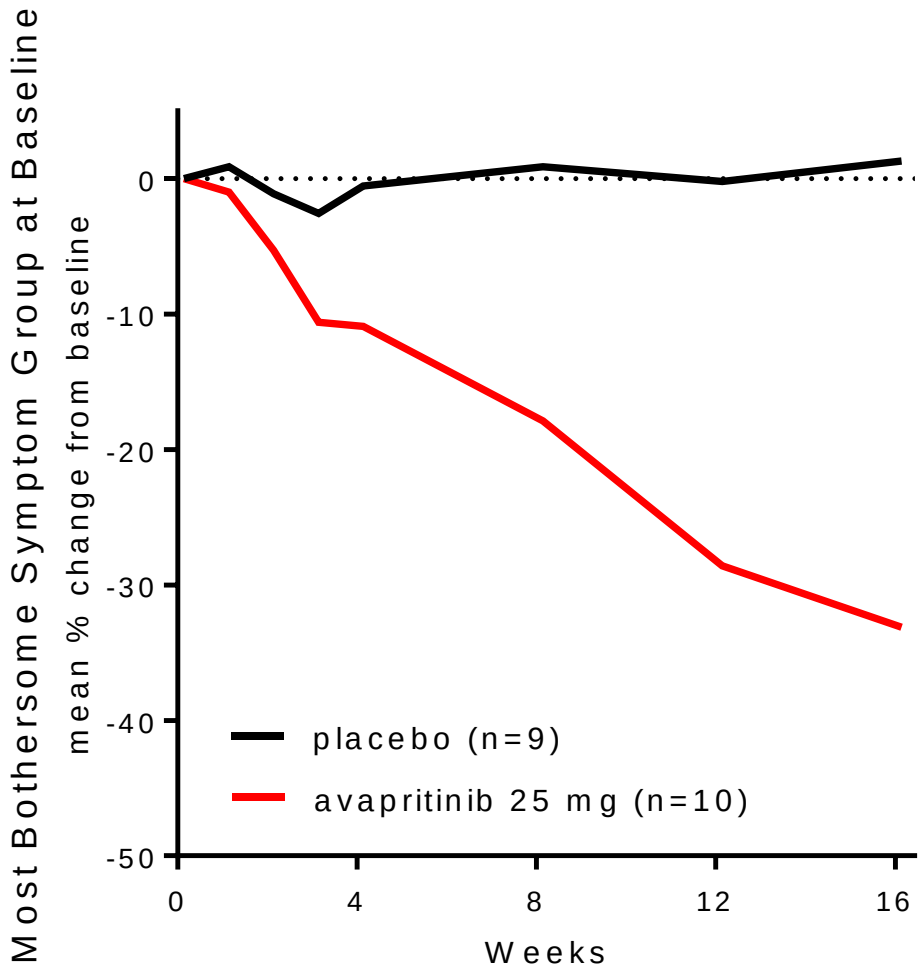
25 mg dose provided similar mean improvements as higher doses with better tolerability

n is number dosed in each cohort

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



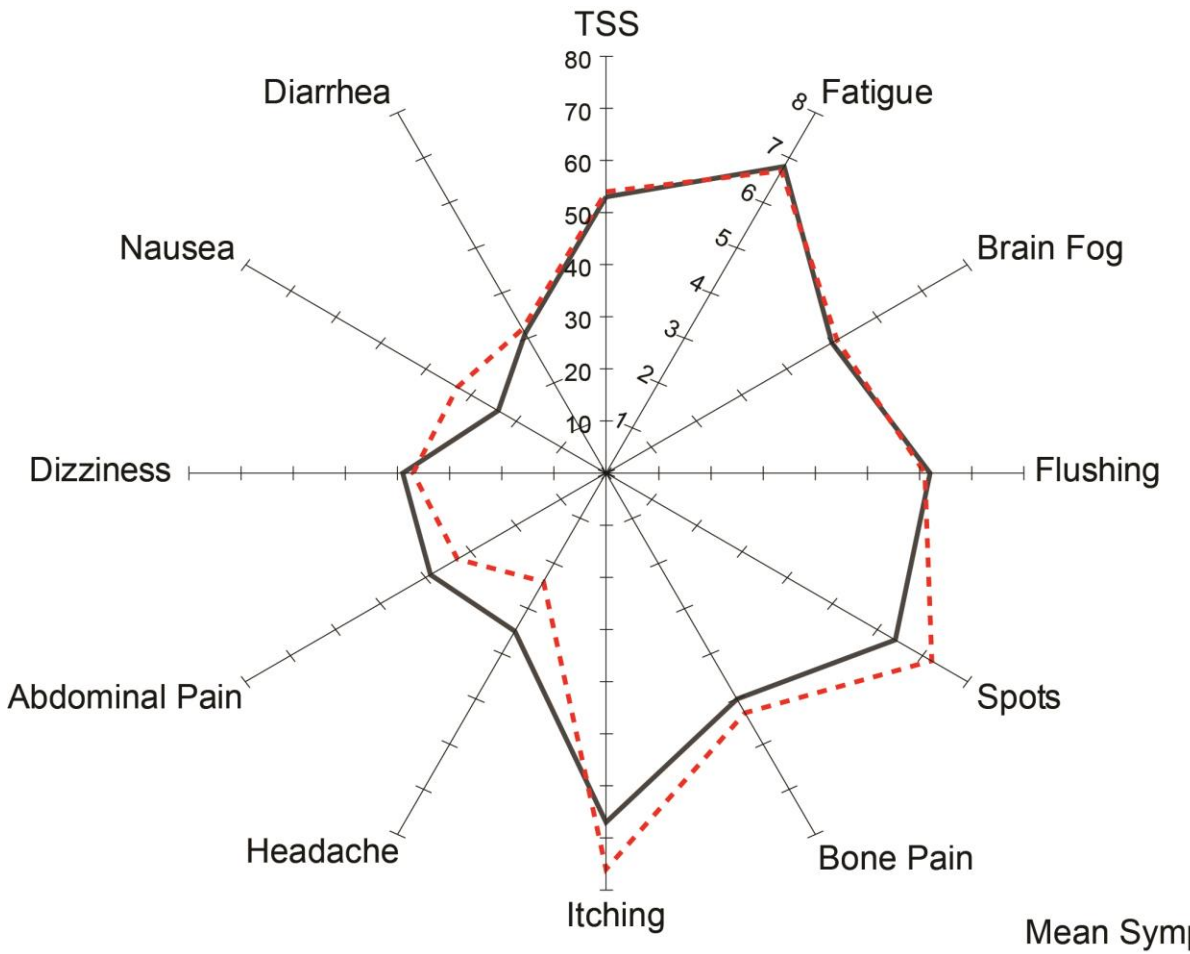
Avapritinib 25 mg QD improves most bothersome symptom group



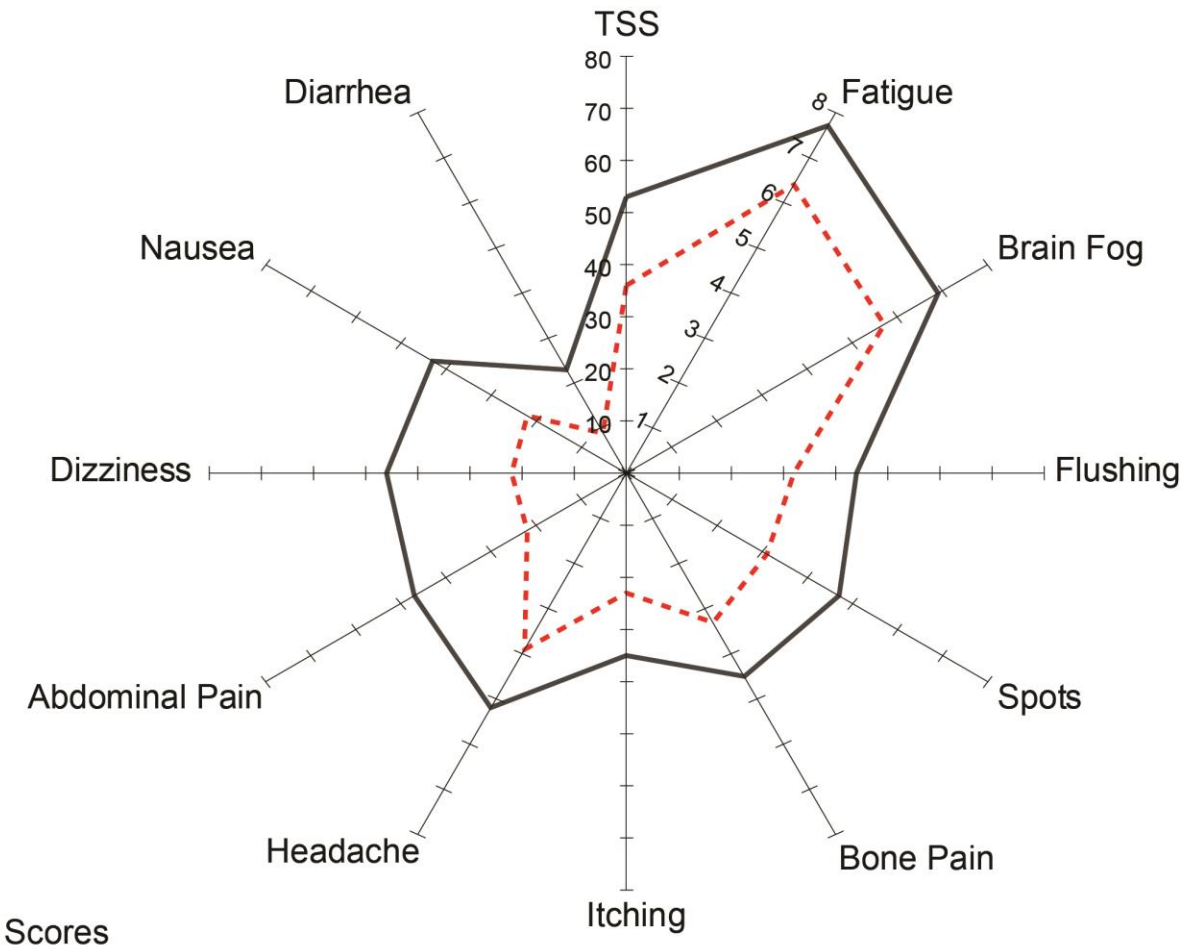
- Improvements in most bothersome symptom group at baseline for each patient
- The most bothersome symptom group for these patients were:
  - 47.4% Skin
  - 47.4% Neurocognitive
  - 5.2% GI

Avapritinib 25mg QD improves individual symptoms compared to placebo

placebo



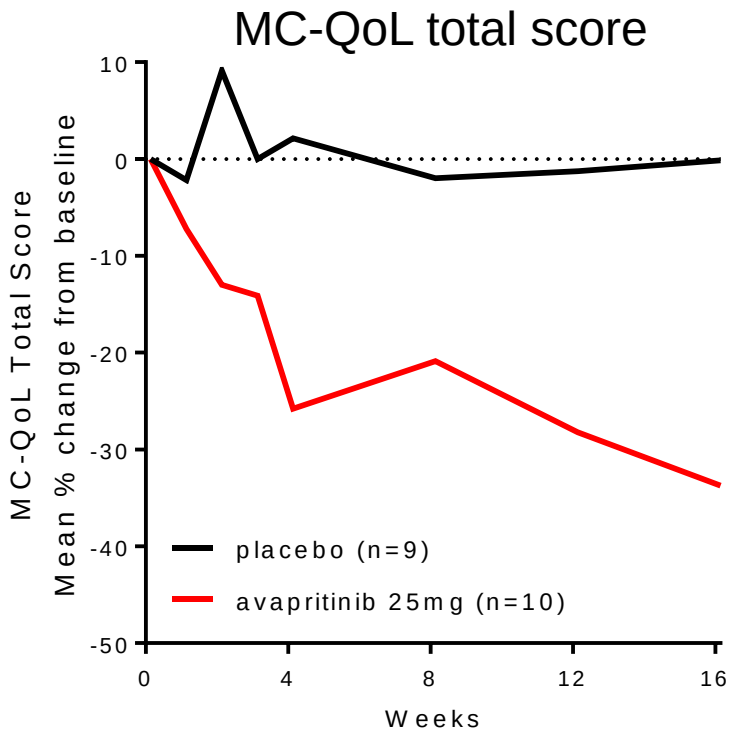
avapritinib 25 mg QD

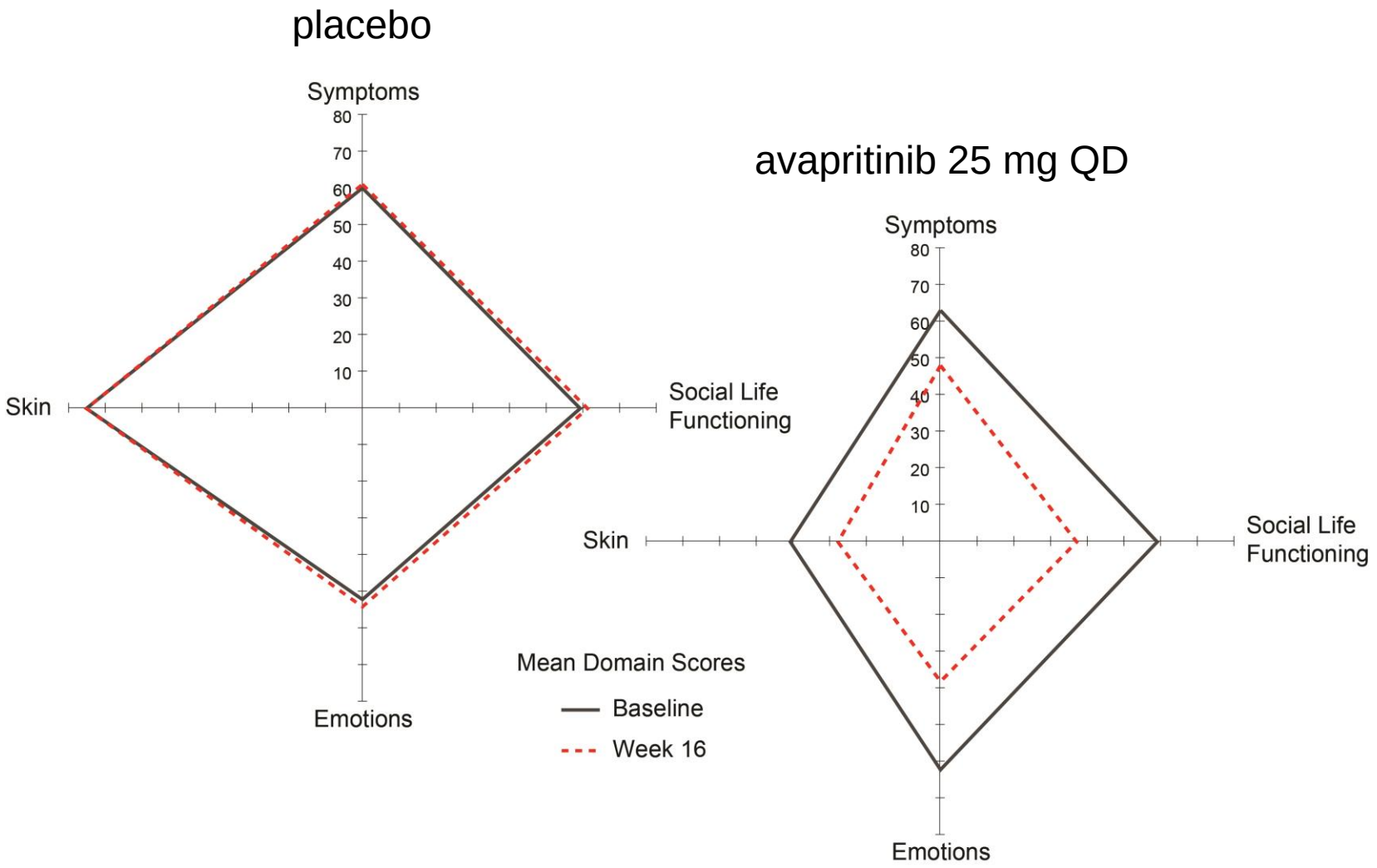


Mean Symptom Scores

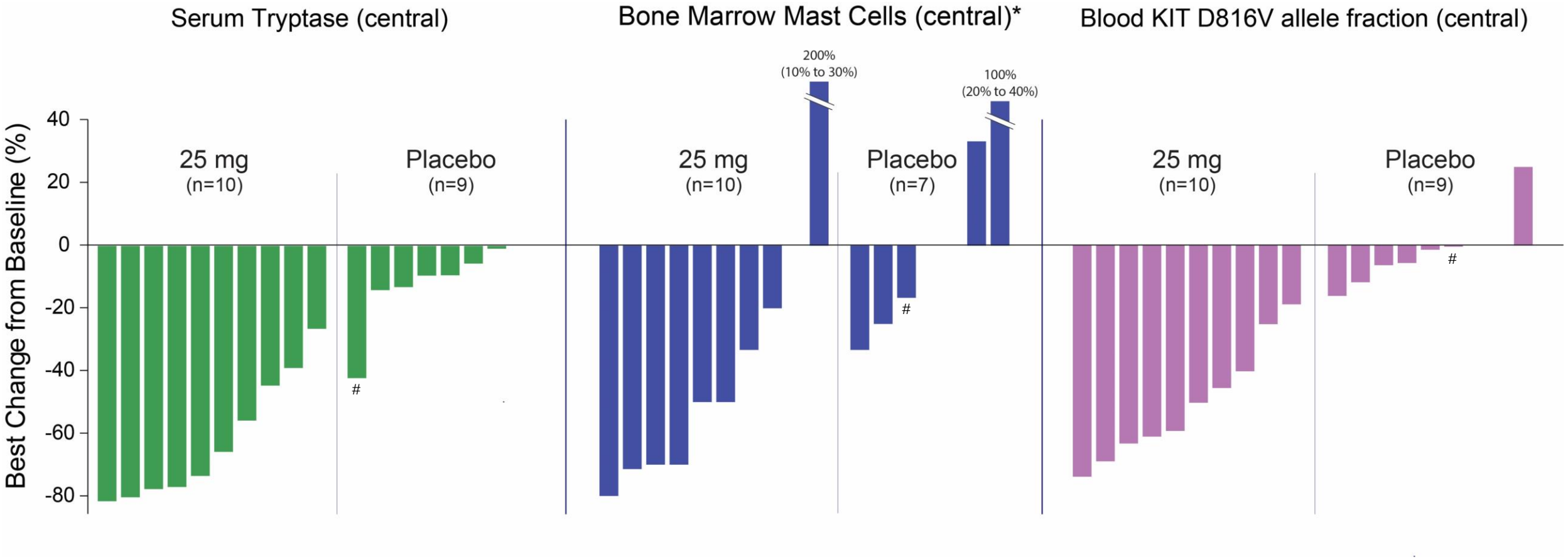
Baseline Week 16

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