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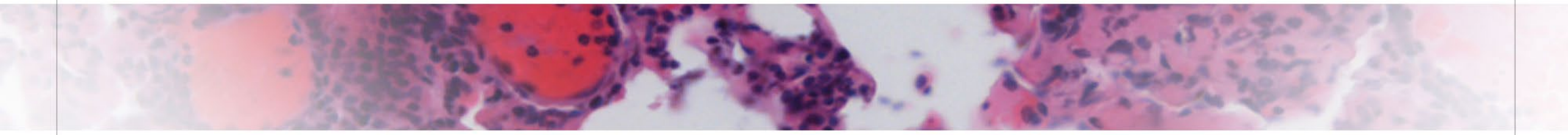

Results from PIONEER: a randomized, double-blind, placebo-controlled, phase 2 study of avapritinib in patients with indolent systemic mastocytosis

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AYVAKIT™ (avapritinib) is approved by the US Food and Drug Administration (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 Europe, AYVAKYT® (avapritinib) is approved by the European Medicines Agency (EMA) for the treatment of adult patients with unresectable or metastatic GIST harbouring the *PDGFRA* D842V mutation.

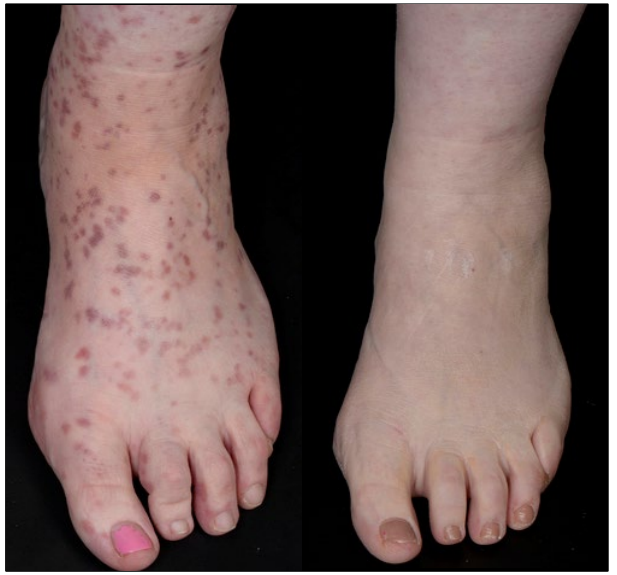
Avapritinib is not approved as safe or effective for use in systemic mastocytosis or any other indication by the FDA, EMA, or any healthcare authority in any jurisdiction.

Systemic mastocytosis is a clonal mast cell neoplasm driven by the *KIT* D816V mutation[1,2]

- **MC hyperactivation, proliferation and mediator release are responsible for debilitating skin, gastrointestinal and neurological symptoms[3–5]**

- **There are no approved disease-modifying therapies for patients with indolent SM**

- **Avapritinib, a highly potent and selective KIT D816V inhibitor, markedly reduced MC burden in the EXPLORER phase 1 study in patients with advanced SM[6,7]**



Baseline On study

PIONEER (NCT03731260) is a randomized, double-blind, placebo-controlled, phase 2 study of avapritinib versus placebo in patients with indolent SM and symptoms inadequately controlled by supportive care

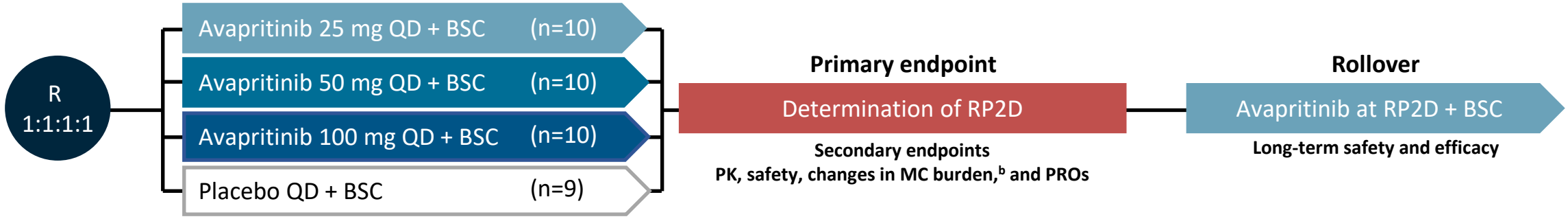
MC, mast cell; SM, systemic mastocytosis.

1. Gulen T et al. *J Intern Med*. 2016;279:211–228; 2. Pardanani A. *Am J Hematol*. 2016;91:1146–1159; 3. Rossignol J et al. *F1000Research*. 2019;8:1961; 4. Pardanani A. *Am J Hematol*. 2019;94:363–377; 5. Valent P et al. *Int J Mol Sci*. 2019;20;789; 6. Evans EK et al. *Sci Transl Med*. 2017;9:eaao1690; 7. Radia D et al. Presented at the 24th European Hematology Association Congress, Amsterdam, Netherlands, June 15, 2019.

PIONEER part 1 study design

Key eligibility criteria

- Age ≥18 years, ECOG PS 0–2
- Indolent SM confirmed by central pathology review of BM biopsy and central review of B- and C-findings, according to WHO criteria
- Moderate-to-severe symptoms[a] despite ≥2 BSC medications



- PIONEER part 2 is currently enrolling, aiming to assess the safety and efficacy of avapritinib RP2D[1]
- Patients who complete PIONEER part 1 or part 2 will be eligible to enter an open-label extension to evaluate the long-term safety and efficacy of avapritinib RP2D
- ISM-SAF is a reliable construct valid PRO tool for indolent SM[2]
  - Clinical benefit measure and primary endpoint in PIONEER part 2
  - Symptoms in 3 domains scored daily from 0–10, to generate a TSS from 0–110, and analyzed as a 14-day moving average

[a]Based on minimum mean TSS over the 14-day eligibility screening period. [b]Measured by reduction of serum tryptase, peripheral blood *KIT* D816V allele fraction and BM MCs.
BM, bone marrow; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PK, pharmacokinetics; PRO, patient reported outcome; QD, once daily; R, randomize; RP2D, recommended phase 2 dose; TSS, total symptom score; WHO, World Health Organization.

1. Akin C et al. Presented at the 62nd American Society of Hematology Annual Meeting. December 5–8, 2020. Abstract 1247; 2. Shields A et al. *Value Health.* 2019;22 (suppl 3):S867–868.

Baseline clinical characteristics and patient disposition

Patient demographic		All doses (n=39)	
Age (years), median (range)		51 (21–75)	
Female, n (%)		30 (77)	
ECOG PS, n (%)			
0		12 (31)	
1		19 (49)	
2		8 (21)	
Mast cell burden		**All doses (n=39)**	
Central diagnosis of indolent SM, 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]**
Detected, n (%)	31 (80)	11 (28)	37 (95)
Median MAF, % (range)	–	11 (1.9–32)	0.36 (0.02–30.22)

SM therapy	All doses (n=39)
Prior cytoreductive therapy, n (%)	6 (15)
Midostaurin, imatinib, dasatinib, masitinib	5 (13)
Interferon-alfa	1 (3)
Baseline supportive care medications, median (range)	4 (2–9)
H1 blockers, n (%)	37 (95)
H2 blockers, n (%)	30 (77)
Leukotriene receptor antagonists, n (%)	23 (59)
Proton pump inhibitors, n (%)	18 (46)
Cromolyn sodium, n (%)	12 (31)
Corticosteroids, n (%)	6 (15)
Omalizumab, n (%)	9 (23)
Patient disposition	**All doses (n=39)**
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

Based on data cut-off date of December 27, 2019

[a]Local quantitative and qualitative *KIT* testing of bone marrow and/or blood, various methods and sensitivities. [b]NGS targeted myeloid panel (central) in bone marrow samples, algorithmic calling sensitivity to 1.0% MAF; median MAF and range at screening. [c]ddPCR 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; ddPCR, droplet digital polymerase chain reaction; MAF, mutation allele fraction; NGS, next generation sequencing; SD, standard deviation.

Avapritinib was well tolerated across all doses

AEs in ≥15% of placebo or combined avapritinib arms (any grade)[a]	Placebo (n=9)		Avapritinib					
			25 mg (n=10)		50 mg (n=10)		100 mg (n=10)	
	Any grade	Grade 3	Any grade	Grade 3	Any grade	Grade 3	Any grade	Grade 3
Patients with AE, %	89	22	100	0	80	20	90	40
Bone pain	22	0	0	0	0	0	0	0
Arthralgia	22	0	10	0	10	0	0	0
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

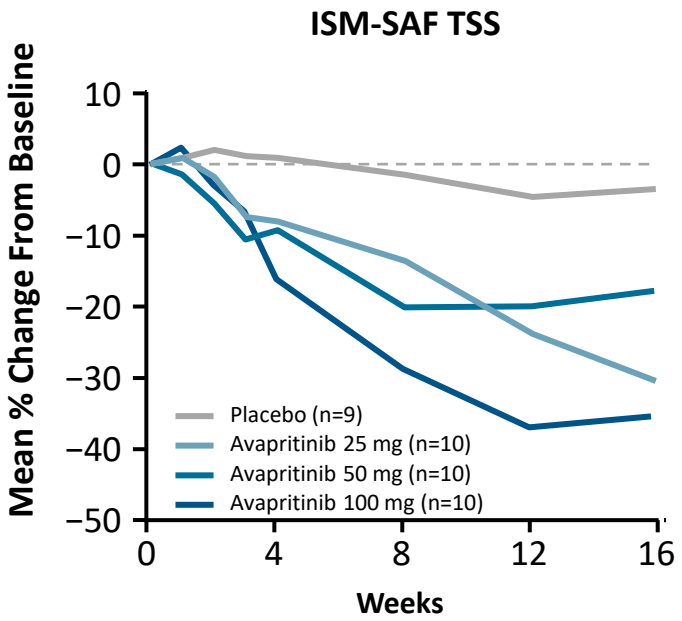
- No Grade 3 AEs or dose modifications were reported in the 25 mg cohort
- No Grade 4 or 5 AEs were reported in the study
- At data cut-off, no patients had discontinued avapritinib due to AEs or progression to AdvSM
- No neutropenia, anemia, thrombocytopenia, or intracranial bleeding was reported
- One Grade 3 cognitive disorder in the 100 mg cohort was resolved following dose modification

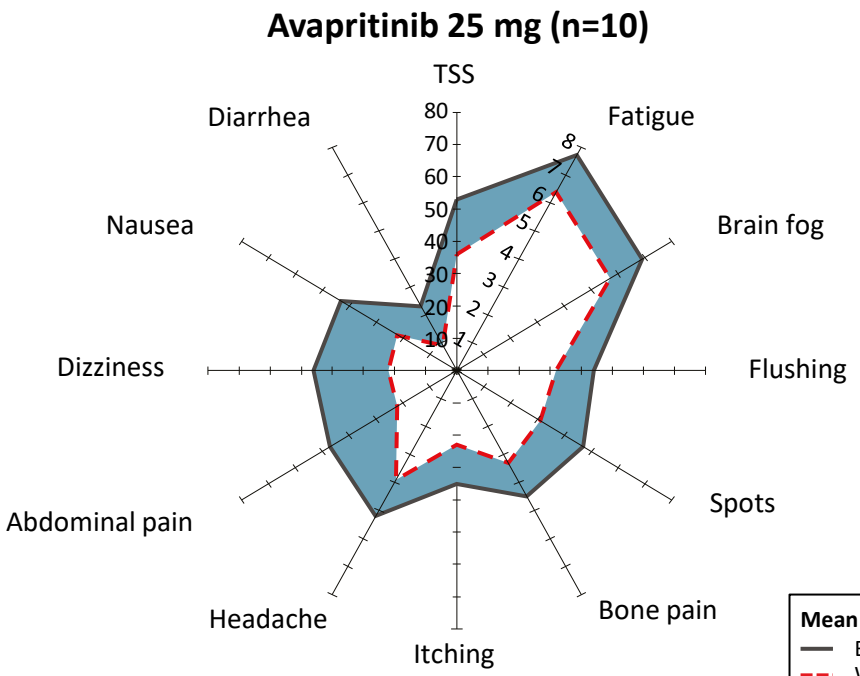
Based on data cut-off date of December 27, 2019

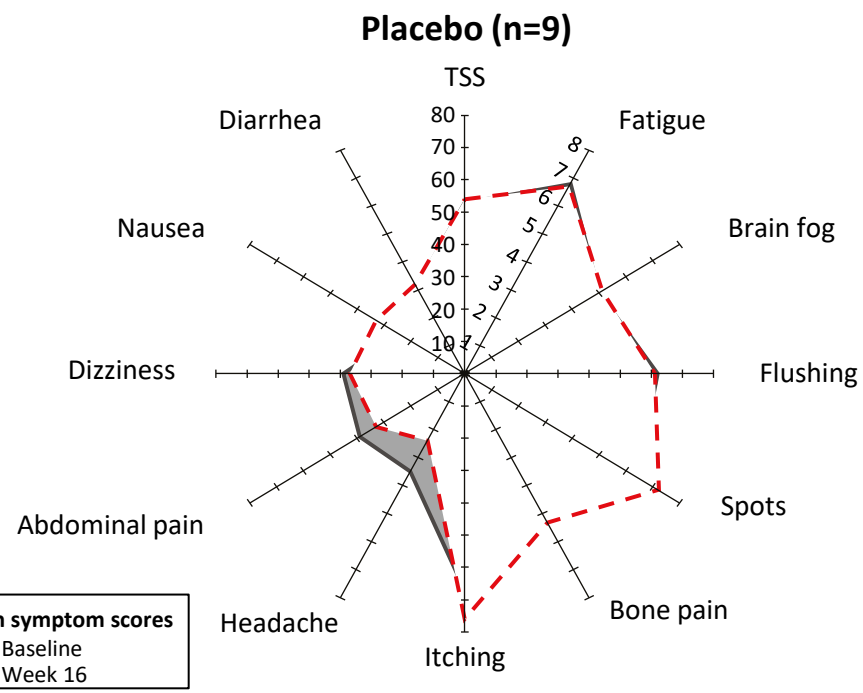
[a]Severity of all AEs were graded according to NCI CTCAE version 5.0.
AEs, adverse events; AdvSM, advanced systemic mastocytosis; NCI CTCAE; National Cancer Institute Common Terminology Criteria for AEs.

Avapritinib improved symptom burden at all doses by ISM-SAF

- Similar temporal improvements in all individual symptoms that comprised TSS were observed across the 3 QD avapritinib doses (line graph)
- Based on tolerability and efficacy findings, avapritinib 25 mg QD was selected as the RP2D
- A significant ~30% mean symptom reduction in ISM-SAF TSS was observed in avapritinib-treated patients (all cohorts combined) versus placebo by Week 16 (*P*=0.001, not shown)
- The most bothersome symptoms domains at baseline (skin and neurological symptoms for 47% of patients) were improved by avapritinib 25 mg versus placebo by Week 16 (radar plots)

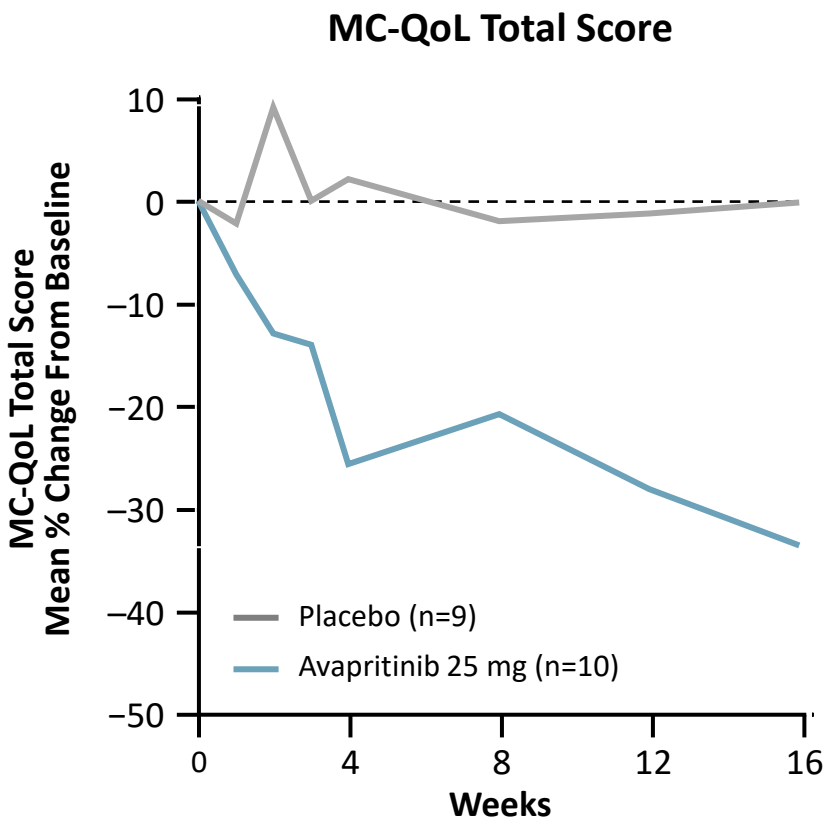


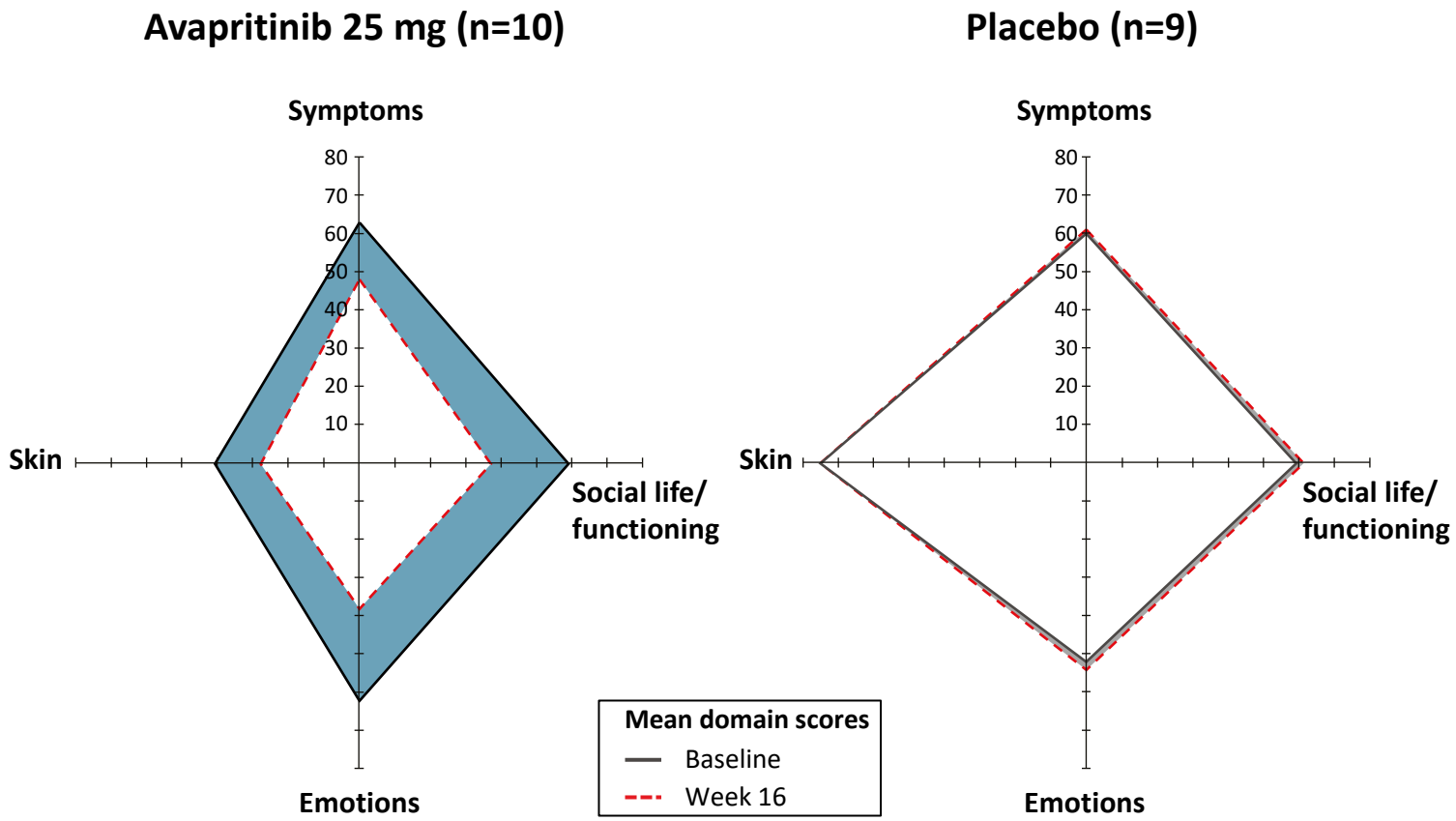




Based on data cut-off date of December 27, 2019

Avapritinib 25 mg QD improved QoL versus placebo by MC-QoL

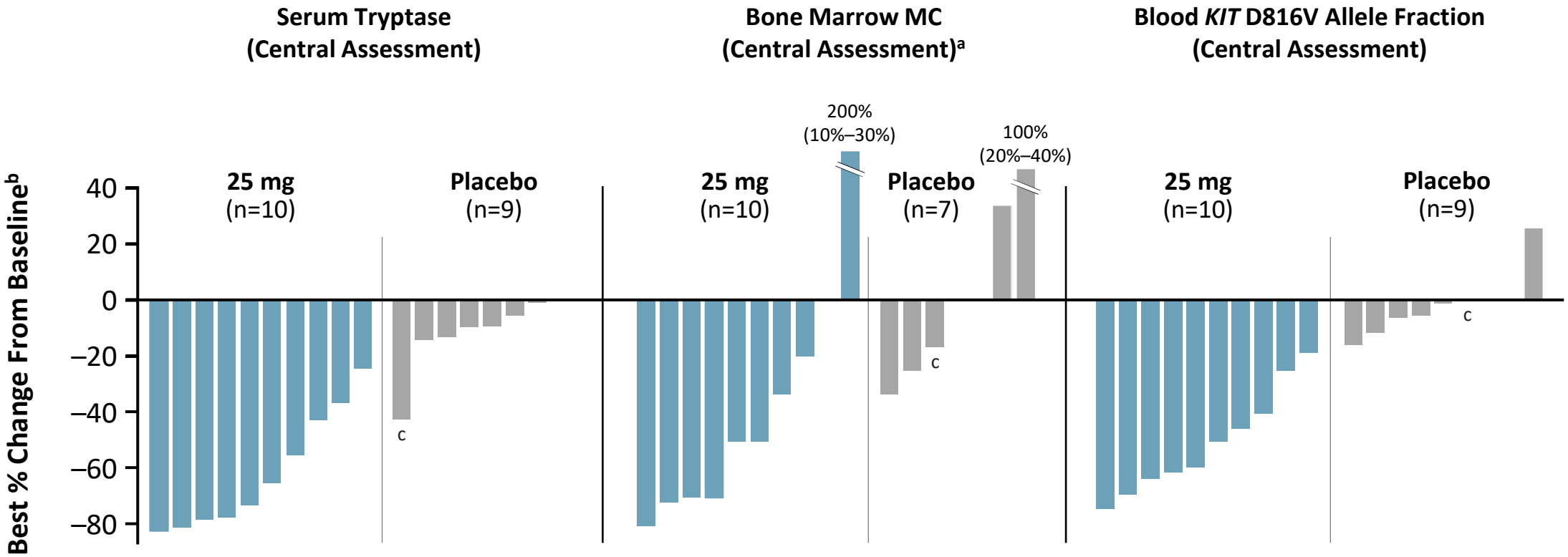




Based on data cut-off date of December 27, 2019

MC-QoL, Mastocytosis Quality of Life Questionnaire

Avapritinib 25 mg QD improved objective measures of MC burden versus placebo



Based on data cut-off date of December 27, 2019

[a]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; [b]Serum tryptase assessments at Weeks 1, 2, 3, 4 and every 4 weeks thereafter; bone marrow assessment at Week 12; mutation burden assessments at Weeks 2 and 4 and every 4 weeks thereafter; [c]Patient received high dose intravenous steroids.

Conclusions

- Avapritinib, a highly potent and selective KIT D816V inhibitor, had a favorable safety profile and demonstrated potential as a new treatment for patients with indolent SM, supporting further evaluation of a continuous dosing regimen
- Avapritinib 25 mg QD was selected as the RP2D; clinically meaningful improvements over baseline at Week 16 were reported at this dose
  - Reductions in TSS and most bothersome symptom group
  - Improvements in QoL, as measured by MC-QoL overall score and all domain scores
  - Reductions in bone marrow MC burden, serum tryptase, and blood *KIT* D816V allele fraction
- Part 2 will be conducted with 25 mg QD; the study is currently enrolling patients in the USA and Europe[1]

1. Akin C et al. Presented at the 62nd American Society of Hematology Annual Meeting. December 5–8, 2020. Abstract 2988

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