# *Avapritinib reduces cutaneous symptoms and mast cell burden in patients with indolent systemic mastocytosis in the PIONEER study*

**Karin Hartmann**[1*], Sigurd Broesby-Olsen[2*], Frank Siebenhaar[3*], Hanneke O. Elberink[4], Jason Gotlib[5], Vito Sabato[6], Mariana Castells[7], Michael W. Deininger[8], Mark L. Heaney[9], Tracy I. George[8], Deepti H. Radia[10], Massimo Triggiani[11], Paul van Daele[12], Daniel J. DeAngelo[13], Oleg Schmidt-Kittler[14], Hui-Min Lin[14], Andrew Morrison[14], Brenton Mar[14], Cem Akin[15**], Marcus Maurer[3**]

[1]University of Basel, Basel, Switzerland; [2]Odense University Hospital, Odense, Denmark; [3]Dermatological Allergology, Allergie-Centrum-Charité-Universitätsmedizin Berlin, Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; [4]University Medical Center Groningen, Groningen, The Netherlands; [5]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, USA; [6]University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; [7]Brigham and Women's Hospital, Boston, USA; [8]University of Utah, Salt Lake City, USA; [9]Columbia University Medical Center, New York, USA; [10]Guy's & St Thomas' NHS Foundation Trust, London, UK; [11]University of Salerno, Salerno, Italy; [12]Erasmus Medical Center, Rotterdam, The Netherlands; [13]Dana-Farber Cancer Institute, Boston, USA; [14]Blueprint Medicines Corporation, Cambridge, USA; [15]University of Michigan, Ann Arbor, USA

6 – 8 June 2020

*,**authors contributed equally

# Disclosures

In relation to this presentation, I declare the following real or perceived conflicts of interest:

| Type | Company |
|---|---|
| Employment full time / part time | University of Basel, Basel, Switzerland |
| Consulting, honoraria and reimbursement of travel expenses | ALK-ABelló, Allergopharma, Blueprint Medicines Corporation, Deciphera, Menarini, Novartis and Takeda |
| Research Grant | Euroimmun, Thermofisher |
| Other research support | None |
| Ownership interest (stock, stock-options, patent or intellectual property | None |

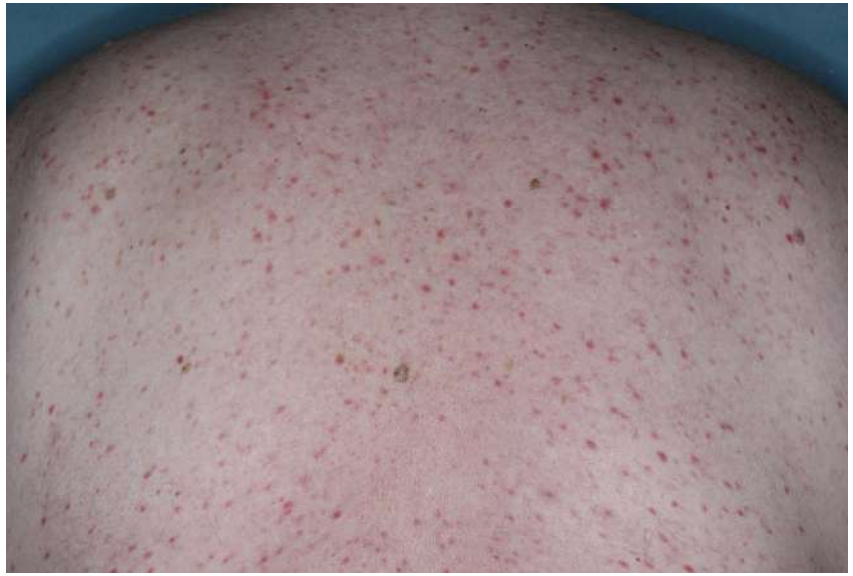
AYVAKIT™ (avapritinib) is approved by the FDA for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations, in the United States. Avapritinib has 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.

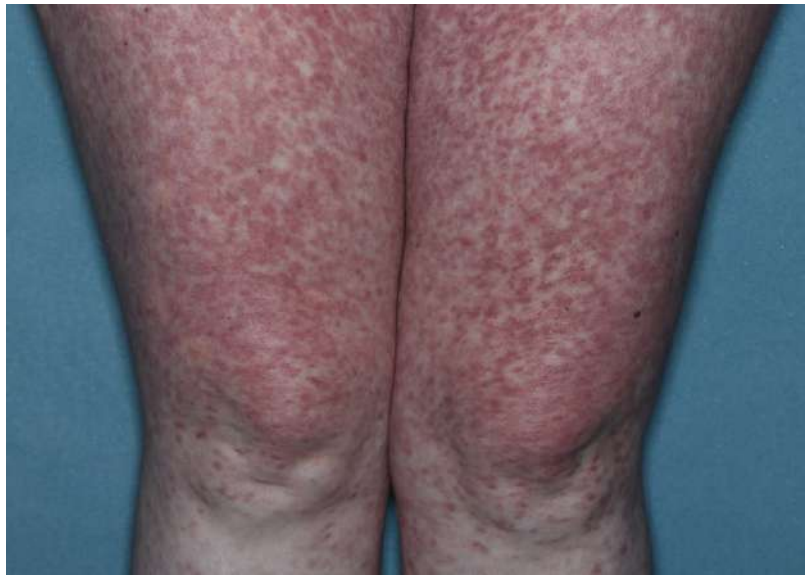


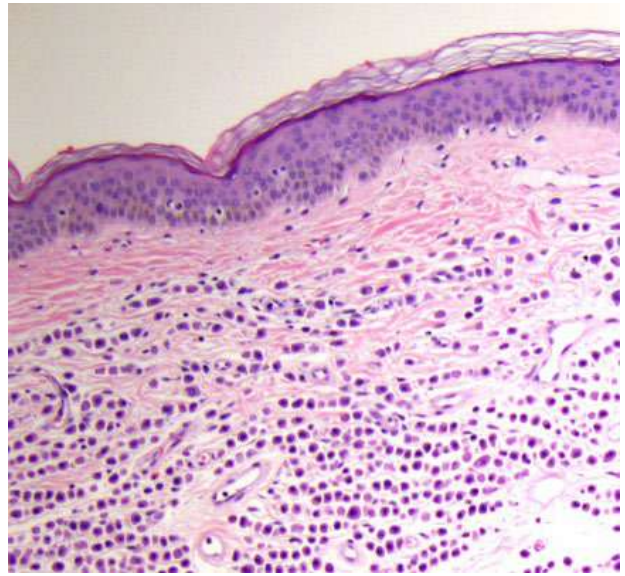
FDA, Food and Drug Administration.

# Systemic mastocytosis is a clonal mast cell neoplasm driven by *KIT* D816V

- ***KIT* D816V** mutation drives **mast cell hyperactivation** and **accumulation** throughout various organs[1]
- This leads to debilitating **skin**, **gastrointestinal**, **neurocognitive** and **systemic** symptoms[2]
- In indolent SM, cutaneous involvement is frequent and is associated with **pruritis, flushing** and **pigmented skin lesions** which can severely impact quality of life[2]







- Currently **no approved therapies** effectively reduce the burden of disease in indolent SM, including the skin lesions[2]

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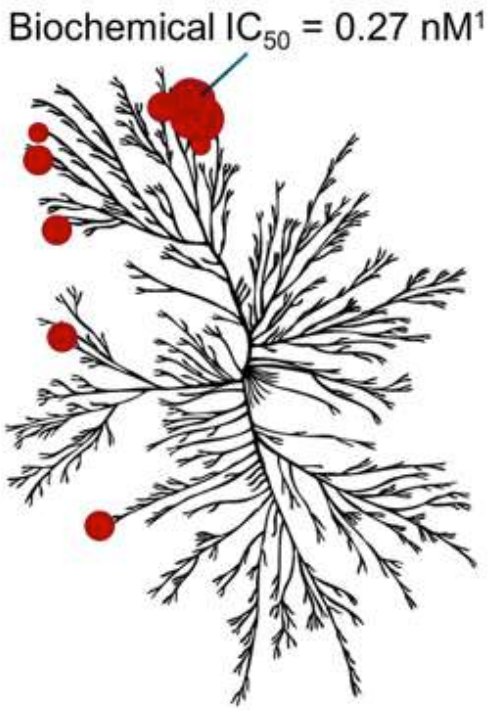
SM, systemic mastocytosis.

1. Rossignol J et al. F1000 Research 2019; 8:1961; 2. Czarny J et al. Adv Dermatol Allergol 2018; 35:541–545.

# Avapritinib targets *KIT* D816V with objective and symptomatic responses in SM

## Avapritinib is a TKI that is highly potent on *KIT* D816V with a highly selective kinome profile[1]

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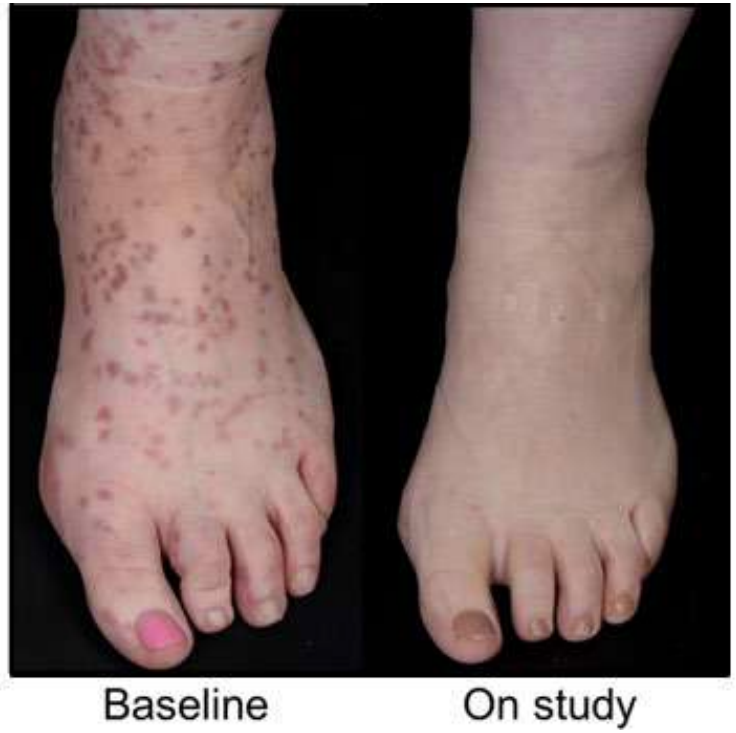
## Phase I EXPLORER trial: confirmed ORR of 77% in AdvSM[2]

FDA breakthrough designation for AdvSM
Phase 2 PATHFINDER in AdvSM enrolling

## Efficacy on AdvSM symptoms including potential for resolution of mastocytosis in skin[2,3]

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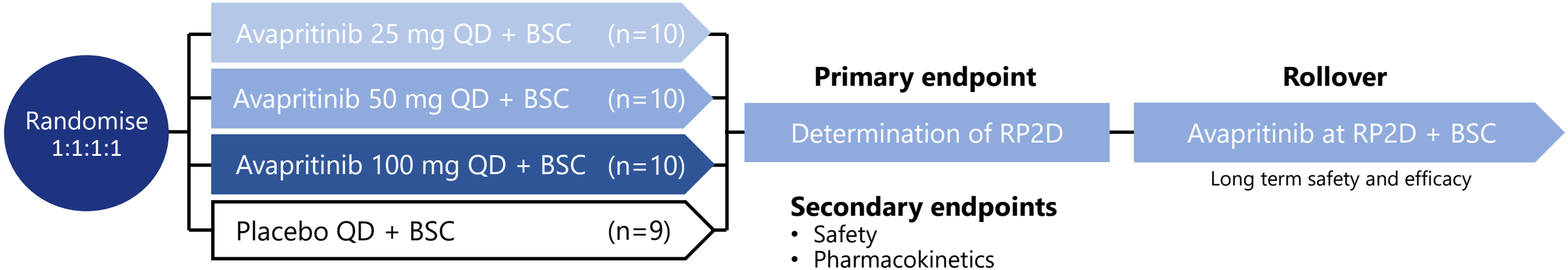
AdvSM, advanced systemic mastocytosis; FDA, Food and Drug Administration; $IC_{50}$, half-maximal inhibitory concentration; ORR, overall response rate; SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor. 1. Evans EK et al. *Sci Transl Med.* 2017;9:eaao1690. 2. Radia D et al. Presented at the 24th European Hematology Association Congress, Amsterdam, the Netherlands, July 1316, 2019. 3. Gotlib JR et al. *Blood.* 2018;132 (suppl 1):351.

# PIONEER Phase II clinical trial of avapritinib in non-advanced SM

## Part 1: dose selection (fully enrolled) – selection of well-tolerated, long-term dose with appropriate benefit–risk for indolent SM




**Secondary endpoints**

- Safety
- Pharmacokinetics
- Changes in mast cell burden*
- Changes in patient-reported outcomes
- Changes in cutaneous disease (photography)
- Changes in skin mast cells (pathology)

RP2D selected as **25 mg QD**
Plan to initiate Part 2 patient screening in June 2020

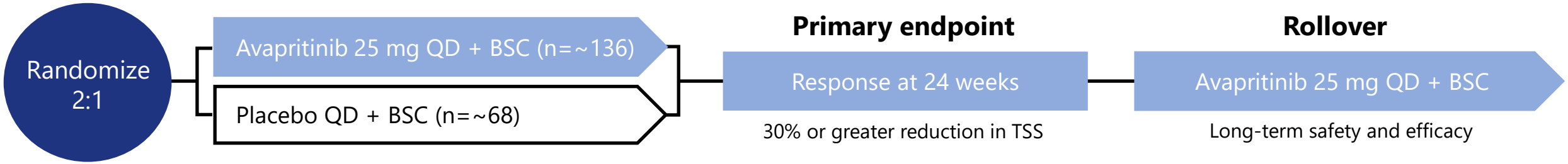


*Measured by reduction of serum tryptase, peripheral blood *KIT* D816V allele fraction and bone marrow mast cells.
BSC, best supportive care; QD, once daily; R2PD, recommended Part 2 dose; SM, systemic mastocytosis.

# PIONEER phase II clinical trial of avapritinib in non-advanced SM

## Part 2: pivotal efficacy (pending) – registration-enabling portion powered to demonstrate efficacy over placebo

*30% or greater reduction in Total Symptom Score (TSS) determined as clinically important response*




### Key secondary endpoints

- Proportions of patients with 50% or greater reduction in:
  - Serum tryptase
  - Peripheral blood KIT D816V allele fraction
  - Bone marrow mast cells
- Mean change in TSS from Baseline to week 24

### 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 BSC medications



BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; QD, once daily; SM, systemic mastocytosis; WHO, World Health Organization.

# Assessment of avapritinib efficacy on cutaneous signs and symptoms

## Patient Reported Outcomes

- Indolent SM-Symptom Assessment Form (ISM-SAF) was completed daily
  - 24-hour recall, analysed as a 14-day average
  - Severity of 11 symptoms ranging from 0 (no symptoms) to 10 (worst imaginable) was asked daily
  - Total Symptom Score (TSS) was the total of all symptoms

## Skin Assessments

- High resolution skin photography (front and rear torso and thighs)
  - Percent affected fractional surface area (as determined by best of four detection methods)
  - Most affected region at baseline as determined by the Skin Assessment Committee
  - Colour change over time as determined by the Skin Assessment Committee

- Mast cell number per $mm^2$ in lesional skin



AEs, adverse events; QD, once daily; R2PD, recommended Part 2 dose; SM, systemic mastocytosis; TSS, total symptom score.

# Baseline characteristics of PIONEER population

| Patient demographics | All doses (n=39) |
|---|---|
| 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 | 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) | | |
| *KIT* D816V mutation | Local[a] | Central NGS[b] | Central ddPCR[c] |
| n (%) detected | 31 (80) | 11 (28) | 37 (95) |
| Median MAF, % (range) | – | 11 (1.9–32) | 0.36 (0.16–30.22) |

| SM therapy, n (%) | All doses (n=39) |
|---|---|
| Prior cytoreductive therapy | 6 (16) |
| Midostaurin, imatinib, dasatinib, masitinib | 5 (13) |
| Interferon-alfa | 1 (3) |
| Baseline supportive care medications, 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 | 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 |

**Data in this presentation are based on a cut-off of 27 December 2019 unless otherwise specified**

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[a]Local quantitative and qualitative KIT testing of bone marrow and/or blood, various methods and sensitivities. [b]NGS 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; ECOG PS, Eastern Cooperative Oncology Group performance status; MAF, mutation allele fraction; MC, mast cells; NGS, next generation sequencing; SD, standard deviation; SM, systemic mastocytosis.

# Avapritinib was well tolerated across all doses with no grade 3 AEs at 25 mg

| | Placebo n=9 | | Avapritinib 25 mg n=10 | | Avapritinib 50 mg n=10 | | Avapritinib 100 mg n=10 | |
|---|---|---|---|---|---|---|---|---|
| **Preferred term** | Any grade | Grade 3 | Any grade | Grade 3 | Any grade | Grade 3 | Any grade | Grade 3 |
| Patients with ≥1 AE, % | **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 |
| Diarrhoea | 11 | 0 | 0 | 0 | 40 | 10 | 30 | 10 |
| Fatigue | 11 | 0 | 40 | 0 | 10 | 0 | 10 | 0 |
| Face oedema | 0 | 0 | 10 | 0 | 0 | 0 | 40 | 0 |
| Peripheral oedema | 0 | 0 | 10 | 0 | 20 | 0 | 20 | 0 |
| Periorbital oedema | 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 AEs or progression to AdvSM
- No neutropenia, anaemia, thrombocytopenia or intracranial bleeding
- One Grade 3 cognitive disorder in the 100 mg cohort resolved following dose modification; patient remains on treatment at 25mg

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

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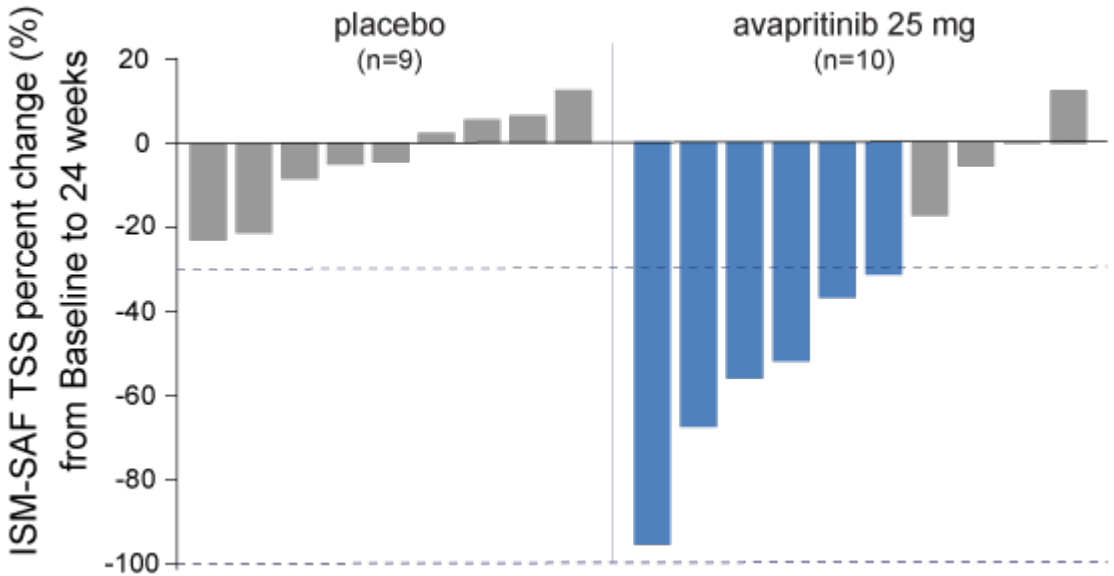
AEs, adverse events; AdvSM, advanced systemic mastocytosis.

# Avapritinib reduces overall signs and symptoms and mast cell burden in indolent SM

*At 25 mg daily, avapritinib induces significant responses in overall symptoms and serum tryptase*

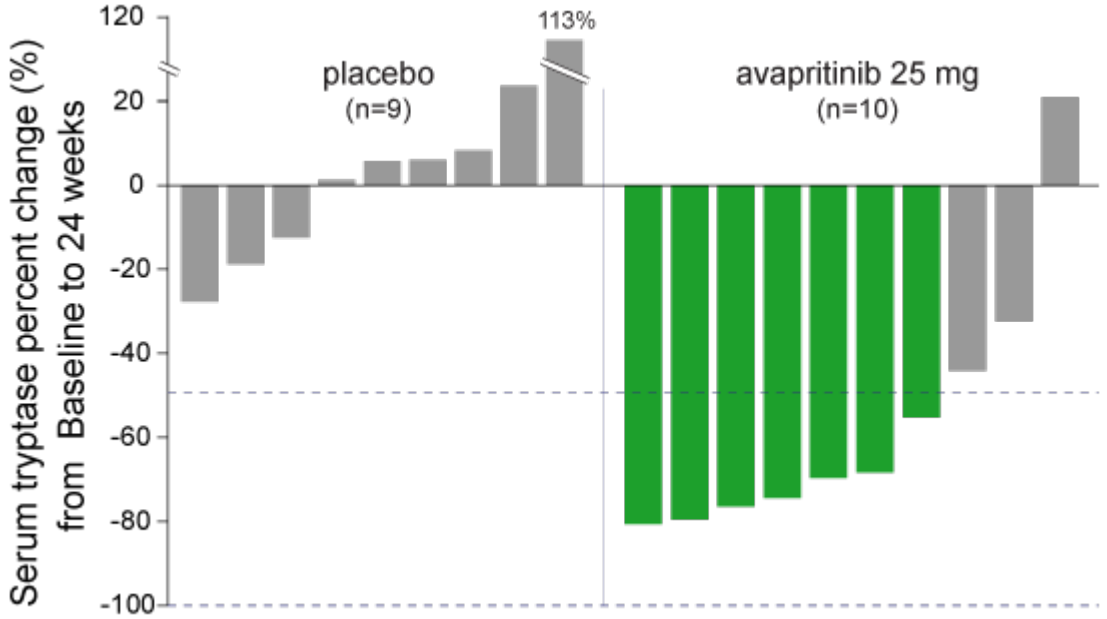
**Part 2 Primary endpoint**

≥30% reduction in ISM-SAF Total Symptom Score at 24 weeks




**Part 2 First key secondary endpoint**

≥50% tryptase reduction at 24 weeks*:




| | | | | |
|---|---|---|---|---|
| **Response rate:** | **0%** | **60%** | **0%** | **70%** |

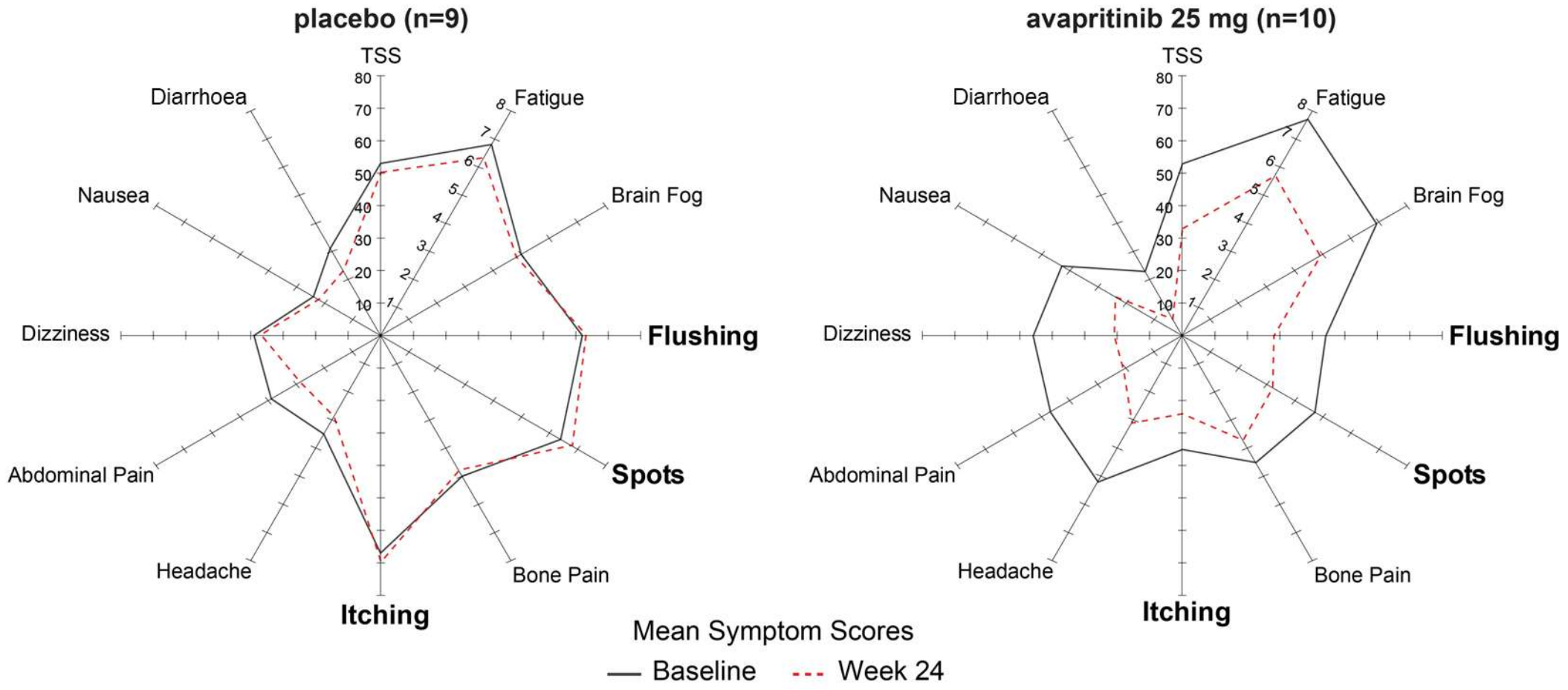
Based on a data cut-off date of 31 March 2020



*24 weeks or last assessment before, if 24 weeks not available.
ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; SM, systemic mastocytosis; TSS, Total Symptom Score.

# Avapritinib reduces individual signs and symptoms in indolent SM

*At 25 mg daily, avapritinib reduced all individual symptoms, including flushing, spots and itching*




Based on a data cut-off date of 31 March 2020

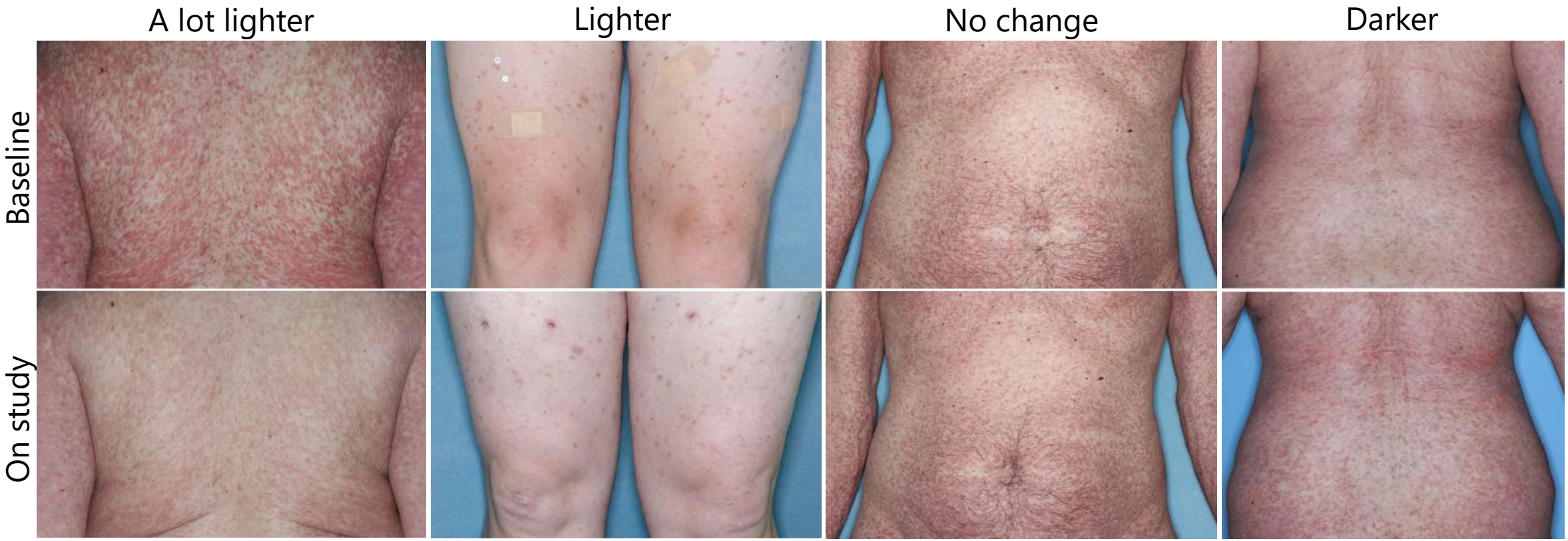


*24 weeks or last assessment before, if 24 weeks not available.
ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; SM, systemic mastocytosis; TSS, Total Symptom Score.

# Skin Assessment Committee assessed photography in a blinded fashion

High resolution skin photographs were taken at baseline and every 12 weeks during treatment in patients with significant cutaneous involvement, who consented to photography (n=26)

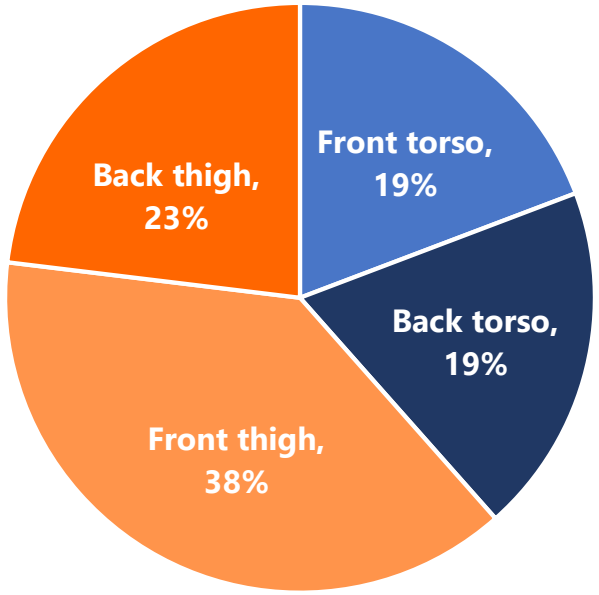
Most affected region at baseline and color change (a lot lighter to darker) was assessed, examples:



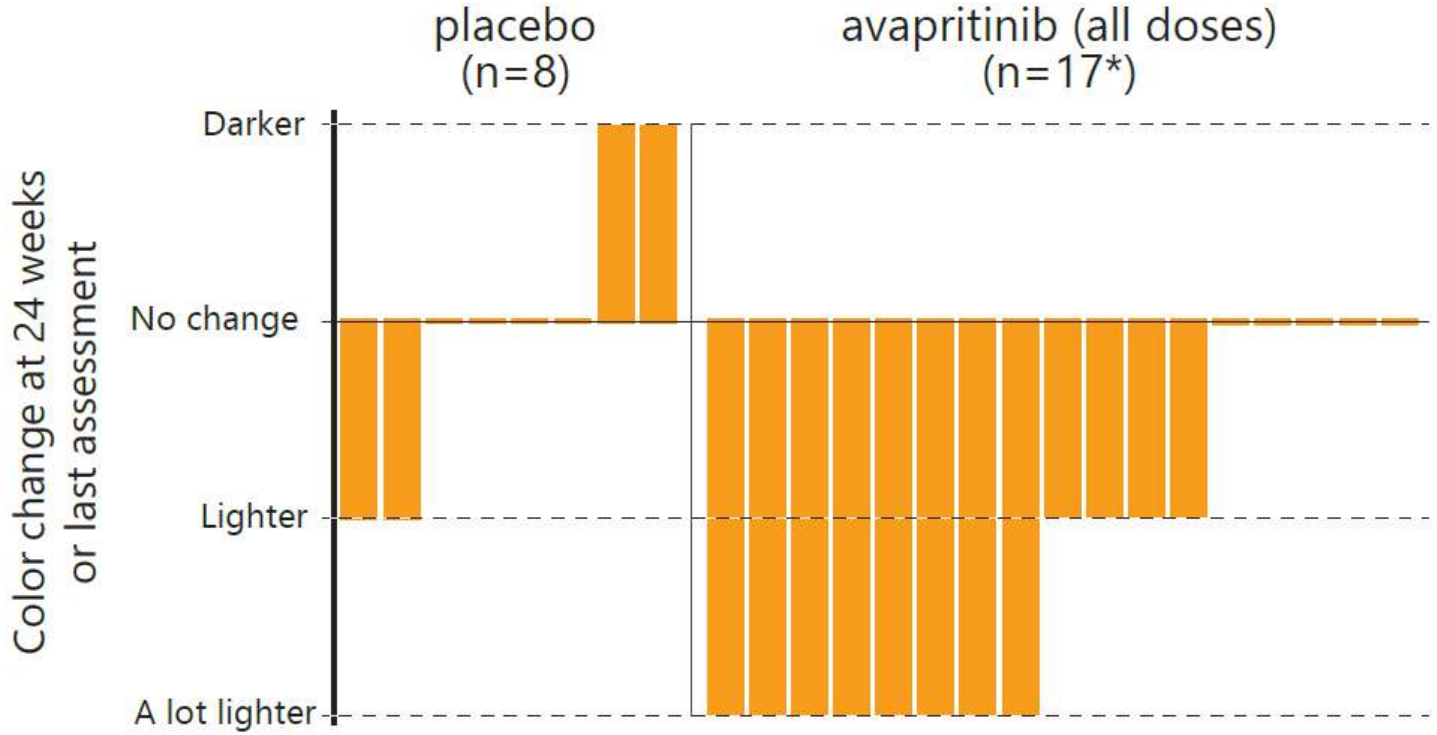

Patients' permission granted for use of photos

# Avapritinib lightens the color of skin lesions

## Most affected skin region




## Most affected skin region

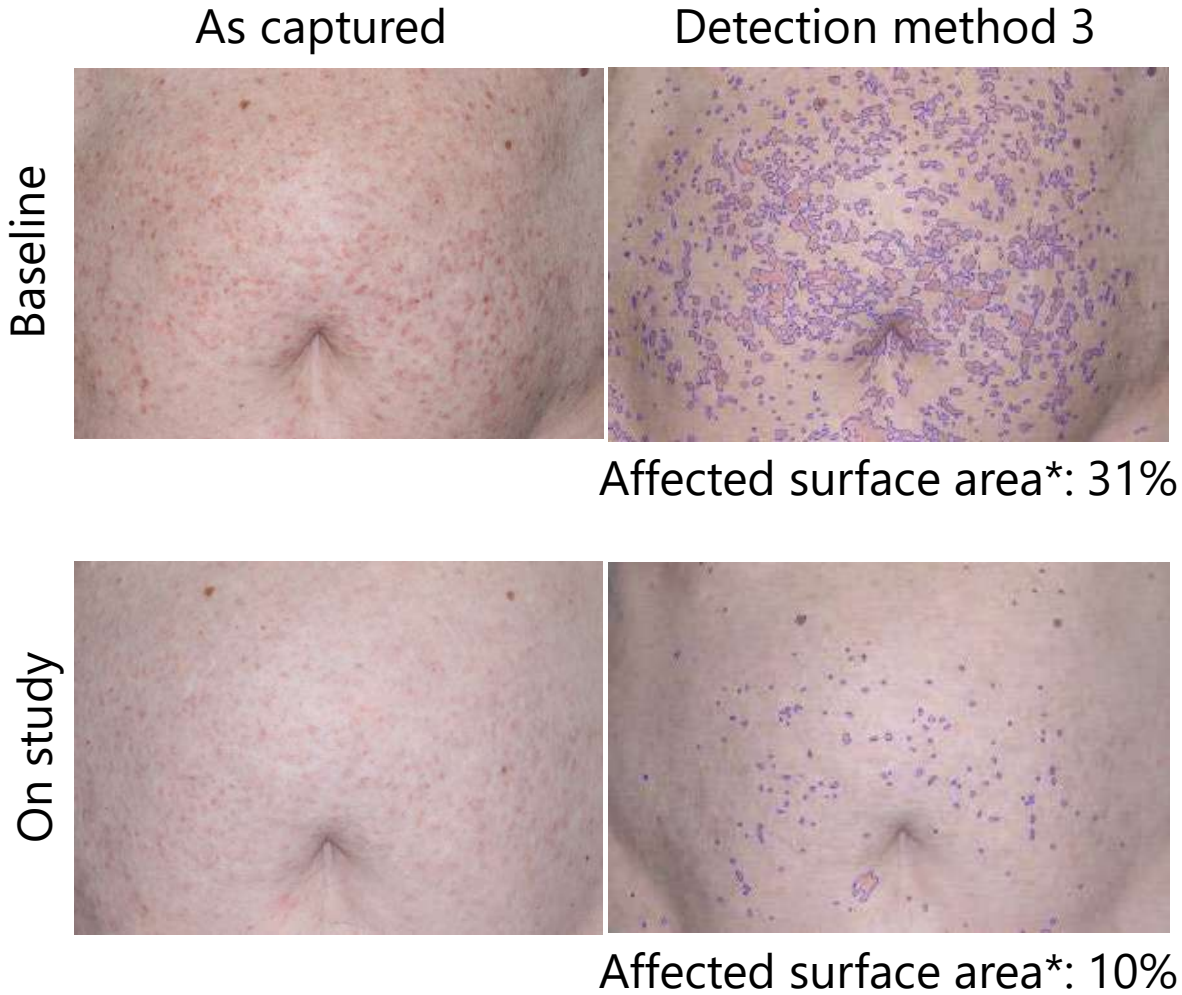



Data based on Skin Adjudication Meeting on 12 May 2020

*One patient could not be assessed for color change.

# Affected surface area determined by image analysis algorithm

- Due to the heterogenous presentation of mastocytosis in skin, four detection methods were developed to determine the affected surface area
- For each individual patient, the Skin Assessment Committee determined the best detection method at baseline
- Affected surface area in defined areas of interest was followed every 12 weeks by photography, using the same method for each patient

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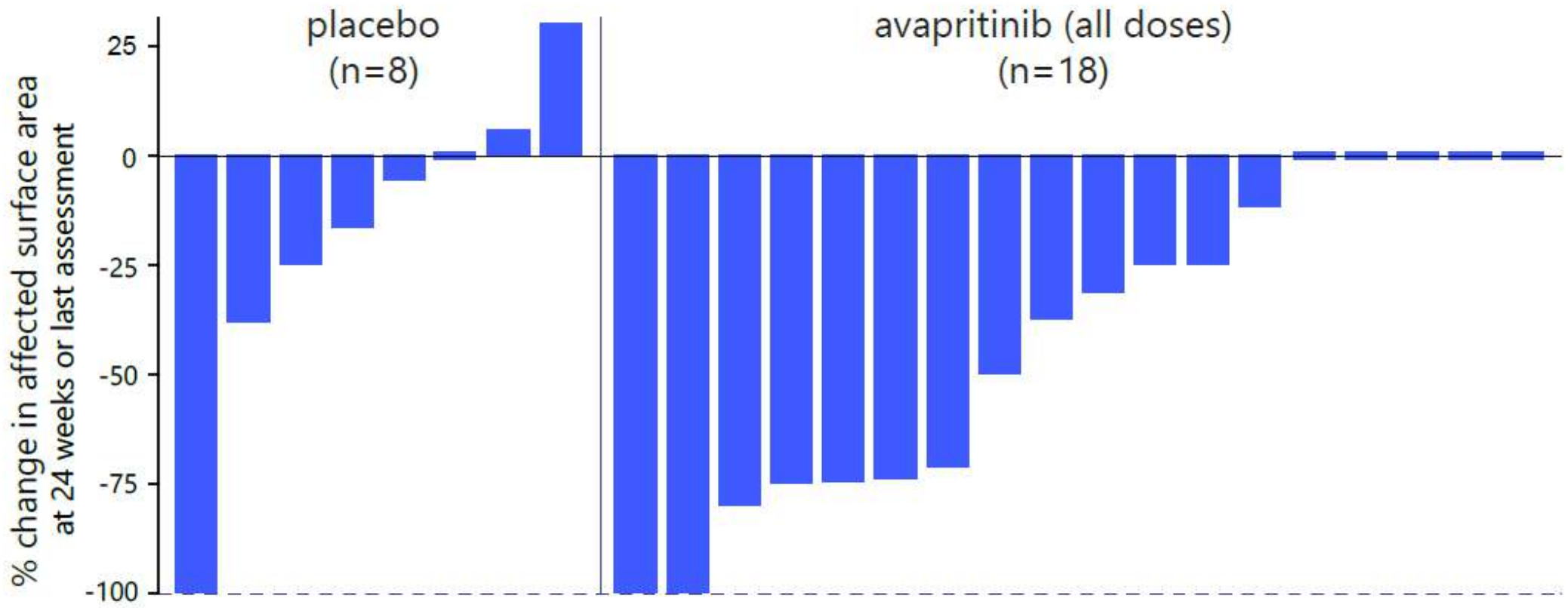
*Fractional surface area determined for entire front torso image, but only a portion shown for privacy reasons.

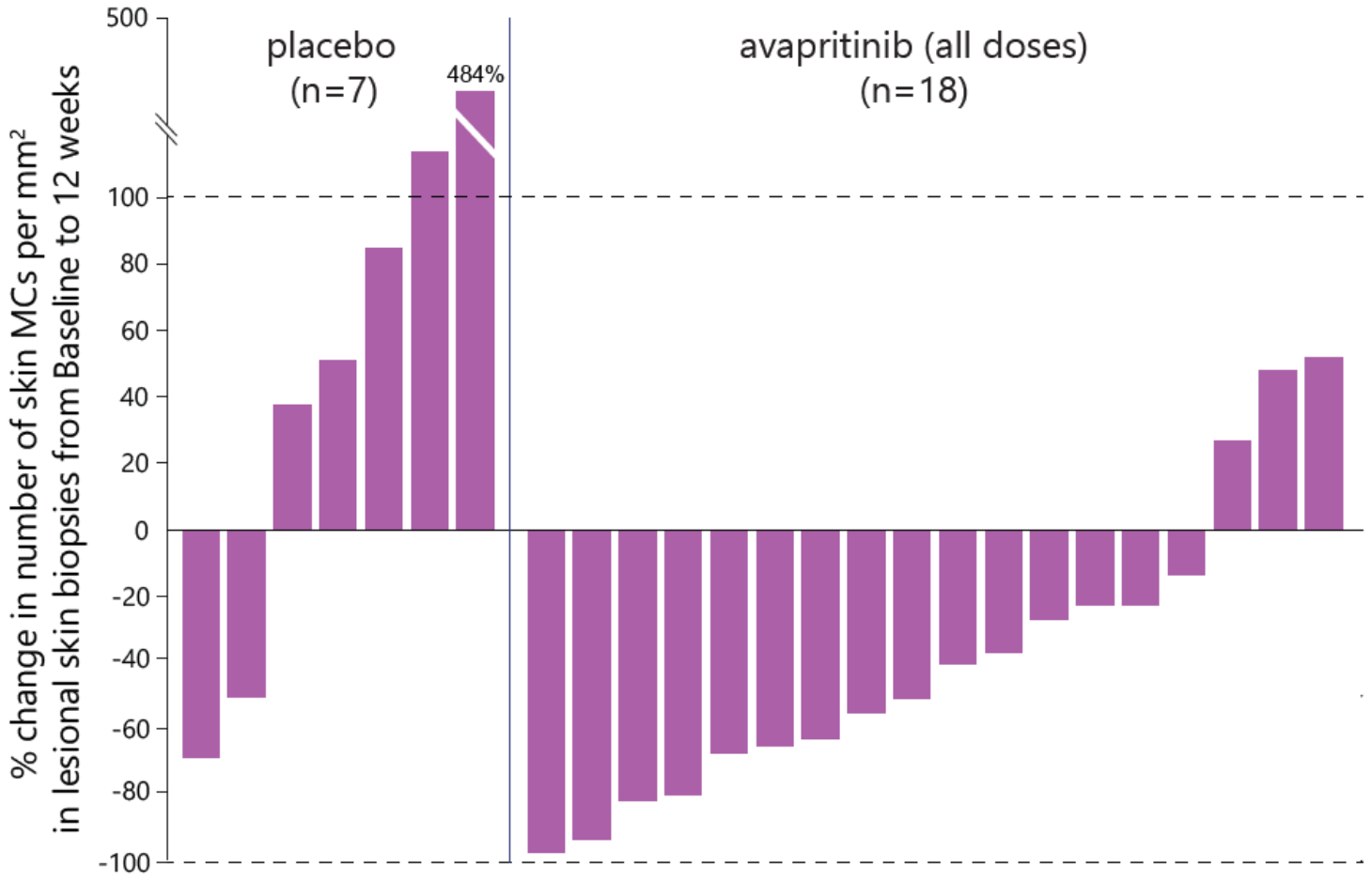
# Avapritinib reduces affected surface area of skin lesions

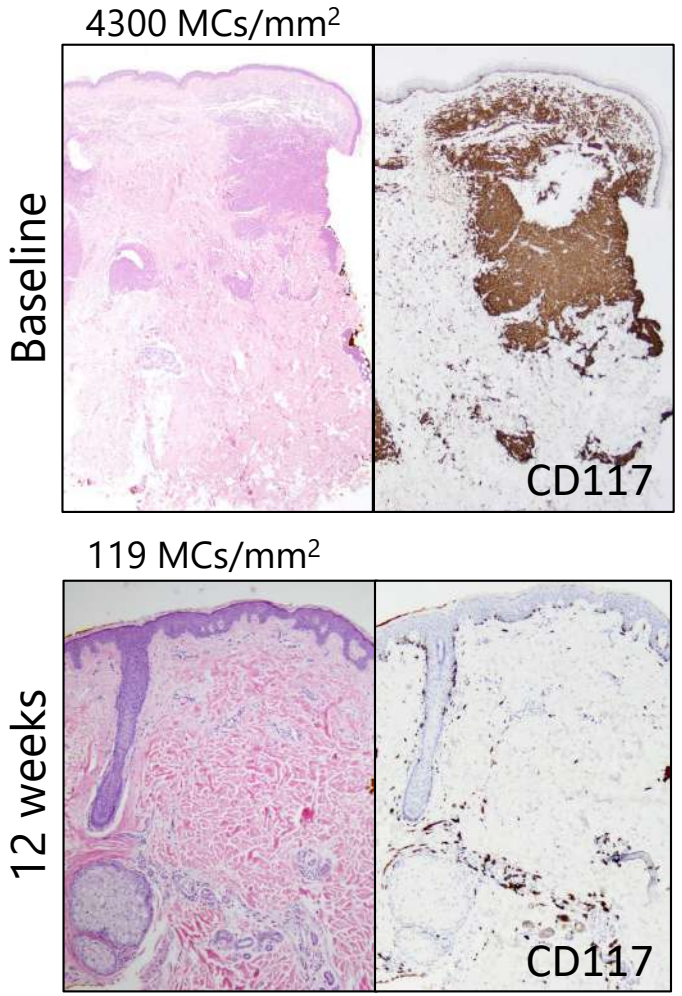
## Most affected skin region




Data based on Skin Adjudication Meeting on 12 May 2020

# Avapritinib reduces mast cell number in lesional skin biopsies






MC, mast cell.

# Avapritinib reduces signs, symptoms and mast cell burden in indolent SM

- **Clinically meaningful reductions in overall symptoms and serum tryptase at RP2D of 25 mg QD**
  - 60% and 70% response rates in TSS and serum tryptase, respectively, versus 0% for placebo

- **Avapritinib reduces the signs, symptoms and pathological findings of skin lesions**
  - Decreased mean severity of all patient-reported symptoms, including itching, flushing and spots
  - Lightens skin lesions and reduces the affected surface area of lesions in most affected regions
  - Reduces the mast cell numbers in lesional skin biopsies

- **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

Part 2 will be conducted with 25 mg daily and is expected to initiate patient screening in June 2020



AEs, adverse events; QD, once daily; R2PD, recommended Part 2 dose; SM, systemic mastocytosis; TSS, total symptom score.

# Acknowledgements


## PIONEER part 1 Investigators

Cem Akin
Hanneke Oude Elberink
Jason Gotlib
Vito Sabato
Mariana Castells
Michael W. Deininger
Mark L. Heaney
Tracy I. George
Deepti H. Radia
Massimo Triggiani
Paul van Daele
Daniel J. DeAngelo

## Skin Assessment Committee

Karin Hartman
Sigurd Broesby-Olsen
Frank Siebenhaar
Marcus Maurer

## Patients and Families

# EAACI

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