Avapritinib improves overall symptoms, skin lesions and quality of life in patients with advanced systemic mastocytosis in the PATHFINDER study

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Disclosure

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

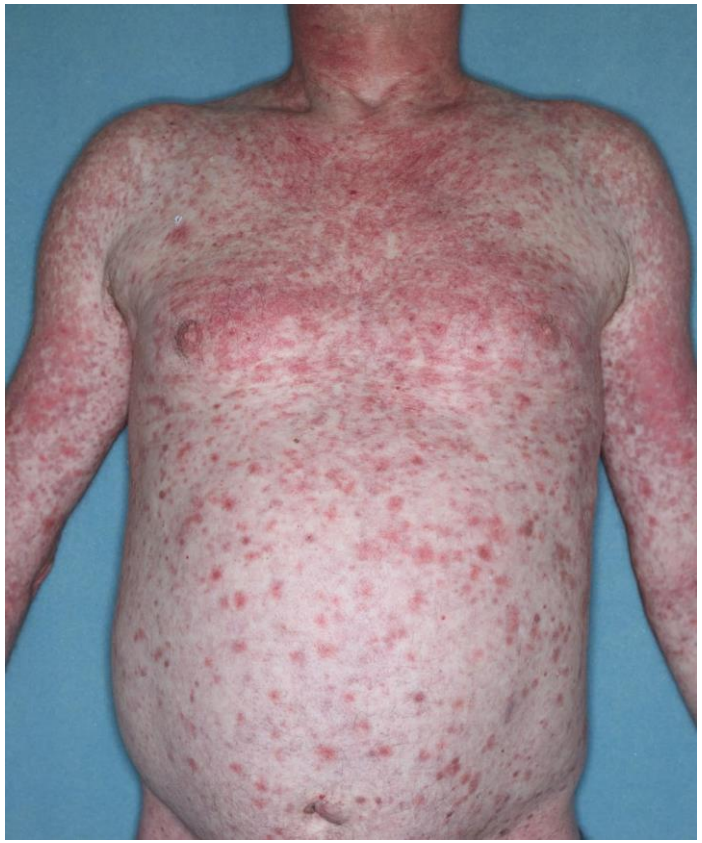
Type	Company
Employment full time/part time	Dermatological Allergology, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin
Consulting, honoraria, reimbursement of travel expenses, and/or institutional grant/research support	Allakos, Amgen, Astra-Zeneca, Bayer, Blueprint Medicines Corporation, Celldex, Dr. Pfleger, FAES, Genentech, GI Innovation, GSK, Innate Pharma, Kyowa Kirin, Lilly, Merckle Recordati, Moxie, Novartis, Regeneron, Roche, Sanofi, Third Harmonic Bio, UCB, and Uriach/
Other research support	None
Ownership interest (stock, stock-options, patent or intellectual property)	None

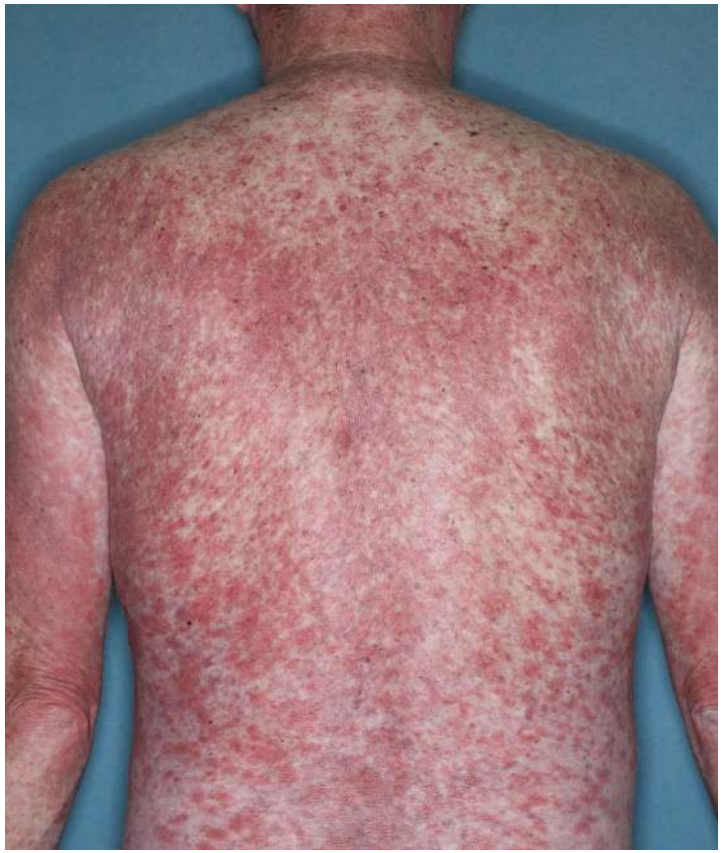
AYVAKIT™ (avapritinib) is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with advanced systemic Mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL). Limitations of Use: AYVAKIT is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50×10^9/L.

Avapritinib is not approved as safe or effective for use in non-advanced systemic mastocytosis by the FDA. Avapritinib is not approved for use in any subtype of systemic mastocytosis by the European Medicines Agency (EMA), or any healthcare authority in any jurisdiction.

1 Systemic mastocytosis (SM) is a rare, clonal mast cell (MC) neoplasm driven by *KIT* D816V mutation in ~95% of cases

- ***KIT* D816V** mutation drives **MC proliferation** and **hyperactivation** in various organs[1]
- **Severe skin**, **gastrointestinal**, **neurocognitive** and **systemic MC mediator** symptoms diminish Quality of Life (QoL)[1,2]
- In **Advanced SM**, MCs lead to organ damage resulting in **poor survival**[3]
- Few effective treatment options[3]





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1. Rossignol J et al. *F1000 Research* 2019; 8:1961; 2. Czarny J et al. *Adv Dermatol Allergol* 2018; 35:541–545; 3. Pardanani A. *Am J Hematol.* 2019;94:363–377.
MC, mast cell; QoL, quality of life.

2

Avapritinib is a potent and selective KIT D816V inhibitor which induced responses across SM subtypes

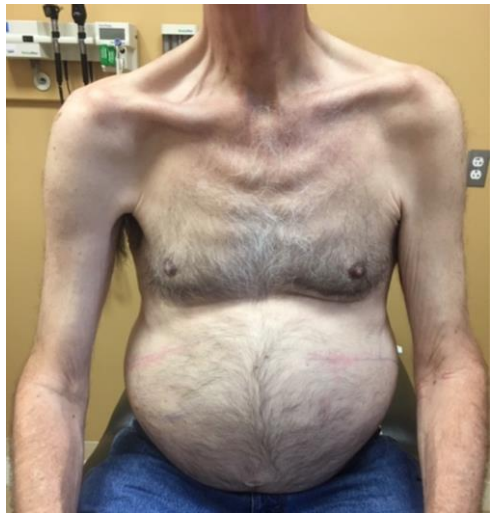
Advanced SM

EXPLORER Phase 1 Study

75% Overall Response Rate[a] per mIWG-MRT-ECNM criteria[1]

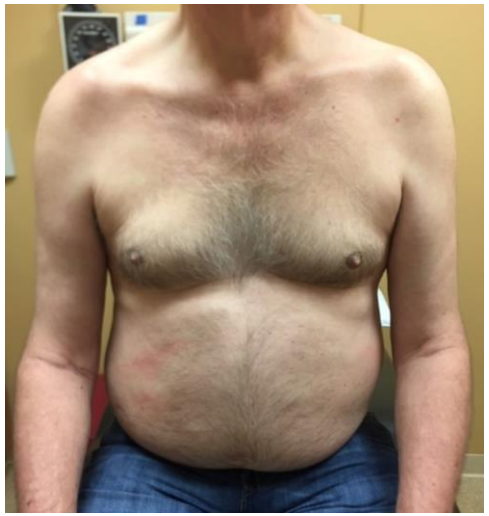
Improvements in MC burden, organ damage and patient symptoms and QoL were observed[2]

Baseline



- Serum tryptase 367 ng/mL
- Weight loss of >50 pounds
- Hypoalbuminemia (2.3 mg/dL)
- Ascites with paracentesis (15 L/week)

On study



- Serum tryptase 1.9 ng/mL
- All weight gained back
- Albumin normalized
- Ascites resolved

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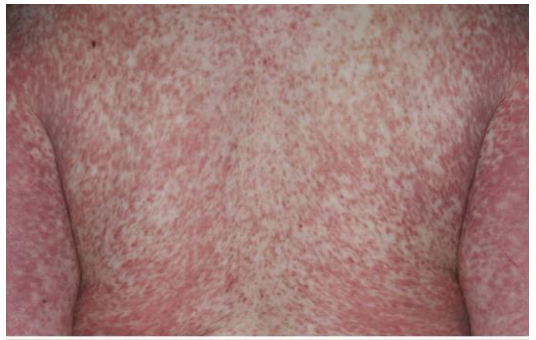
Non-Advanced SM

PIONEER Phase 2 Study (Part 1)

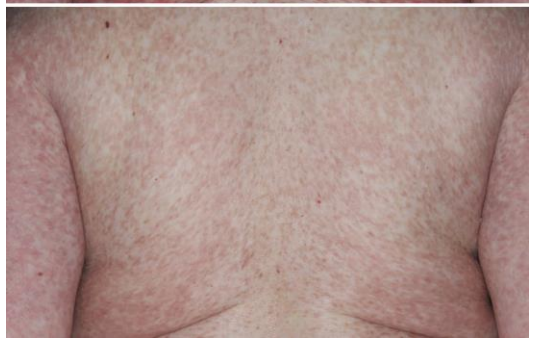
60% Response[b] in Total Symptom Score (TSS) at 24 weeks[3]

Reductions in lesion surface area, color and skin MC number[3]

Baseline



On study



[a]Overall Response Rate includes CR+CRh+PR+CI. [b]≥30% reduction in TSS. 1. Radia D et al. British Society of Hematology Annual Meeting 2021. 2. Gotlib J et al. American Society of Hematology Annual Meeting 2018. 3. Hartman K et al. European Academy of Allergy and Clinical Immunology Annual Meeting 2020. CI, clinical improvement; CR, complete remission; CRh, CR with partial hematologic recovery; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; PR, partial remission.

3 PATHFINDER Phase 2 pivotal study in Advanced SM (AdvSM)

- Central diagnosis of AdvSM
- ≥18 years of age
- ECOG PS 0–3

- Platelets <50×10^9/L excluded

Avapritinib 200[a] mg QD starting dose

Enrolled (N=62)

mIWG Evaluable, Cohort 1 (n=52)
AdvSM with ≥1 evaluable C-finding[b]

mIWG Non-Evaluable, Cohort 2 (n=10)
AdvSM without any evaluable C-findings[b]

Primary Endpoint (Cohort 1)

- Adjudicated ORR by mIWG-MRT-ECNM criteria

Response primarily based on resolution of organ damage (C-findings)

Secondary Endpoints (both cohorts)

- Reduction in MC burden (including serum tryptase)
- Safety

Symptom-related Secondary Endpoints (both cohorts)

- **Total Symptom Score** of the AdvSM-Symptom Assessment Form (AdvSM-SAF), mean change from baseline
- **Global symptom severity** by Patient Global Impression of Symptom Severity (**PGIS**) Questionnaire
- **QoL** on the EORTC QLQ-C30 survey

Symptom-related Exploratory Endpoints

- **Cutaneous disease** in patients by photography

Based on data cut-off date of June 23, 2020

[a]60 patients received 200 mg and 2 patients received 100 mg. [b]Per mIWG-MRT-ECNM criteria, response assessment requires ≥1 evaluable C-finding at baseline. MCL without an evaluable C-finding may be assessed for response based on disease burden alone (Gotlib et al. *Blood*. 2013;21:2393–2401). ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire- core questionnaire 30; MCL, mast cell leukemia; QD, once-daily.

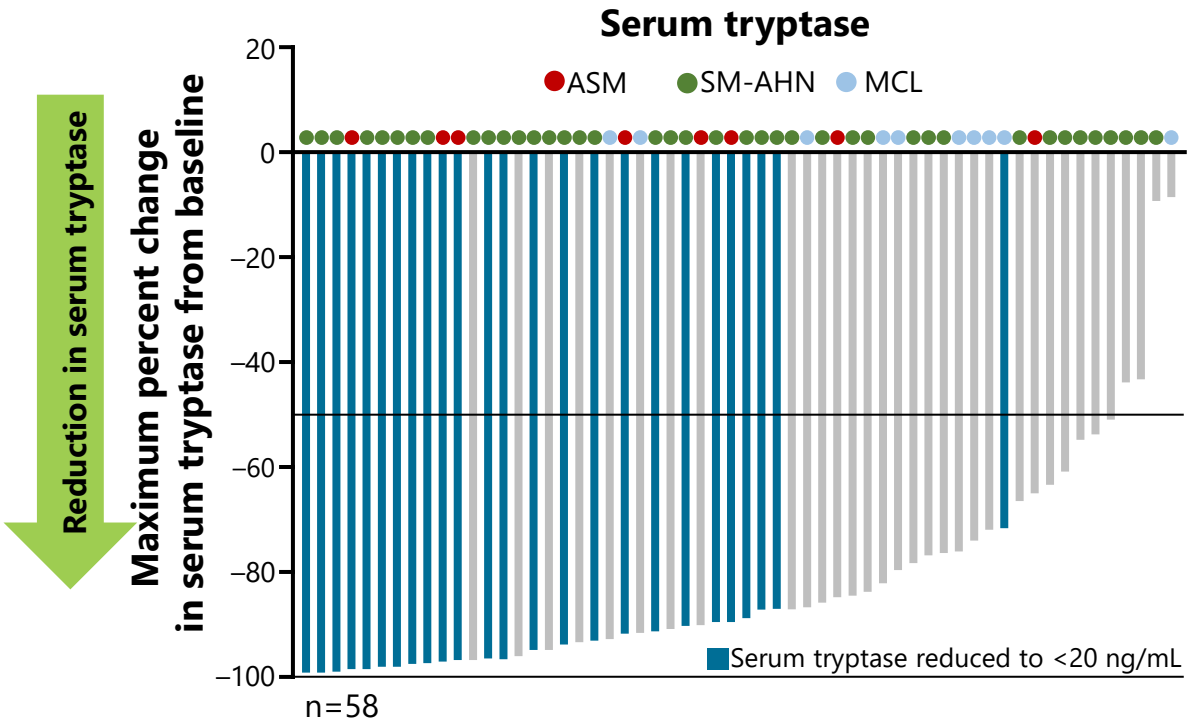
4 Baseline characteristics of PATHFINDER population

Patient demographics	All doses (n=62)
Age (years), median (range)	69 (31–88)
Sex, n (%), female	28 (45)
ECOG PS, n (%)	
0–1	43 (69)
2–3	19 (31)
AdvSM subtype per central assessment, n (%)	
ASM	9 (15)
SM-AHN	43 (69)
MCL	10 (16)
Bone marrow biopsy MC burden median percent (range)	45 (1–95)
Serum tryptase level, median ng/mL (range)	283 (24–1600)
KIT D816V positive in peripheral blood by central ddPCR, n (%)	59 (95)
Prior anti-neoplastic therapy, n (%)	42 (68)
Midostaurin	34 (55)
Cladribine	8 (13)
Baseline supportive medications, median (range)	3 (0–11)
H1 antihistamines	36 (58)
H2 antihistamines	24 (39)
Leukotriene receptor antagonists	12 (19)
Proton pump inhibitors	10 (16)
Cromolyn sodium	6 (10)
Corticosteroids (systemic)	20 (32)
Other	19 (31)

ASM, aggressive systemic mastocytosis; ddPCR, droplet digital polymerase chain reaction; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

5 PATHFINDER high confirmed response rate of avapritinib in AdvSM

- 75% confirmed ORR per mIWG-MRT-ECNM criteria
- 93% of patients achieved ≥50% reduction in serum tryptase



- Overall, 43% of patients achieved reduction to <20 ng/mL

- Avapritinib was generally well tolerated; only 3 (5%) patients discontinued due to treatment-related AEs
- Cytopenias are the most common Grade ≥3 AEs

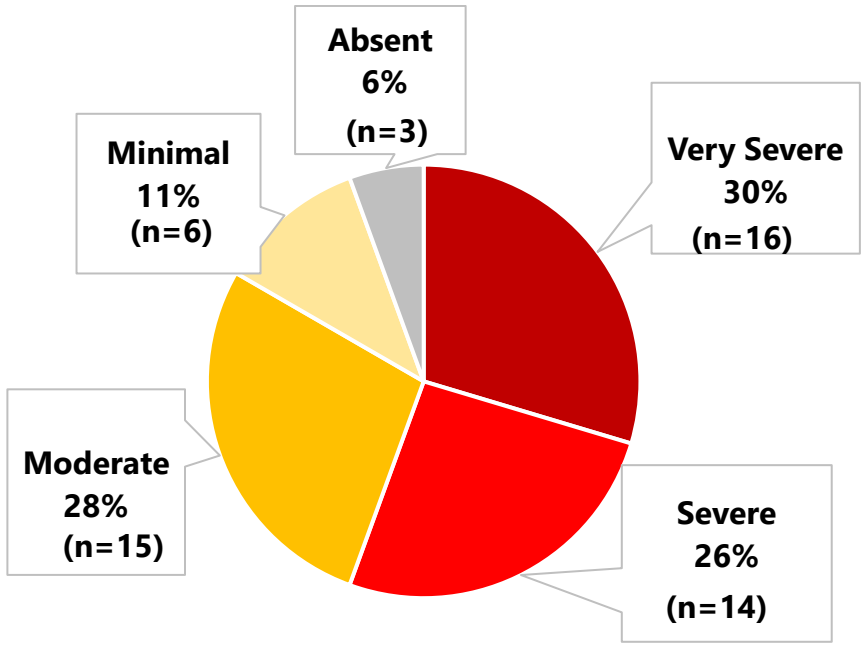
Adverse Events (AEs) in ≥15%	Any-cause AEs	
Non-hematologic, n (%)	**Any Grade**	**Grade 3/4**
Peripheral edema	31 (50)	2 (3)
Periorbital edema	30 (48)	2 (3)
Diarrhea	14 (23)	1 (2)
Nausea	11 (18)	1 (2)
Vomiting	11 (18)	1 (2)
Fatigue	9 (15)	2 (3)
Hematologic, n (%)		
Thrombocytopenia	28 (45)	10 (16)
Anemia	20 (32)	10 (16)
Neutropenia	15 (24)	15 (24)[a]

AE table includes pooled similar AE terms for periorbital edema, thrombocytopenia, anemia, and neutropenia.

[a]Five (8%) patients had Grade 4 neutropenia.
AEs, adverse events. DeAngelo et al. Presented at the American Association for Cancer Research Annual Meeting, virtual format, April 10–15, 2021.

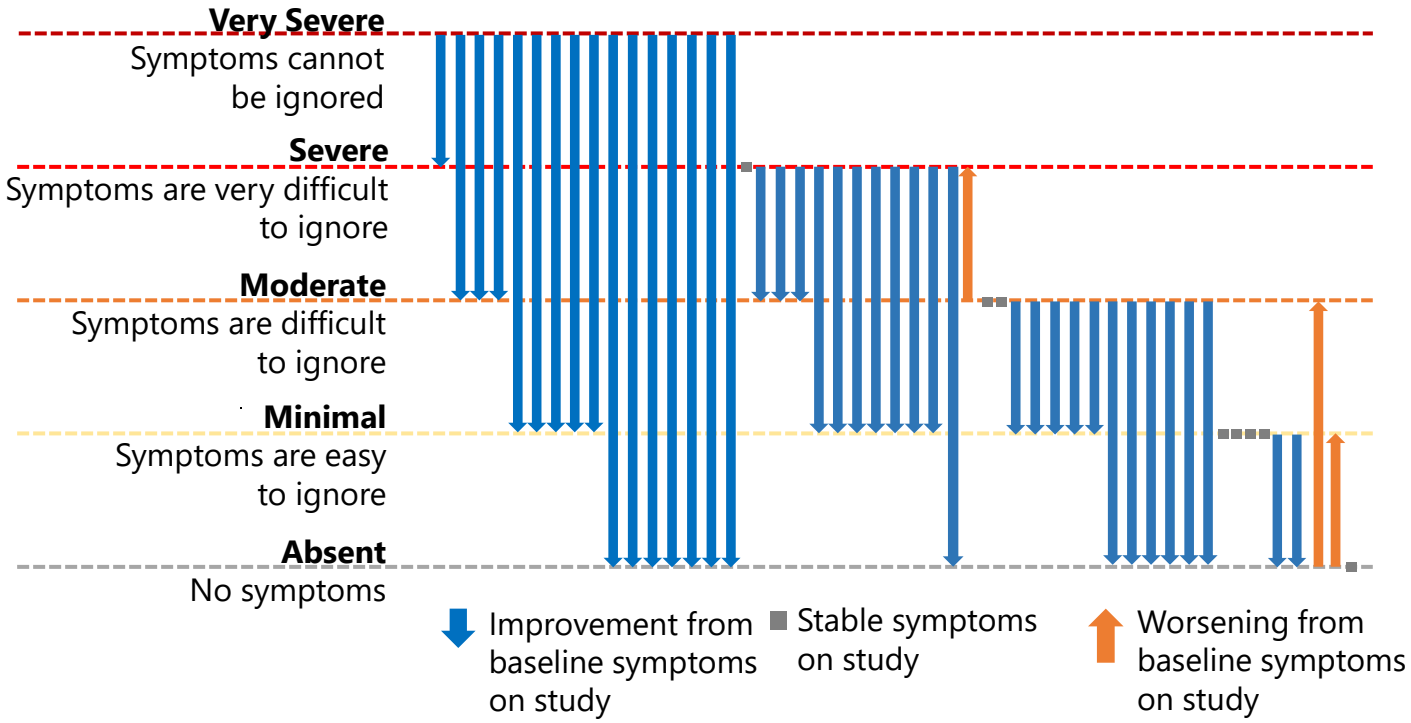
6 Patients with AdvSM, including highly symptomatic patients at baseline, improved on avapritinib

Baseline PGIS score (n=54)



- Majority of patients reported severe (26%) or very severe (30%) SM symptoms at baseline

Maximum change in global symptoms from baseline[a]



- 78% of patients with improvement from baseline in global symptom severity
- 71% of patients with severe/very severe symptoms improved to minimal/absent

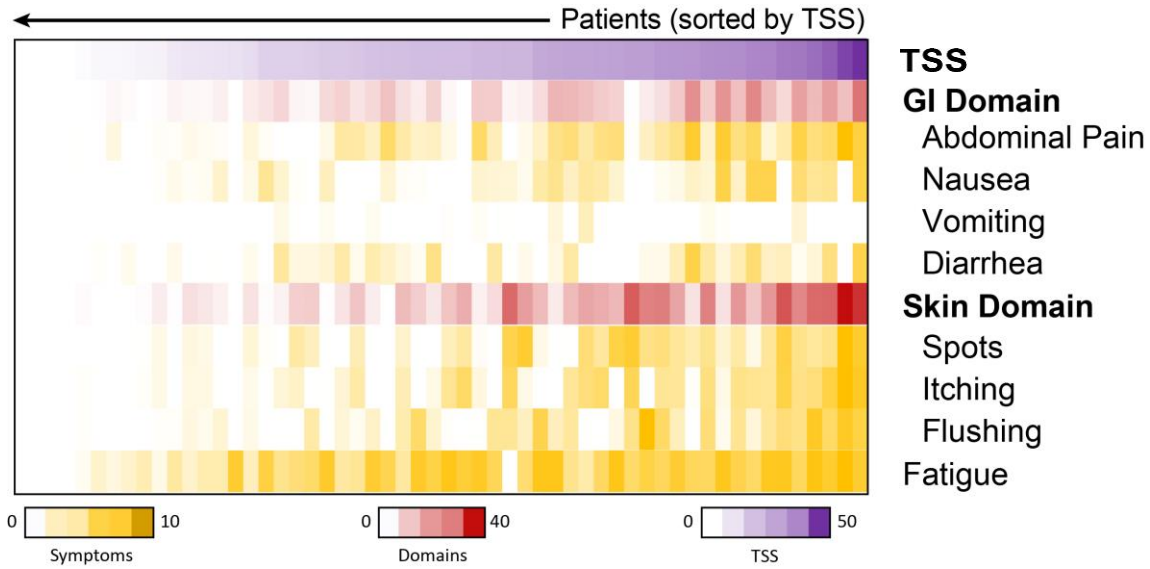
[a]Includes patients with baseline and post-baseline assessments (n=51). PGIS was administered to patients at baseline and after 2, 4, 8, 16, 24, 32, and 40 weeks of therapy, and then every 12 weeks.

7 Patients reported a broad range of specific symptoms at baseline on the Advanced SM-Symptom Assessment Form (AdvSM-SAF)

AdvSM-SAF: Validated patient-reported outcome tool in AdvSM[a]

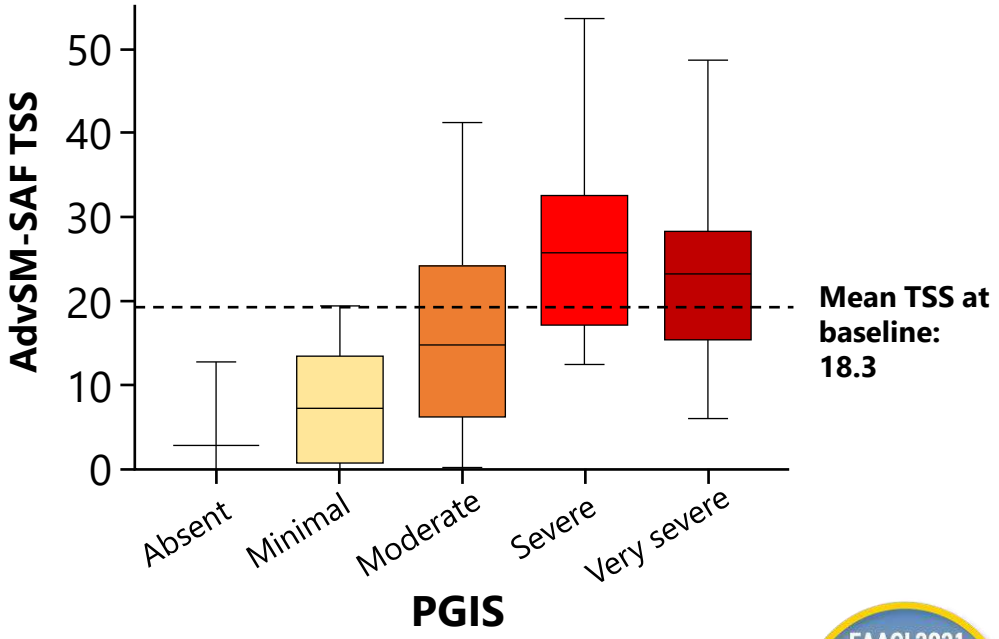
- A total of 8 symptoms were scored (0–10) daily on an eDiary
- Scores were averaged over 7 days for analysis
- Patients have heterogenous symptoms in number and severity

Baseline AdvSM-SAF symptom scores



- A mean TSS of 18 is correlated to moderate to severe symptom burden on the PGIS

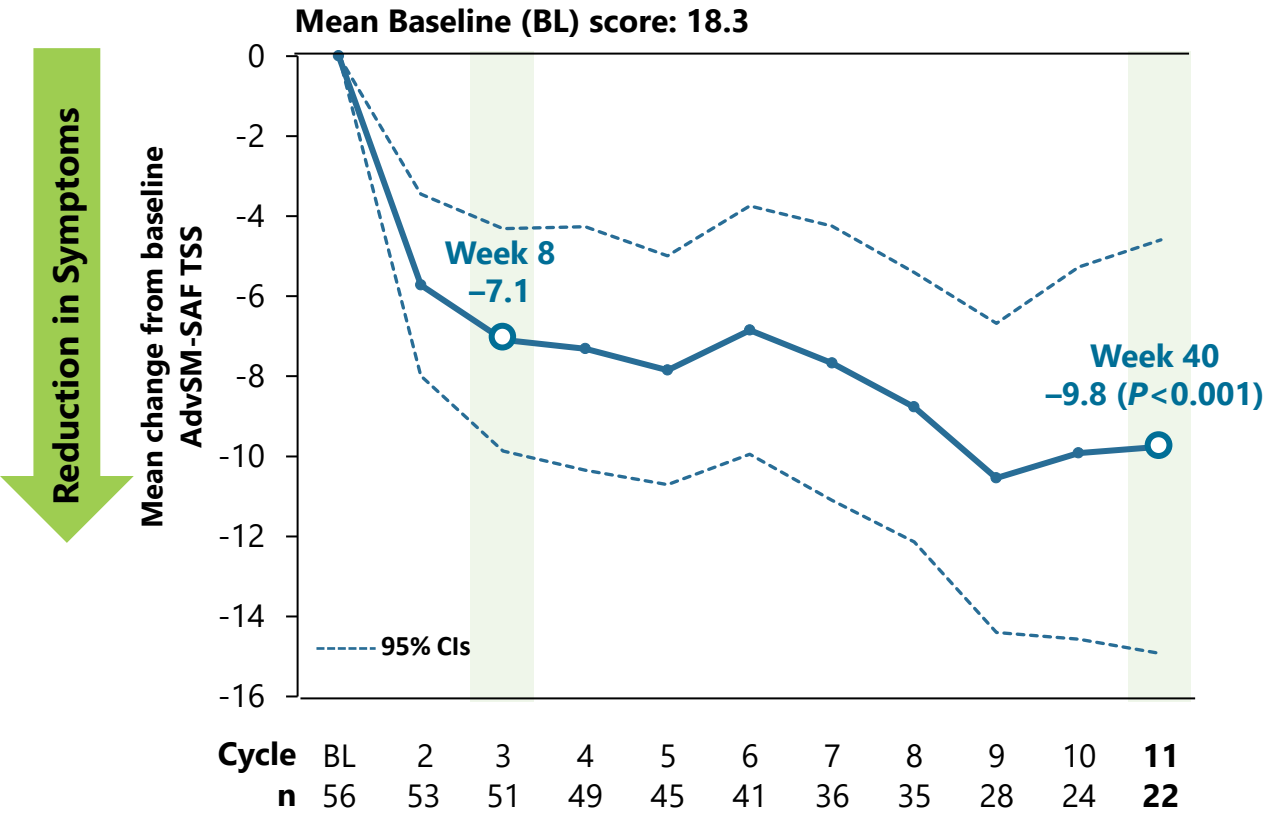
Concordance of AdvSM-SAF with PGIS



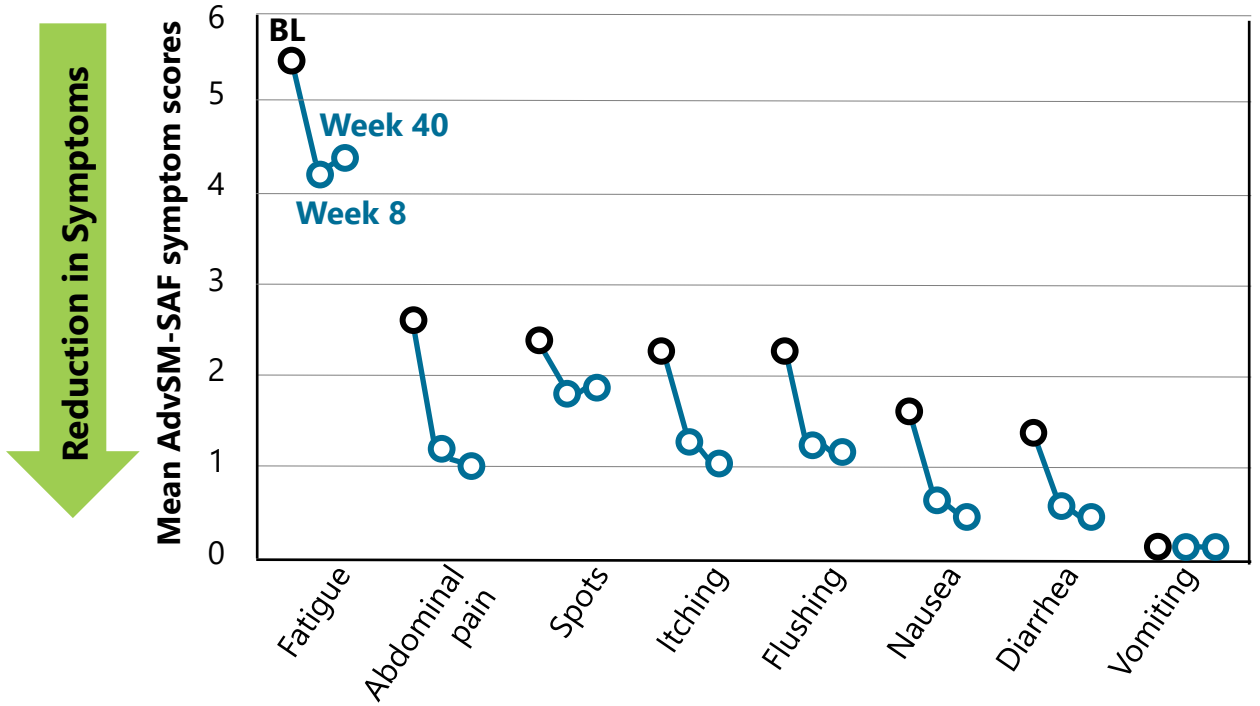
[a]Taylor F et al. 2019 The Professional Society for Health Economics and Outcomes Research EU [Poster PRO143]

Avapritinib led to rapid and durable reduction in AdvSM symptoms

Significant reduction in TSS



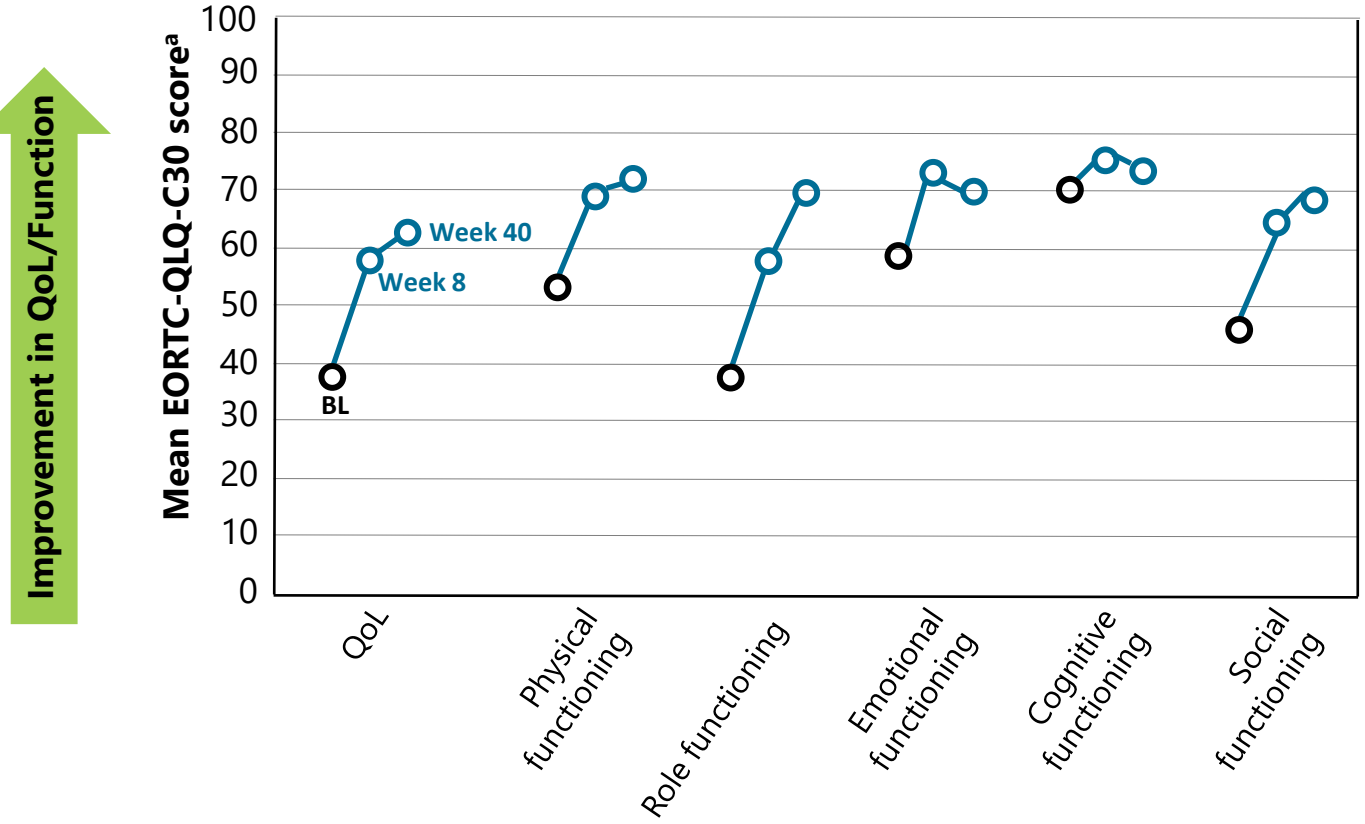
Individual Symptom Scores



BL, baseline; CI, confidence interval.

Avapritinib led to rapid and durable improvement in QoL and functional impairment

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C30)

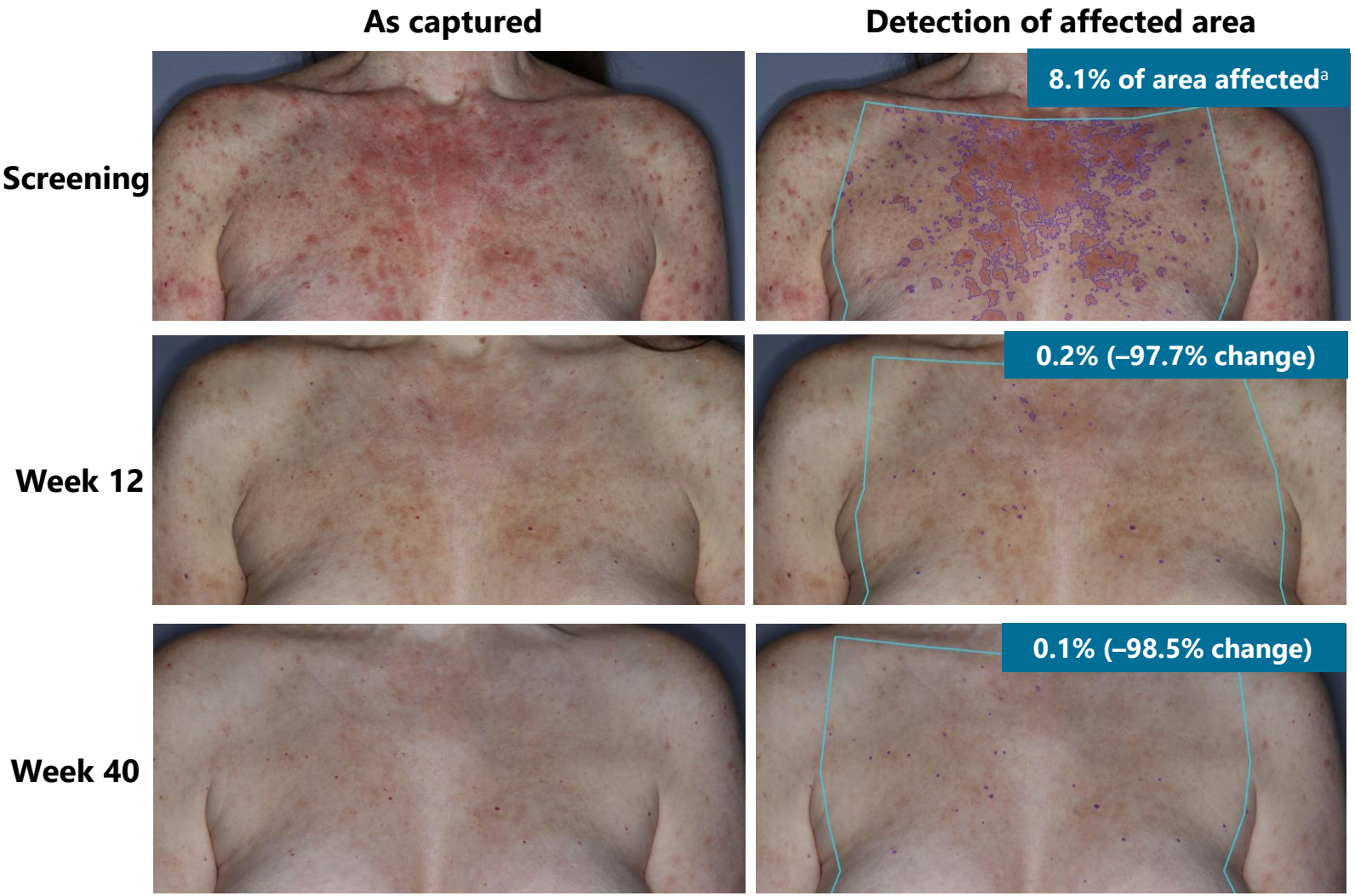


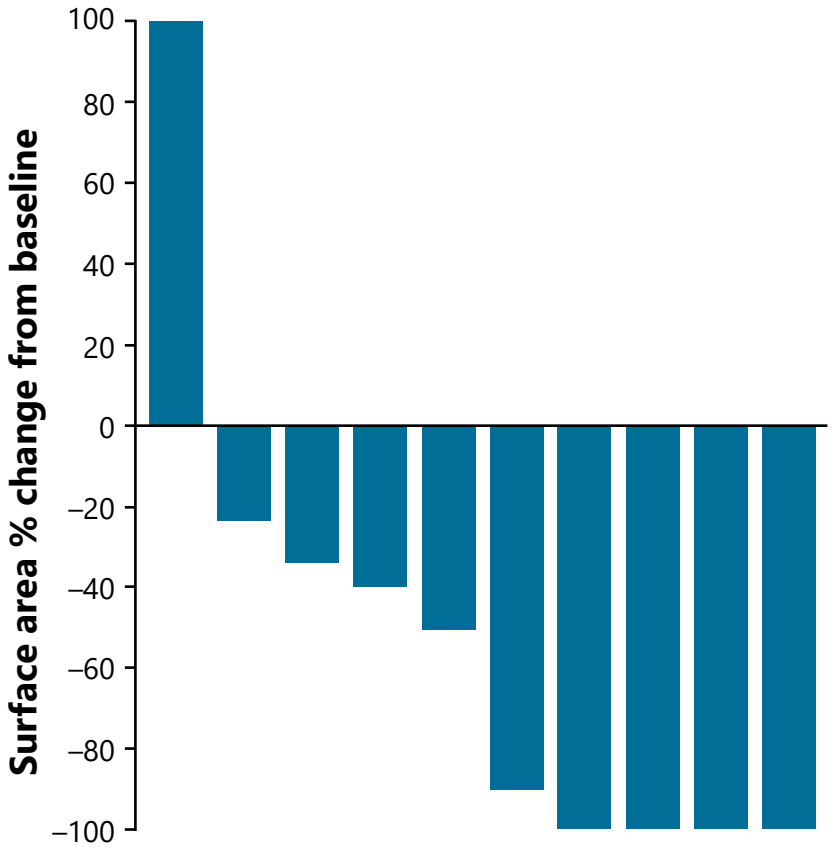
- AdvSM patients have poor QoL and functional impairment at Baseline
- Rapid improvement in QoL by week 8
- Sustained improvement at week 40, approaching scores in healthy patients from a historical study[1]
- Improvements seen in all facets of QoL

[a]BL (n=54); Week 8 (n=45); Week 40 (n=9).

1. Hinz A et al. *Acta Oncologica*. 2014;53:958–965.

Avapritinib reduced size of skin lesions in AdvSM





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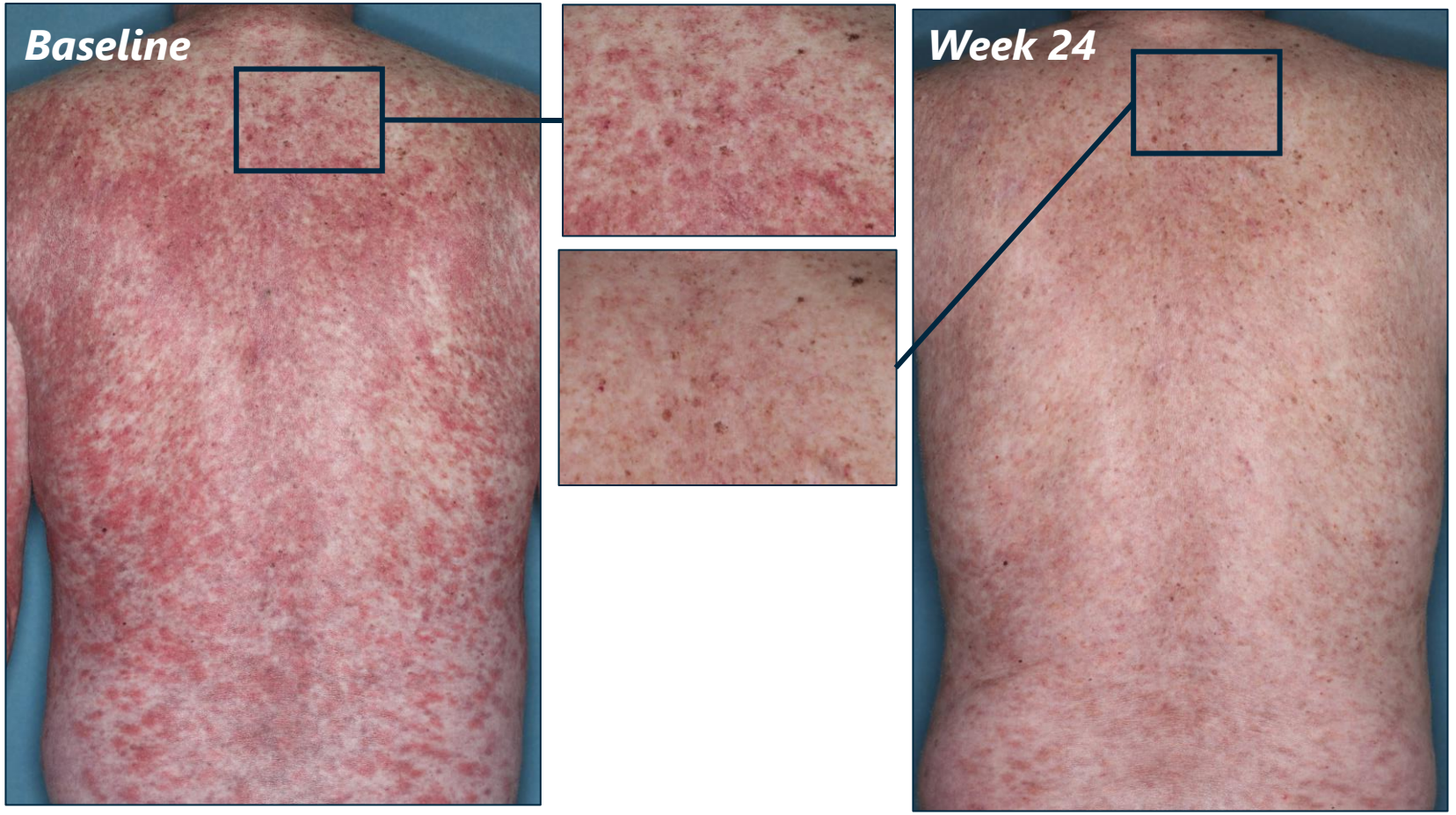
[a]Only a portion of the analyzed front torso is shown.

Avapritinib reduced skin lesion color intensity

- Color change was judged by the Skin Assessment Committee



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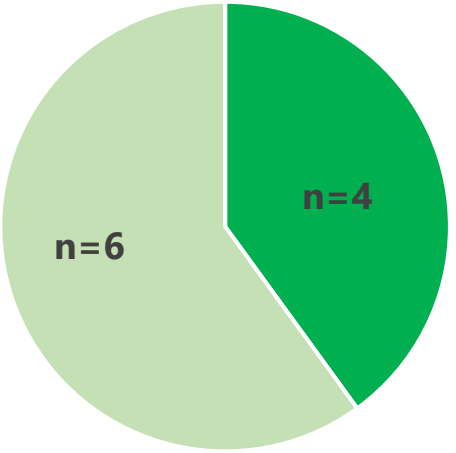

Lighter A lot lighter

- No patients were assessed as "no change", "darker" or "a lot darker"

Avapritinib led to profound reduction of disease burden and symptom improvement

- 75% confirmed ORR with significant reductions in serum tryptase in 93% of patients
- Reduced overall patient-reported symptom burden, with rapid and durable improvement in QoL and functional domains in patients with AdvSM
- Reduced affected area and lightened color of SM skin lesions
- Avapritinib was generally well tolerated; cytopenias were the most common Grade 3+ AEs
- Avapritinib for the treatment of AdvSM has been submitted to the EMA for approval

Acknowledgements

- Participating patients and families
- PATHFINDER Investigators
- Skin Assessment Committee

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Pivotal part 2 of PIONEER phase 2 study in Indolent SM now enrolling globally

PIONEER
Indolent SM

For more information email:
medinfo@blueprintmedicines.com

Complete list of enrolling sites at: clinicaltrials.gov/ct2/show/NCT03731260