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CHALLENGING CASES

Hematologic Disorders

Challenging Cases in… Hematologic Disorders

Presented by Dr. Hunter

Program Disclosures

Consulting/Honoraria: GSK, Cogent Biosciences, PharmaEssentia, Blueprint Medicines, Sobi

Research support: Incyte, Cogent Biosciences, Ascentage Pharma, Blueprint Medicines, Syntrix Biosystems, Novartis, PharmaEssentia

The information presented is consistent with FDA Guidelines and includes the latest clinical trial data

This program has been provided as an opportunity for discussion and learning, with insights from key opinion leaders

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Challenging Cases in… Hematologic disorders

Note: Aggregated results and discussion based on 5 practices (≤21 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated.
Programs conducted May – June 2024

Systemic Mastocytosis

Patient case: untreated disease

- Systemic Mastocytosis (SM) is classified as a Myeloid Neoplasm by WHO
- Prevalence of SM is estimated at ~1 in 10,000 adults
- 80% to 90% of cases are non-advanced SM (Indolent SM or Smoldering SM)

- *How can we reduce patient referral times?*
- *What is the optimal patient identification process?*
- *High sensitivity KIT D816V testing awareness?*

SM, systemic mastocytosis; **WHO**, World Health Organization.

REFERENCES: **1**. Swerdlow SH et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. Lyon, France: International Agency for Research on Cancer; 2017. **2**. Sperr WR et al. *Lancet Haematol*. 2019;6(12):e638-e649. **3**. Cohen SS et al. *Br J Haematol*. 2014;166(4):521-528. **4**. Brockow K. *Immunol Allergy Clin North Am*. 2014;34(2):283-295.

Patient History

71-year-old man

History of hypertension, dyslipidemia, cataract surgeries

Referred to hematology

Patient reported fatigue, headaches, intermittent episodes of diarrhea, and noticing macular spots x 6 months

No anaphylaxis

Diagnostics

Initial lab results:

December 10, 2022:

WBC 5, Hgb 13.4, Platelets 171

June 17, 2023:

WBC 7, Hgb 13.9, Platelets 196

July 28, 2023:

ultrasound showed spleen 14 cm in length. Liver was normal.

How are patients most often referred to you for potential SM?

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Polling Question

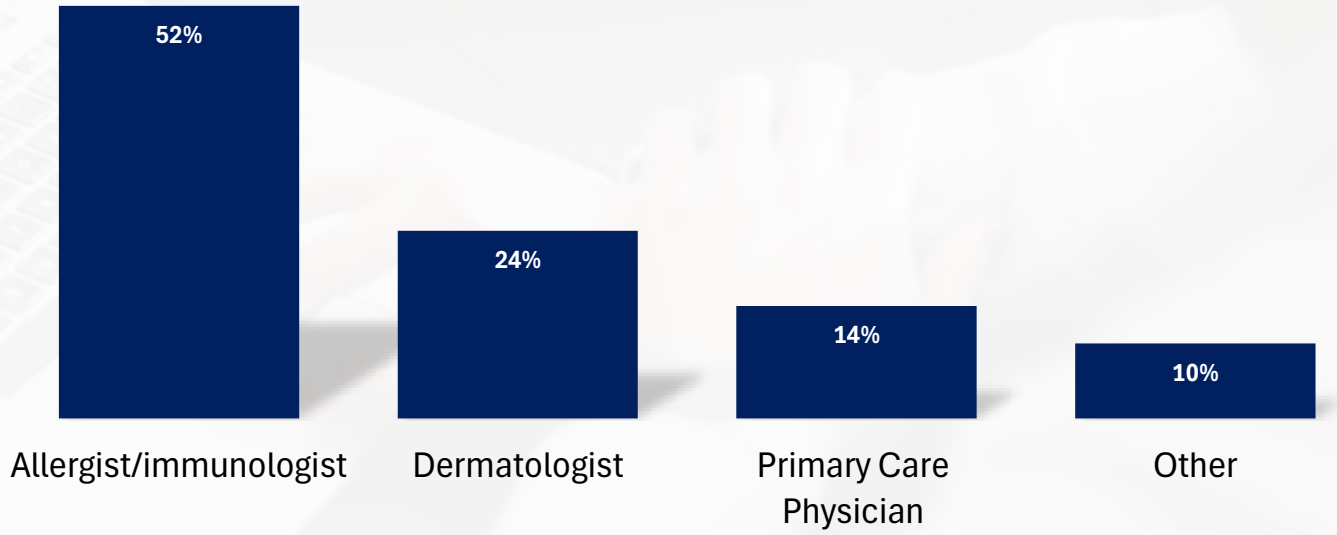
How are patients most often referred to you for potential SM?

1. Allergist/immunologist
2. Dermatologist
3. Gastroenterologist
4. Primary Care Physician
5. Other

Discuss: What is your experience with patients who are suspected or diagnosed with SM?

Poll Results from HCP Participants

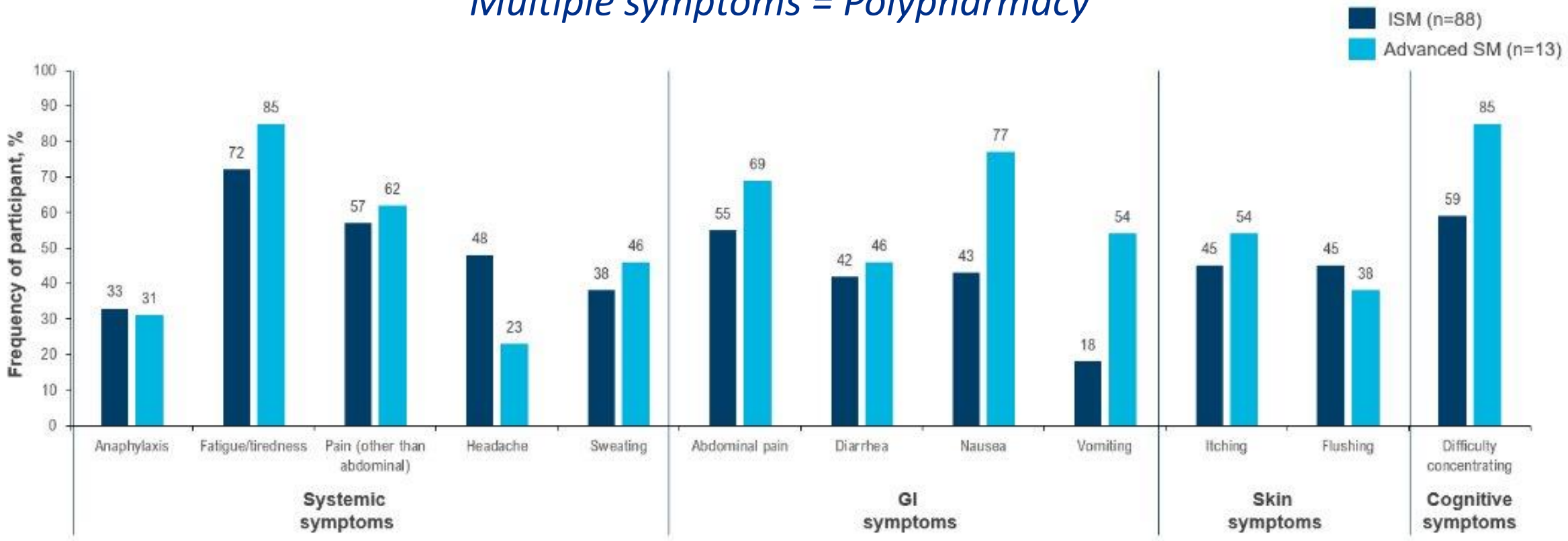
How are patients most often referred to you for potential SM?



Spectrum of Symptom Burden for SM

Patients with ISM and advanced SM may experience severe symptoms

Multiple symptoms = Polypharmacy



Jennings SV et al. Immunol Allergy Clin North Am. 2018;38(3):505-525.

Does the spectrum of symptom burden for ISM surprise you?

Discussion with HCP Participants

How are patients most often referred to you for potential SM?

Does the spectrum of symptom burden for ISM surprise you?

- *In general, patients are referred by allergist/immunologist or dermatologist*
  - *Occasionally referrals come from a pulmonologist or cardiologist*
- *Most do not have a lot of experience with SM; Few practices have patients currently diagnosed with indolent SM*
- *Some surprised by the symptom burden of disease for ISM*
  - *Symptom overlap with many different diseases and the variation between patients was noted; all agree that it is not surprising that ISM can be undiagnosed for an extended period of time*

KOL insights:

- Given the spectrum of symptom burden for Indolent SM, patients are often on a lot of mediator therapies which can mask the disease
- Trigger avoidance is important
- If multiple symptoms and a borderline tryptase level, then it is important to do a bone marrow biopsy for KIT testing

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ultrasound showed spleen 14 cm in length. Liver was normal.

How do you currently assess patients for potential mast cell disease?

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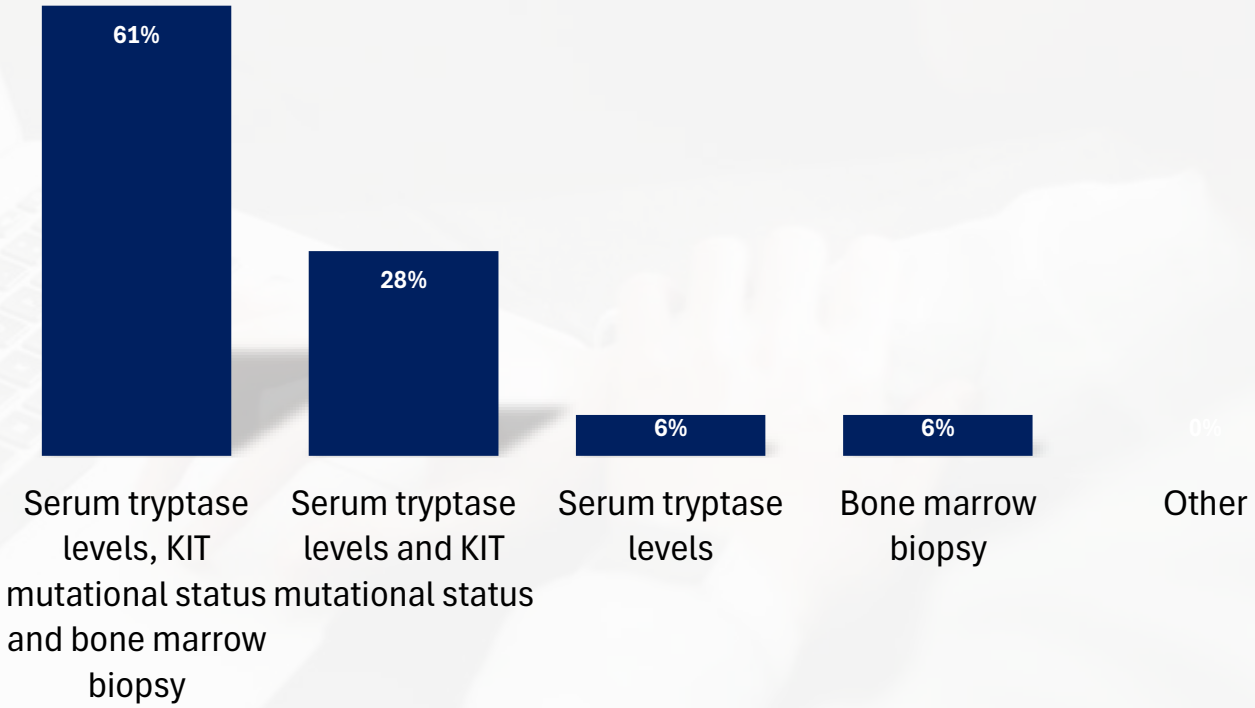
Polling Question

How do you currently assess patients for potential mast cell disease?

1. Serum tryptase levels
2. Serum tryptase levels and KIT mutational status
3. Bone marrow biopsy
4. Serum tryptase levels, KIT mutational status and bone marrow biopsy
5. Other

Poll Results from HCP Participants

How do you currently assess patients for potential mast cell disease?



Discussion with HCP Participants

How do you currently assess patients for potential mast cell disease?

- *In general, evaluation of serum tryptase levels, KIT mutational status and a bone marrow biopsy are done to assess patients for potential mast cell disease*

KOL insights:

- Serum tryptase levels can be used as an initial screening test but, regardless of result, if unexplained symptoms it is important to follow up
- Noted that it is important for the pathologist to be able to identify between the different mast cell disorders
- Archival bone marrow biopsy, skin and or GI biopsy can be utilized for high sensitivity KIT mutational status testing
- Indicate on test request for "high sensitivity droplet PCR" as well as "bone marrow CD25, CD2 stain"
- Occasionally, a bone biopsy due to an unexplained fracture can result in a diagnosis of SM
- Antihistamines (for symptoms, chronic allergies) do not impact testing or testing results
- Steroids can affect the bone marrow but in general can still detect on testing especially with a flare up of symptoms

NCCN Guidelines for Diagnosis of SM

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Systemic Mastocytosis

NCCN Guidelines Index
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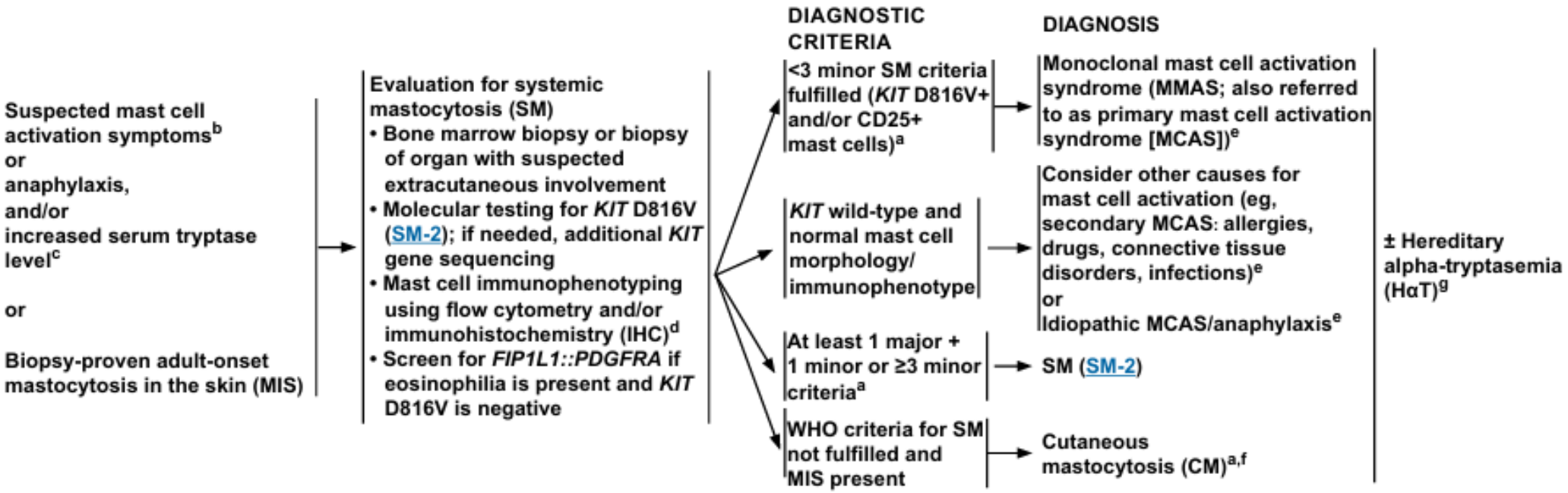
Discussion

DIAGNOSTIC ALGORITHM FOR THE PATIENT PRESENTING WITH SIGNS OR SYMPTOMS OF MASTOCYTOSIS[a]



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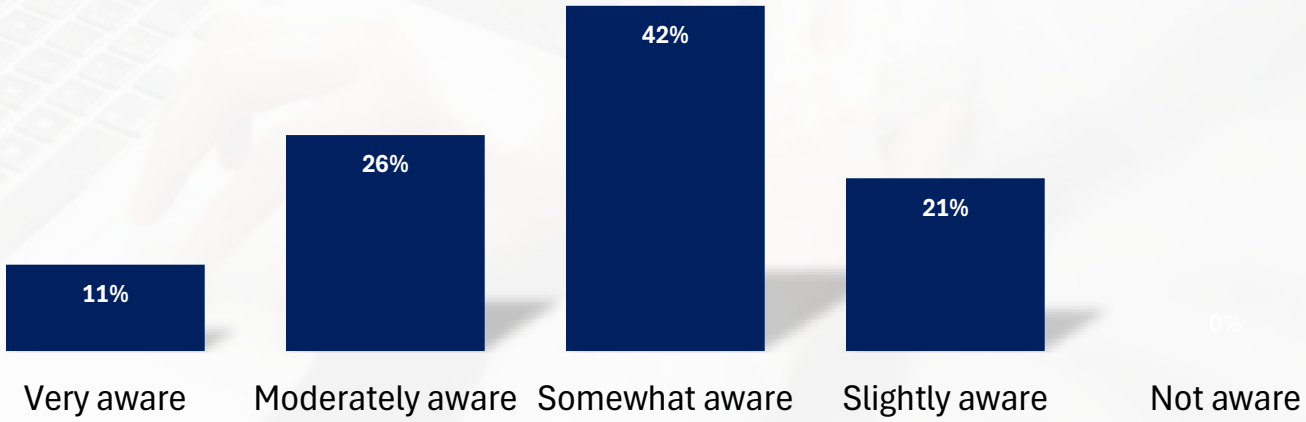
Polling Question

How aware are you of the WHO Criteria for SM?

1. Very aware
2. Moderately aware
3. Somewhat aware
4. Slightly aware
5. Not aware

Poll Results from HCP Participants

How aware are you of the WHO Criteria for SM?



WHO Criteria

WHO Criteria for Diagnosis of SM:

1 Major criterion and **1 Minor** criterion **OR ≥ 3 Minor** criteria

Major criterion

- Multifocal dense infiltrates of mast cells (≥15 mast cells/aggregate) detected in bone marrow and/or extracutaneous organs

Minor criterion

- Detection of *KIT* 816V in bone marrow, blood or an extracutaneous organ
- Serum tryptase >20 ng/mL (unless associated myeloid neoplasm is present)
- >25% of infiltrating mast cells are spindle-shaped or atypical on biopsy of bone marrow or extracutaneous organ or >25% of all mast cells in bone marrow aspirate smears are immature or atypical
- Mast cells in bone marrow, blood or extracutaneous organ express CD2, CD25, and/or CD30

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Discussion with HCP Participants

How aware are you of the WHO Criteria for SM?

- *In general, most have to review the WHO criteria for SM given the lack of experience and rarity of the disease*

KOL insights:

- Highlighted that serum tryptase levels are a minor criteria, noting that serum tryptase levels of <20 ng/ml do not necessarily rule out indolent SM (See PIONEER trial baseline characteristics)
- Highlighted that detection of KITG816V could be at any level with high sensitivity testing and indicates a positive result (See PIONEER trial baseline characteristics)

SM subtypes

Non-advanced

Indolent SM: Meets the general criteria for systemic mastocytosis; <2 B-findings; No C-findings; Low mast cell burden; No evidence of an associated hematologic neoplasm; Skin lesions are frequently present

Smoldering SM: Meets the general criteria for systemic mastocytosis; ≥2 B-findings; No C-findings; No evidence of an associated hematologic neoplasm; Does not meet the criteria for mast cell leukemia

Advanced

Aggressive SM: Meets the general criteria for systemic mastocytosis; ≥1 C-finding; Does not meet the criteria for mast cell leukemia; Skin lesions are usually absent

SM with an associated hematologic neoplasm: Meets the general criteria for systemic mastocytosis; Meets the criteria for an associated neoplasm

Mast Cell Leukemia: Bone marrow aspirate smears show ≥20% mast cells; In classic cases, mast cells account for ≥10% of the peripheral blood white blood cells, but the aleukemic variant (in which mast cells account for <10%) is more common; Skin lesions are usually absent; Mast cell variants include:

- Acute MCL [≥1 C-finding(s)] vs. chronic MCL (no C-findings)
- MCL with an AHN vs. MCL without an AHN
- Primary (de novo) vs. secondary MCL (arising from another SM variant)

Evaluation of B- and C- findings and organ involvement

- **B-Findings: Indicate a high burden of MCs and expansion of the neoplastic process into multiple hematopoietic lineages, without evidence of organ damage**
  - High mast cell burden (shown on bone marrow biopsy): >30% infiltration of cellularity by MCs (focal, dense aggregates) AND serum total tryptase >200 ng/mL.
  - Signs of dysplasia or myeloproliferation in non-mast cell lineage(s), but criteria are not met for definitive diagnosis of an AHN, with normal or only slightly abnormal blood counts.
  - Hepatomegaly without impairment of liver function, palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging

- **C-Findings: Are indicative of organ damage produced by MC infiltration (should be confirmed by biopsy if possible)**
  - Bone marrow dysfunction caused by neoplastic mast cell infiltration, manifested by ≥1 cytopenia; absolute neutrophil count <1.0 x 10^9/L, hemoglobin level <10 g/dL, and/or platelet count <100 x 10^9/L
  - Palpable hepatomegaly with impairment of liver function, and/or ascites, and/or portal hypertension
  - Skeletal involvement, with large osteolytic lesions (if the size of the lesion is ≥2 cm, it is considered large) with or without pathologic fractures (pathologic fractures caused by osteoporosis do not qualify as a C-finding). Small osteolytic and/or sclerotic lesions do not define advanced SM.
  - Palpable splenomegaly with hypersplenism
  - Malabsorption with weight loss due to gastrointestinal mast cell infiltrates

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ISM is Primarily Driven by the *KIT* D816V Mutation

- The ***KIT* D816V** mutation is present in **~95%** of patients with ISM and is an underlying driver of disease[1]
- The D816V mutation causes structural changes that result in constitutive activation of *KIT*[2]
- **Mast cells harboring the *KIT* D816V mutation have constitutive *KIT* activation/signaling resulting in uncontrolled mast cell proliferation and activation**[3,4]

Methods to detect KIT D816V include:

- ✓ ASO-qPCR
- ✓ ddPCR

ISM in PIONEER Trial	Local assessment n (%)[1]	TruSight NGS n (%)[1]	ddPCR n (%)[1]
KIT D816V detected	31 (80)	11 (28)	**37 (95)**
KIT D816V not detected	8 (20)	28 (72)	2 (5)
Patients analyzed	39	39	39

The high-sensitivity ddPCR assay method demonstrated:

- KIT D816V mutation detection in 95% of peripheral blood samples from patients with previously confirmed ISM
- 30-fold greater sensitivity over NGS for measuring MAF; median percentage MAF (range) was 0.36 (0.02–30.22) by ddPCR and 11 (1.9–32) by NGS
- Greater diagnostic sensitivity for ISM compared with serum tryptase >20 ng/mL (77%) and presence of bone marrow mast cell aggregates (90%)

1. Garcia-Montero AC et al. Blood. 2006;108(7):2366-2372.
2. Laine E et al. PLoS Comput Biol. 2011;6:e1002068.
3. Cruse G et al. Immunol Allergy Clin North Am. 2014;34(2):219-237.
4. Theoharides TC et al. N Engl J Med. 2015;373(2):163-172.

Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2022.

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Patient History

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ultrasound showed spleen 14 cm in length. Liver was normal.

What treatment do you recommend?

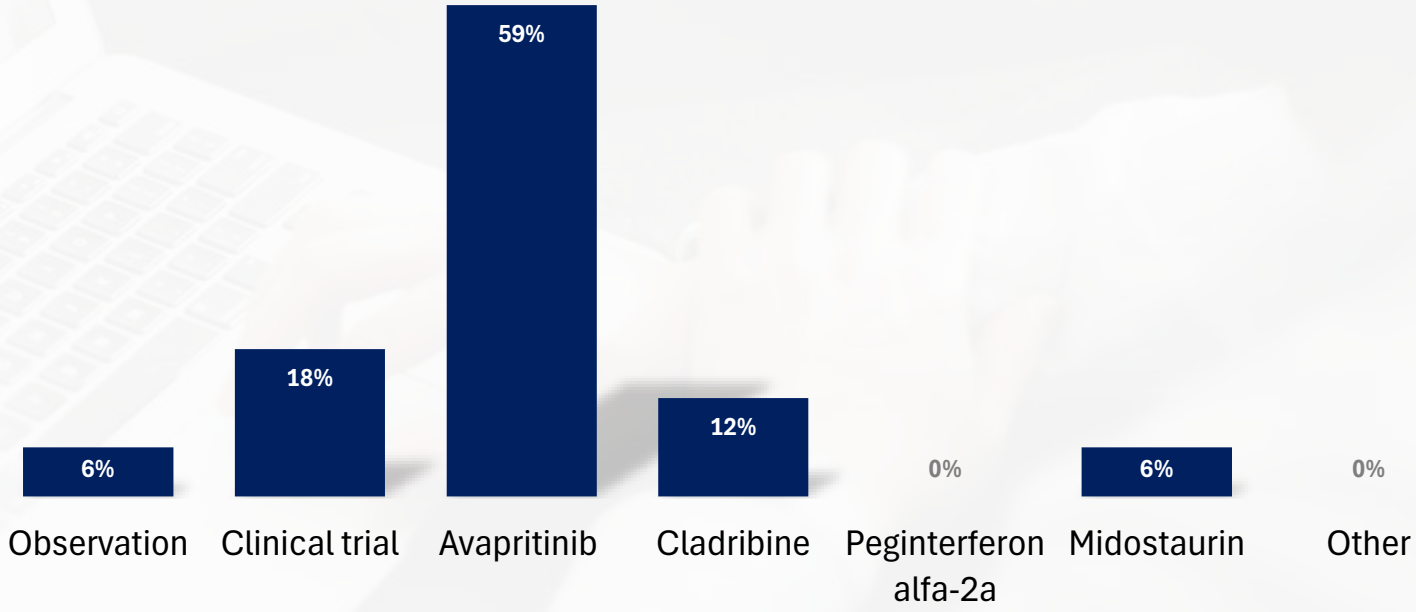
Polling Question

What treatment do you recommend?

1. Observation
2. Clinical trial
3. Avapritinib
4. Cladribine
5. Peginterferon alfa-2a
6. Midostaurin
7. Other

Poll Results from HCP Participants

What treatment do you recommend?



Discussion with HCP Participants

What treatment do you recommend?

- *In general, participants would recommend avapritinib as their treatment of choice for patients with ISM*
  - *One participant indicated that a patient was diagnosed with SM prior to the approval of avapritinib*

- *Timing of avapritinib approval for ISM was noted:*

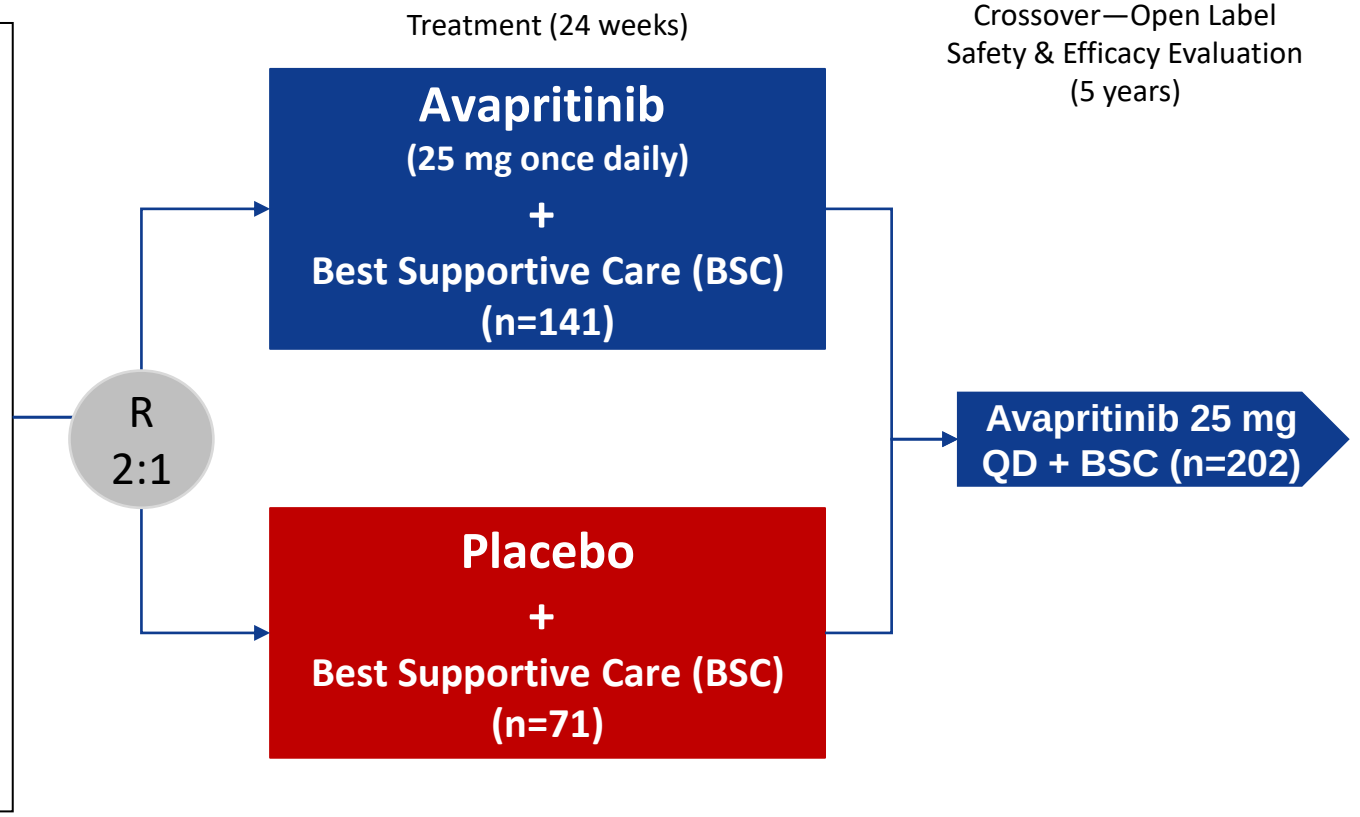
  - *On May 22, 2023 the FDA approved AYVAKIT® (avapritinib) for the treatment of adults with indolent systemic mastocytosis (ISM), supported by data from the PIONEER trial*

PIONEER

Study Design: randomized double-blind, placebo-controlled, multipart Phase 2 trial

- Patients with indolent systemic mastocytosis (SM) confirmed by Central Pathology Review of BM biopsy, and central review of B- and C-findings by WHO diagnostic criteria
- Patient must have moderate-to-severe symptoms based on minimum mean total symptom score (TSS of ≥28; scores range from 0 to 110, with higher numbers indicating more severe symptoms) of the ISM Symptom Assessment Form (ISM-SAF) over the 14-day eligibility screening period
- Patient must have failed to achieve adequate symptom control for 1 or more Baseline symptoms
- For patients receiving corticosteroids, the dose must be ≤ 20 mg/d prednisone or equivalent, and the dose must be stable for ≥ 14 days
- ECOG PS of 0 – 2

N =212



Primary endpoint: Mean change in total symptom score (TSS) based on the 14-day average of patient-reported severity of 11 symptoms at 24 weeks

Secondary endpoints: Reductions in serum tryptase and blood KIT D816V variant allele fraction (≥50%), reductions in TSS (≥50% and ≥30%), reduction in bone marrow mast cells (≥50%), and quality of life measures

PIONEER

Baseline Characteristics

Characteristic	Avapritinib (n=141)	Placebo (n=71)
Age – Years, Median (range)	50.0 (18–77)	54.0 (26–79)
Female — n (%)	100 (70.9)	54 (76.1)
Ethnicity — n (%)		
• Hispanic or Latino	6 (4.3)	1 (1.4)
• Not Hispanic or Latino	99 (70.2)	58 (81.7)
• Not reported	22 (15.6)	10 (14.1)
• Unknown	14 (9.9)	2 (2.8)
Tryptase (central) — ng/ml, mean (SD)	57.6 (54.4)	67.6 (74.2)
• Baseline — median (range)	38.4 (3.6–256.0)	43.7 (5.7–501.6)
• ≥20 — n (%)	113 (80.1)	56 (78.9)
• <20 — n (%)	28 (19.9)	15 (21.1)
TSS		
• Baseline — mean (SD)	50.2 (19.1)	52.4 (19.8)
• <28 — n (%)	14 (10.1)	4 (5.6)
• ≥28 to <42 — n (%)	38 (27.3)	22 (31.0)
• ≥42 — n (%)	87 (62.6)	45 (63.4)

A total of two patients in the avapritinib group had missing baseline TSS values; therefore, the denominator was on the basis of patients with available data at baseline (n=139).

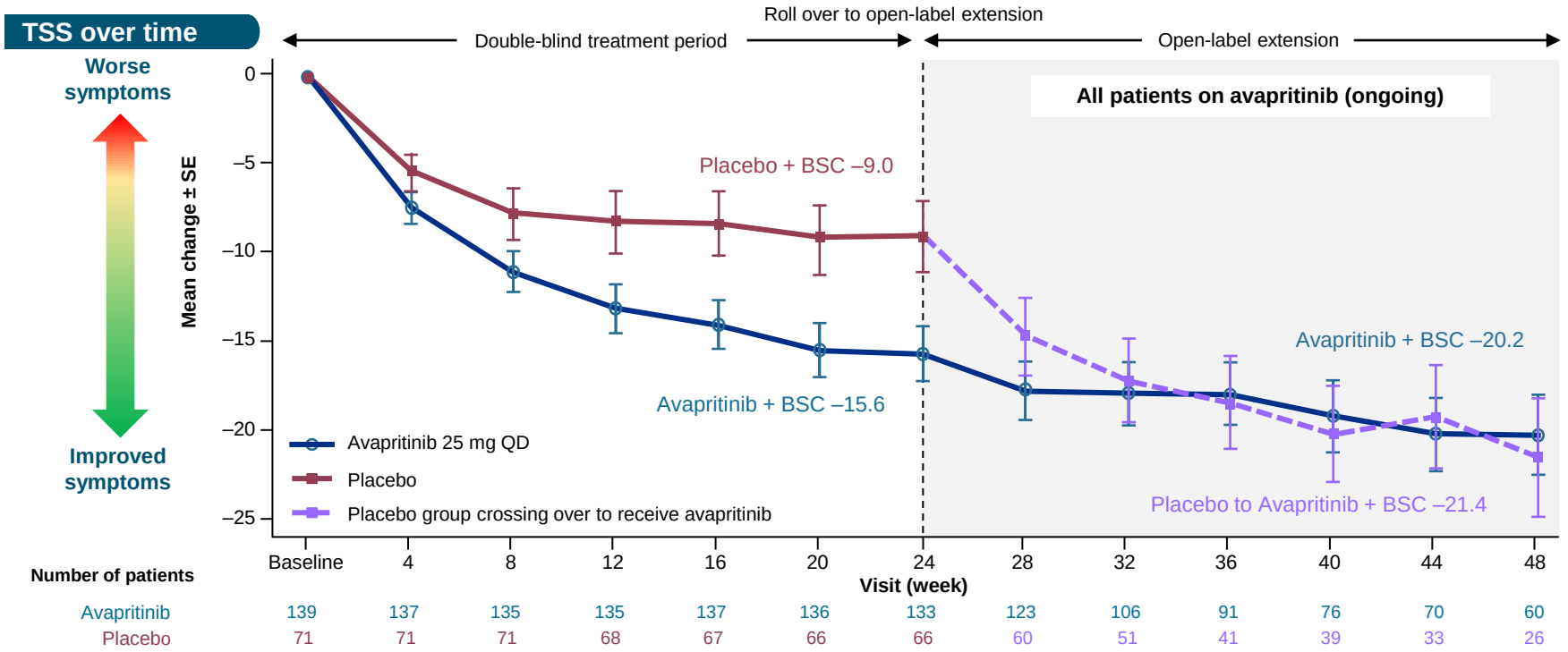
Characteristic	Avapritinib (n=141)	Placebo (n=71)
Bone marrow biopsy mast cells (central)		
• Mean (SD) — %	11.0 (11.1)	12.2 (12.6)
• Median (range) — %	7.0 (1.0–50.0) 106	7.0 (1.0–70.0)
• Mast-cell aggregates present — n (%)	(75.2)	57 (80.3)
KIT D816V VAF in peripheral blood		
• Below level of detection (<0.02%) — n (%)	23 (16.3)	8 (11.3)
• ≥0.02% to <1% — n (%)	78 (55.3)	37 (52.1)
• ≥1% — n (%)	40 (28.4)	26 (36.6)
• Median VAF (range)	0.4 (0.02–41.3)	0.3 (0.02–36.7)
Prior cytoreductive therapy — n (%)	19 (13.5)	7 (9.9)
Prior TKI therapy — n (%)	10 (7.1)	4 (5.6)
Number of BSC treatments — median (range)	3 (0–11)	4 (1–8)

All patients had at least two BSC prior to or at screening. A total of 10 (7.1%) patients treated with avapritinib and 5 (7.0%) patients treated with placebo had less than two BSC at the start of the trial.

ClinicalTrials.gov ID NCT03731260

PIONEER

Primary Endpoint: Indolent Systemic Mastocytosis Symptom Assessment Form Total Symptom Score over Time with Avapritinib versus Placebo



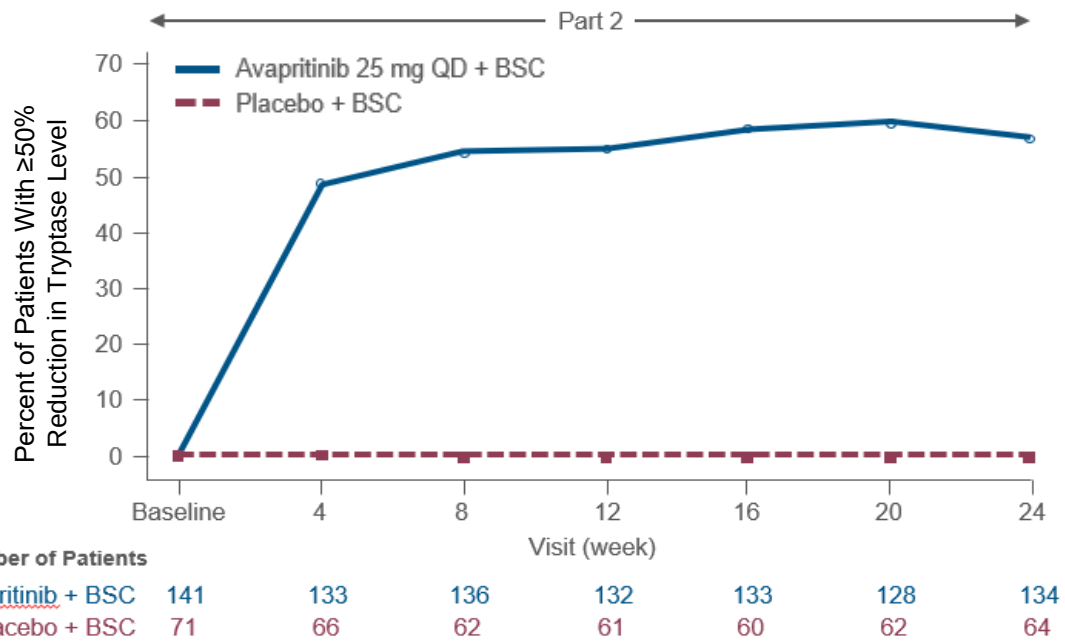
	Avapritinib 25 mg (N=128)	Placebo (N=65)	P-value
Mean Change in TSS (95% CI)	-15.58 (-18.61, -12.55)	-9.15 (-13.12, -5.18)	0.003

ClinicalTrials.gov ID NCT03731260

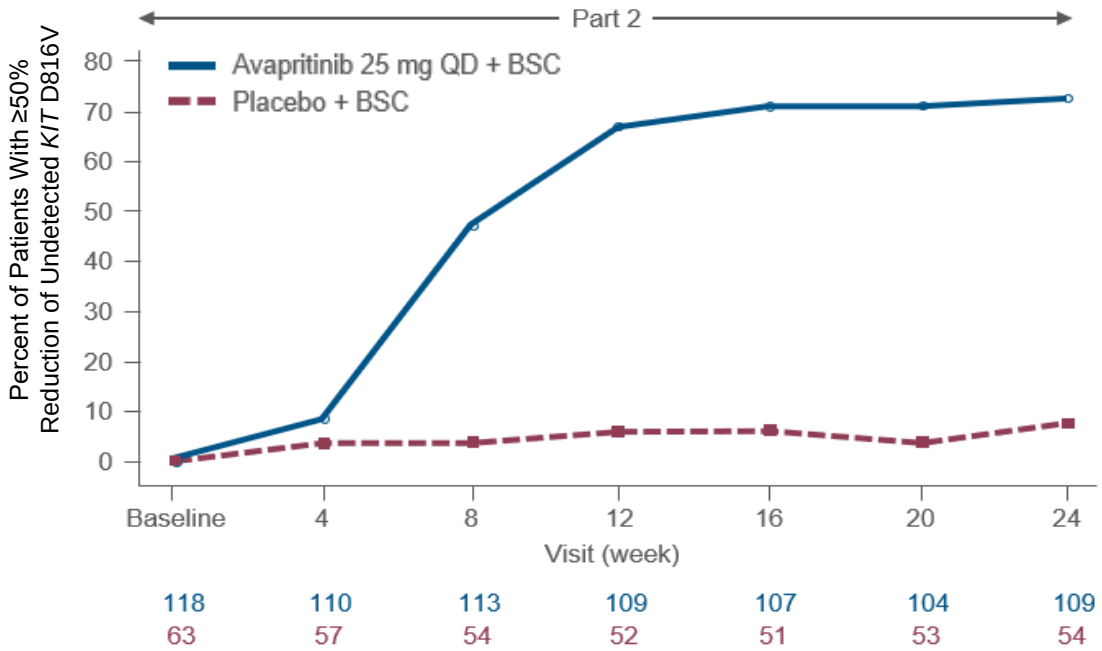
PIONEER

Secondary Endpoints

≥50% Reduction in Serum Tryptase over Time



≥50% Reduction in KIT D816V Variant Allele Fraction over Time



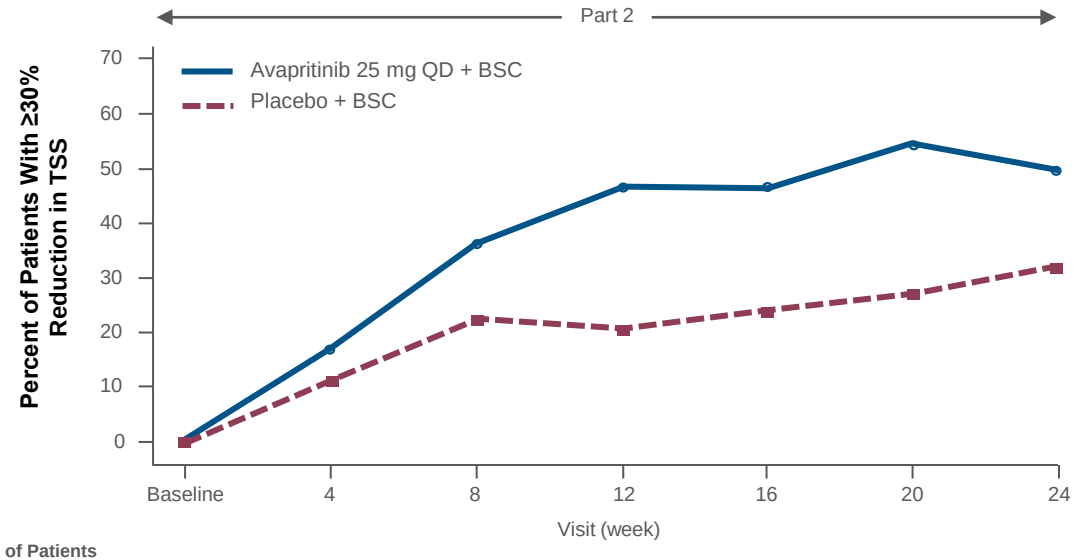
	Avapritinib 25mg (n=128)	Placebo (n=65)	P-value
≥50% Reduction in Serum Tryptase (95% CI)	**53.9%** (45.3, 62.3)	**0.0%** (0.0, 5.1)	<0.0001
≥50% Reduction in *KIT* D816V VAF (95% CI)	**67.8%** (58.6, 76.1)	**6.3%** (1.8, 15.5)	<0.0001

ClinicalTrials.gov ID NCT03731260

PIONEER

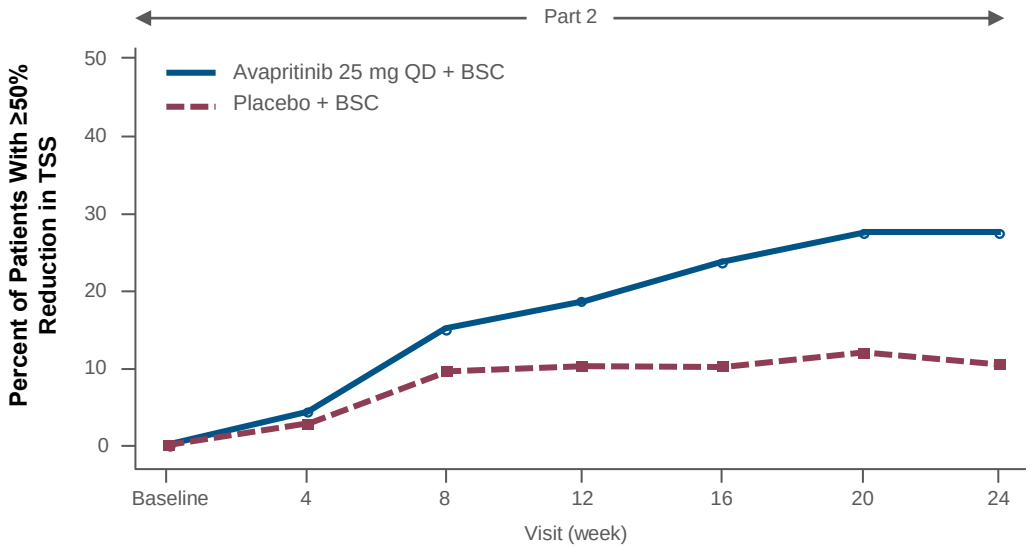
Secondary Endpoints

≥30% Reductions in Indolent Systemic Mastocytosis Symptom Assessment Form Total Symptom Score over Time with Avapritinib versus Placebo



No. of Patients							
Avapritinib + BSC	139	135	133	133	135	134	131
Placebo + BSC	71	71	71	68	67	66	66

≥50% Reductions in Indolent Systemic Mastocytosis Symptom Assessment Form Total Symptom Score over Time with Avapritinib versus Placebo



	139	135	133	133	135	134	131
	71	71	71	68	67	66	66

	Avapritinib 25mg (n=128)	**Placebo** (n=65)	P-value
≥30% Reduction in TSS (95% CI)	**45.4%** (37.0, 54.0)	**29.6%** (19.3, 41.6)	0.009
≥50% Reduction in TSS (95% CI)	**24.8%** (17.9, 32.8)	**9.9%** (4.1, 19.3)	0.005

ClinicalTrials.gov ID NCT03731260

PIONEER

Safety

	Avapritinib 25 mg QD + BSC (N=141)	Placebo + BSC (N=71)
Any AEs[a,b], n (%)	128 (90.8)	66 (93.0)
• Grade 1–2 AEs	98 (69.5)	51 (71.8)
• Grade 1–2 related AEs	74 (52.5)	30 (42.3)
• Grade ≥3 AEs	30 (21.3)	15 (21.1)
• Grade ≥3 related AEs	3 (2.1)	2 (2.8)
Any grade TRAEs	77 (54.6)	32 (45.1)
Most frequently reported TRAEs (≥5% of patients)		
• Headache	1 (7.8)	7 (9.9)
• Nausea	9 (6.4)	6 (8.5)
• Peripheral edema	9 (6.4)	1 (1.4)
• Periorbital edema	9 (6.4)	2 (2.8)
• Dizziness	4 (2.8)	5 (7.0)
AEs leading to discontinuation	3 (2.1)	1 (1.4)
• TRAEs leading to discontinuation	2 (1.4)	1 (1.4)

- Majority of AEs were Grade 1 or 2 with a low rate of discontinuation
- SAEs were reported more frequently in the placebo arm (no treatment-related SAEs in either arm)
- Edema events were slightly higher in the avapritinib group (majority Grade 1 and did not result in discontinuation)
- Very few TRAEs on avapritinib vs placebo required dose interruption (3.5 vs 5.6% respectively) or reduction (0.7% vs 1.4%, respectively)

ClinicalTrials.gov ID NCT03731260

Polling Question

How will the PIONEER trial data and avapritinib impact your assessment and treatment of patients with suspected ISM?

1. My testing and prescribing behavior will change
2. My testing and prescribing behavior will stay the same
3. Unsure

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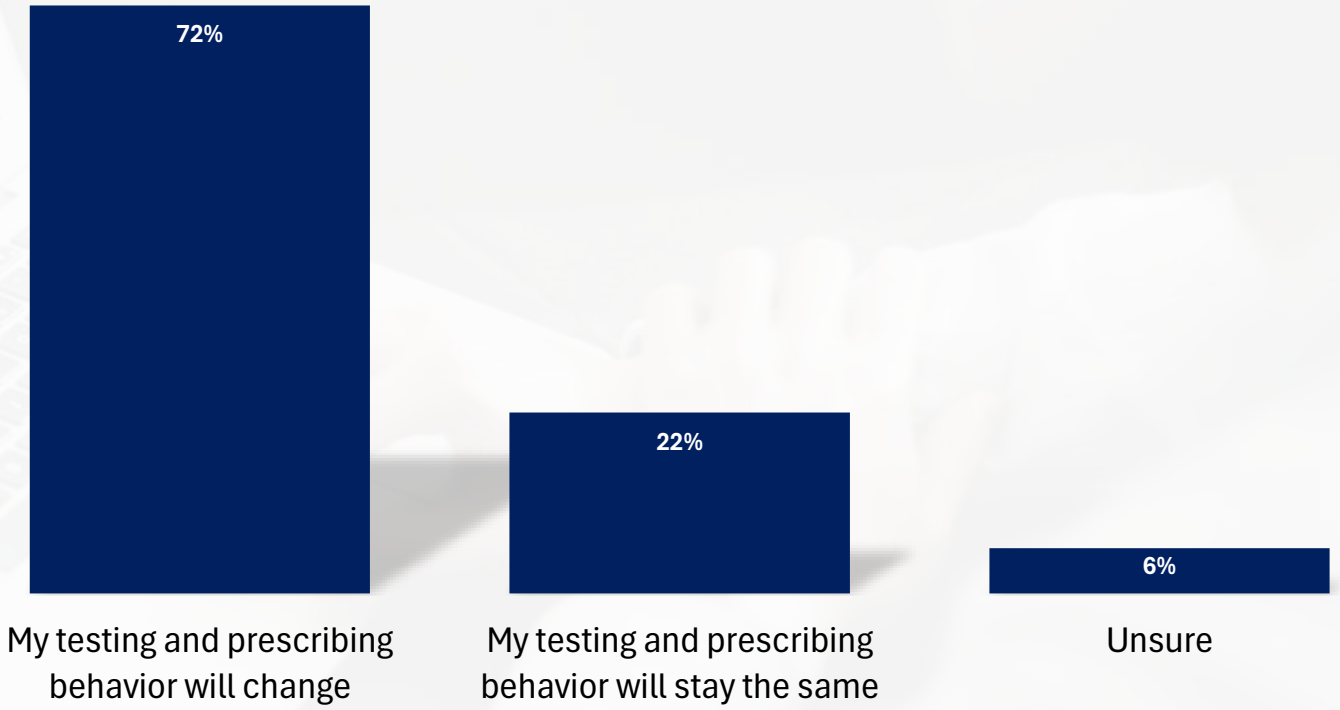
Poll Results from HCP Participants

How will the PIONEER trial data and avapritinib impact your assessment and treatment of patients with suspected ISM?



Discussion with HCP Participants

How will the PIONEER trial data and avapritinib impact your assessment and treatment of patients with suspected ISM?

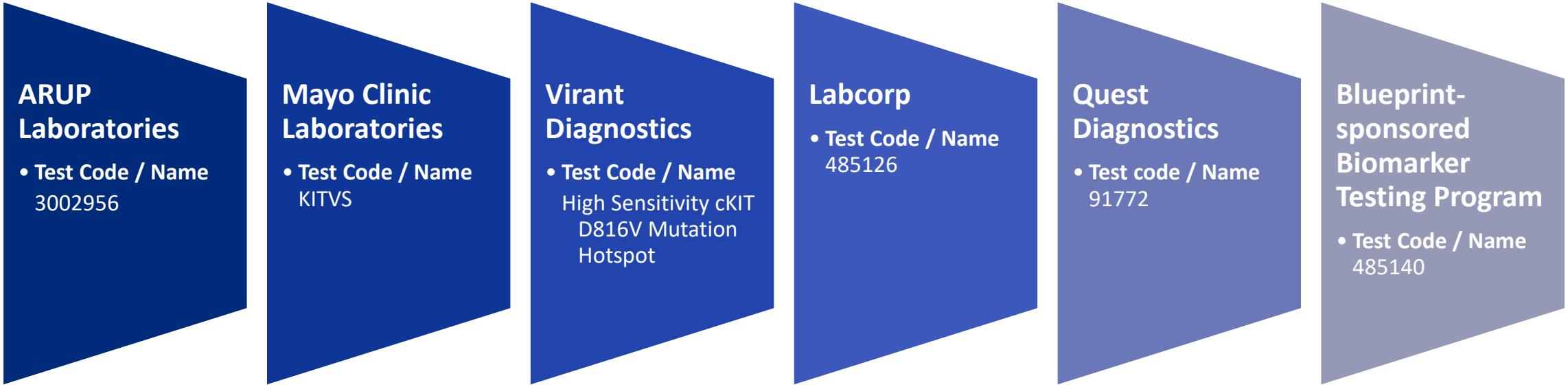
- *In general, most agreed that the presented PIONEER trial data as well as the testing information would change their assessment and treatment of patients with suspected ISM*

KOL insights:

- Important to wait at least 8 – 12 weeks in order to see the impact of treating with avapritinib
- In general, do not increase the dose of avapritinib but would consider increasing to 50 mg per day for patients with highly symptomatic disease after 8 -12 weeks at a dose of 25 mg; would wait a least 6 months before increasing to 50 mg if less symptomatic

Molecular testing for KIT D816V

- NCCN Guidelines recommends a highly sensitive assay such as ASO-qPCR or digital droplet PCR on peripheral blood for initial screening
- A thorough analysis of KIT mutational status should include bone marrow evaluation



[Precision Medicine - Cornerstone Specialty Network (cornerstoneoncology.com)]

Key Takeaways

Systemic Mastocytosis

- *Identification of patients is key to reduce impact on patient quality of life and reduce the time to diagnosis*
- *Coordination with other specialists from PCPS to allergist/immunologist, dermatologist and pathologists*
- *Awareness of WHO criteria*
- *High sensitivity KIT D816 testing*
- *Avapritinib is the only approved treatment for ISM*

Thank you!