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Cancer Institute



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# Systemic Mastocytosis: Diagnostic and Therapeutic Updates

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## Disclosure Information

The following relationships exist related to this presentation:

- I serve as a consultant for Amgen, Autolos, Agios, Blueprint, Forty-Seven, Gilead, Incyte, Jazz, Novartis, Pfizer, Servier, and Takeda
- I receive research funding from Abbvie, Glycomimetics, Novartis and Blueprint Pharmaceuticals
- I am on the DSMB for Daiichi-Sankyo, Fibrogen. Mt Sinai MPN Consortium
- I am the Co-Chair of the NCI (CTEP) Leukemia Steering Committee

### Off-Label/Investigational Discussion

In accordance with CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during their presentations. **Avapritinib in Indolent SM**

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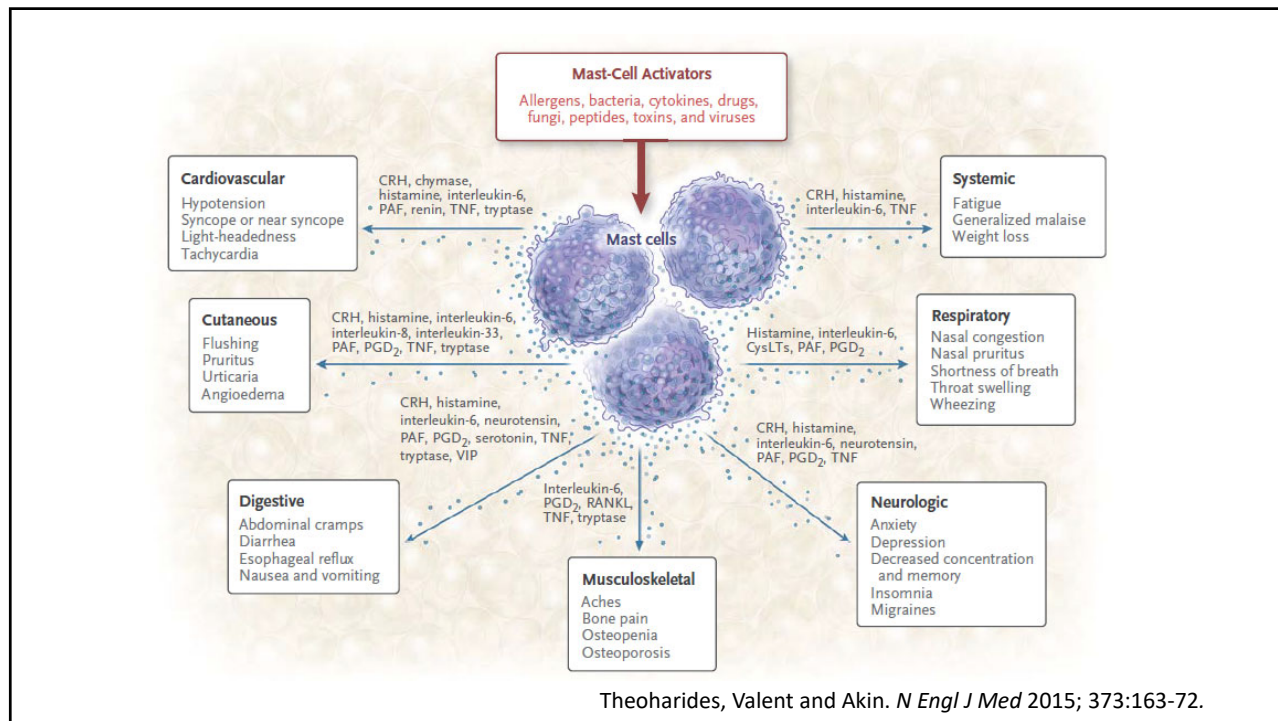
# What are Mast Cells?

First discovered by Paul Ehrlich – named these cells “mastzellen”.



Ehrlich, P. Beitrage zur Kenntnis der Anilinfarbbungen und ihrer Verwendung in der mikroskopischen Technik. Arch. mikr. Anat. 1877. 13: 263–277

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## Diagnostic Criteria of SM: WHO 2016 Update

Major	Multifocal dense infiltrates of mast cells
Minor	<ol style="list-style-type: none"><li>&gt; 25% mast cells with atypical morphology</li><li>D816 KIT mutation</li><li>CD25 <b>with or without</b> CD2</li><li>Serum total tryptase &gt;20 ng/mL (unless associated myeloid disorder)</li></ol>

**1 Major + 1 Minor**

**OR**

**3 Minor criteria**

Arbor D, et al. *Blood*. 2016;127(20):2391-2405.

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## B and C-Findings in Systemic Mastocytosis

**B-Findings** = Indication of high burden of MCs, and expansion of the genetic defect into various myeloid lineages without impairment of organ function  
B = Borderline Benign

- Infiltration grade (MCs) in bone marrow > 30% in histology and serum total tryptase level > 200 ng/mL
- Hypercellular marrow with loss of fat cells, discrete signs of dysmyelopoiesis without substantial cytopenias or WHO criteria for an MDS or MPD
- Organomegaly: palpable hepatomegaly, splenomegaly, or lymphadenopathy (on CT or US: > 2 cm) without impaired organ function

**C-Findings** = Indication of impaired organ function due to MC infiltration (has to be confirmed by biopsy in most cases)  
C = Consider Cyto-reduction

- Cytopenia(s): ANC < 1000/ $\mu$ L or Hb < 10 g/dL or Plt < 100,000/ $\mu$ L
- Hepatomegaly with ascites and impaired liver function
- Palpable splenomegaly with hypersplenism
- Malabsorption with hypoalbuminemia and weight loss
- Skeletal lesions: large-sized osteolyses or/and severe osteoporosis causing pathologic fractures
- Life-threatening organopathy in other organ systems that is definitively caused by an infiltration of the tissue by neoplastic MCs

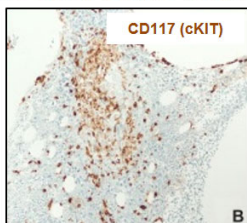
Valent P, et al. *Leuk Res*. 2001;25(7):603-625.

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## Systemic mastocytosis (SM)

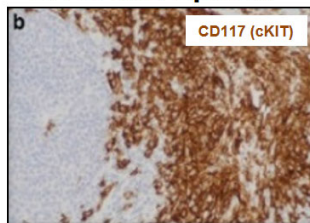
**Advanced systemic mastocytosis**  
*ASM, SM-AHN and MCL*

**Bone and bone marrow\***



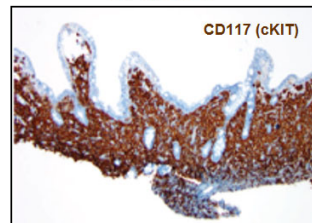
**Osteolytic bone lesions**  
**Cytopenias**

**Liver and spleen†**



**Liver function abnormalities,**  
**Ascites, or Hypersplenism**

**GI tract‡**



**Hypoalbuminemia**  
**Weight loss**

### **C-findings**

AdvSM, advanced SM; ASM, aggressive systemic mastocytosis; GI, gastrointestinal; MCL, mast cell leukemia; SM-AHN, SM-associated hematologic neoplasm.

Images reproduced with permission from: \*Metcalfe Blood (2008) 112:4; †Ammanagari N et al Ann Hematol (2013) 92:1573–1575; ‡Behdad A., Owens SR Arch Pathol Lab Med (2013) 137:1220–1223;

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## The Spectrum of Mast Cell disorders

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## Mast Cell Activation Syndrome

- Mediator-positive
  - Classic symptoms of mast cell disease and response to anti-mast cell mediator treatment with at least one positive lab finding (tryptase, histamine, PGD<sub>2</sub>, PGF<sub>2</sub>, +RAST, IgE)
- Mediator-negative
  - Classic symptoms and response to treatment without positive lab findings

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The screenshot displays the homepage of The New England Journal of Medicine. At the top left is the journal's logo, a circular seal with the text 'THE NEW ENGLAND JOURNAL OF MEDICINE' and 'FOUNDED 1827'. To the right of the logo is the journal's name: 'The NEW ENGLAND JOURNAL of MEDICINE'. Below the name is a navigation bar with links for 'HOME', 'ARTICLES & MULTIMEDIA', 'ISSUES', 'SPECIALTIES & TOPICS', 'FOR AUTHORS', and 'CME'. The main content area features an 'INTERACTIVE MEDICAL CASE' section. The title of the case is 'A Stinging Sensation'. Below the title are the authors' names: 'Kathleen Lee-Sarwar, M.D., Anand Vaidya, M.D., Min Shi, M.D., Ph.D., and Cem Akin, M.D., Ph.D.' and the publication information: 'N Engl J Med 2015; 372:e35 | June 25, 2015 | DOI: 10.1056/NEJMc1411027'. There are social media sharing icons for Facebook, Twitter, YouTube, LinkedIn, and a plus sign. Below the text is a 'Case' tab and a 'Metrics' tab. The 'Case' tab is active, showing a text block and an image. The text block describes a 45-year-old man stung by a yellow jacket, with symptoms of light-headedness, nausea, and erythema. The image shows a man in profile holding a smartphone, with a large, detailed illustration of a yellow jacket wasp overlaid on the right side of the image. At the bottom of the text block is a link: 'Learn more about Interactive Medical Cases'.

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## Cutaneous Mastocytosis



Hartmann K, et al. *J Allergy Clin Immunol.* 2016;137:35-45.

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## Cutaneous Mastocytosis (urticaria pigmentosa)



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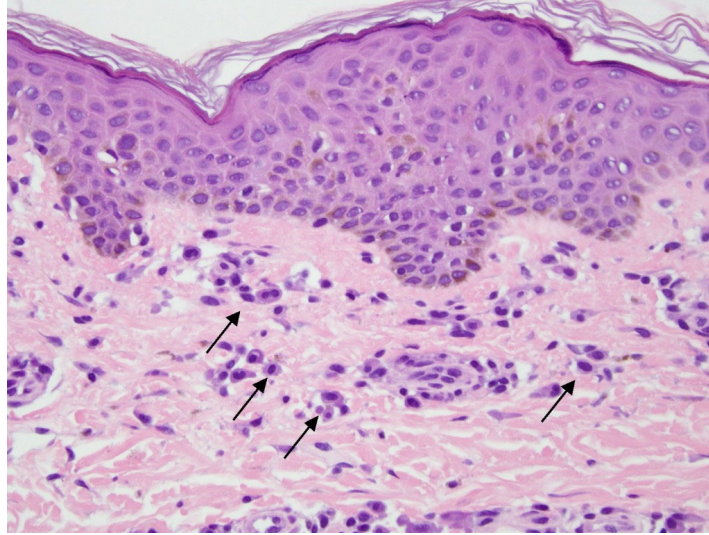
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### Darier Sign

Hartmann K, et al. *J Allergy Clin Immunol.* 2016;137:35-45.

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## Urticaria Pigmentosa



<http://www.skinpathology.org/>

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## Urticaria Pigmentosa



<http://www.skinpathology.org/>

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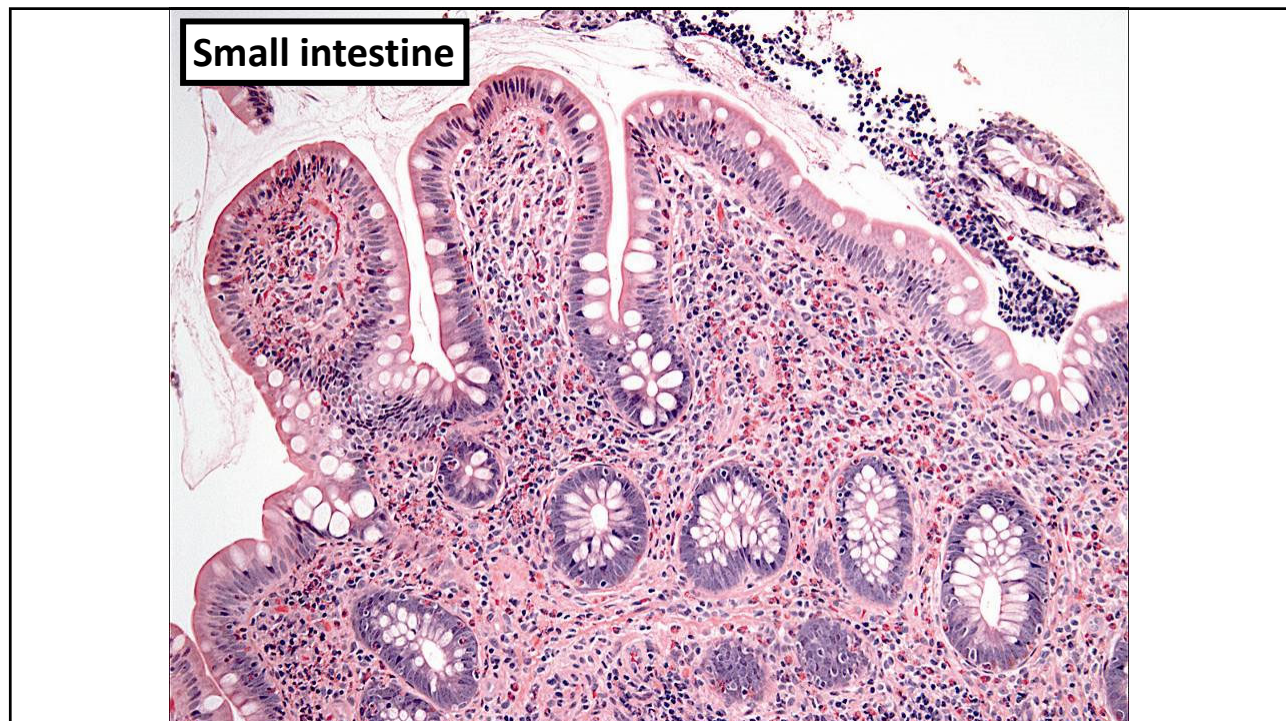


## Gastrointestinal symptoms of mast cell disease\*

<u>Symptom</u>	<u>Presumed etiology</u>
Abdominal pain	Altered gut motility-mediators
<b>Diarrhea</b>	Altered gut motility-mediators
Nausea	↑ H+ secretion, delayed stomach emptying
Vomiting	Delayed stomach emptying
Peptic Ulcer disease	Histamine induced H+ secretion
G I Bleeding	Histamine induced acid secretion, heparin
<b>Weight loss, malnutrition</b>	Mast cell infiltration

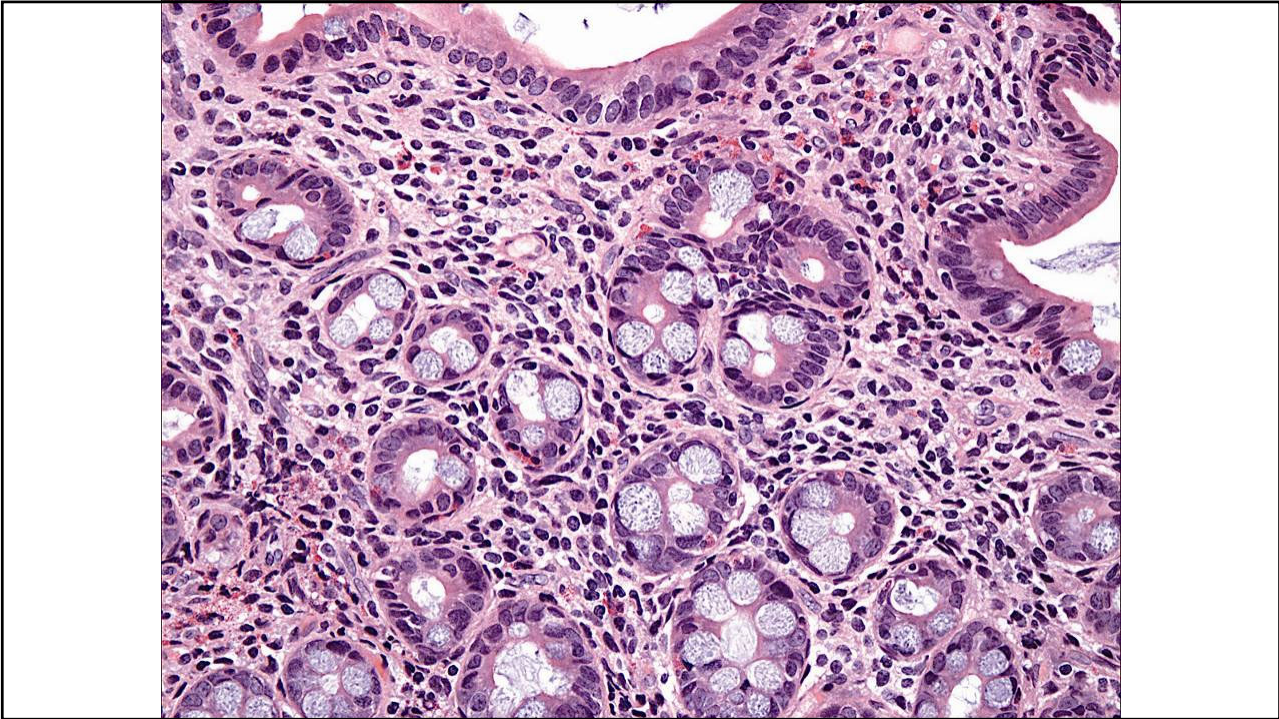
\* May occur without involvement of other organs

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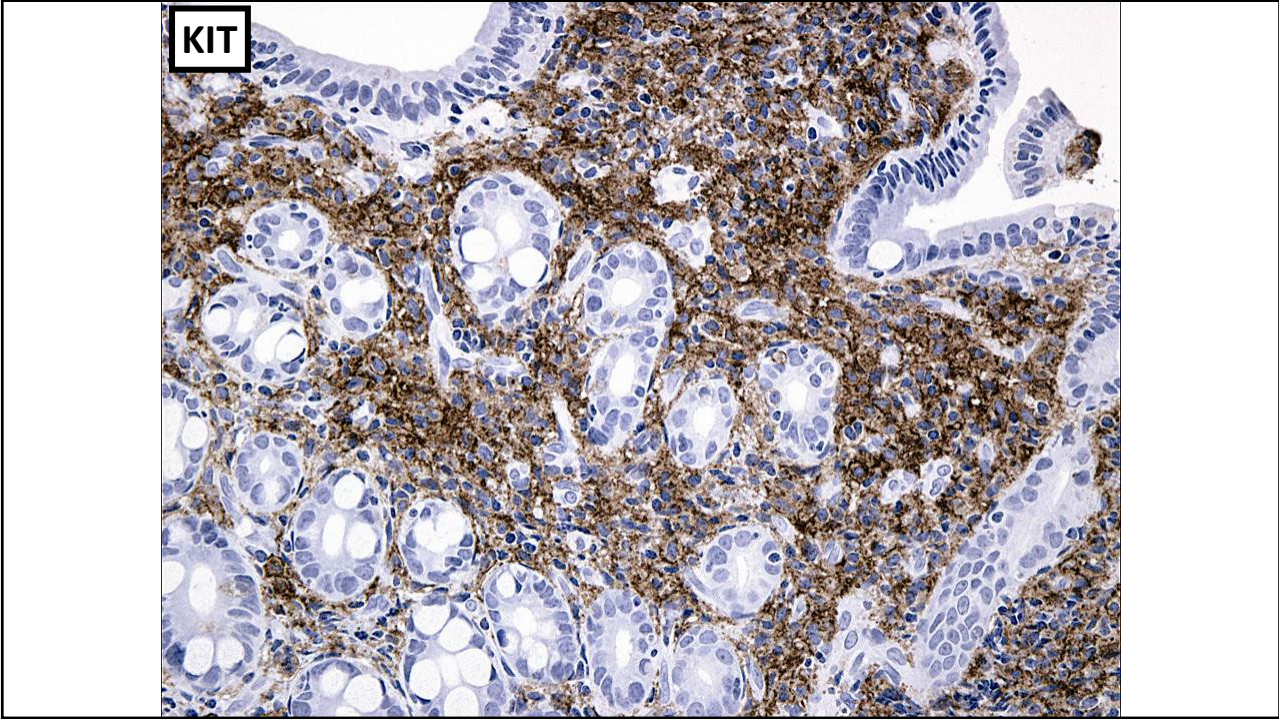


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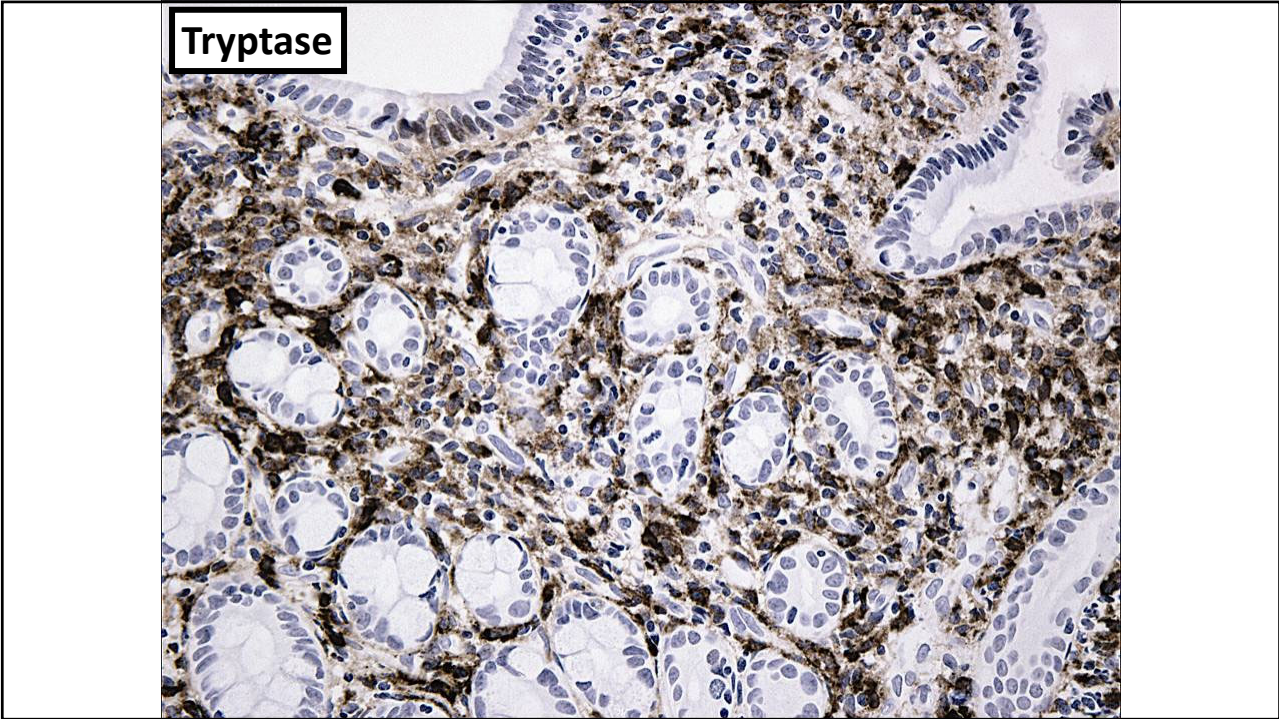


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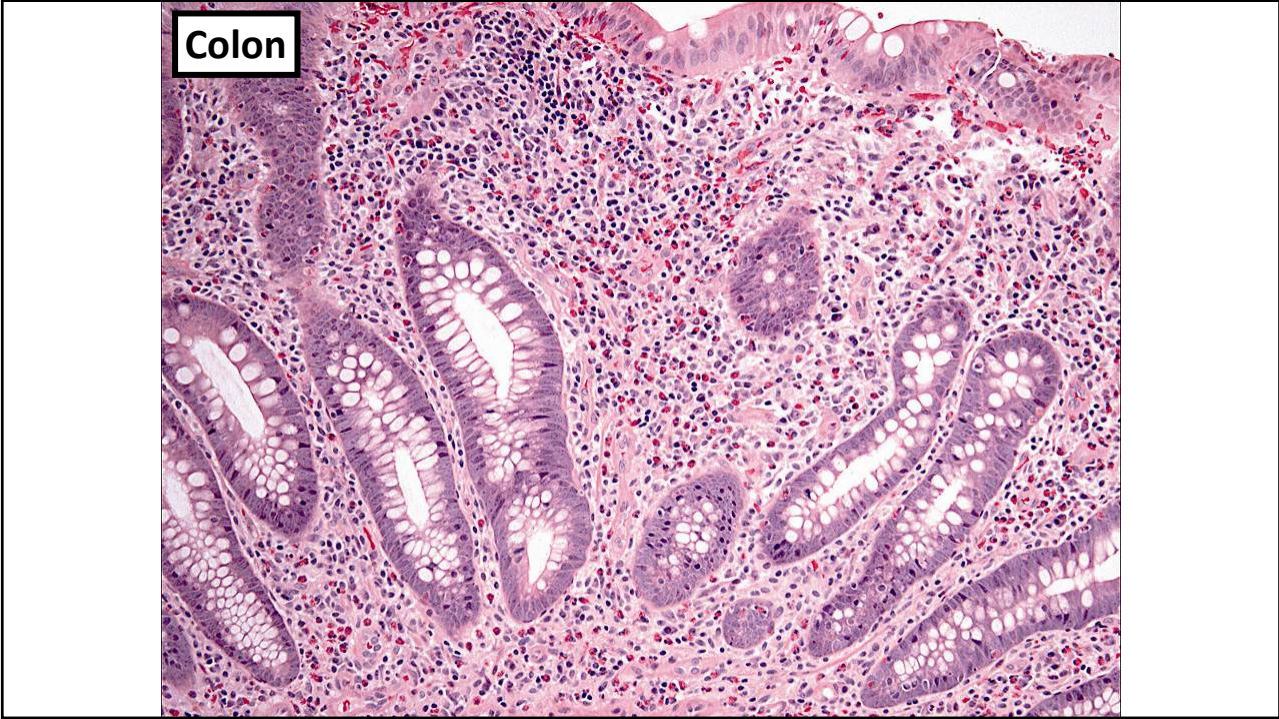


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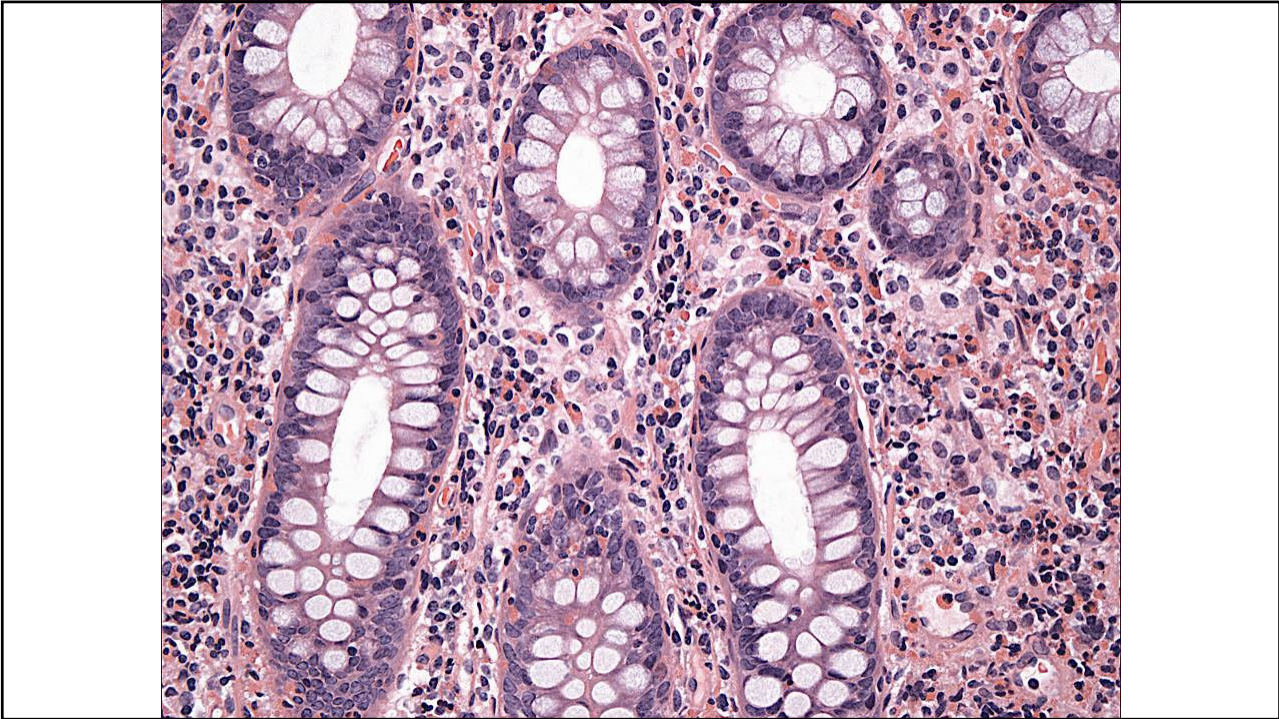


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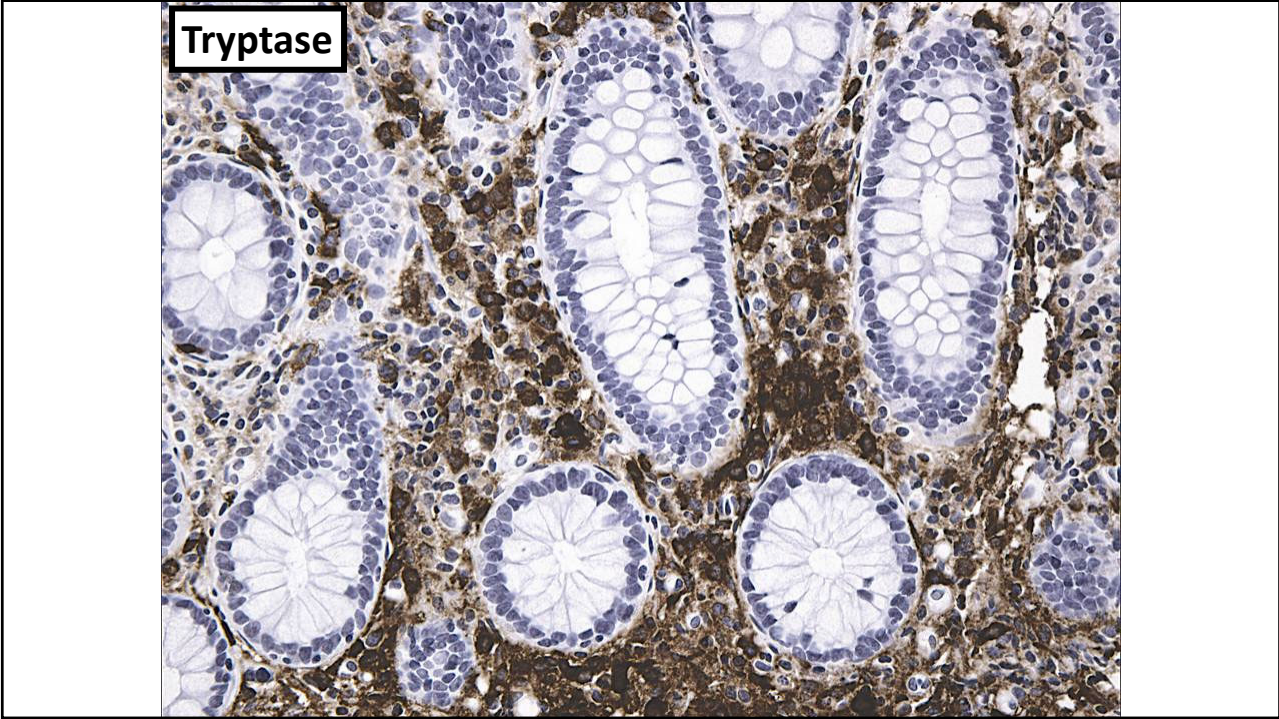


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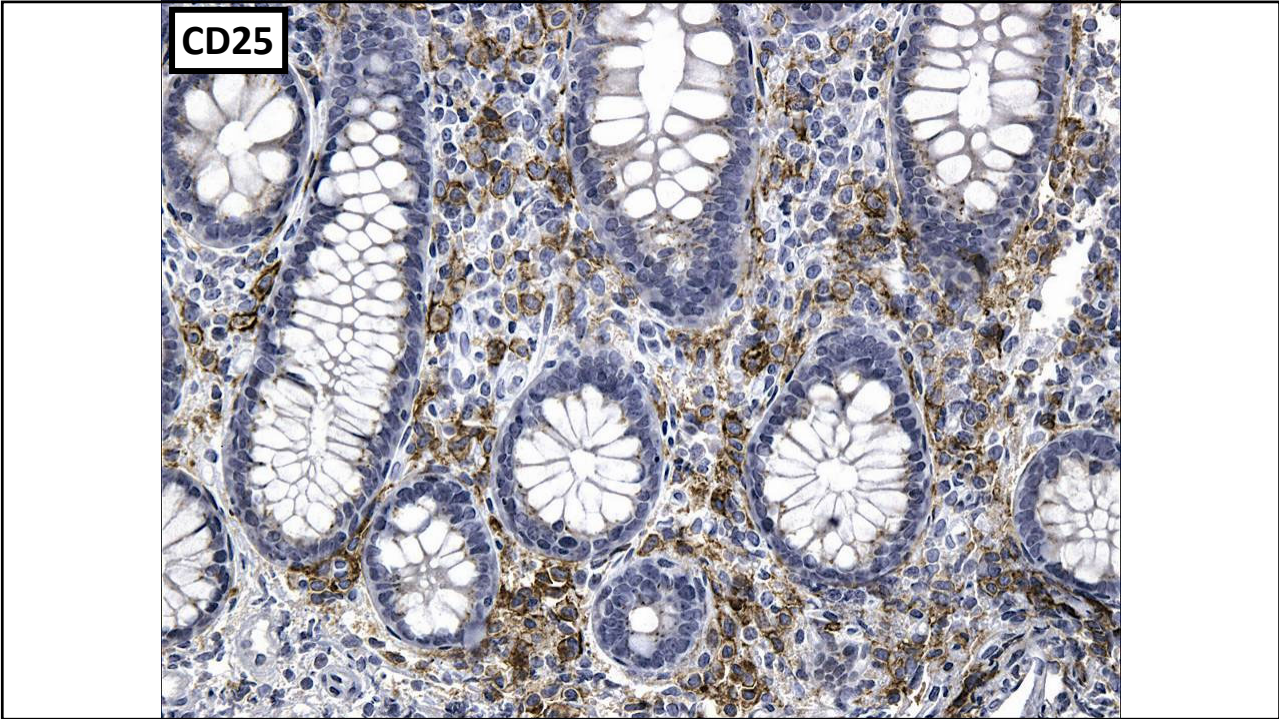


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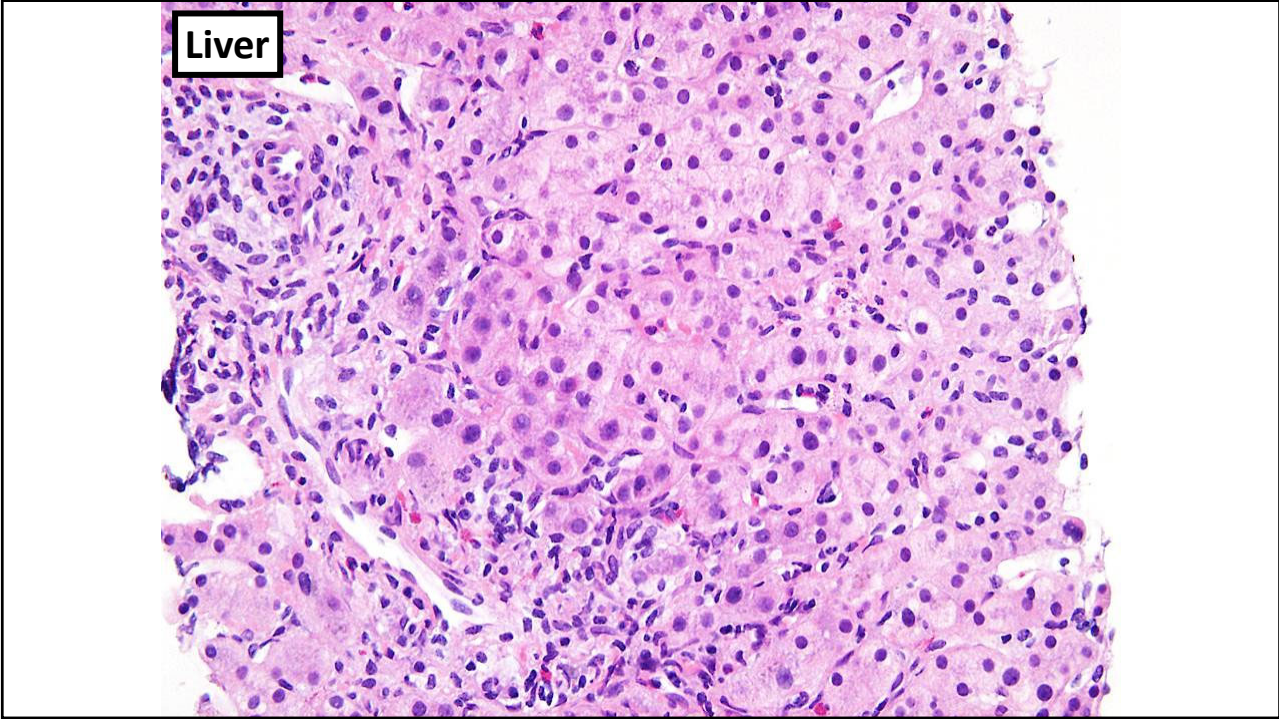


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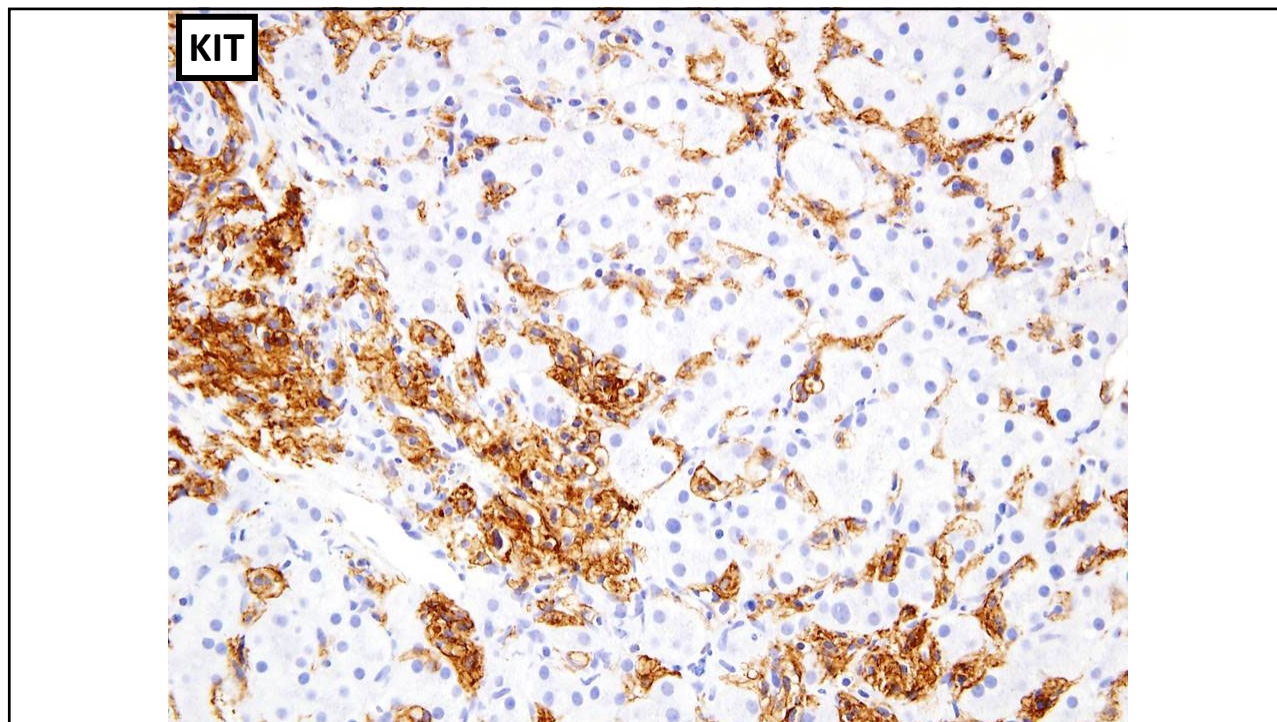
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## WHO 2016 Classification of Mastocytosis

### Diagnostic criteria of subtypes (variant forms) of systemic mastocytosis (SM)

<b>Indolent systemic mastocytosis (ISM)</b>	Non-Advanced
<ul style="list-style-type: none"> <li>SM diagnostic criteria; no "C" findings</li> </ul>	
<b>Smoldering systemic mastocytosis (SSM)</b>	Non-Advanced
<ul style="list-style-type: none"> <li>SM diagnostic criteria plus two or more "B" findings; no "C" findings</li> </ul>	
<b>Aggressive systemic mastocytosis (ASM)</b>	Advanced
<ul style="list-style-type: none"> <li>SM diagnostic criteria plus "C" findings; no features of mast cell leukemia</li> </ul>	
<b>Mast cell leukemia (MCL)</b>	
<ul style="list-style-type: none"> <li>SM diagnostic criteria plus features of MCL</li> </ul>	Advanced
<b>Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN)</b>	
<ul style="list-style-type: none"> <li>SM diagnostic criteria plus clonal hematologic nonmast cell lineage disorder (eg, MDS, MPN, AML, lymphoma, other)</li> </ul>	

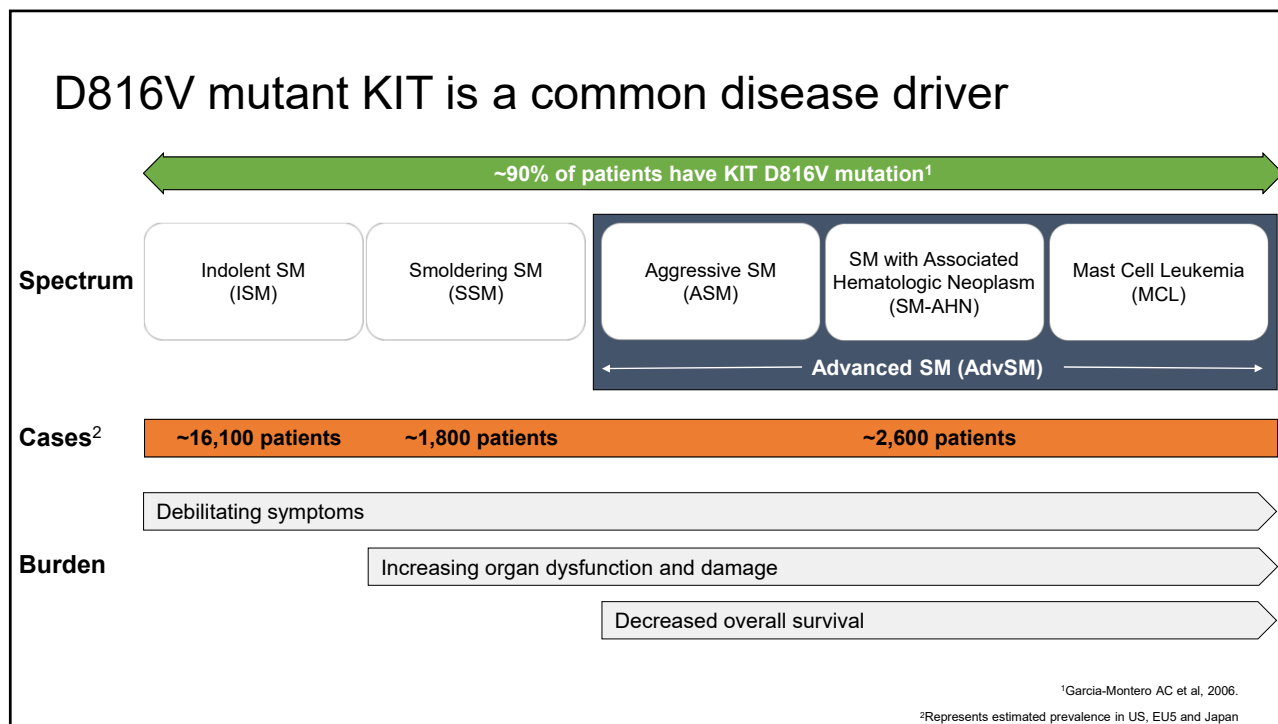
Modified with permission from: Horny HP, Metcalfe DD, Bennet JM, et al. Mastocytosis. In: WHO classification of tumours of haematopoietic and lymphoid tissues, 4th ed, Swerdlow SH, Campo E, Harris NL, et al (Eds), IARC: Lyon, 2008. Copyright © 2008.

Additional data from:

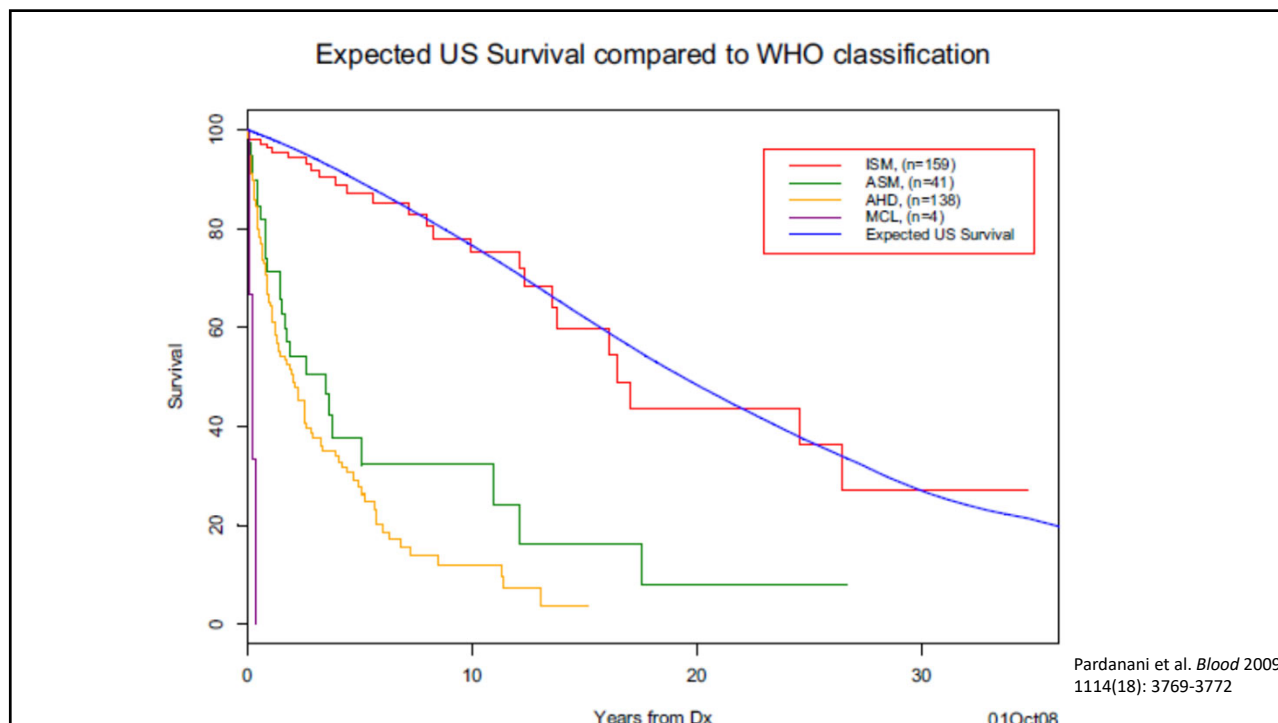
- Arber DA, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127:2391.

*Provisional: Bone Marrow Mastocytosis (indolent clinical course)*

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## Mutational Profile of SM

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### KIT mutation

- KITD816V
  - Approximately 90-95% of all SM patients
  - **Diagnostic** marker and **therapeutic** target
  - Poor oncogenic driver mutation
    - Associated mast cell phenotype
      - Promote mast cell *differentiation*
      - Little effects on mast cell proliferation and oncogenesis

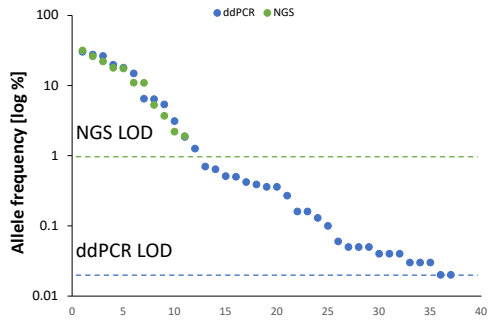
***Are there additional driver mutations that potentiate malignant transformation?***

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## Recommendations for Histopathology and *KIT* D816V Mutation Testing

- Increased detection of *KIT* D816V mutation in peripheral blood samples using digital droplet PCR (ddPCR) compared with next-generation sequencing (NGS) in patients with indolent systemic mastocytosis



***KIT* D816V:  
28%(NGS) vs 95% (ddPCR)**

George TI, et al. ASH 2020. Abstract 3004.

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Leukemia (2016) 30, 136–143  
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www.nature.com/leu

### ORIGINAL ARTICLE

## Additional mutations in *SRSF2*, *ASXL1* and/or *RUNX1* identify a high-risk group of patients with *KIT* D816V<sup>+</sup> advanced systemic mastocytosis

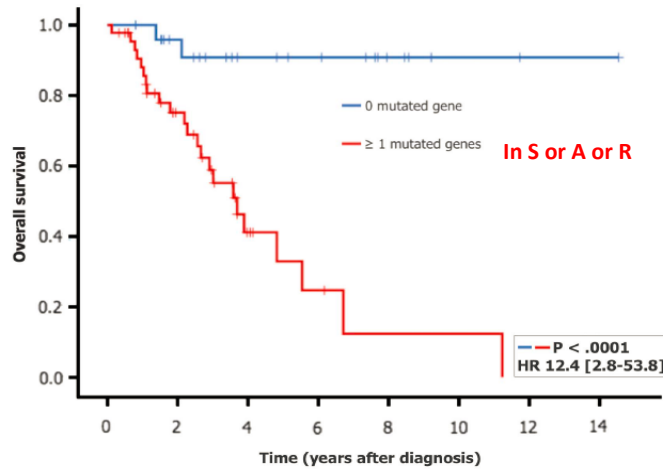
M Jawhar<sup>1</sup>, J Schwaab<sup>1</sup>, S Schnittger<sup>2</sup>, M Meggendorfer<sup>2</sup>, M Pffirmann<sup>3</sup>, K Sotlar<sup>4</sup>, H-P Horny<sup>4</sup>, G Metzgeroth<sup>1</sup>, S Kluger<sup>1</sup>, N Naumann<sup>1</sup>, C Haferlach<sup>2</sup>, T Haferlach<sup>2</sup>, P Valent<sup>5</sup>, W-K Hofmann<sup>1</sup>, A Fabarius<sup>1</sup>, NCP Cross<sup>6,7</sup> and A Reiter<sup>1</sup>

- N= 70 patients with AdvSM
- NGS for potential oncogenic mutations
- Correlate mutational status with OS

Jawhar et al., *Leukemia* (2016) 30, 136–143.

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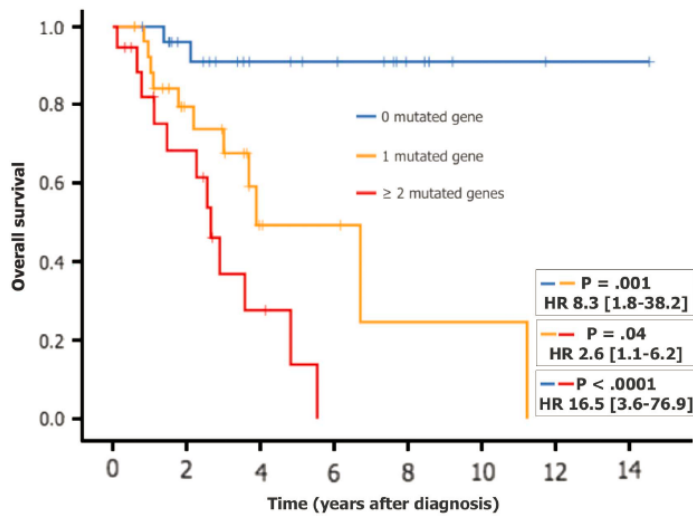
### *SARSF2, ASXL1, RUNX1*: High-Risk Mutations in SM



Jawhar et al., *Leukemia* (2016) 30, 136–143.

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### *SARSF2, ASXL1, RUNX1*: High-Risk Mutations in SM



Jawhar et al., *Leukemia* (2016) 30, 136–143

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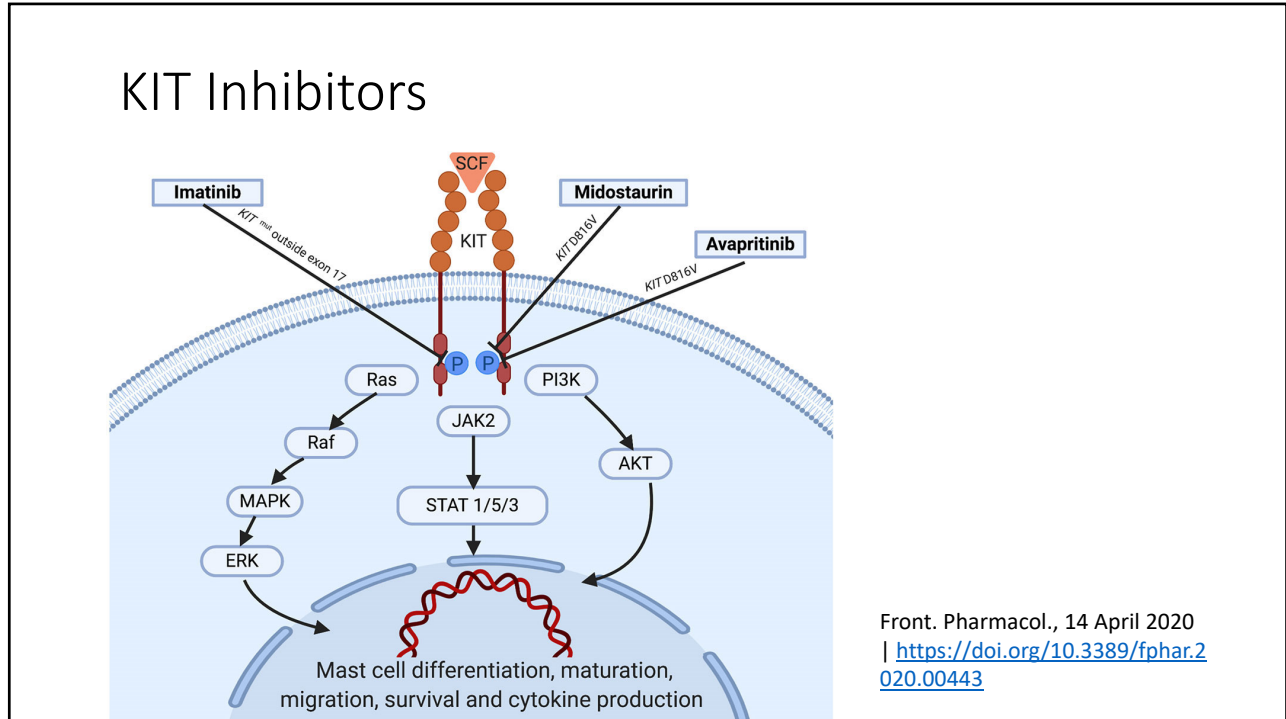
## Clinical Strategies

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### Mast Cell Supportive Therapy

- H1-antihistamines (cetirizine, fexofenadine, etc)
- H2-antihistamines (famotidine, etc)
- Cysteinyl leukotriene inhibitors (montelukast)
- Mast cell stabilizers (GI symptoms)
  - Cromoglicic Acid (Cromolyn; Gastrocrom)
    - Oral bioavailability is about 1%
- Corticosteroids (systemic steroid bursts)
- Aspirin
- Omalizumab (Xolair; Anti-IgE)
- Epinephrine pen
- “ER” sheet
- List of medications to avoid

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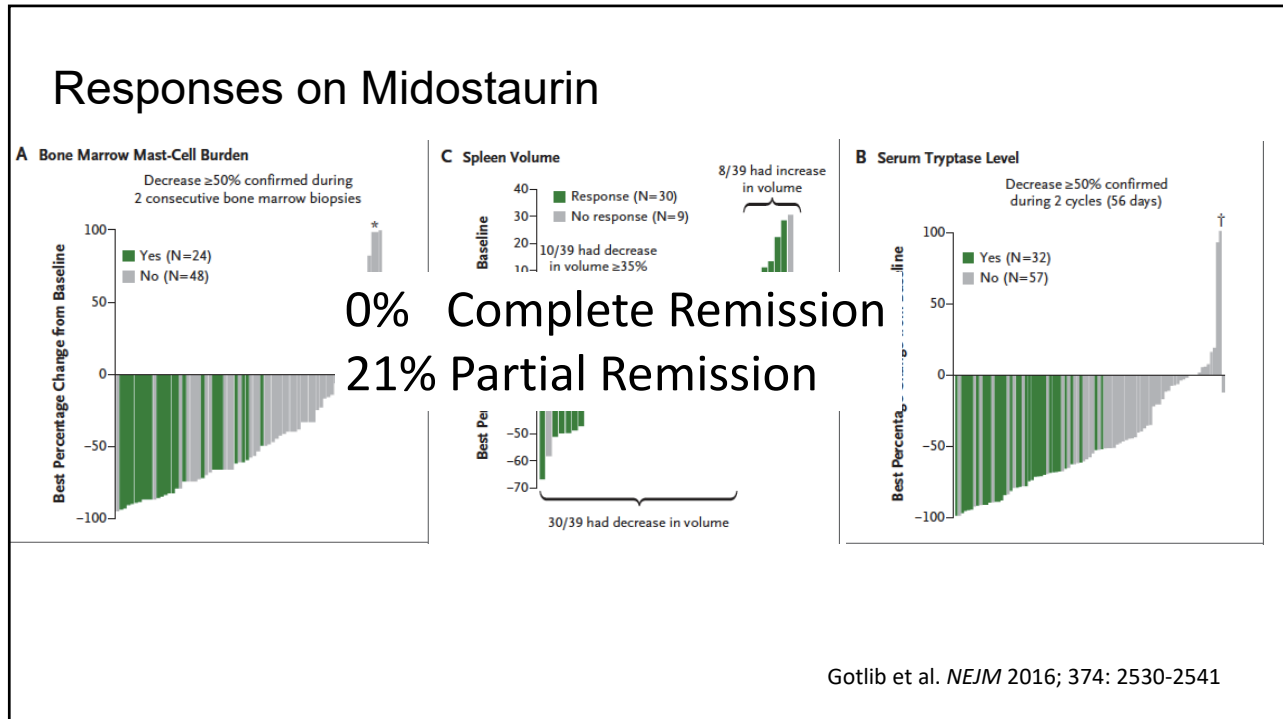
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis

Jason Gotlib, M.D., Hanneke C. Kluijn-Nelemans, M.D., Ph.D., Tracy I. George, M.D., Cem Akin, M.D., Ph.D., Karl Sotlar, M.D., Olivier Hermine, M.D., Ph.D., Farrukh T. Awan, M.D., Elizabeth Hexner, M.D., Michael J. Mauro, M.D., David W. Sternberg, M.D., Ph.D., Matthieu Villeneuve, M.Sc., Alice Huntsman Laped, Ph.D., Eric J. Stanek, Pharm.D., Karin Hartmann, M.D., Hans-Peter Horny, M.D., Peter Valent, M.D., and Andreas Reiter, M.D.

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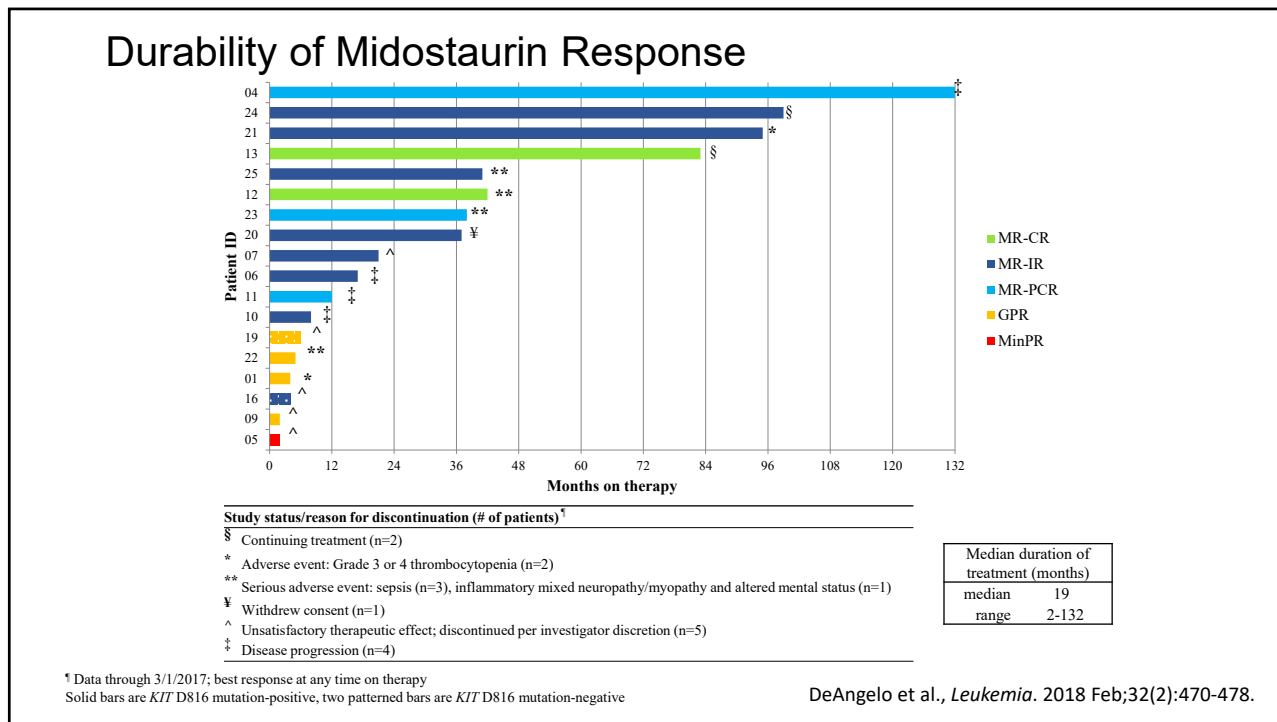
Leukemia (2017), 1–9  
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[www.nature.com/leu](http://www.nature.com/leu)

**ORIGINAL ARTICLE**

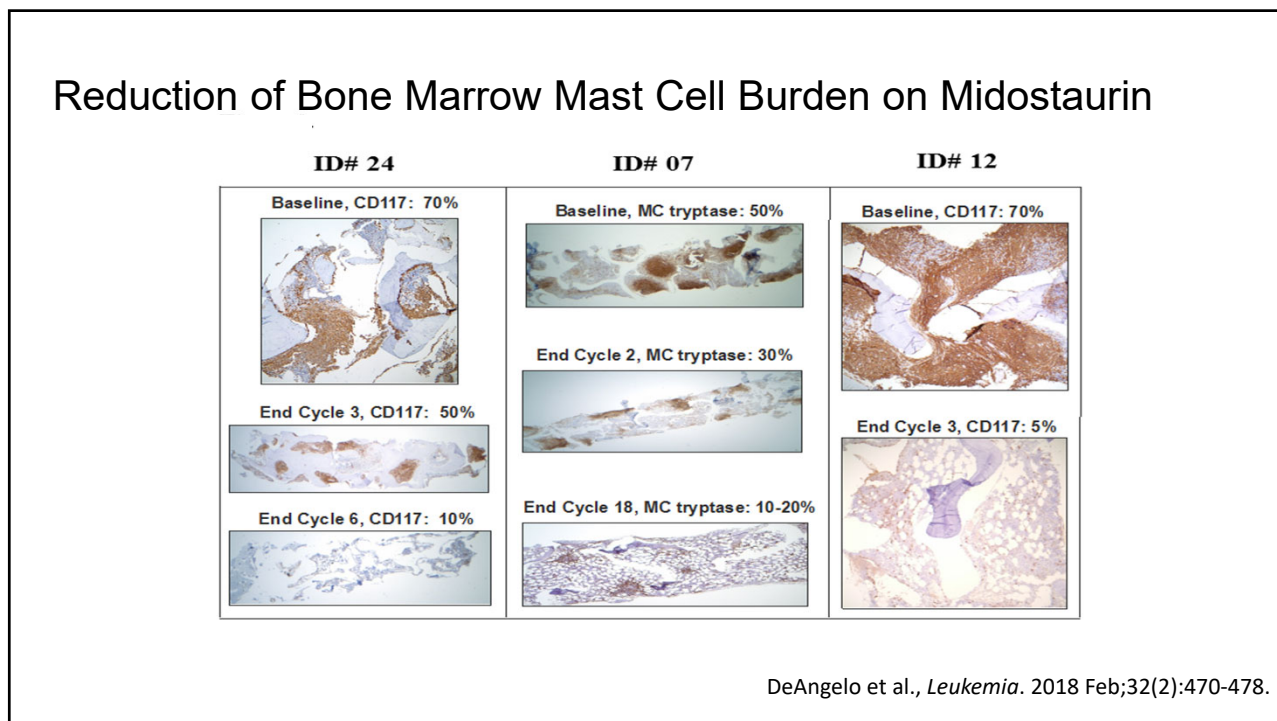
## Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial

DJ DeAngelo<sup>1</sup>, TI George<sup>2</sup>, A Linder<sup>3</sup>, C Langford<sup>3</sup>, C Perkins<sup>3</sup>, J Ma<sup>3</sup>, P Westervelt<sup>4</sup>, JD Merker<sup>5</sup>, C Berube<sup>3</sup>, S Coutre<sup>3</sup>, M Liedtke<sup>3</sup>, B Medeiros<sup>3</sup>, D Sternberg<sup>6,7</sup>, C Dutreix<sup>6,7</sup>, P-A Ruffie<sup>6,7</sup>, C Corless<sup>8</sup>, TJ Graubert<sup>9</sup> and J Gotlib<sup>3</sup>

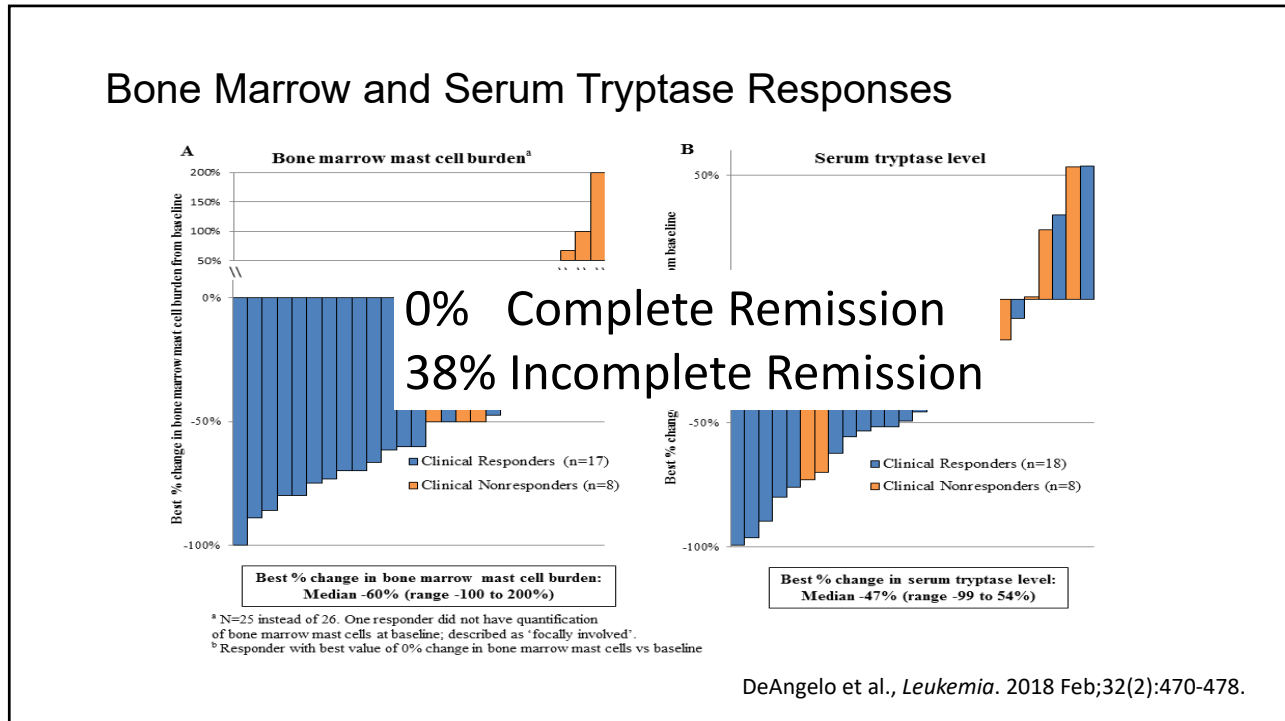
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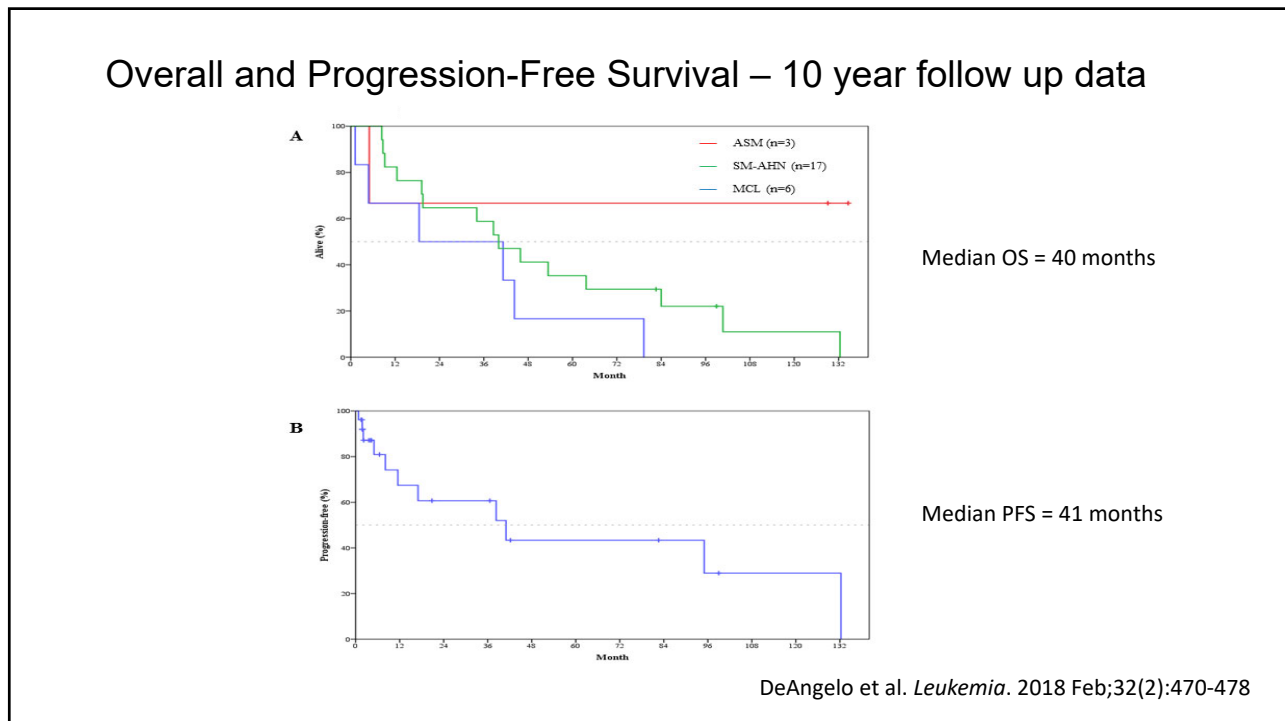
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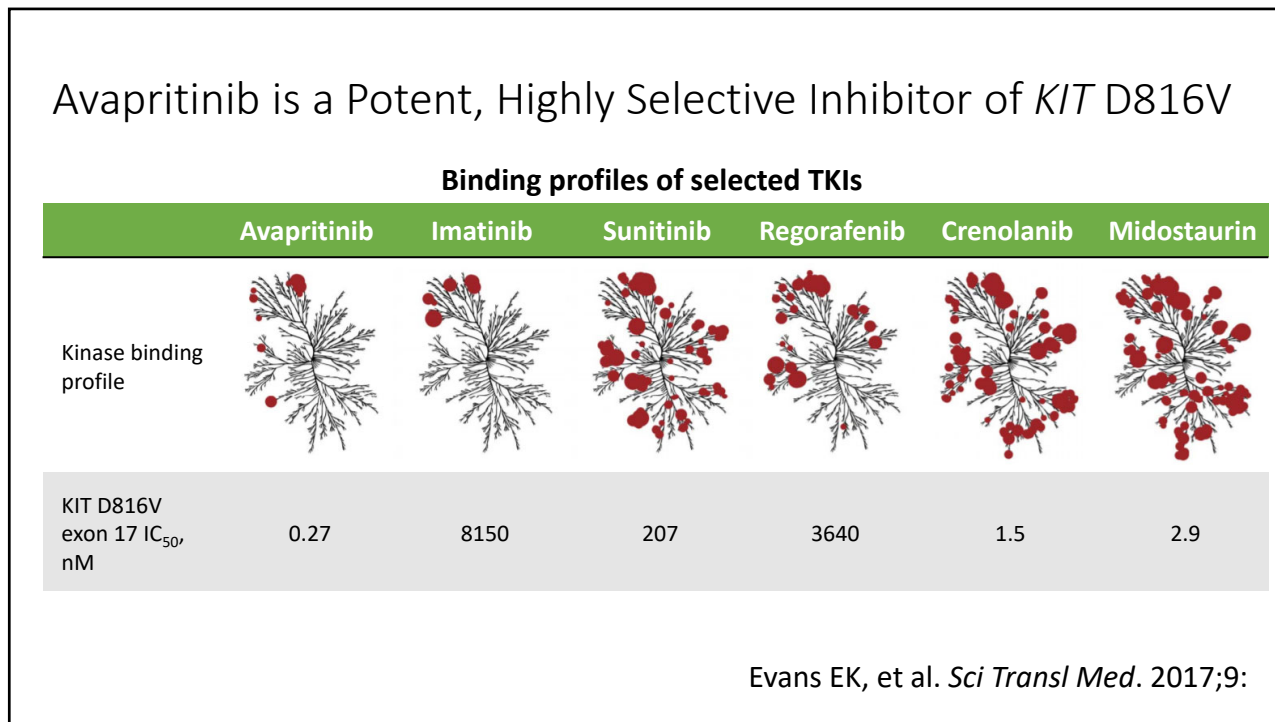
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**ARTICLES**

<https://doi.org/10.1038/s41591-021-01538-9>



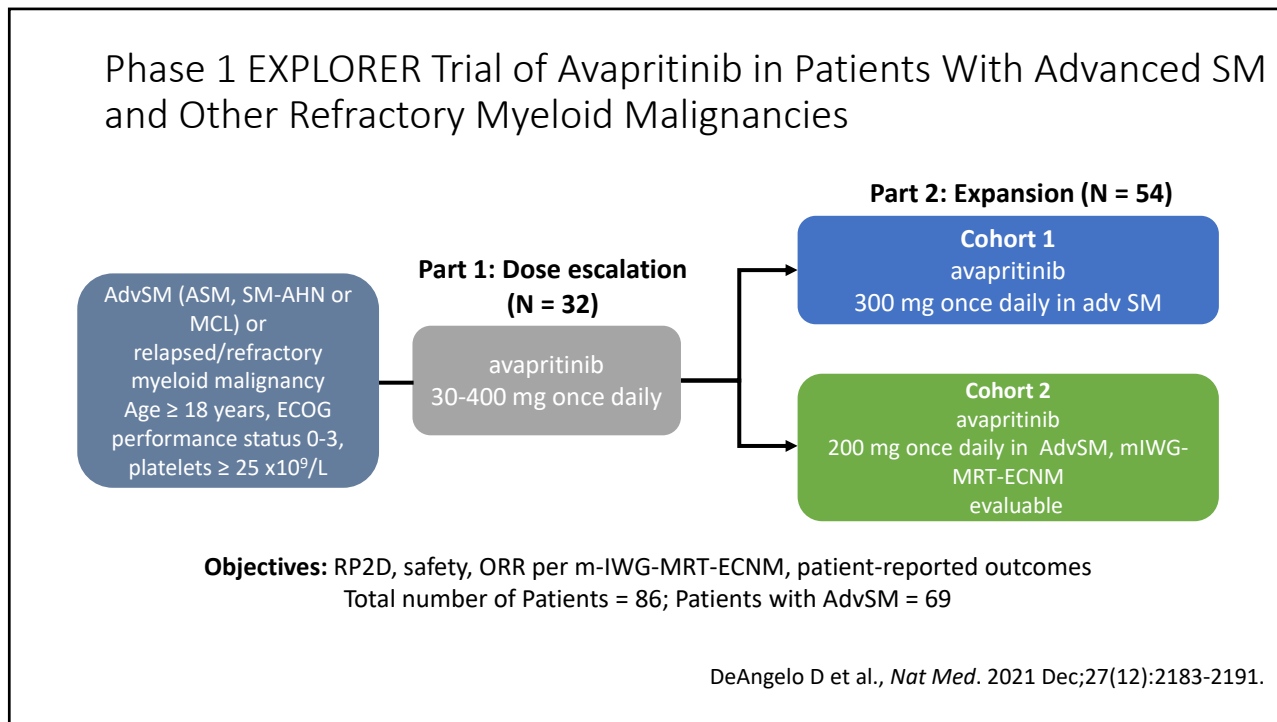
## OPEN Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial

Daniel J. DeAngelo <sup>1</sup>✉, Deepti H. Radia<sup>2</sup>, Tracy I. George <sup>3</sup>, William A. Robinson<sup>4</sup>, Albert T. Quiery<sup>5</sup>, Mark W. Drummond<sup>6</sup>, Prithviraj Bose <sup>7</sup>, Elizabeth O. Hexner <sup>8</sup>, Elliott F. Winton<sup>9</sup>, Hans-Peter Horny<sup>10</sup>, Meera Tugnait<sup>11</sup>, Oleg Schmidt-Kittler<sup>11</sup>, Erica K. Evans<sup>11</sup>, Hui-Min Lin<sup>11</sup>, Brenton G. Mar<sup>11</sup>, Srdan Verstovsek <sup>7</sup>, Michael W. Deininger <sup>12,14</sup> and Jason Gotlib <sup>13,14</sup>

DeAngelo D et al., *Nat Med.* 2021 Dec;27(12):2183-2191.

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## EXPLORER

### Baseline Characteristics of the AdvSM Patients

Parameter	Adv SM Pts (N = 69)	mIWG Evaluable Pts (N = 53)
Median age, years (range)	67 (34-83)	65 (34-83)
SM subtype, n (%)		
• ASM	8 (12%)	3 (6%)
• SM-AHN	48 (70%)	37 (70%)
• MCL	13 (19%)	13 (25%)
ECOG PS, n (%)		
• 0-1	48 (70%)	36 (68%)
• 2-3	21 (30%)	17 (32%)
Any prior therapy, %	41 (59%)	32 (60%)
• Prior midostaurin	23 (33%)	17 (32%)
• Prior cladribine	10 (14%)	7 (13%)
Median bone marrow mast cell burden, % (range)	40 (5 – 95)	50 (5 – 95)
Median serum tryptase, µg/L (range)	173 (12 – 1414)	182 (21 – 765)
KIT D816V allele fraction, median % (range)	14 (0 – 81)	17 (0 – 81)

DeAngelo D et al., *Nat Med.* 2021 Dec;27(12):2183-2191.

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### Treatment-emergent adverse events (AEs)

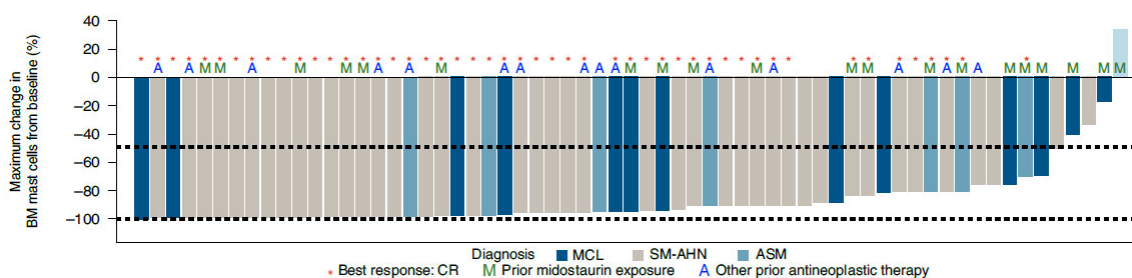
Adverse event, n (%)	Any Grade	Grade 3/4
<b>NON-HEMATOLOGICAL AEs &gt;15% (N=86)</b>		
Periorbital edema	59 (69)	2 (2)
Diarrhea	39 (45)	1 (1)
Nausea	38 (44)	3 (3)
Fatigue	35 (41)	8 (9)
Peripheral Edema	34 (40)	0
Vomiting	31 (36)	4 (5)
Arthralgia	24 (28)	3 (3)
Hair color changes	22 (26)	1 (1)
Memory impairment*	20 (23)	0
Abdominal pain	19 (22)	1 (1)
Dizziness	19 (22)	2 (2)
Decreased appetite	20 (23)	1 (1)
Pruritis	16 (19)	0
Constipation	19 (22)	1 (1)
Dysgeusia	16 (19)	0
<b>HEMATOLOGICAL AEs &gt;10% (N=86)</b>		
Anemia	47 (55)	26 (30)
Thrombocytopenia	33 (44)	29 (34)
Neutropenia	17 (20)	13 (15)

- Most AEs were grade 1 or 2
- Cytopenias were most common  $\geq$  grade 3 treatment-related AE
- No grade 5 treatment-related AEs
- 17% (15/86) discontinued due to treatment-related AEs
  - Refractory ascites, encephalopathy and ICB
- Cognitive impairment occurred in 21 patients
  - Mostly grade 1 (20%) or Grade 2 (7%)
- Intracranial bleeding (ICB) occurred in 9 patients (13%)\*\*
  - 5 of 9 patients resumed therapy
  - No new ICB events reported since implementing dose modifications for thrombocytopenia
- 41% (28/69) with AdvSM remain on treatment

AEs of note: ascites (n=6 [9%]; n=1 [1%] at  $\geq$  grade 3), pleural effusion (n=9 [13%], n= 1[1%] at  $\geq$  grade 3)  
 \*Cognitive effects include cognitive disorder, confusional state, memory impairment and encephalopathy  
 \*\*1 ICB was in setting of severe head trauma

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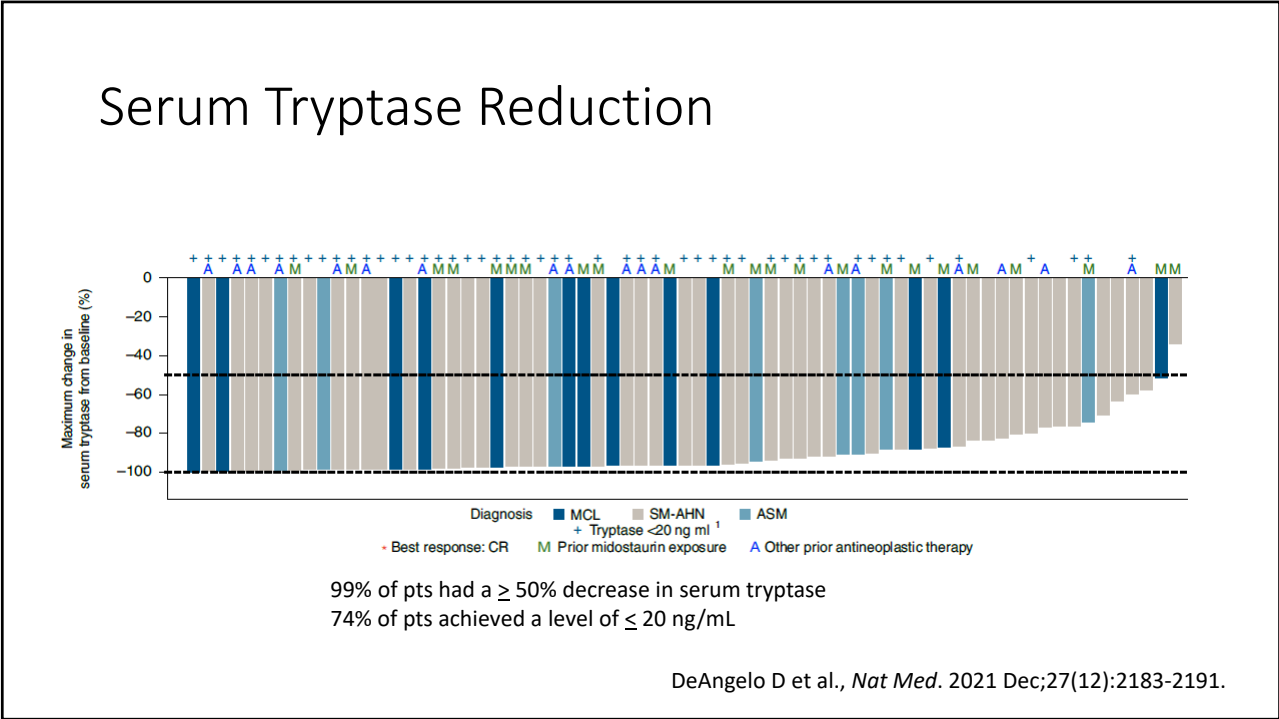
### BM Mast Cell Reduction



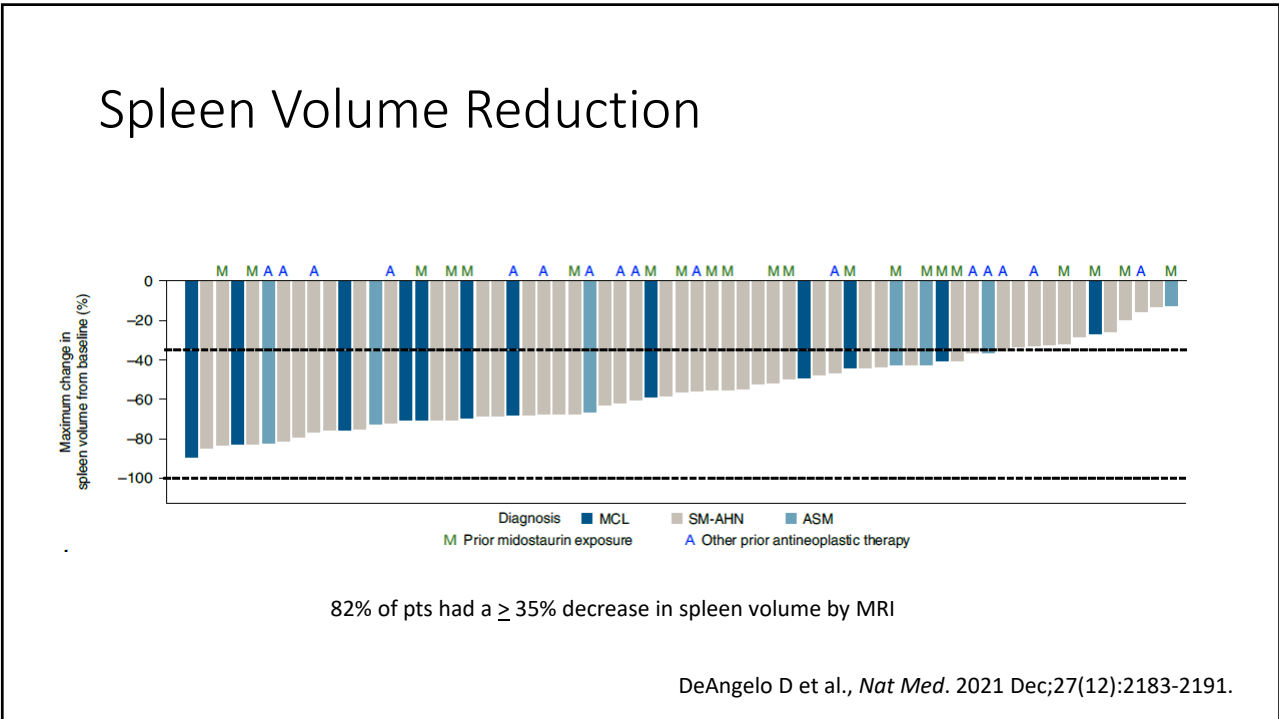
92% of pts had a  $\geq$  50% decrease in MC burden  
 77% had complete elimination

DeAngelo D et al., *Nat Med.* 2021 Dec;27(12):2183-2191.

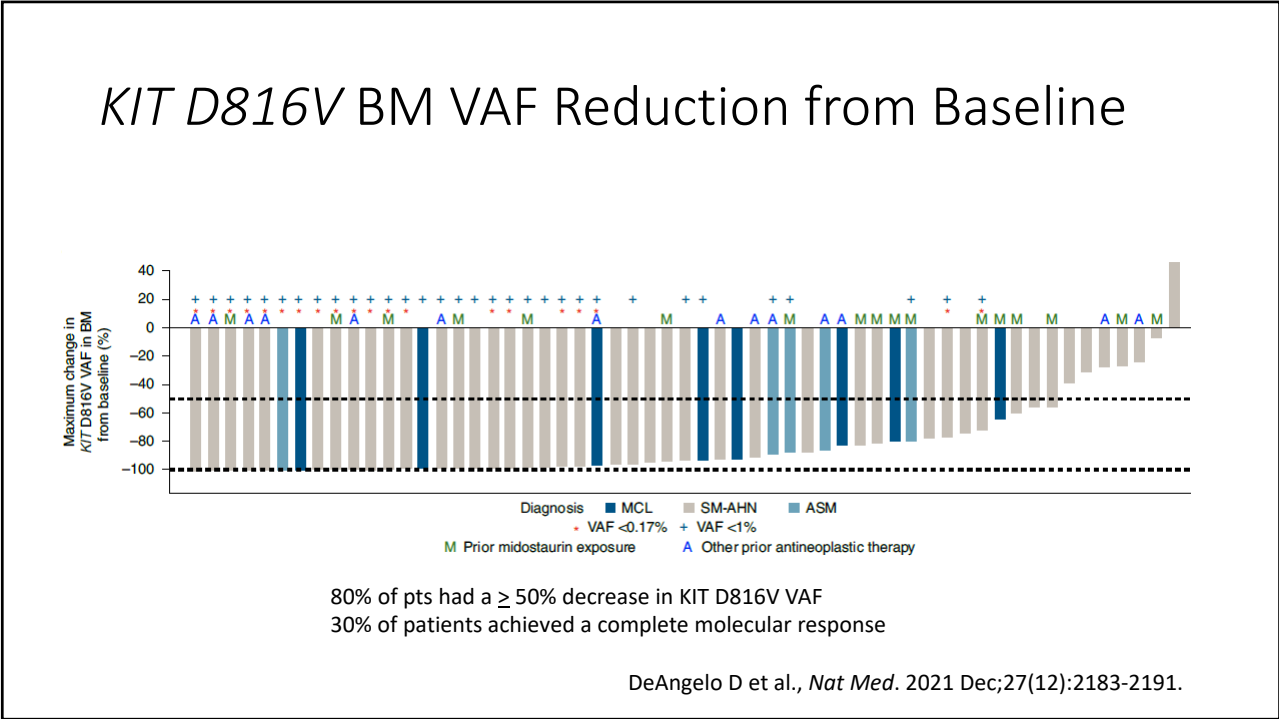
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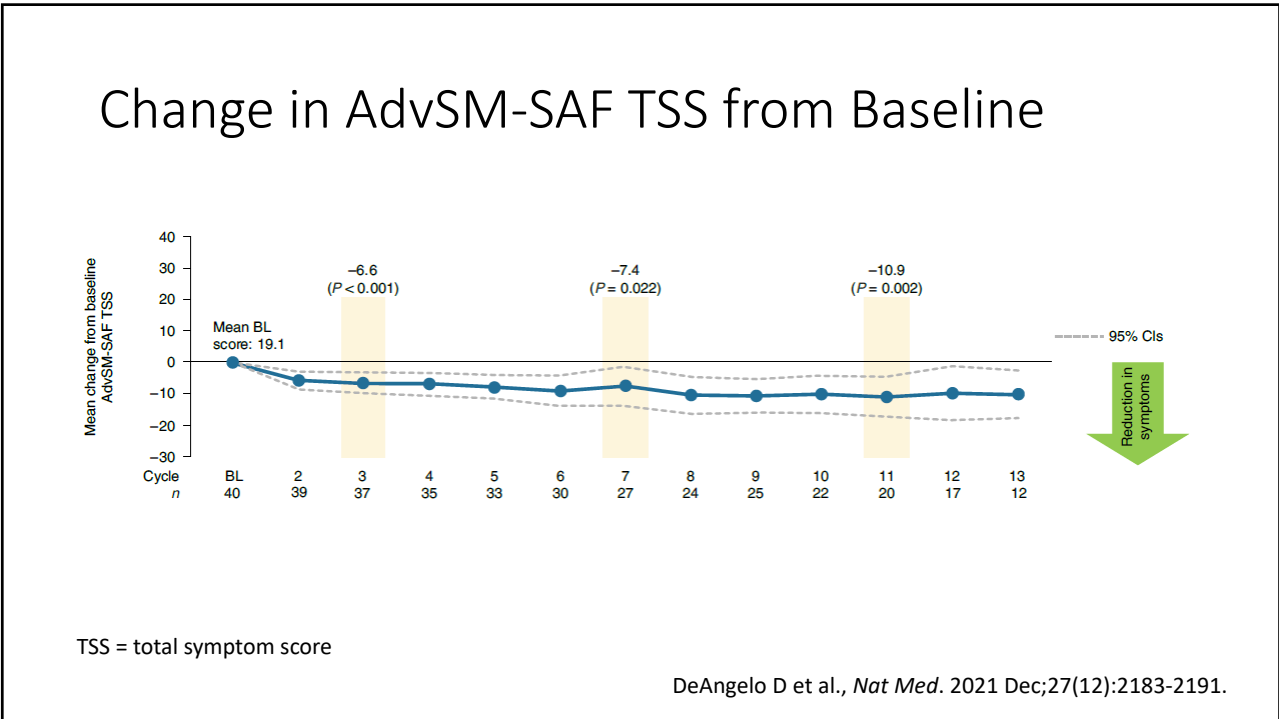
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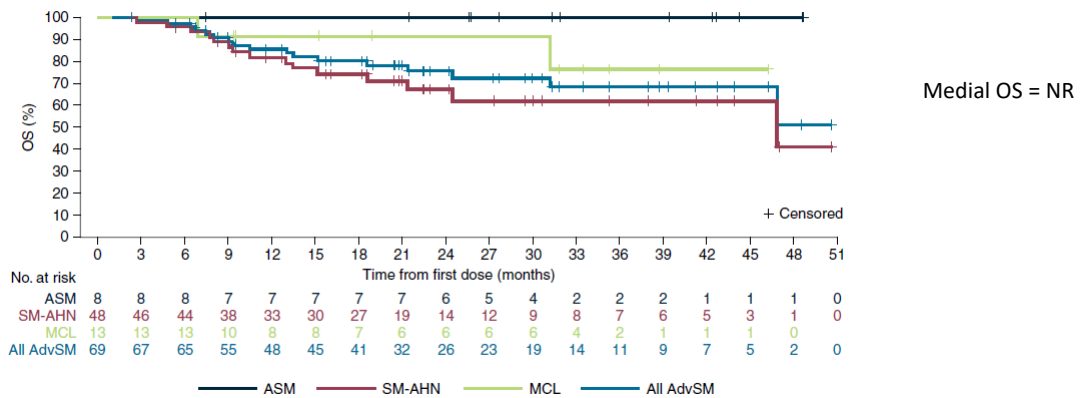
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## Overall Responses by Central Review per mIWG

Best confirmed response by mIWG-MRT-ECNM criteria, n (%)	By AdvSM subtype				All AdvSM, by midostaurin history		All AdvSM, by prior therapy history	
	All AdvSM (n=53)	ASM (n=3)	SM-AHN (n=37)	MCL (n=13)	Prior midostaurin exposure (n=17)	Midostaurin naïve (n=36)	Any prior therapy (n=32)	No prior therapy (n=21)
ORR (CR+CRh+PR+CI), n (%)	40 (75)	3 (100)	28 (76)	9 (69)	10 (59)	30 (83)	22 (69)	18 (86)
95% CI	62-86	29-100	59-88	39-91	33-82	67-94	50-84	64-97
<b>Best response</b>								
CR or CRh	19 (36)	2 (67)	14 (38)	3 (23)	3 (18)	16 (44)	9 (28)	10 (48)
CR	8 (15)	0	5 (14)	3 (23)	2 (12)	6 (17)	4 (13)	4 (19)
CRh	11 (21)	2 (67)	9 (24)	0	1 (6)	10 (28)	5 (16)	6 (29)
PR	18 (34)	1 (33)	13 (35)	4 (31)	6 (35)	12 (33)	11 (34)	7 (33)
CI	3 (6)	0	1 (3)	2 (15)	1 (6)	2 (6)	2 (6)	1 (5)
SD	12 (23)	0	8 (22)	4 (31)	6 (35)	6 (17)	9 (28)	3 (14)
PD	0	0	0	0	0	0	0	0
NE	1 (2)	0	1 (3)	0	1 (6)	0	1 (3)	0


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## Overall Survival




DeAngelo D et al., *Nat Med.* 2021 Dec;27(12):2183-2191.

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**ARTICLES**

<https://doi.org/10.1038/s41591-021-01539-8>



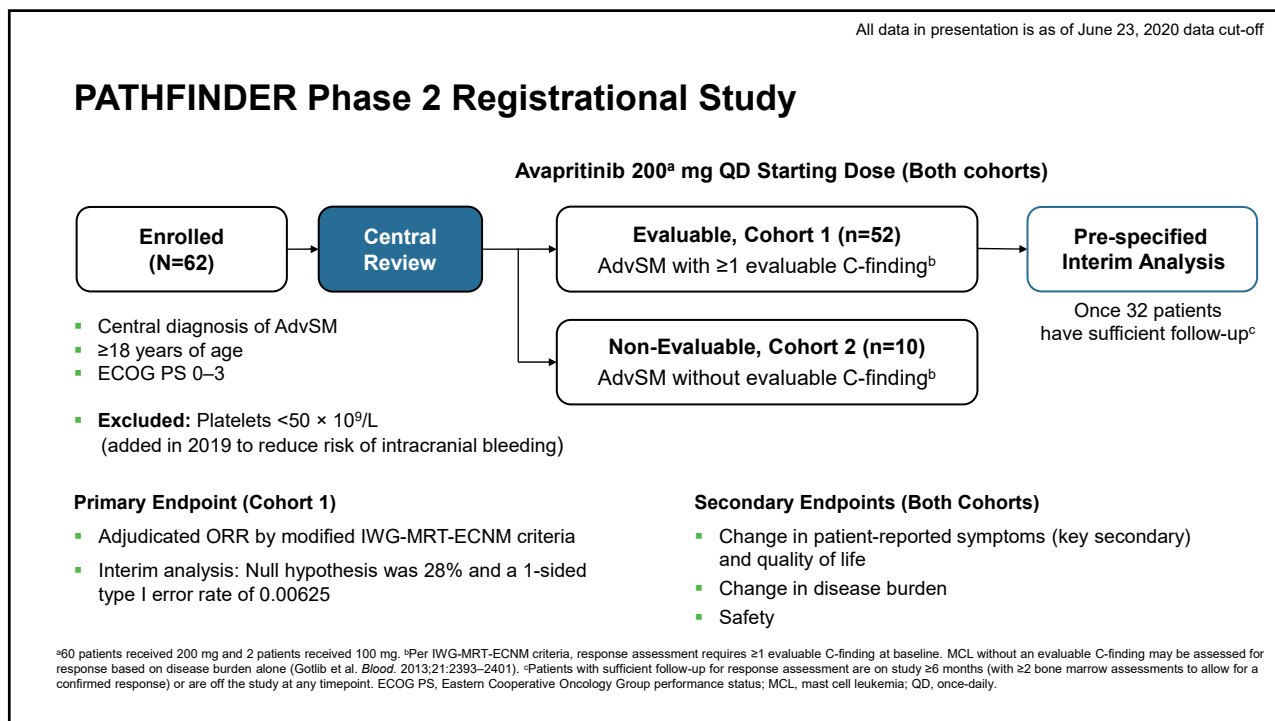
**OPEN**

## Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial

Jason Gotlib<sup>1,23</sup>✉, Andreas Reiter<sup>2,23</sup>, Deepti H. Radia<sup>3</sup>, Michael W. Deininger<sup>4</sup>, Tracy I. George<sup>5</sup>, Jens Panse<sup>6</sup>, Alessandro M. Vannucchi<sup>7</sup>, Uwe Platzbecker<sup>8</sup>, Iván Alvarez-Twose<sup>9</sup>, Andrzej Mital<sup>10</sup>, Olivier Hermine<sup>11</sup>, Ingunn Dybedal<sup>12</sup>, Elizabeth O. Hexner<sup>13</sup>, Lisa K. Hicks<sup>14</sup>, Lambert Span<sup>15</sup>, Ruben Mesa<sup>16</sup>, Prithviraj Bose<sup>17</sup>, Kristen M. Pettit<sup>18</sup>, Mark L. Heaney<sup>19</sup>, Stephen T. Oh<sup>20</sup>, Jayita Sen<sup>21</sup>, Hui-Min Lin<sup>21</sup>, Brenton G. Mar<sup>21</sup> and Daniel J. DeAngelo<sup>22</sup>

Gotlib j et al., *Nat Med.* 2021 Dec;27(12):2192-2199.

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All data in presentation is as of June 23, 2020 data cut-off

## Efficacy of Avapritinib 200 mg QD in Interim Analysis

Best Confirmed Response, n (%)	All AdvSM (n=32) <sup>a</sup>
<b>Overall Response Rate</b> (CR + CRh + PR + CI)	24 (75)
<b>CR or CRh</b>	6 (19)
Complete Remission (CR)	0
CR with partial hematologic recovery	6 (19)
Partial Remission (PR)	10 (31)
Clinical Improvement (CI)	8 (25)
Stable Disease (SD)	4 (13)
Progressive Disease (PD)	1 (3)
Not Evaluable (NE)	3 (9) <sup>b</sup>

Interim analysis: passed ( $P=1.60E-9$ )

**CRh (mIWG-MRT-ECNM) requires**

- Full resolution of all evaluable C-findings
- BM MC aggregates eliminated
- Serum tryptase <20 ng/mL
- Resolution of palpable hepatosplenomegaly

**Partial hematologic recovery**

- ANC >0.5 × 10<sup>9</sup>/L with normal differential
- Platelet count >50 × 10<sup>9</sup>/L
- Hgb level >8.0 g/dL

**PR requires**

- Full resolution of ≥1 evaluable C-findings
- ≥50% reduction in BM MCs, serum tryptase

<sup>a</sup>One patient in evaluable population started at 100 mg QD. <sup>b</sup>Three (9%) of 32 patients in the interim analysis were assessed as not evaluable for response due to coming off study for AE before 13 weeks. ANC, absolute neutrophil count; BM, bone marrow; Hgb, hemoglobin; MC, mast cells.

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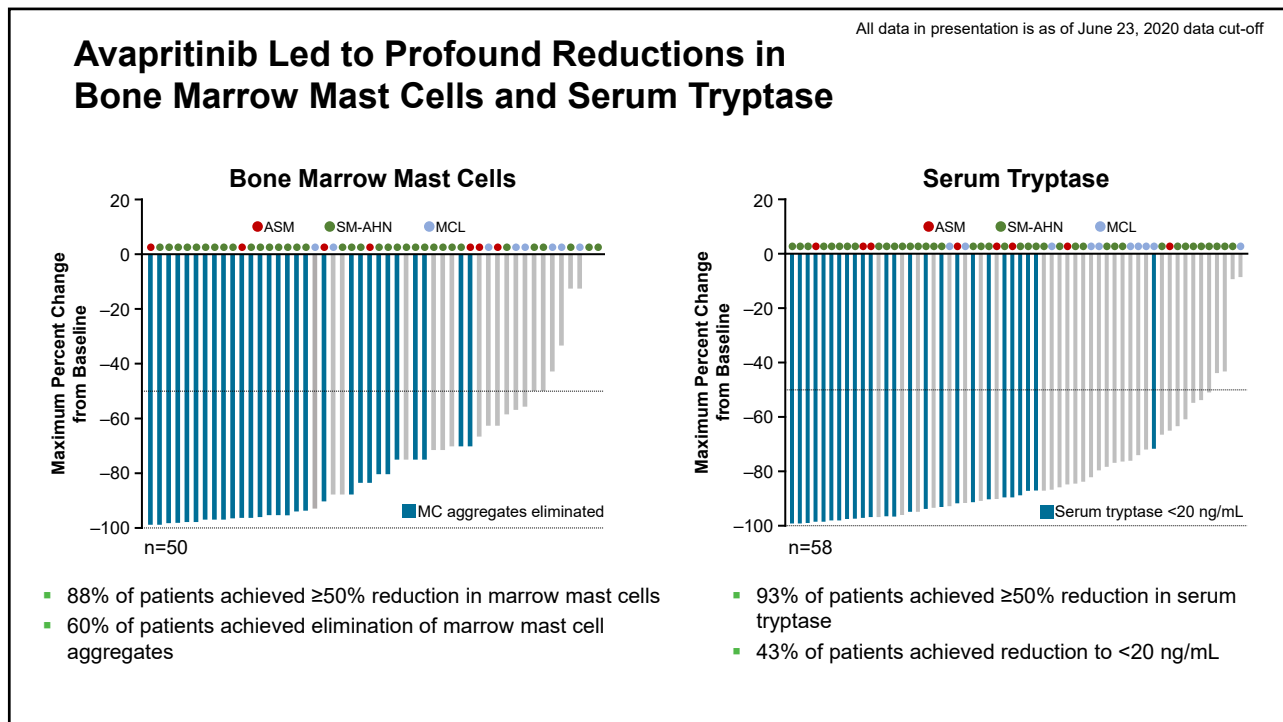
All data in presentation is as of June 23, 2020 data cut-off

## Responses in All Subtypes of AdvSM, Regardless of Prior Therapy

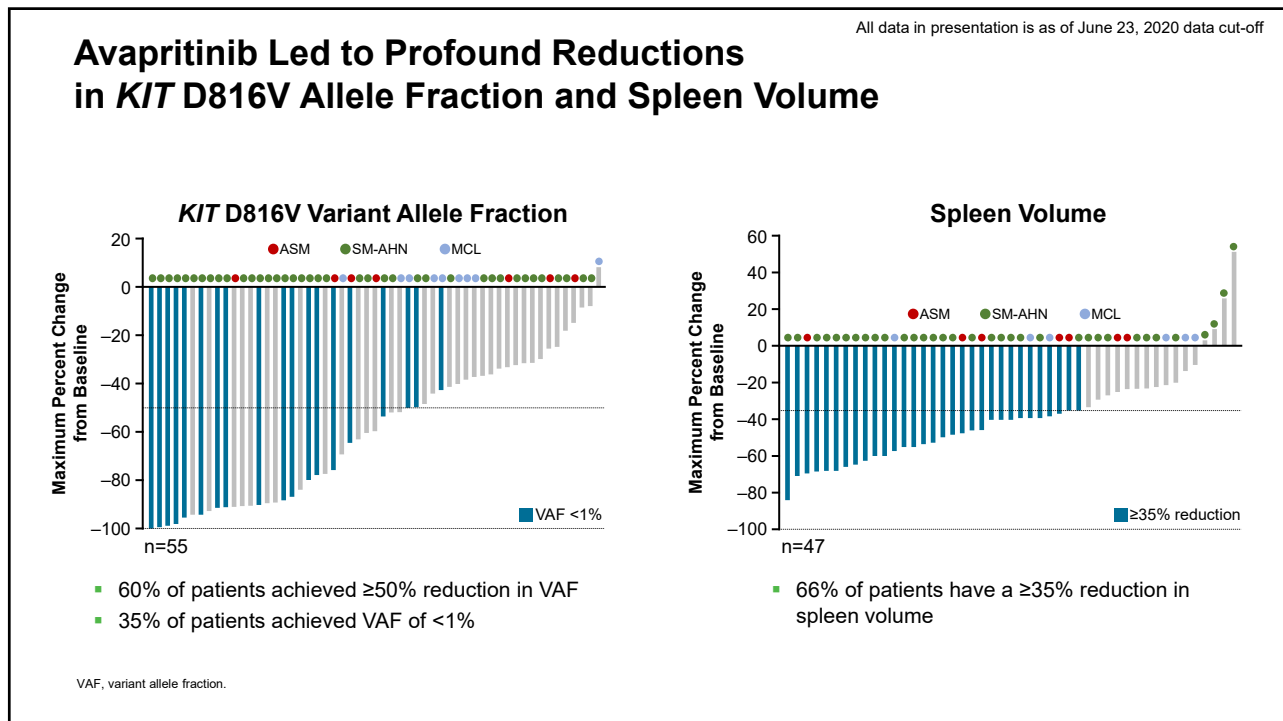
Best Confirmed Response, n (%)	All AdvSM (n=32) <sup>a</sup>	AdvSM Subtype			Any Prior Therapy	
		ASM (n=2)	SM-AHN (n=26)	MCL (n=4)	Yes (n=23)	No (n=9)
<b>Overall Response Rate</b> (CR + CRh + PR + CI)	24 (75)	2 (100)	21 (81)	1 (25)	17 (74)	7 (78)
<b>CR or CRh</b>	6 (19)	1 (50)	5 (19)	0	3 (13)	3 (33)
Complete Remission (CR)	0	0	0	0	0	0
CR with partial hematologic recovery	6 (19)	1 (50)	5 (19)	0	3 (13)	3 (33)
Partial Remission (PR)	10 (31)	1 (50)	8 (31)	1 (25)	7 (30)	3 (33)
Clinical Improvement (CI)	8 (25)	0	8 (31)	0	7 (30)	1 (11)
Stable Disease (SD)	4 (13)	0	2 (8)	2 (50)	2 (9)	2 (22)
Progressive Disease (PD)	1 (3)	0	0	1 (25)	1 (4)	0
Not Evaluable (NE)	3 (9) <sup>b</sup>	0	3 (12)	0	3 (13)	0

<sup>a</sup>One patient in evaluable population started at 100 mg QD. <sup>b</sup>Three (9%) of 32 patients in the interim analysis were assessed as not evaluable for response due to coming off study for AE before 13 weeks.

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# Avapritinib Approved for Advanced Systemic Mastocytosis

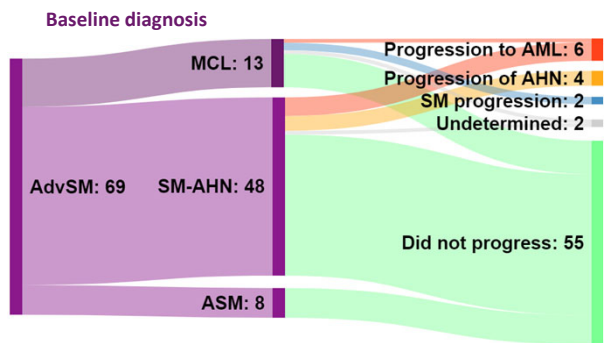
SUNDAY, JUNE 27, 2021

The U.S. Food and Drug Administration (FDA) has approved avapritinib for the treatment of adult patients with advanced systemic mastocytosis (SM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).

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## Exploratory analysis of reasons for progression

- EXPLORER (NCT02561988) is a phase I dose escalation study of avapritinib in 86 patients with local diagnosis of AdvSM, of which 69 were centrally confirmed<sup>1</sup>
- Avapritinib 30–400 mg was studied with expansion cohorts at 200 mg and 300 mg QD



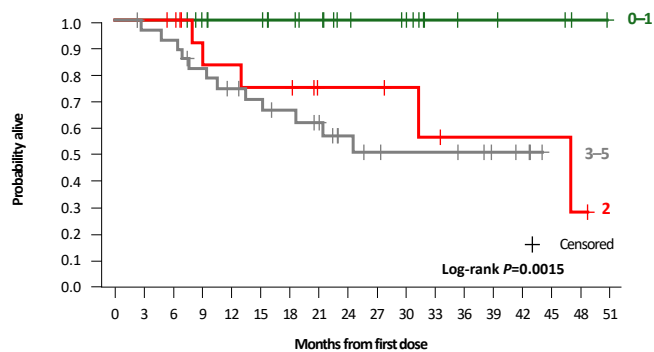
- Only **14 (20%)** patients had clinical progression<sup>a</sup> on treatment
  - 10 (21%) patients with SM-AHN, 4 (31%) with MCL, and 0 with ASM had clinical progression
- Median duration of treatment was 9.5 months
- The majority were AHN or AML progressions in patients with baseline AHN
- Only 2 patients, both with MCL, had a SM progression

Data cut-off: May 27, 2020 (median follow-up of 23 months).  
<sup>a</sup>As determined by investigator: a subset with AML met the mlWG-MRT-ECNM criteria definition for progressive disease.  
AML, acute myeloid leukemia; mlWG-MRT-ECNM, (modified) International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis; QD, once-daily.  
1. DeAngelo D et al. *Nat Med*. 2021.

Deininger et al., ASH 2021

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**Overall survival is more favorable in patients with a low baseline Mutation-Adjusted Risk Score (MARS)**



MARS<sup>1</sup> is a validated, WHO-independent prognostic score based on 5 parameters:

- 1) >60 years of age
- 2) Anemia (Hgb <10 g/dL)
- 3) Thrombocytopenia (Plts <100×10<sup>9</sup>/L)
- 4) 1 S/A/R mutation
- 5) ≥2 S/A/R mutations

MARS category	0-1	25	25	25	22	19	19	17	15	12	11	9	5	4	4	3	3	1	0
3-5	2	15	15	14	11	10	9	9	5	5	5	4	3	2	2	2	2	1	0
	29	27	26	22	19	17	15	12	9	7	6	6	5	3	2	0			

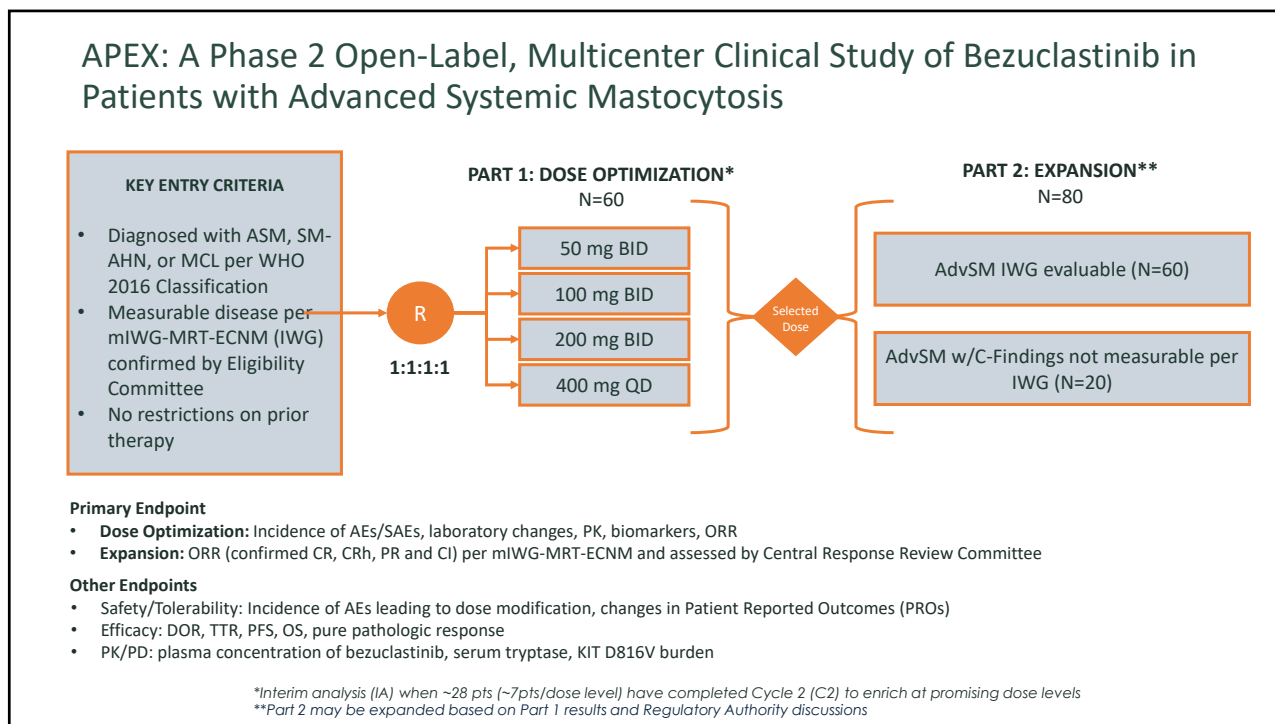
Hgb, hemoglobin; Plts, platelets; WHO, World Health Organization.  
1. Jawhar M et al. *J Clin Oncol*. 2019;37:2846–2856.

Deininger et al., ASH 2021

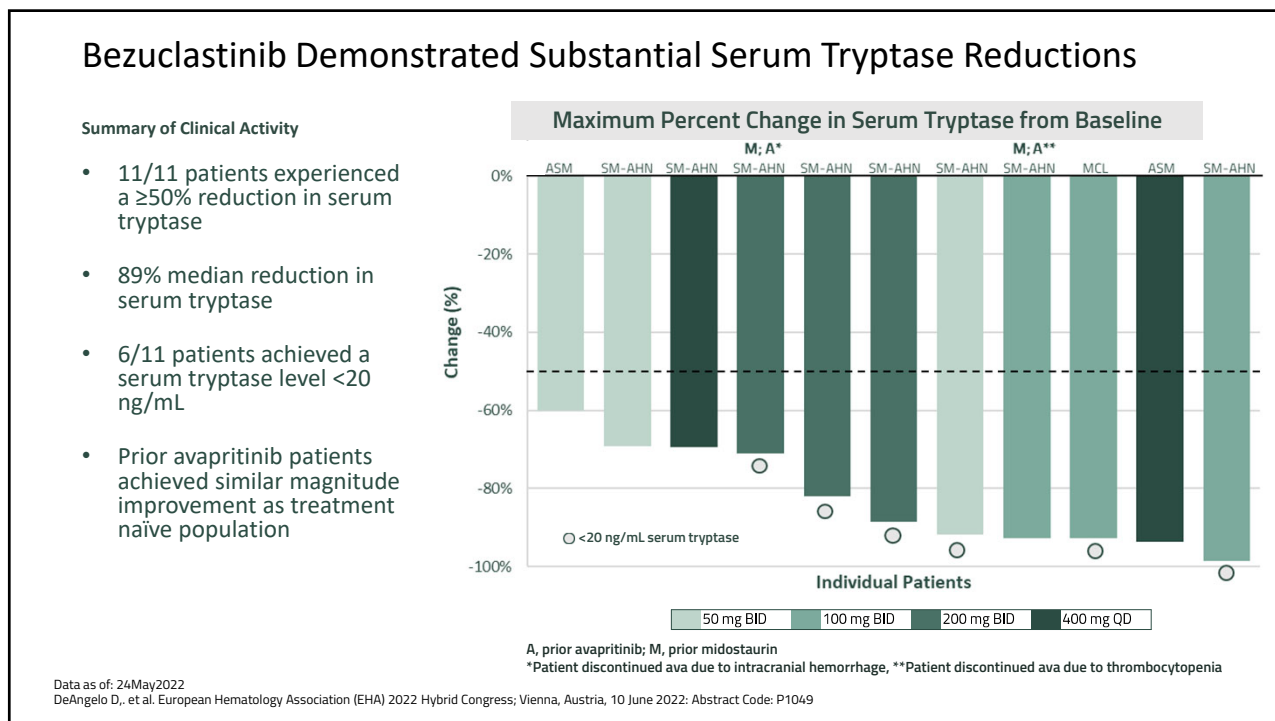
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**Newer Strategies**

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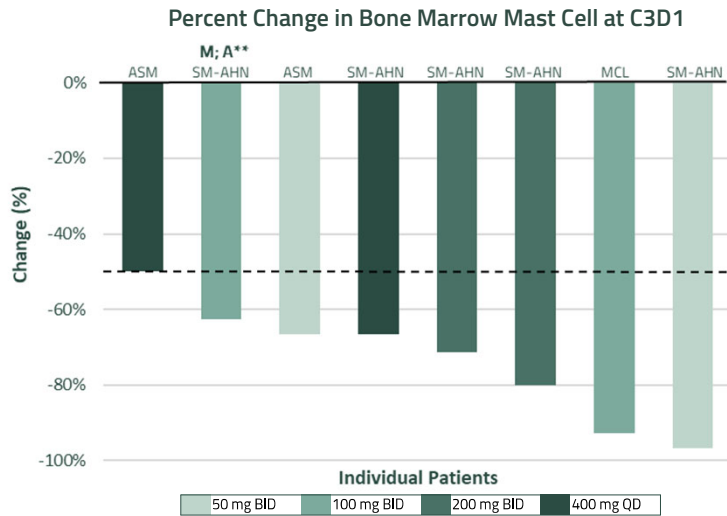


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### Bezuclastinib Demonstrated Impressive Bone Marrow MC Reductions

**Summary of Clinical Activity**

- 8/8 patients with ≥2 cycles of treatment and available Cycle 3, Day 1 (C3D1) data achieved ≥50% reduction in bone marrow mast cells
- 6/8 patients (C3D1) achieved complete clearance of mast cell aggregates by central review



A, prior avapritinib; M, prior midostaurin  
 \*\*Patient discontinued avapritinib due to thrombocytopenia

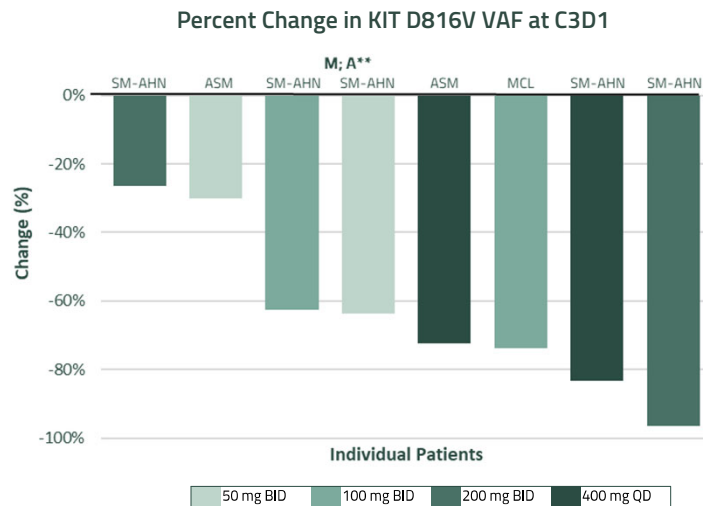
Data as of: 24May2022  
 DeAngelo D., et al. European Hematology Association (EHA) 2022 Hybrid Congress; Vienna, Austria, 10 June 2022; Abstract Code: P1049

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### Bezuclastinib Demonstrated Impressive KIT D816V VAF Reductions

**Summary of Clinical Activity**

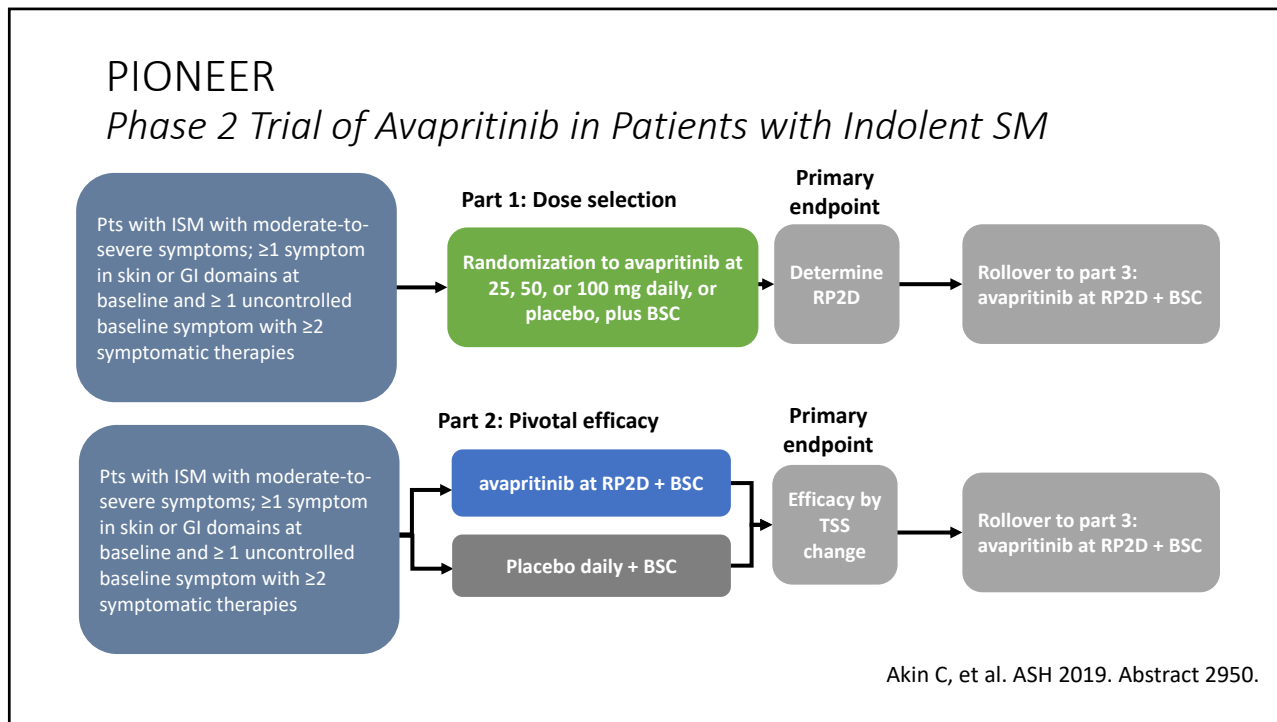
- 8/8 patients (C3D1) demonstrated decreases in KIT D816V variant allele fraction (VAF) by ddPCR



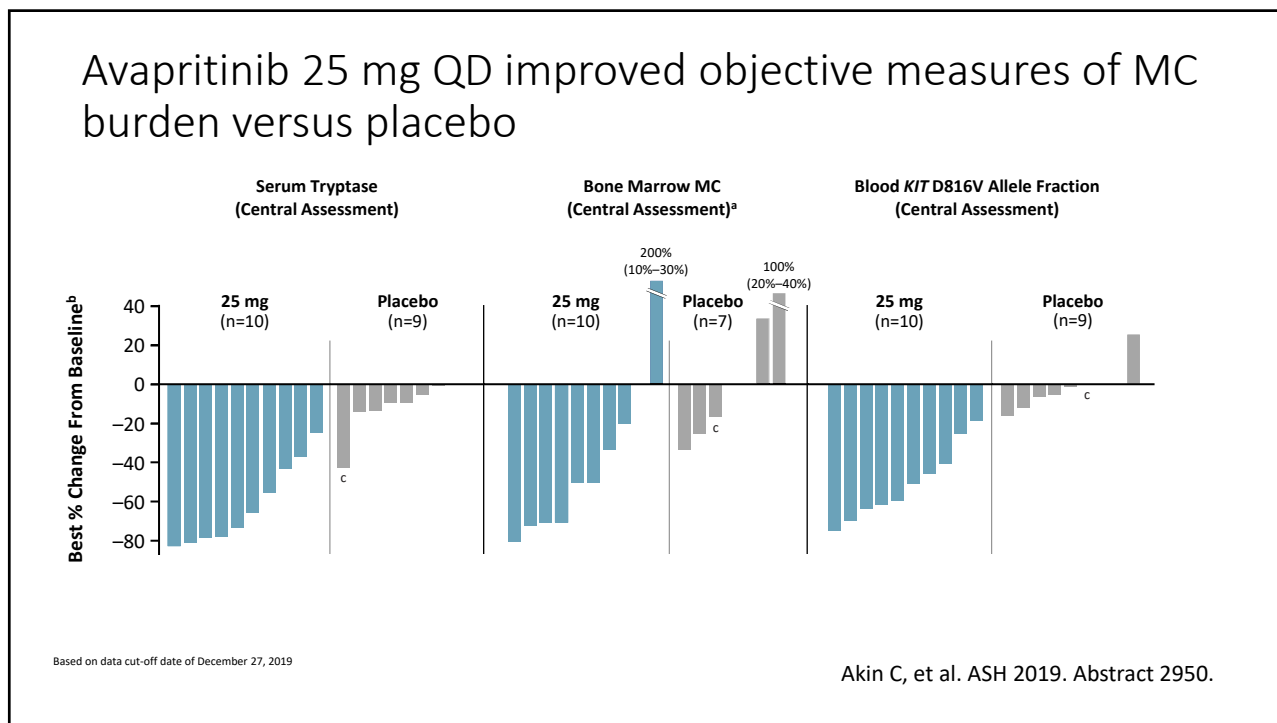
A, prior Avapritinib; M, prior midostaurin  
 \*\*Patient discontinued Avapritinib due to thrombocytopenia

Data as of: 24May2022  
 DeAngelo D., et al. European Hematology Association (EHA) 2022 Hybrid Congress; Vienna, Austria, 10 June 2022; Abstract Code: P1049

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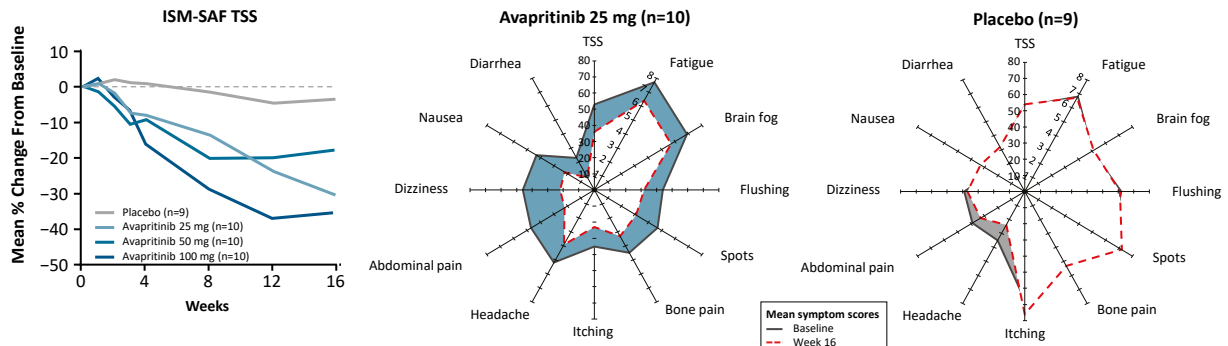
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## Avapritinib Improved Symptom Burden at all Doses by ISM-SAF

- 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)
- By Week 16, avapritinib 25 mg improved the most bothersome symptoms (47% of patients at baseline) in the skin and neurological domains versus placebo (Radar plots)



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

Akin C, et al. ASH 2019. Abstract 2950.

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## Some Unanswered Questions

- What is the best approach for patients with SM-AHN?
  - Combination therapy?
  - Stem cell transplantation? If so, when?
- What is the mechanism of drug resistance to avapritinib?
- What is the best approach for patients with indolent or smoldering SM?
  - What about mast cell activation syndrome (MCAS)?

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## Next Steps

- Derive and validate pure pathologic response criteria for SM
- Establish new response criteria for SM-AHN
- Compare Avapritinib versus Best Available Therapy
- Await final readout of the Indolent SM (Pioneer) trial
- New Agents
  - **Bezuclastinib (CPT-9486) APEX trial in Adv SM now enrolling**

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## Summary

- Systemic mastocytosis is a clinico-pathologic entity
- Clinical subtypes have been revised and correlate with prognosis (WHO 2016)
- *KIT D816V* is a pathognomonic mutation
- *KIT* mutation is a late event → phenotypic modification towards mast cells
- Midostaurin and Avapritinib are safe and effective targeted therapies for advanced SM

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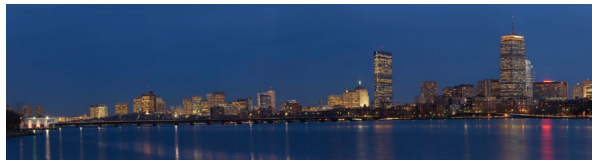
## Acknowledgements

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Ellen Toomey-Mathews, RN  
Kelly Ling, PA  
Patrice O'Sullivan, NP



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## *The End: Questions?*

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