Systemic Mastocytosis
Diagnosis and Treatment

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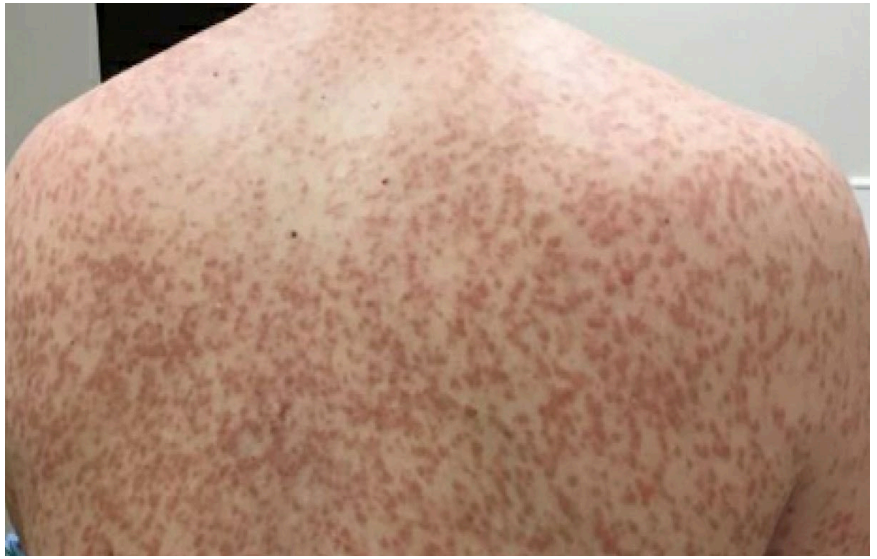
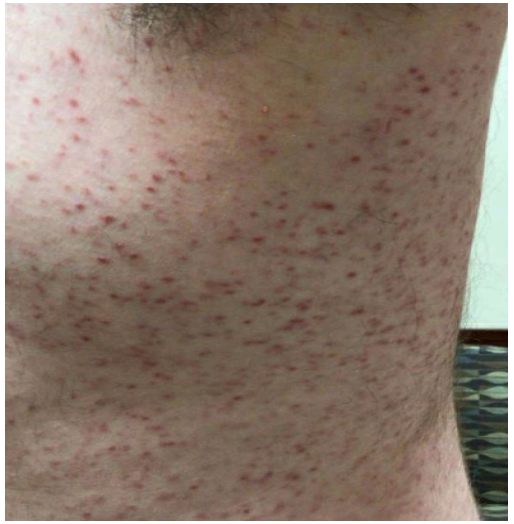
Case-1

- A 49-year-old man presents with diffuse skin spots after skin biopsies showing “**urticaria pigmentosa**”.
  - skin flushing, intolerant to heat, fatigue, and long-standing diarrhea.
- Physical exam - a palpable spleen 4 cm below the costal margin.



- Labs:
  - WBC of 8.9 K/mcl, Hb of 14.1 g/dl, Hct of 43%, MCV of 90 FL, and platelet of 225 K/mcl.
    - ANC 3400/mcl, ALC 2100/mcl, and monocyte count of 400/mcl.
  - Chemistry: Unremarkable



Systemic Mastocytosis

- An MPN, characterized by pathological accumulation of clonal mast cells in different extracutaneous tissues.
- Mast cell degranulations can lead to mediator symptoms
- A gain-of-function mutation in *KIT*, exon 17 (D816V) is found in ~85-90% of SM

- It is a rare disease and true incidence is unknown, as it is often underdiagnosed.
  - One study reported that in 140 SM patients, 36% were not diagnosed properly and 20% were overlooked[1].

[1]Schwaab J et al, J allergy Clin Immunol Pract, 2020; 8(9) 3121-3127

Diagnosis of Systemic Mastocytosis

Diagnosis is based on WHO criteria, updated in 2022, 5th edition

- **Major criteria:**
  1. Multifocal dense mast cell aggregates (>15 cells/aggregate) in bone marrow or other involved organs

- **Minor criteria:**
  1. >25% of all mast cells have spindled-shaped morphology
  2. Any *KIT*-activating mutation
  3. Mast cell express CD2, CD25 and/or CD30
  4. Serum tryptase > 20 ug/L *(not applicable for SM-AHN; In case of known HaT, levels should be adjusted)*

- For SM diagnosis – ***Major + 1 minor*** *or* ***3 minor criteria***
- *If* ***only the major,*** *or* ***only 2 minor*** *criteria –* ***monoclonal MCAS***

Khoury JD et al, Leukemia. Jul 2022;36(7)

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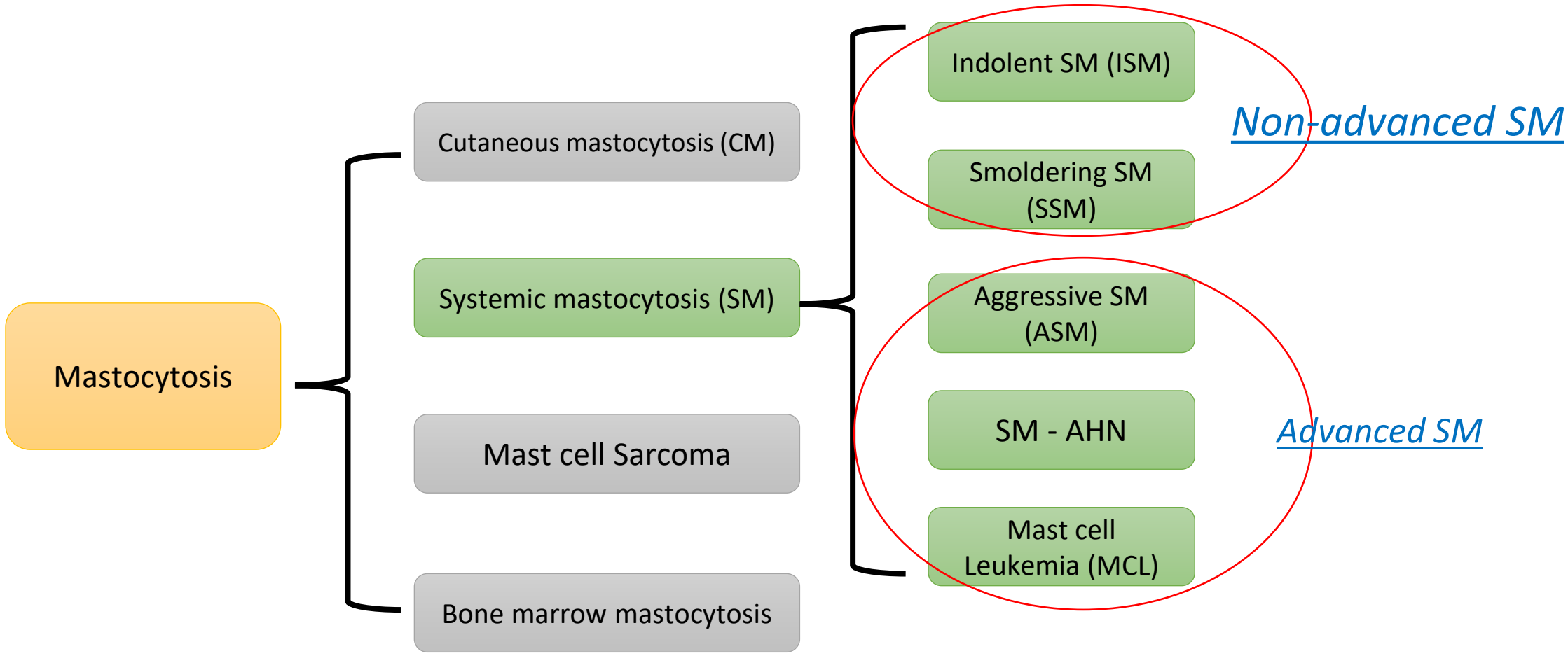
2022 WHO classification of Mastocytosis



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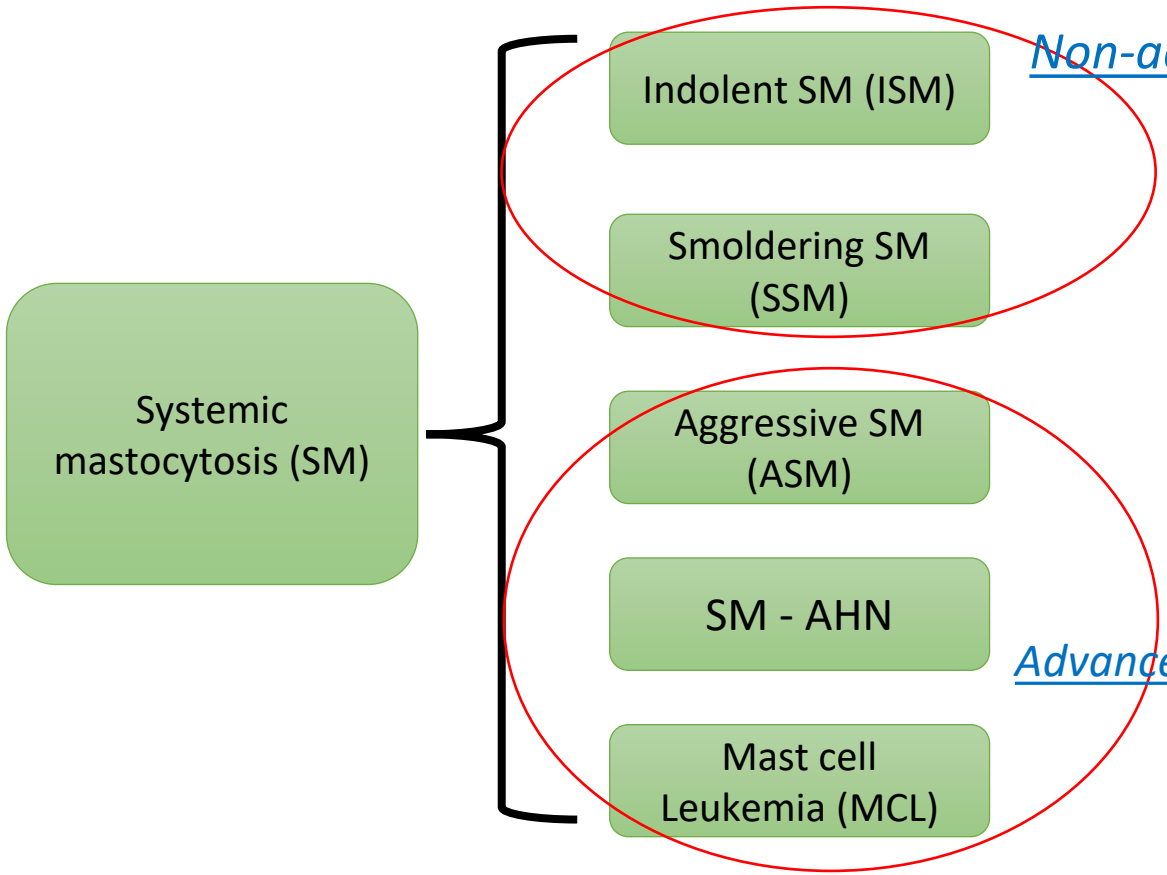


B-findings

(0-1: ISM)

(>2: SSM)

1. High mast cell burden
   a) >30% of cellularity and
   b) Serum tryptase > 200 ug/L
2. Signs of dysplasia or myeloproliferation but not sufficient for MDS or MPN diagnosis
3. Hepatomegaly, splenomegaly and/or lymphadenopathy, without functional impairment
4. *KIT* mutation VAF > 10%

C-findings

Only 1 required

Bone marrow	Bone marrow dysfunction caused by MC infiltration: ANC < 1 x 10^9/L, Hb < 10 g/dl or platelets < 100 x 10^9/L)
Liver	Hepatomegaly with impairment of liver function, ascites and/or portal hypertension
Spleen	Palpable splenomegaly with hypersplenism (platelet < 100 x 10^9/L)
GI	Gastrointestinal MC infiltrates causing malabsorption with weight loss > 10%
Skeletal	Skeletal involvement with large osteosclerotic or lytic lesion (>2cm) and/or with pathologic fractures due to the lesions.
Other	Any other life-threatening organ damage caused by the neoplastic MC infiltration

Khoury JD et al, Leukemia. Jul 2022;36(7)

Clinical work-up for SM

- **Serum tryptase level and KIT D816V by ddPCR (peripheral blood)**
- **Bone marrow biopsy**
  - Establish SM diagnosis and evaluation for AHN if present
- **Complete Blood Count with WBC differential**
  - CBC abnormalities could be from SM, AHN, or other etiologies
- **Liver Function Tests**
  - LFT abnormalities could be from MC infiltration of the liver or other etiologies
- **CT or MRI of the abdomen**
  - Assess liver and spleen sizes, adenopathy, ascites
- **Bone density scan**
  - Screen for osteoporosis
- **Skeletal X-ray**
  - Assess for skeletal involvement with osteolytic or sclerotic lesions
- **GI work-up if needed for GI symptoms**

…Case continued

- A serum ***tryptase*** value was ***48 ug/L*** (normal <11 ug/L)
- A bone marrow biopsy was done:
  - 60% cellularity; mast cells ~ 10% of the cellularity. The ***majority of MC are spindled*** shaped, ***expresses CD25***.
  - ***KIT D816V*** mutation was ***detected*** at VAF of 1.2%. No other somatic mutations

- Abdominal CT showed fatty liver, ***spleen size at 16cm*** craniocaudal. No other abnormalities.
- DEXA scan showed vertebral T-score of -2.3.
- The whole-body bone survey was unremarkable.
- EGD and colonoscopy - colon biopsies showed few scattered areas of mast cells

- **SM diagnosis criteria:** >25 MC are spindled; Express CD25, KIT D816V+, Tryptase – 48. *(all 4 minor criteria)*
- B-findings – *Splenomegaly*
- C-findings – *None*
- Diagnosis – **Indolent Systemic Mastocytosis**

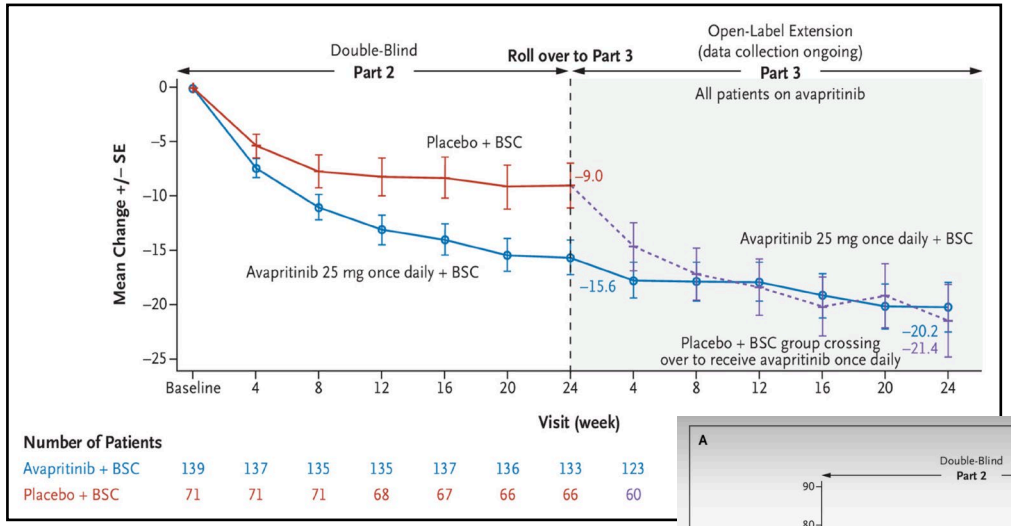
Management of Indolent SM

- **The goal of therapy is symptom management and QoL improvement.**
- **Best supportive medications:**
  - Antihistamines - H1 blockers; H2 blockers
  - Antileukotrienes - Montelukast
  - Mast cell stabilizers - Cromolyn sodium, Ketotifen
  - Anti-IL5 therapy - Omalizumab

- **For significant symptomatic patients - definitive therapy with TKI**
  - Avapritinib
  - Midostaurin

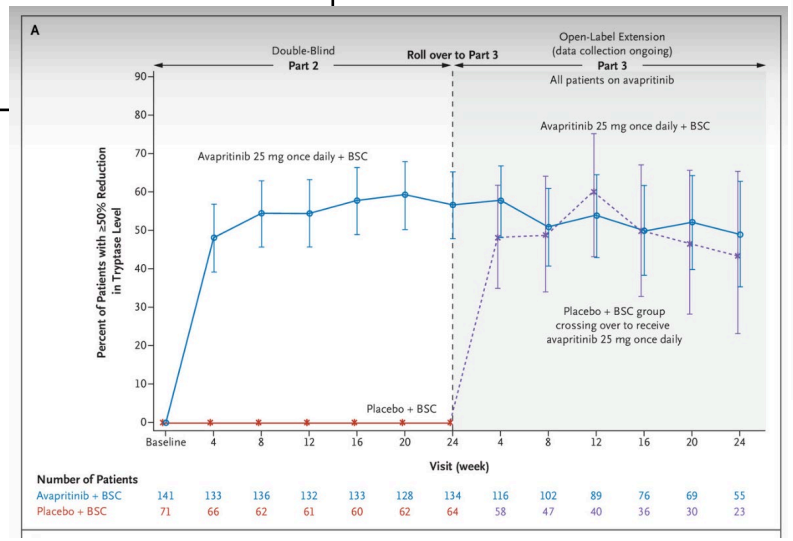
PIONEER study (Avapritinib in ISM)

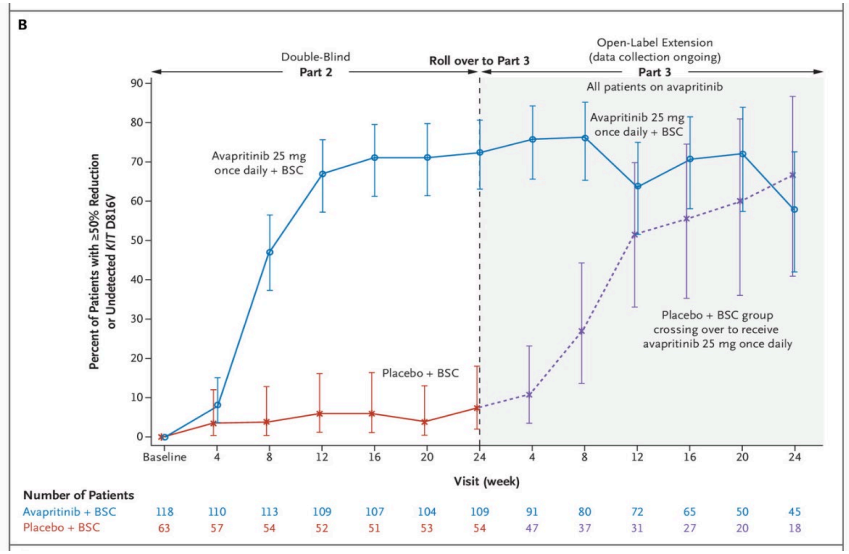
- A randomized phase 2, double blind, placebo controlled study of avapritinib in indolent systemic mastocytosis (N=212)



Primary Endpoint:

- Decrease in total symptoms score at week 24
- *15.6 versus 9.2 (p=0.003)*





Gotlib J et al, NEJM Evidence 2023; 2(6)

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…Case continued

- Started on cetirizine 10mg BID, famotidine 40mg BID, Cromolyn sodium 200mg QID
- Endocrinology referral - started on calcium and vitamin D supplements, bisphosphonates for osteoporosis

- **After 3 months:**
  - Symptoms of flushing and diarrhea were less frequent but not resolved, but his skin spots remained the same, brain fog and fatigue was persistent
  - Started on avapritinib 25mg daily

- All the symptoms gradually got better over the next 4 months. Skin spots have started to fade. He discontinued cromolyn sodium and decreased cetirizine to once a day.
- Serum tryptase is now 10ug/L.

Case - 2

- A 61-year-old woman is fatigued and has a poor appetite.
- Physical exam - palpable spleen 4 cm below the costal margin.
- **Labs showed**
  - WBC - 3.1 K/mcl, Hb/Hct: 10.2 / 31, MCV -90 FL, and platelet - 92 K/mcl.
  - ANC 890/mcl, ALC 1200/mcl, and monocyte count of 1300/mcl.

- **Bone marrow biopsy:**
  - 50% cellularity with 15% mast cells, spindled shaped and aggregates;
  - Multilineage dysplasia and granulocytic left shift; 2% blasts.
  - *KIT* D816V mutation was detected with VAF of 19%, along with *U2AF1* at 31%, *SRSF2* at 27% and *TET2* at 14%.

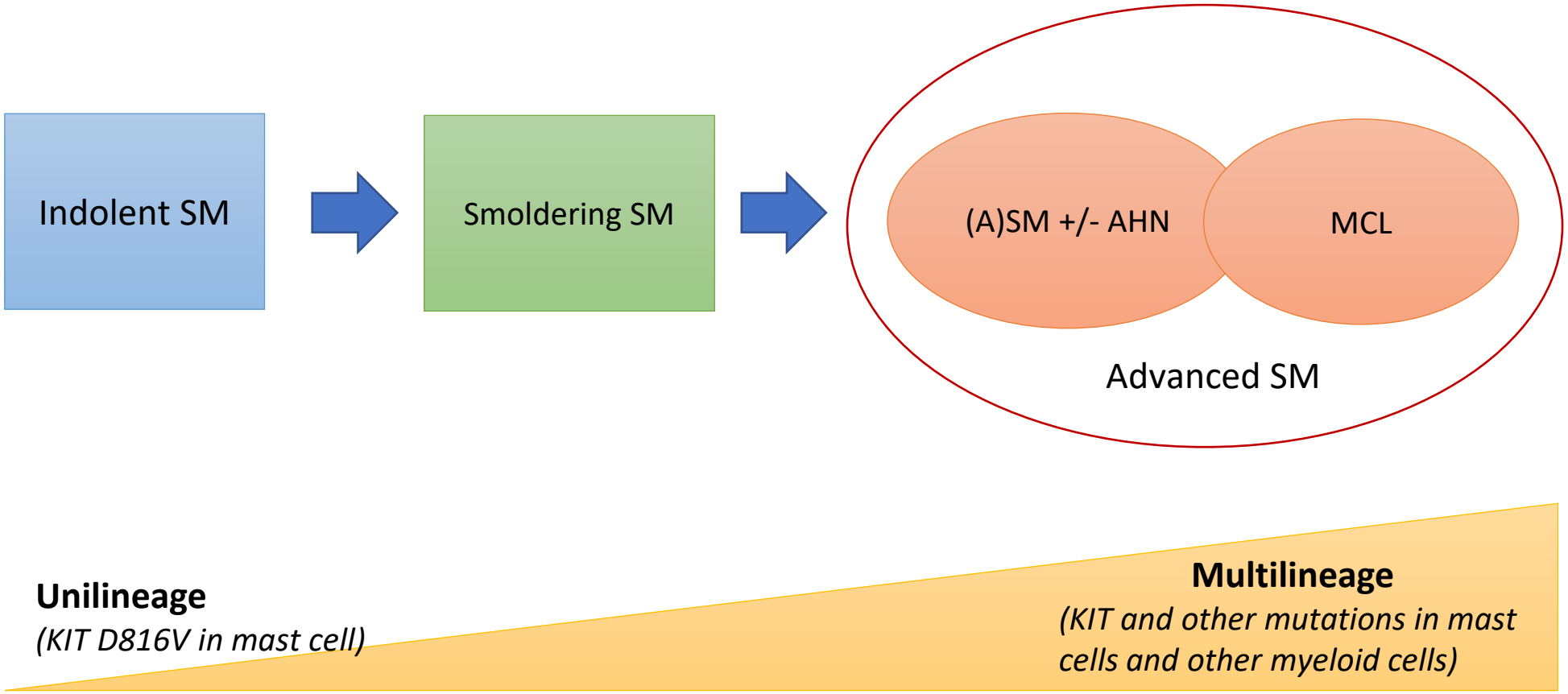
…Case - 2

- Serum tryptase – 125 ug/L
- Abdominal CT showed spleen size at 19cm craniocaudal. No other abnormalities.
- DEXA scan showed vertebral T-score of -1.8
- The whole-body bone survey was unremarkable.

- **SM diagnostic criteria:** Major ***(MC aggregates)*** + Minor ***(spindled MC, KIT+, MC expresses CD25)***
    - *Bone marrow is also consistent with* ***MPN/MDS (CMML).***

- C-findings – *Splenomegaly with cytopenia; Bone marrow involvement with cytopenia*
- Diagnosis – **Systemic mastocytosis with associated hematological neoplasm (SM-AHN) (MDS/MPN)**

Molecular profiles of SM and its subtypes



Clinical features of Advanced SM

Presenting symptoms can be highly variable

- **Mediator release symptoms**
  - Skin rash and flushing, dizziness, neurocognitive symptoms, GI symptoms – diarrhea, among others.
- **Symptoms from end-organ damage from clonal mast cell infiltration**
  - The “C”-findings
- **Symptoms and signs of Associated Hematologic Neoplasm**
  - Blood count abnormalities
  - Constitutional symptoms, splenomegaly

AGGRESSIVE SM

- Comprises 20-25% of AdvSM
- Presence of a C-finding ***(required)***
- No evidence of AHN
- Mainly a KIT-driven process
- Risk of progression to MCL
- ASM with > 5% MC in BM aspirate is called ASM-t (in transformation)

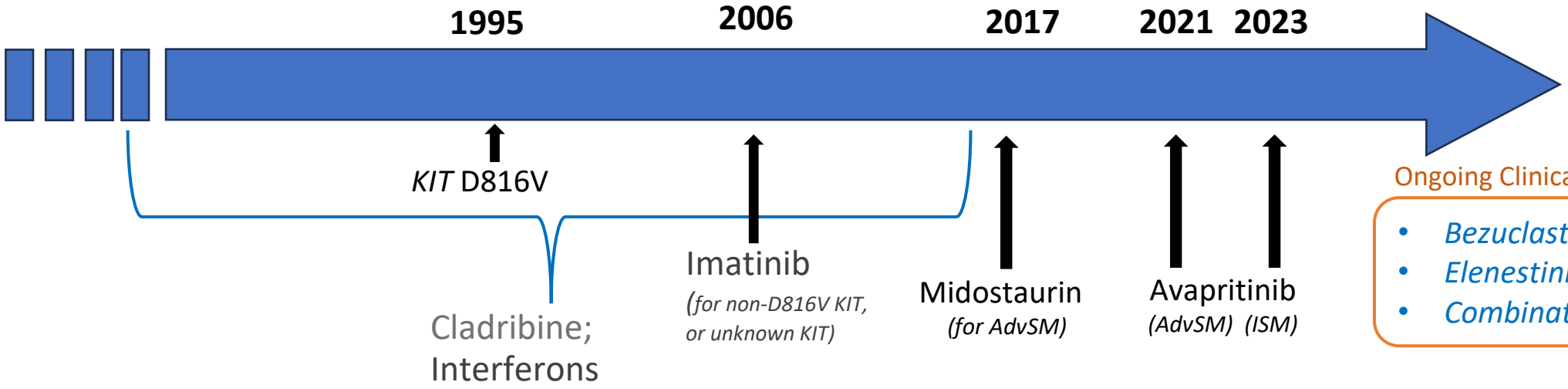
SM-AHN

- Comprises 70-75% of AdvSM
- *If no C-findings – Unevaluable* (ISM-AHN)*
- AHN is mainly myeloid
  - *CMML; MDS/MPN most common*
  - *2022 ICC named "SM-AMN"*
- Multilineage; can have multiple somatic mutations
- Sometimes, AHN can be subtle
- Eosinophilia is common, need to rule out other eosinophilic conditions

MCL

- Comprises <5% of AdvSM
- >=20% immature MC on the BM aspirate ***(required)***
- May have C-finding ***(not required)***
- Can be **acute/chronic**, **leukemic/aleukemic**, **de-novo/secondary**, **+/- AHN**
- Poor prognosis: < 2 years

Treatment history timeline in SM



Ongoing Clinical Trials AdvSM

- *Bezuclastinib (APEX)*
- *Elenestinib (AZURE)*
- *Combination therapies*

Cladribine:

- *Overall response rate of 30-60%*
- *Prolonged myelosuppression, toxic*

Interferons:

- *All partial responses*
- *Mood disorders, poor tolerance*

- Largely historical
- Cladribine may be rarely indicated if there is an acute need for cytoreduction

Ongoing Clinical Trials ISM

- *Bezuclastinib (SUMMIT)*
- *Elenestinib (HARBOR)*
- *Lirentelimab (AK002)*
- *TL-895*

Imatinib

- FDA approved for SM lacking the KIT D816V mutation, or unknown KIT mutation status.
  - Approval was based on case reports and small case series

- Response rate ranges 40-80% *(based on historical data)*

- Imatinib response likely relies on presence of imatinib-sensitive genetic defect (either known or still unidentified), rather than lack of *KIT* D816V per se.

Alvarez-Twose, I et al, Oncotarget, 2017; Sep 15; 8(40)

Midostaurin

- Approved in 2017 for AdvSM (CONSORT trial; N=116)
- Overall Response – 60%
  - (75% ASM, 58% SM-AHN, 50% MCL)
    - There were no CRs
    - Incomplete CRs: 21%
    - Partial response: 15%
    - Stable disease: 12%
- Median OS: 28.7 months
  - (ASM-NR, SM-AHN-20.7m, MCL-9.4m)

- Toxicity:
  - Nausea (79%)/Vomiting (66%)/diarrhea (54%)
  - Fatigue (28%)
  - Cytopenias (50-60%)
- 72% discontinued treatment
  - 20% discontinued due to toxicities
  - 35% had progressive disease

Gotlib J et al, NEJM, 2016; 374:2530-2541

Avapritinib

- Avapritinib – first potent and selective *KIT* D816V inhibitor (IC_{50}=0.27nM)
- Evaluated in **EXPLORER** trial (Phase 1) and **PATHFINDER** trial (Phase 2)

- **EXPLORER** trial (Phase 1); n = 69; Dose ranged 30 - 400mg daily.
  - ORR – 75%; (36% CR/CRh, 34% PR)
  - Responses were rapid (Median follow-up 23 m)

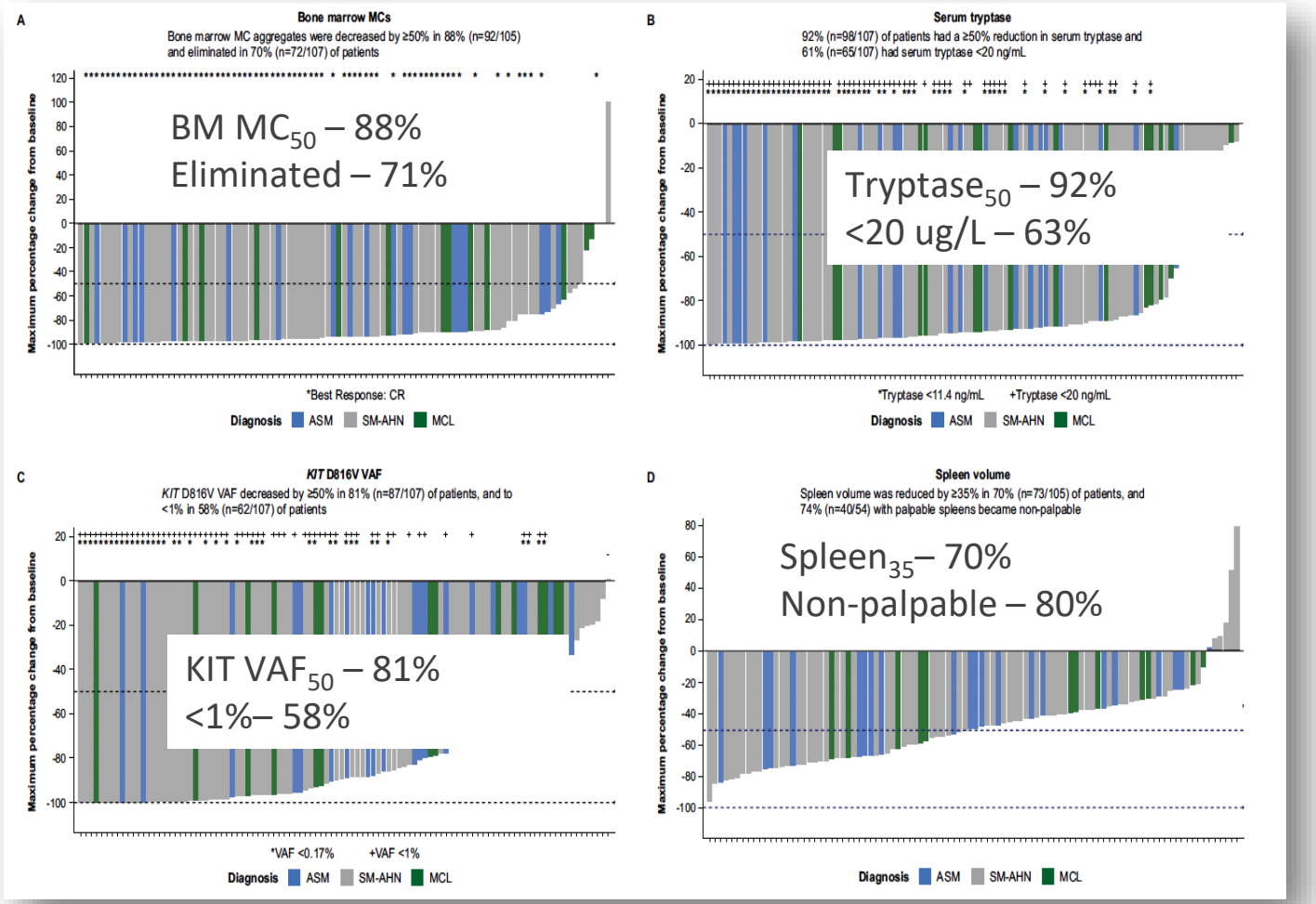
- Toxicity:
  - Periorbital edema (65%); Cytopenia (50-60%), peripheral edema (45%), hair and skin color changes (19%), neurocognitive changes (30%)
  - ICH– in 9 patients (13%), 5/9 were grade 1, all but one had low platelets

- Recommended phase 2 dose: 200mg daily

DeAngelo D et al, Nat Med 2021; 27(12): 2183–2191

PATHFINDER study – interim results (>3-years)

- Phase 2 study, N=107 patients
- Over 3-year follow-up data
  - ORR **73%** (63 – 83); CR/CRh **29%**
    - ORR 87%; with CR/CRh of 43% in treatment-naïve
  - Median OS and PFS: not reached
    - 2-year OS: 79%
    - 2-year PFS: 76%



Reiter A, et al, EHA Annual meeting, 2024 – Oral presentaiton

PATHFINDER – interim results

- Decrease in monocytosis in CMML and eosinophilia

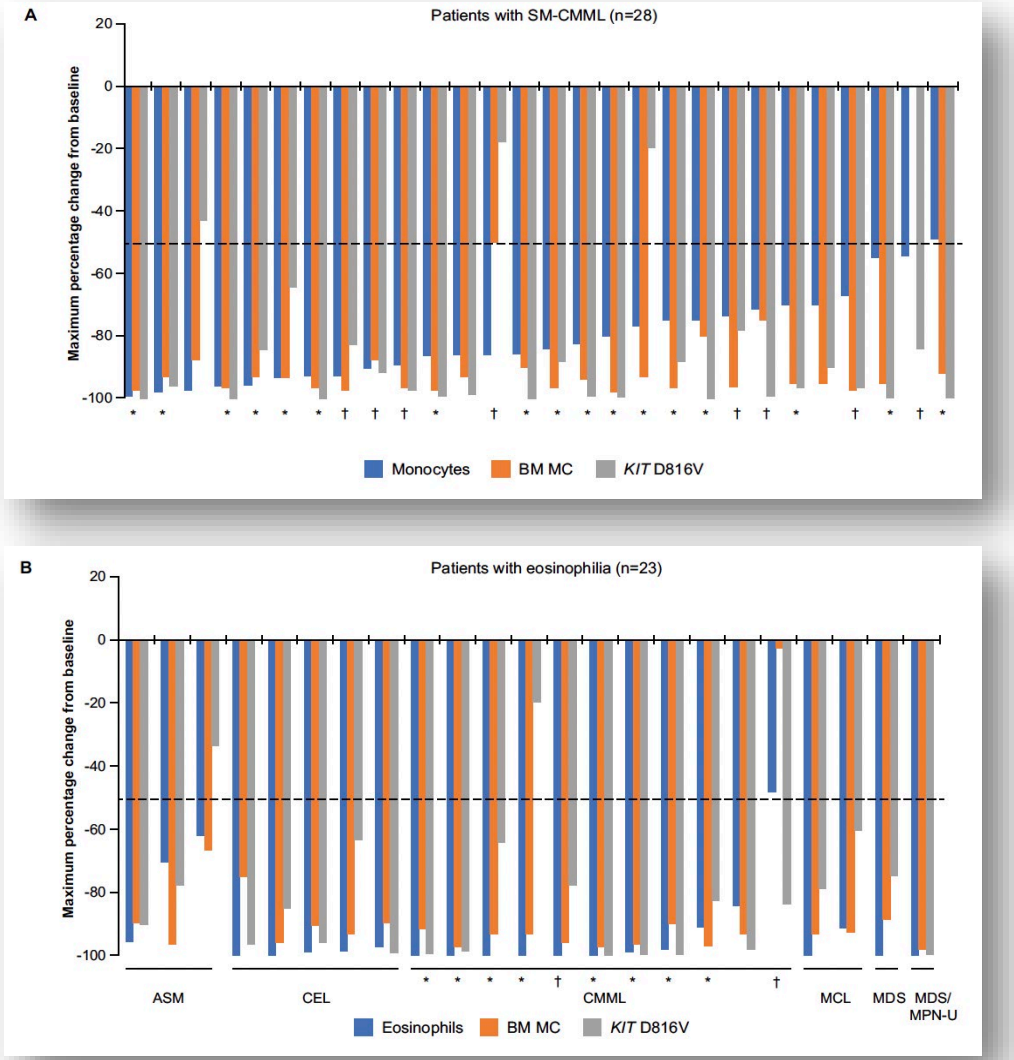
- Toxicities:

  Peripheral edema, Cognitive disorder, Cytopenias

  ICH occurred in 4 patients (3.7%), resolved after discontinuation

- **US FDA approved avapritinib for advanced SM in 2021**

- ***PATHFINDER now closed***
  - ***Final data analysis forthcoming***



Reiter A, et al, EHA Annual meeting, 2024

Progression of AHN

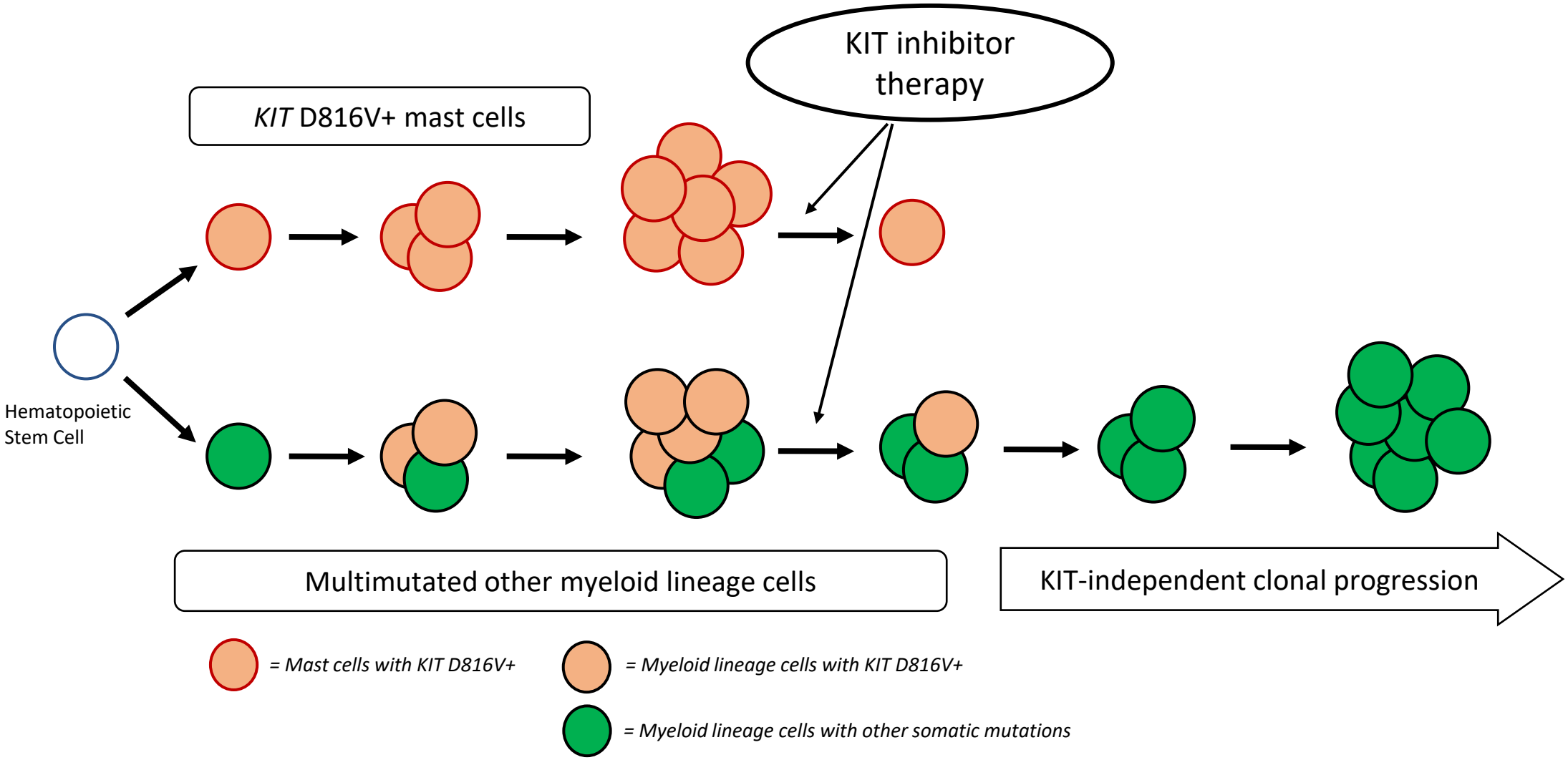
- KIT inhibitor therapy is effective for SM, but its effect on AHN remains unclear.
  - *May delay progression, as reduction in monocytosis is seen in CMML in avapritinib trials*
  - *AHN tends to progress over time, and under the selective pressure of KIT inhibition, AHN progression may be KIT-independent*

- Data from midostaurin studies, the rate of leukemic transformation ranges 11 – 16%, and majority of them (>80%) are in SM-AHN patients
  - Presence of *SRSF2, ASXL1 or RUNX1 (S/A/R)* conferred higher risk of progression
  - Acquisition of new mutations in *K/NRAS, RUNX1 and IDH2*

- From avapritinib studies – 18% (AHN 72%) *(combined EXPLORER and PATHFINDER)*
  - *Pre-existing germline variant, acquisition of new mutations*

Gotlib J et al, NEJM, 2016; 374:2530-2541; Jawhar M et al, Blood 2017; 130(2) 137-145; George T, AIM Meeting 2024

Model of clonal evolution in SM-AHN with KIT inhibitor therapy



Tashi T et al, Immunol & Allergy Clinics 2023 Nov;43(4):723-741.

Challenges in SM-AHN management

- ***Which to treat first – SM or AHN ?***
  - Depends on the primary cause of the symptoms and organ damage; Often it may be difficult to discern which one is the cause
  - Often reasonable to treat SM first, unless AHN is high-risk, such as AML, or MDS excess blast

- ***When to treat the AHN?***
  - Treat AHN when it shows signs of progression
  - Clinical progression? Clonal progression? New mutations?

- ***What if both need treatment at the same time?***
  - No data yet for combination therapies – clinical trials !
  - Risk of using avapritinib in cytopenic patients, especially thrombocytopenia

Tashi T et al, Immunol & Allergy Clinics 2023 Nov;43(4):723-741.

Challenges in SM-AHN management

- ***When to transplant?***
  - Data are from pre-KIT inhibitor era
  - Pre-transplant response to KIT inhibitor seems to be a main predictor of outcome
  - Referral to BMT should be considered for
    - All SM-AHN, MCL patients
      - SM-AHN when AHN shows signs of progression/high-risk molecular features
      - When AHN is a high-grade myeloid neoplasm or AML
      - Acute MCL

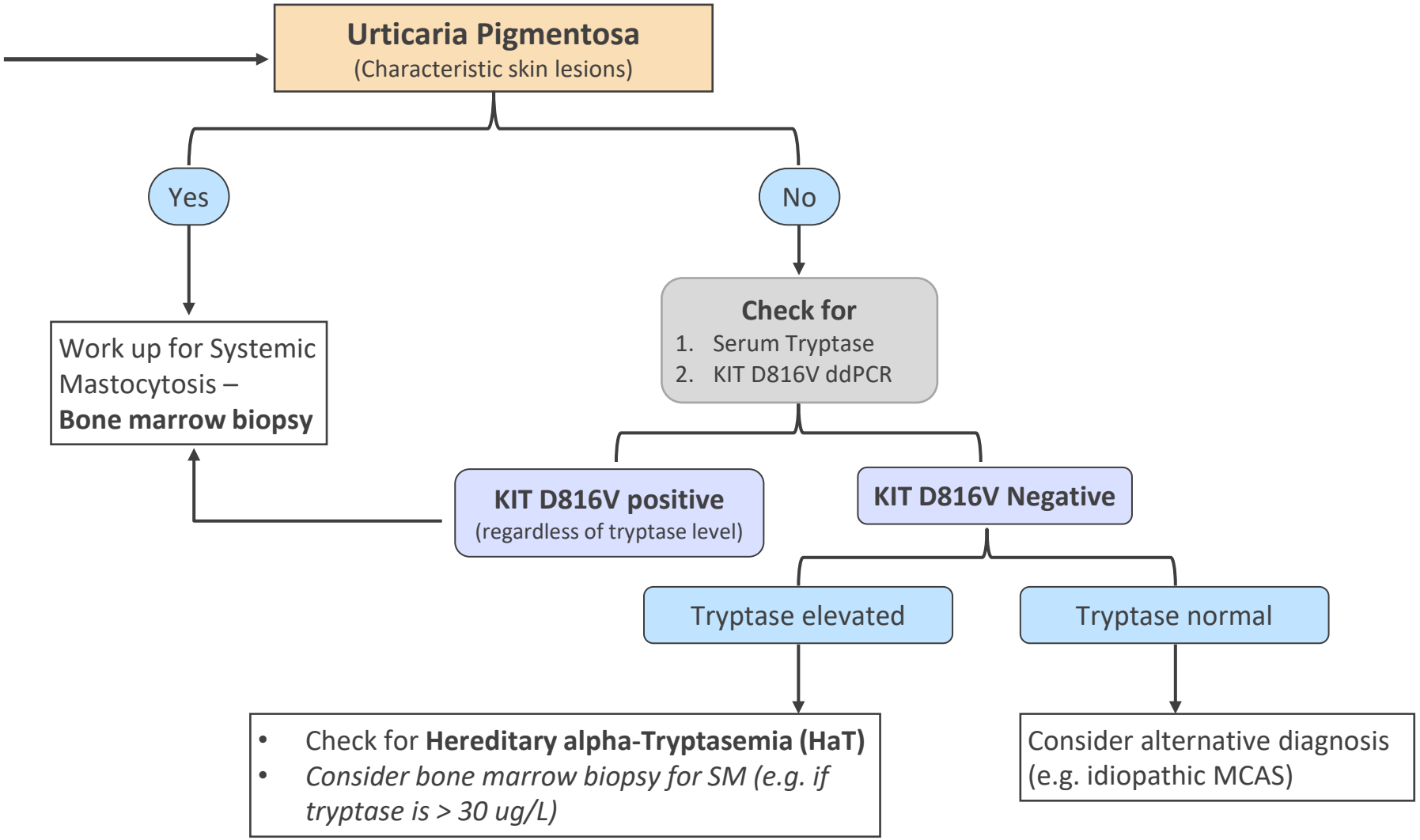
- **Referral to academic centers with expertise in SM**
- **Enroll in clinical trials !!**

Utsun C et al, J Clin Oncol. Oct 10 2014;32(29):3264-74; Lubke J. et al, *Leukemia,* 2024 Apr;38(4):810-821

Testing for Mast cell disorders

Indications for testing

- Mediator-release symptoms
- Skin flushing, diarrhea, anaphylaxis etc



Hereditary alpha-tryptasemia (HaT)

- Extra copy number of alpha-tryptase gene
- Reported prevalence of 4-6% of all Western population (Caucasians only so far).
- Autosomal dominant, 100% penetrant (*all have high sBT*) but variable expression *(variable phenotype)*
- Elevation in basal tryptase has a gene dosage relation
- Most common symptoms
    - Flushing, urticaria, IBS-like GI symptoms, joint pains, fibromyalgia, POTS, retained primary dentition, neuropsychiatric symptoms.
- In SM patients, prevalence about 10-12%
    - Increased mediator symptoms
- HaT patients are managed by allergist
- **Testing:**
    - ***Gene by Gene®***
    - ***ARUP laboratories*** *(TPSAB1 copy number analysis by PCR)*

Summary

- SM is a rare clonal mast cell disorder, driven by *KIT* D816V mutation in 85-90% of the cases, and includes **Non-Advanced** (Indolent SM, Smoldering SM), and **Advanced SM** (Aggressive SM, SM-AHN and MCL)
- Diagnosis is established by WHO 2022 criteria
- None or 1 B-findings define ISM, while >2 B-findings define smoldering SM
- The presence of mast cell-induced organ damage (C-findings) establishes the diagnosis of AdvSM
- In SM-AHN, AHN is usually a myeloid neoplasm, with CMML being the most common
- Symptom improvement is the primary goal of therapy in ISM, with antihistamines. Avapritinib, a KIT inhibitor is approved for ISM
- Midostaurin and avapritinib are the two kinase inhibitors approved for AdvSM.
- KIT inhibitors are effective for SM, but their effect on AHN is unclear, and AHN is treated per AHN-specific therapy
- Studies are ongoing for combination therapies *(with AHN therapies)* and other novel KIT inhibitors

- Hereditary alpha-tryptasemia (HaT) causes elevated basal tryptase levels, can co-exist with SM, and can modify SM symptoms.

Thank you for your attention!