

# **Diagnosis and Management of Patients with Mastocytosis**



**Peter Valent**

**ECNM Homepage Update 2013**

**Peter Valent**

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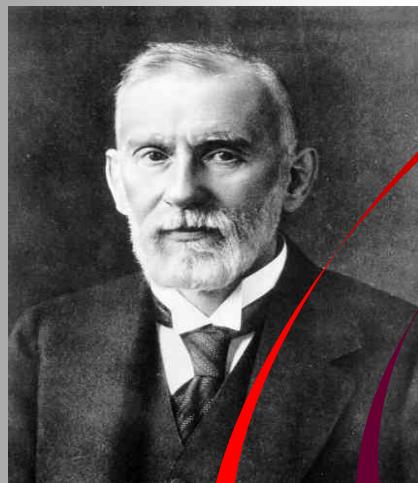
**Department of Internal Medicine I  
Medical University of Vienna**

[www.ecnm.net](http://www.ecnm.net)



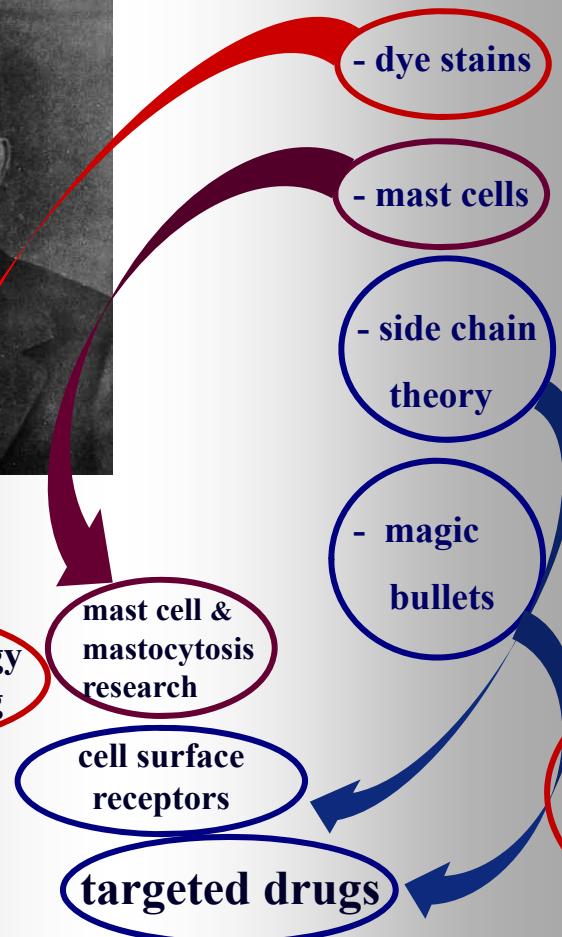
# HISTORY: MAST CELLS and MASTERS

## PAUL EHRLICH (1854-1915)



modern hematology  
& immunostaining

2013  
2015

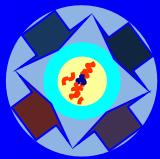


- 1869 - Nettleship Rare Form of Urticaria
- 1878 - Sangster Urticaria Pigmentosa UP
- 1879 - Ehrlich Mast Cells (Mastzellen)
- 1887 - Unna Mast Cells in UP
- 1949 - Ellis Systemic Mastocytosis
- 1966 Ishizakas Detection of IgE etc 
- 1979 - Lennert Kiel Classification
- 1991 - Metcalfe Consensus Classification
- 1995 - Nagata KIT D816V in SM
- 1998 - Escribano CD2/CD25 on MC in SM
- 1990-2000 Criteria Established
- 2000 Working Conference
- 2001 WHO Classification
- 2002 ECNM

# HISTORY: Year 2000 Working Conference on Mastocytosis – Vienna September 2000



# History 1990 - 2000 - 2002 - 2011



## Activities in the ECNM:

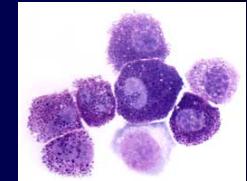
- Annual Meetings (9)
- Centers (25)
- Publications (20)
- Homepage

[www.ecnm.net](http://www.ecnm.net)



Working Conference  
on Standards and Standardization  
in Mastocytosis

Multicenter Trials to determine disease related markers and criteria 1995-2000



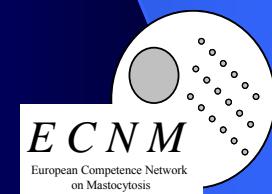
WHO - Year 2000 Working Conference on Mastocytosis – Vienna

## WHO Consensus Classification

WHO Classification of Tumors;  
IARCPress Lyon 2001



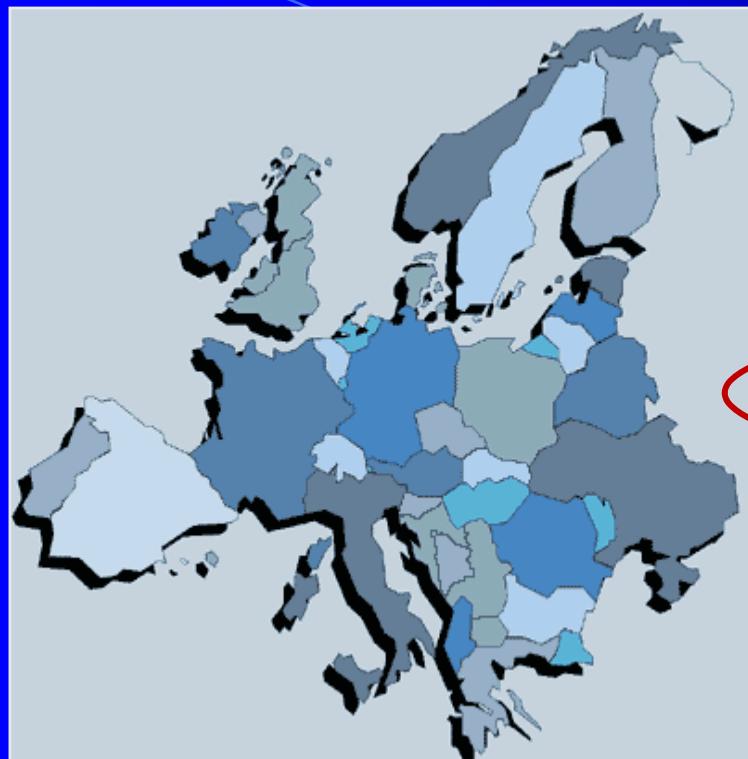
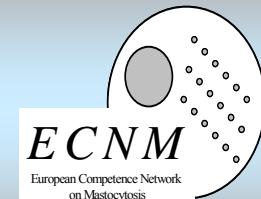
ECNM – European Competence Network on Mastocytosis 2002



Response Criteria (2003) →  
Standardization Conference 2005 →  
WHO Update 2008 → WoCo 2010



# ECNM – THE EUROPEAN COMPETENCE NETWORK ON MASTOCYTOSIS



[www.ecnm.net](http://www.ecnm.net)

## Multi-Center European Initiative to

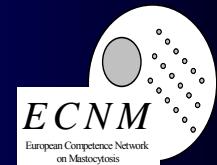
- Improve Recognition, Diagnosis & Therapy in Mastocytosis
- Provide all available Information to Patients and Doctors
- Study the Incidence and Epidemiology of Mastocytosis
- Start Cooperative Research-Projects on Mastocytosis in Europe
- Prepare and Conduct Clinical Trials
- ECNM Registry

# ECNM – Structure and Centers



Annual ECNM  
Meeting 2013:  
London (Sep 19-21)

[www.ecnm.net](http://www.ecnm.net)



## Structure of the ECNM: Center Types

### 1) Center of Excellence

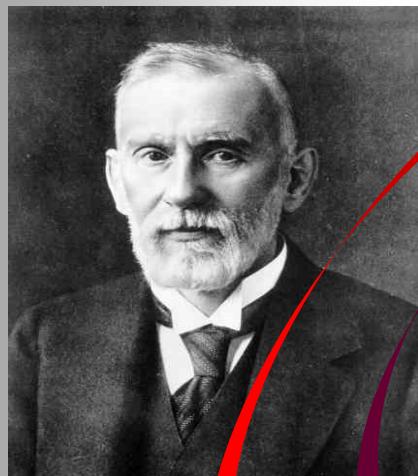
- Referral Center for all Patients
- All Major Diagnostics available
- All types of Therapy offered
- At least one COE per country = Aim
- Typically 3-4 Departments cooperate

### 2) Reference Center

- Focus on one major aspect
- Referral Center for Material etc
- Assists in developing Standards
- Usually Major Research Center

# MAST CELLS FORM A UNIQUE LINEAGE WITHIN THE HEMATOPOIETIC SYSTEM

PAUL EHRLICH (1854-1915)



modern hematology  
& immunostaining

2013

mast cell &  
mastocytosis  
research

cell surface  
receptors

targeted drugs

- dye stains

- mast cells

- side chain  
theory

- magic  
bullets

## Mast Cells

KIT+

IL-3R-

IL-4R+

IgER+

Histamine+

Tryptase+

Chymase+/-

Heparin+

Basogranulin+

CD63+

CD203c+/-

## Basophils

KIT-

IL-3R+

IL-4R+

IgER+

Histamine+

Tryptase+/-

Chymase-

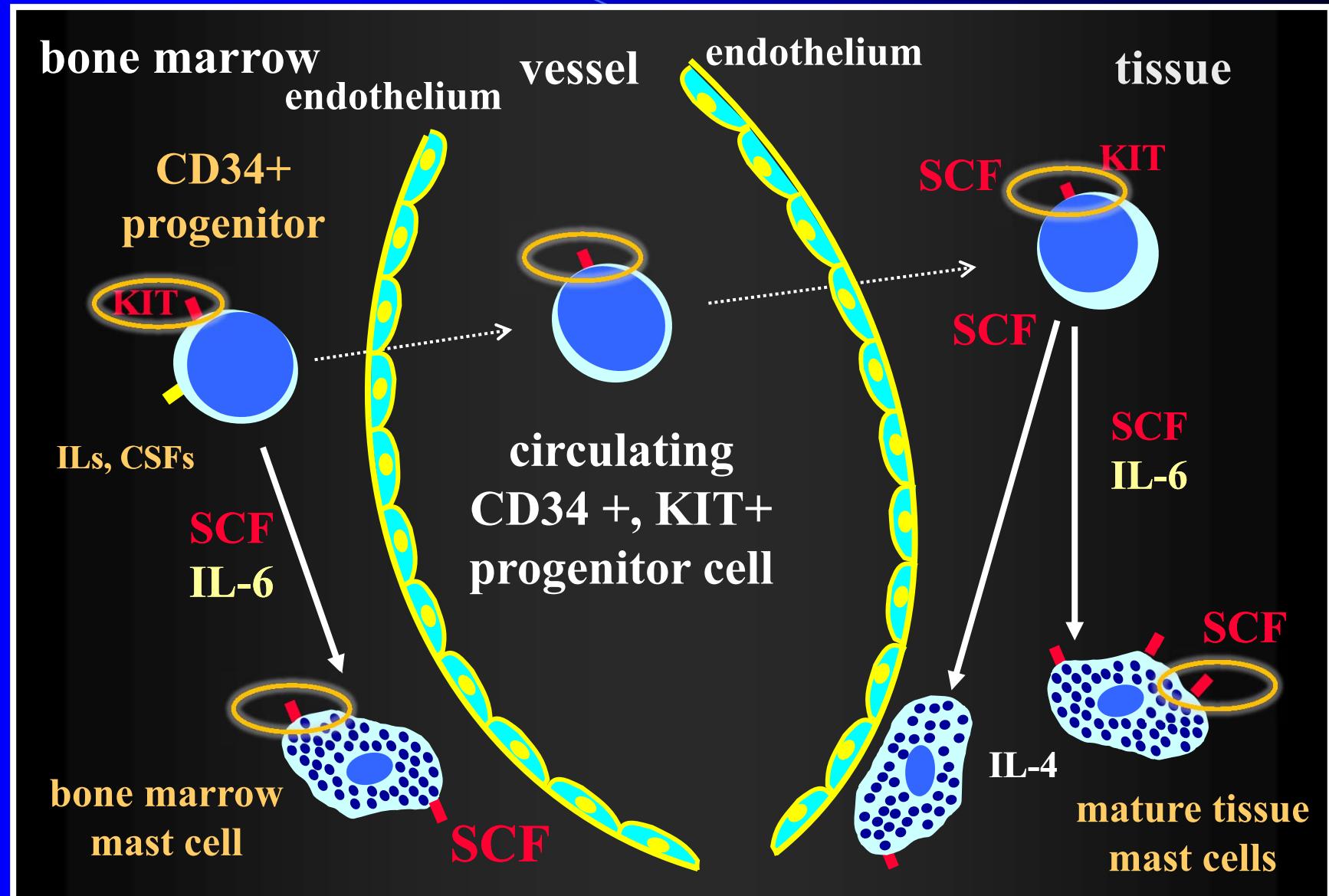
Heparin-

Basogranulin+

CD63+

CD203c+

# DIFFERENTIATION OF MAST CELLS



# Cutaneous Mastocytosis (CM) vs Systemic Mastocytosis (SM) !



Hartmann. & Henz, Br J Derm 2001;144:682

**Mostly Children** (*KIT*<sub>mut</sub>≈40%)

**Diagnosis:** Skin only

- Biopsy of Skin
- Serum Tryptase
- Usually no BM Biopsy

Cutaneous Mastocytosis



Wolff et al, Leuk Res 2001;25:519

**Mostly Adults** (*KIT D816V*)

**Diagnosis:** >80% !

- Biopsy of BM (and Skin)
- Apply SM Criteria
- Define SM Variant

Systemic Mastocytosis

# WHO CLASSIFICATION



- **Cutaneous Mastocytosis (CM)**
- **Indolent Systemic Mastocytosis (ISM)**
- **SM with an Associated Hematologic non Mast Cell Lineage Disease (SM-AHNMD)**
- **Aggressive Systemic Mastocytosis (ASM)**
- **Mast Cell Leukemia (MCL)**
- **Mast Cell Sarcoma (MCS)**
- **Extracutaneous Mastocytoma**

# WHO Classification: Criteria for Systemic Mastocytosis (SM-Criteria)



## Major Criteria

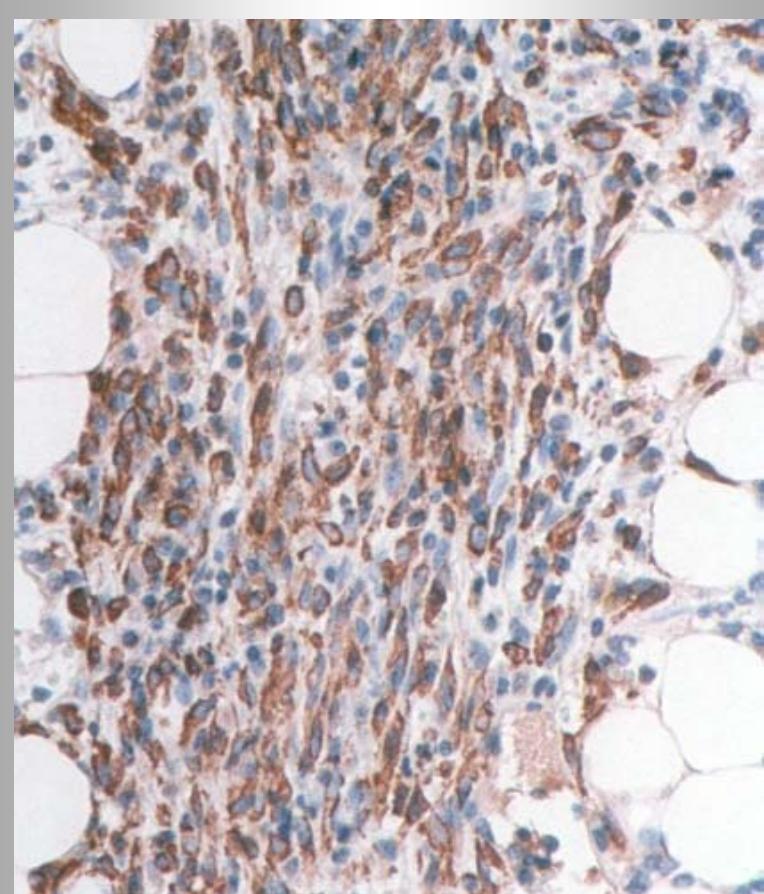
- Multifocal dense mast cell (MC) infiltrates ( $\geq 15$  MC/infiltrate) in the bone marrow or in another extracutaneous organ

## Minor Criteria

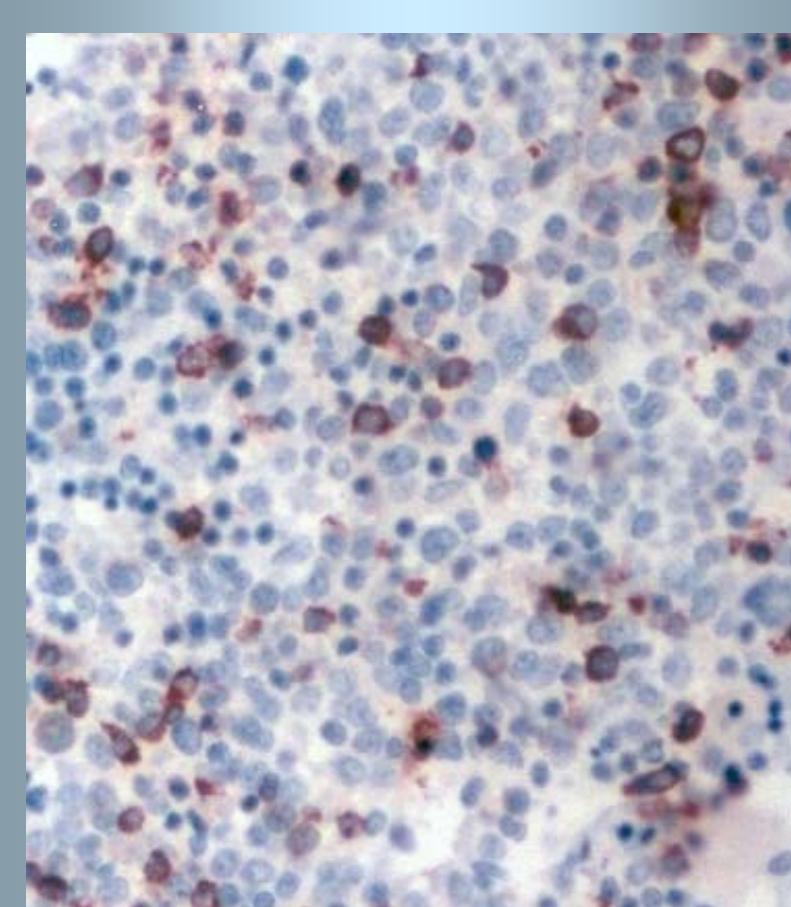
- $>25\%$  spindle-shaped cells in MC-infiltrates; or  $>25\%$  of all MC are atypical MC (type I and/or type II) in bone marrow smears
- Expression of CD2 and/or CD25 in bone marrow MC
- Serum tryptase level  $>20$  ng/ml (does not count in cases with an AHNMD)
- *KIT* point mutation at codon 816 (mostly D816V) in bone marrow or in another extracutaneous organ

The diagnosis Systemic Mastocytosis is established if at least 1 major and 1 minor or 3 minor criteria are fulfilled

# Analysis of Bone Marrow Sections: Tryptase-Immunohistochemistry



Systemic Mastocytosis



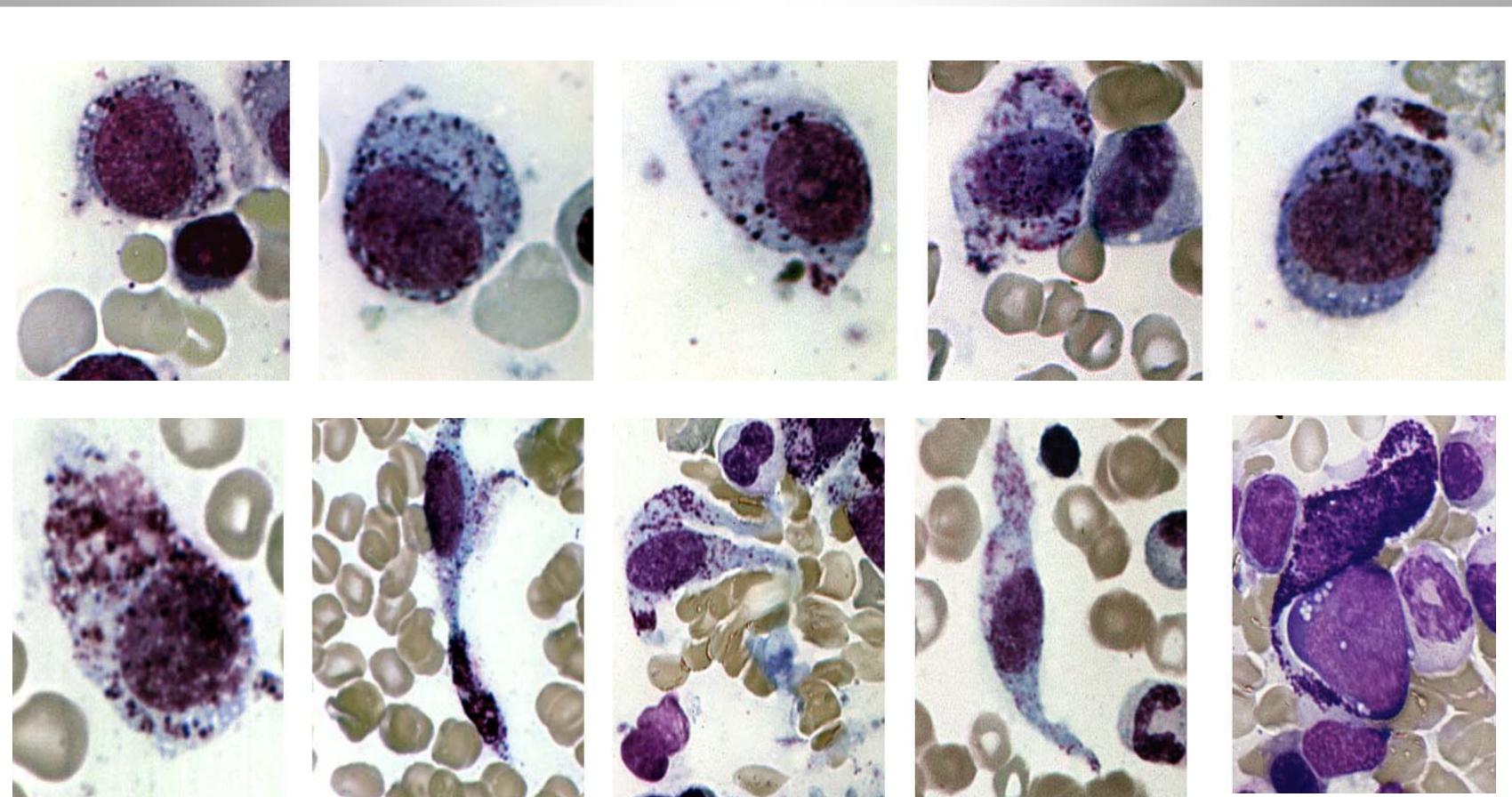
SM-AHNMD ? Myelomastocytic ?

# Bone Marrow Smear: Atypical Mast Cells in Systemic Mastocytosis



Criteria for Atypical Mast Cells Type I in Bone Marrow Smears:

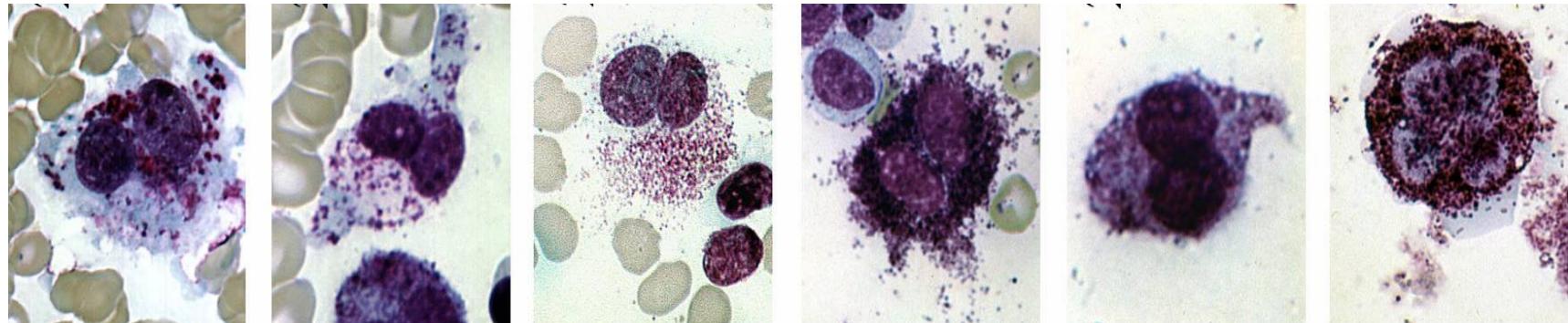
**A: Oval Nucleus, B: Cytoplasmic Extensions, C: Hypogranulated (2/3)**



# Bone Marrow Smear: Atypical Mast Cells Type II and Metachromatic Blasts

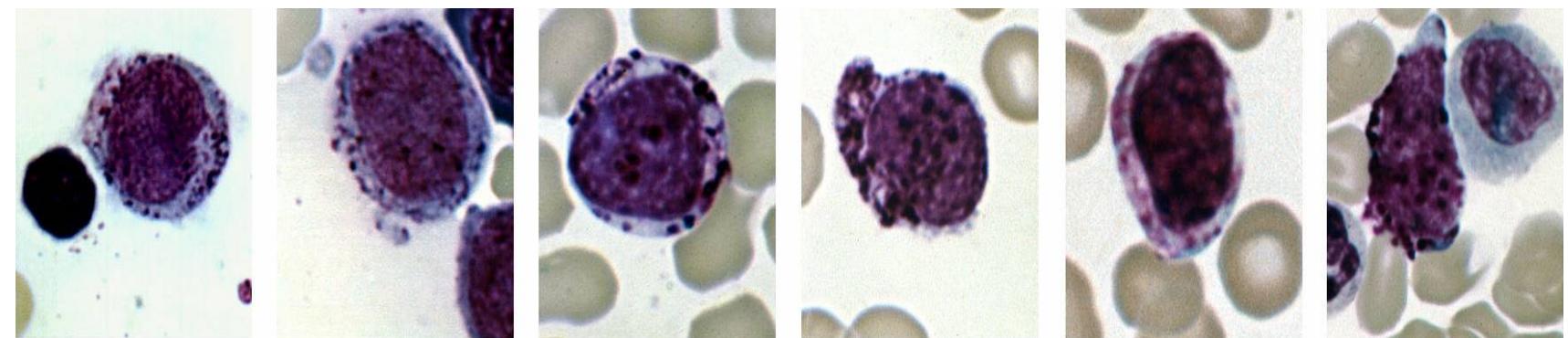


Atypical Mast Cells Type II = Promastocytes in Bone Marrow Smears



Sperr et al, Leuk Res 2001;25:529

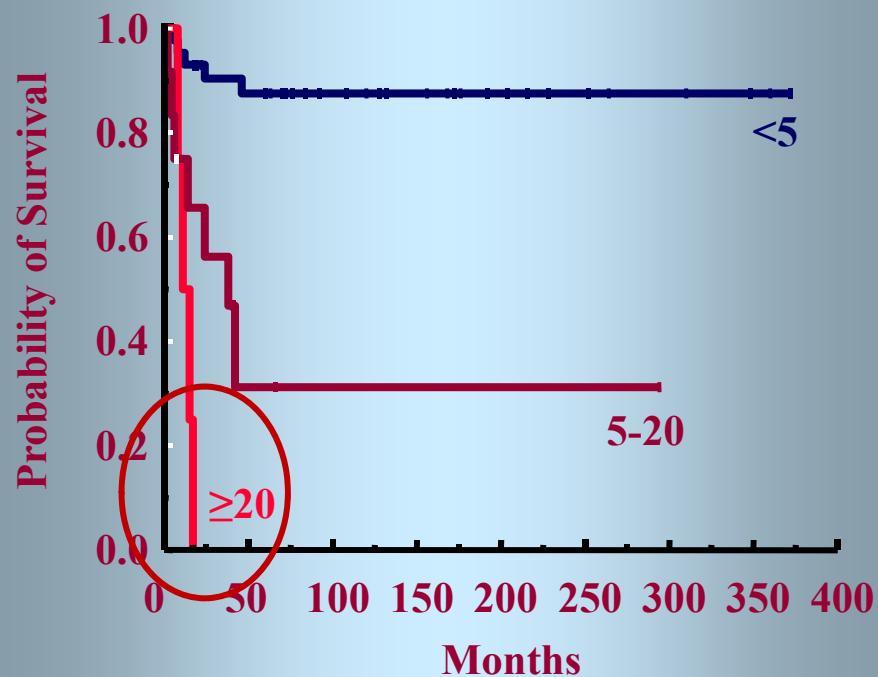
Metachromatic Blasts in Bone Marrow Smears



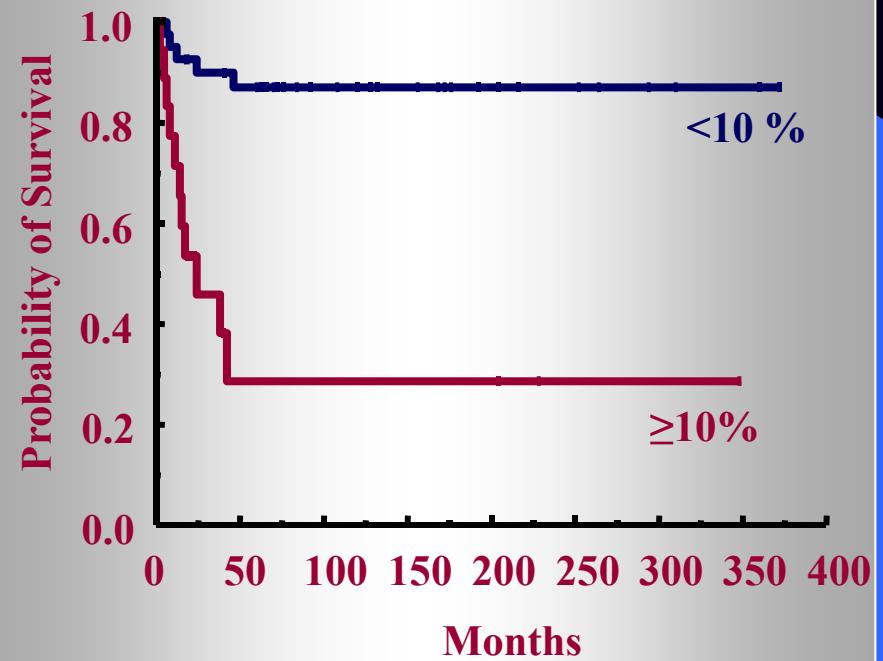
# Mast Cell Numbers in Bone Marrow Smears in Patients with SM: Clinical Significance



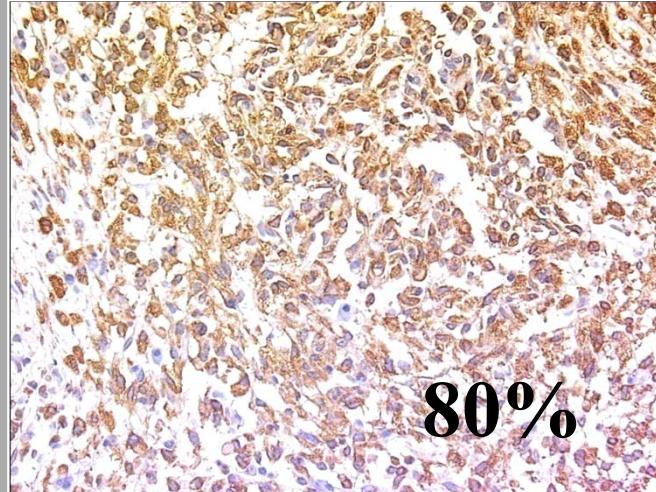
Survival of patients with varying percentages of mast cells (of all nucleated cells) in bm smears



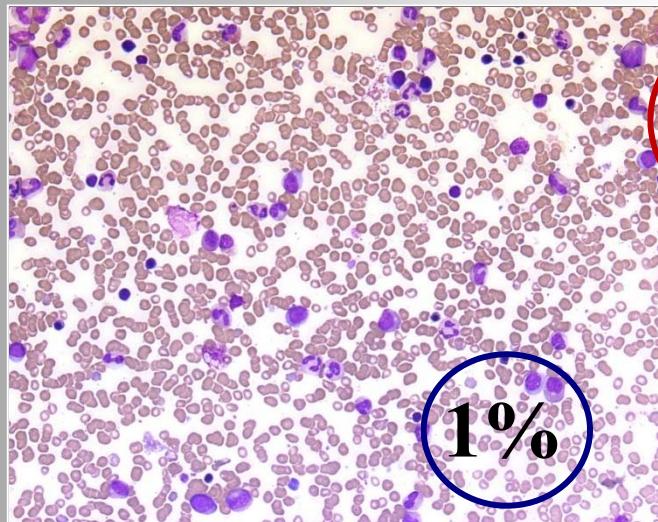
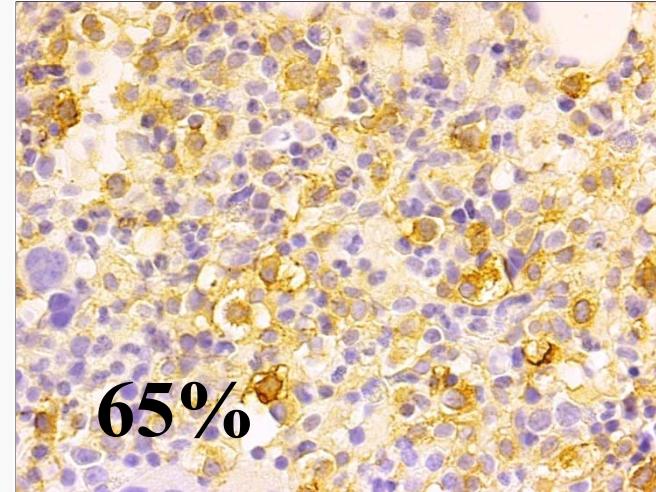
Survival of patients with varying percentages of pro-mastocytes (of all mast cells) in bone marrow smears



# Impact of the Mast Cell Count in the BM Smear in SM

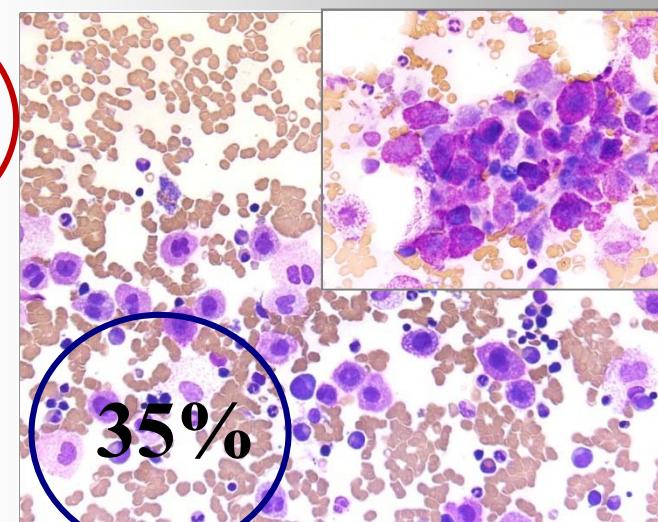


BM  
Section  
IHC  
(tryptase)



BM  
smear

!



survival: >20 years, alive SSM

survival: <1 year (MCL)

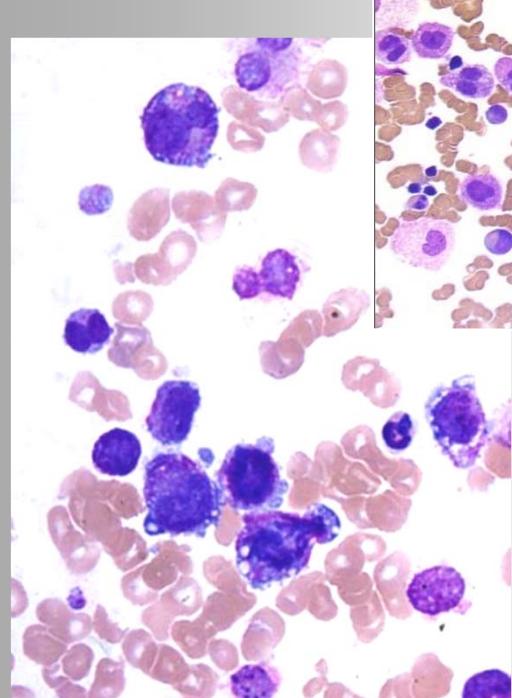
# Impact of Mast Cell Morphology in Patients with MCL (>20% MC in BM Smears)



**Acute MCL:**

**>20% MC in BM Smears**

**C-Findings**



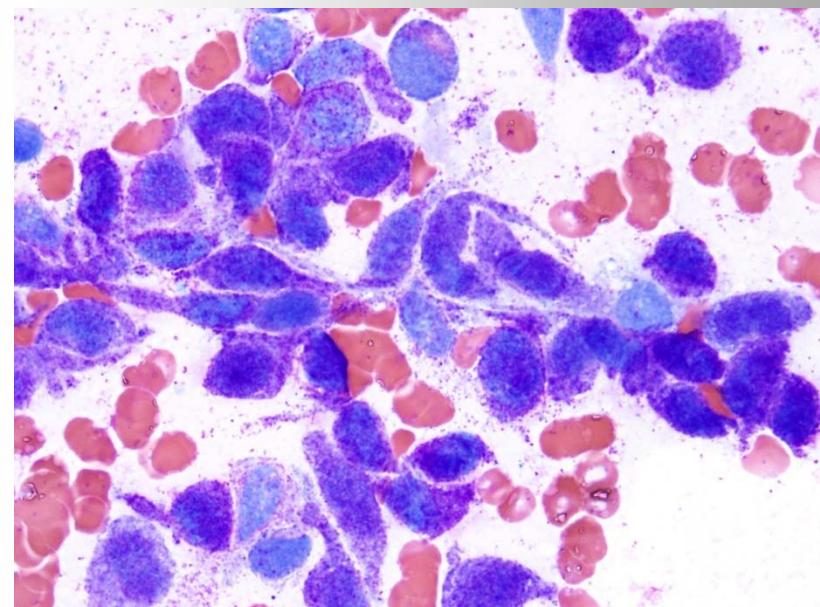
**'Hyperacute'**  
**MCL**  
**KIT D816H+**

**survival: <1 year**

**Chronic MCL:**

**>20% MC in BM Smears**

**No C-Findings**



**survival: >1 year**

# WHO Classification: Criteria for Systemic Mastocytosis (SM-Criteria)



## Major Criteria

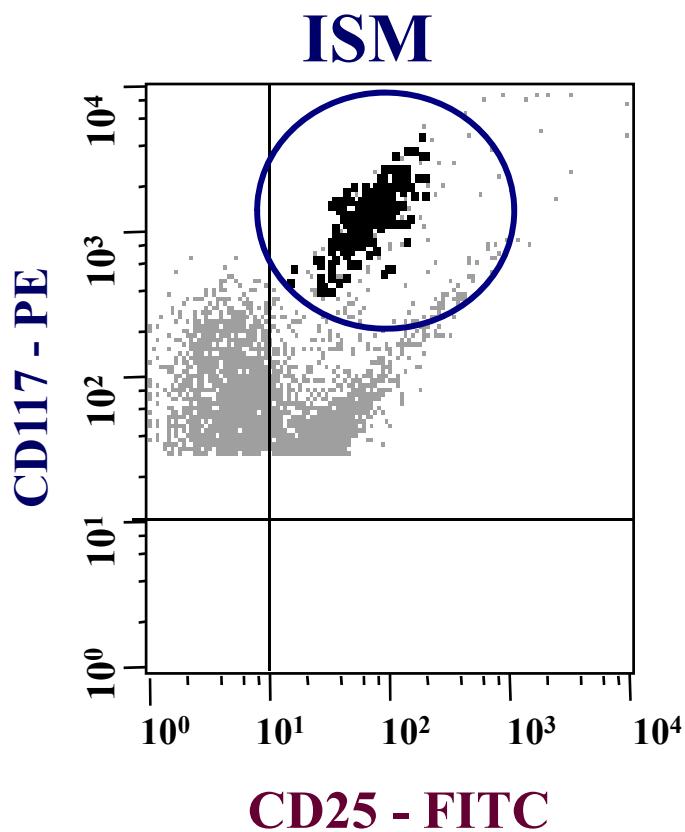
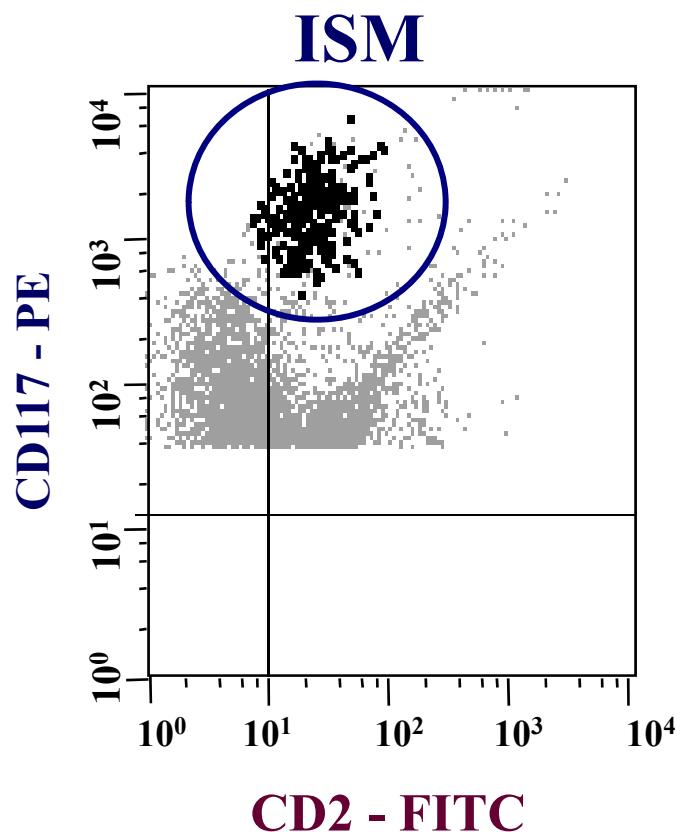
- Multifocal dense mast cell (MC) infiltrates ( $\geq 15$  MC/infiltrate) in the bone marrow or in an other extracutaneous organ

## Minor Criteria

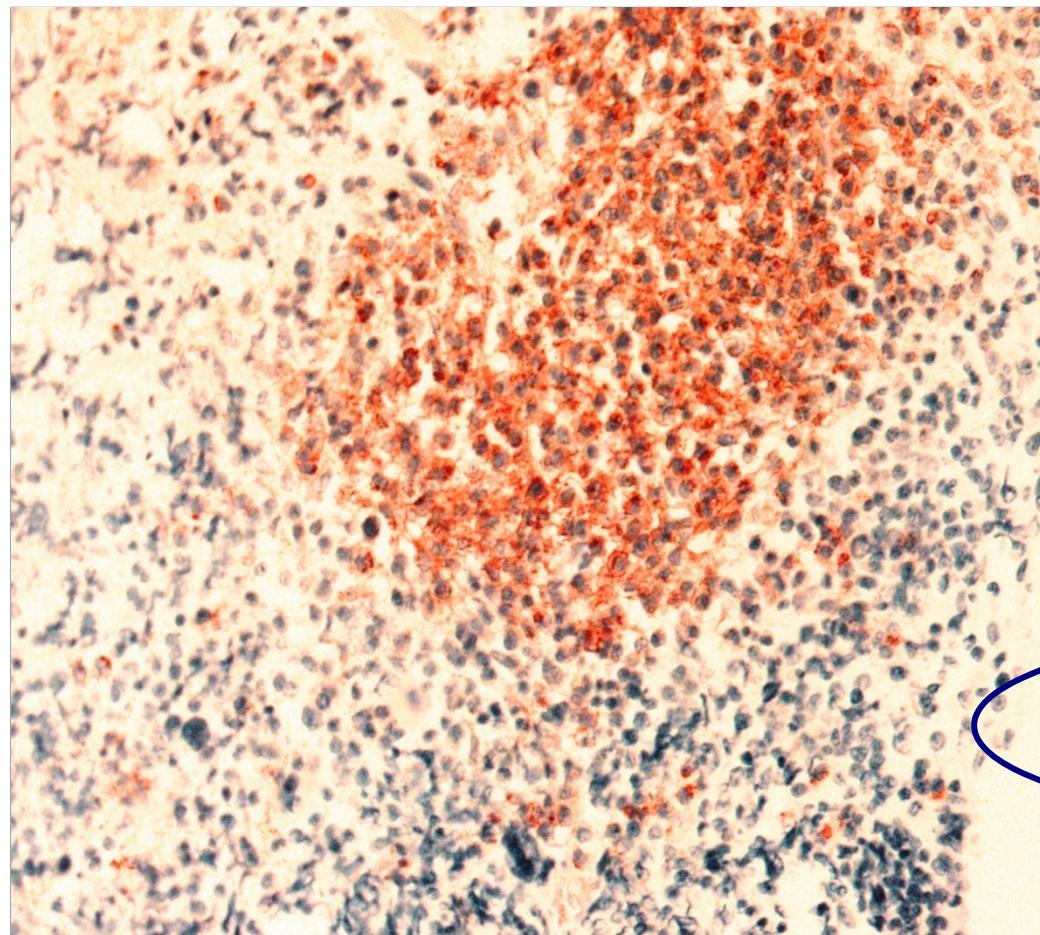
- $>2\%$  spindle-shaped cells in MC-infiltrates; or  $>25\%$  of all MC are atypical MC (type I and/or type II) in bone marrow smears
- **Expression of CD2 and/or CD25 in bone marrow MC**
- Serum tryptase level  $>20$  ng/ml (does not count in cases with an AHI > MD)
- *c-KIT* point mutation at codon 816 (mostly D816V) in bone marrow or in another extracutaneous organ

**The diagnosis Systemic Mastocytosis is established if at least 1 major and 1 minor or 3 minor criteria are fulfilled**

# Expression of CD2 and CD25 on Bone Marrow Mast Cells in a Patient with SM - Flow Cytometry



# Detection of CD25 in Neoplastic Bone Marrow Mast Cells by Immunohistochemistry (IHC)



## CD25-IHC:

- Simple Test
- Highly Specific (>95%) for neoplastic MC in SM
- MC in Myelomastocytic Leukemia & reactive MC Hyperplasia are CD25-
- Highly Sensitive and superior to CD2
- IHC regarded equally diagnostic compared to flow-cytometry

# WHO Classification: Criteria for Systemic Mastocytosis (SM-Criteria)



## Major Criteria

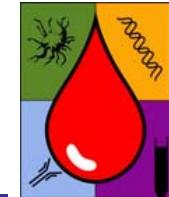
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- Expression of CD2 and/or CD25 in bone marrow MC
- Serum tryptase level  $>20$  ng/ml (does not count in cases with an AHNMD)
- c.61 point mutation at codon 816 (mostly D816V) in bone marrow or in another extracutaneous organ

The diagnosis Systemic Mastocytosis is established if at least 1 major and 1 minor or 3 minor criteria are fulfilled

# Serum Tryptase Levels in Controls



**Healthy controls:**

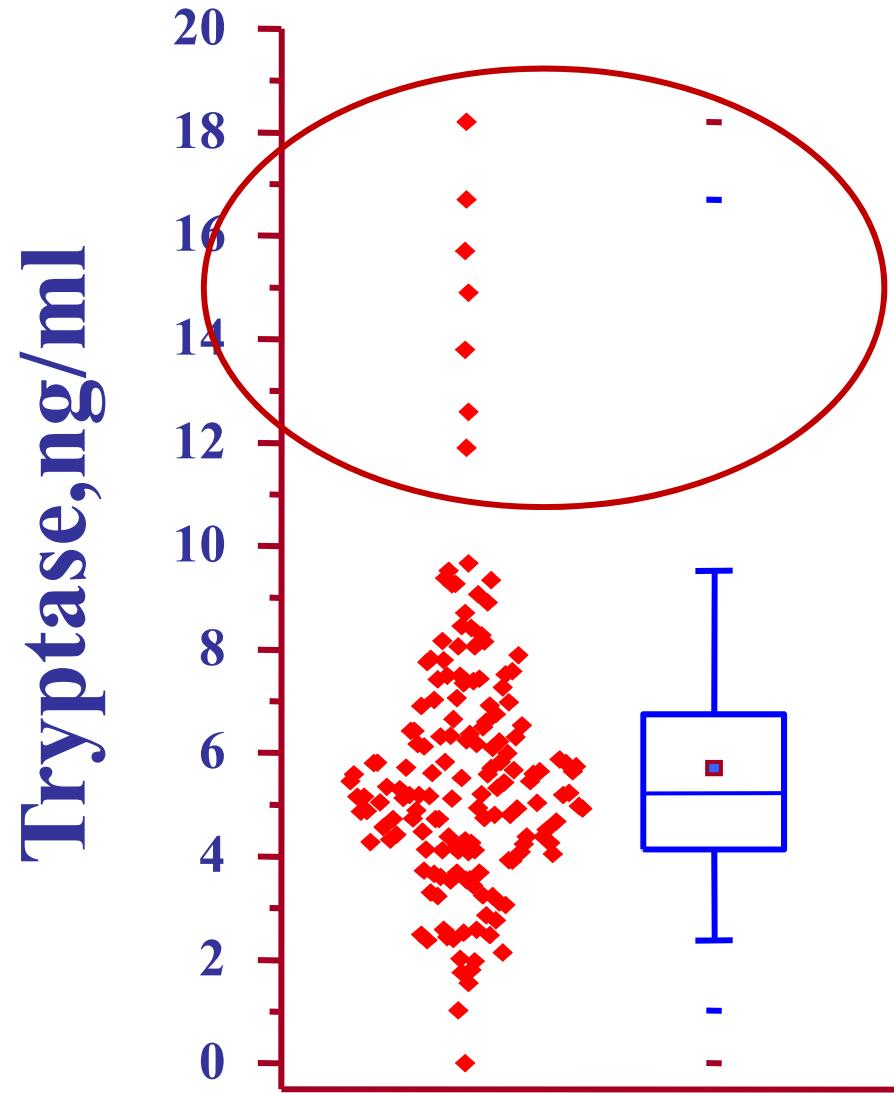
**Age:** range 5-83 yrs

**Serum tryptase levels:**

**Mean $\pm$ S.D.:**  $5.7\pm2.7$  ng/ml

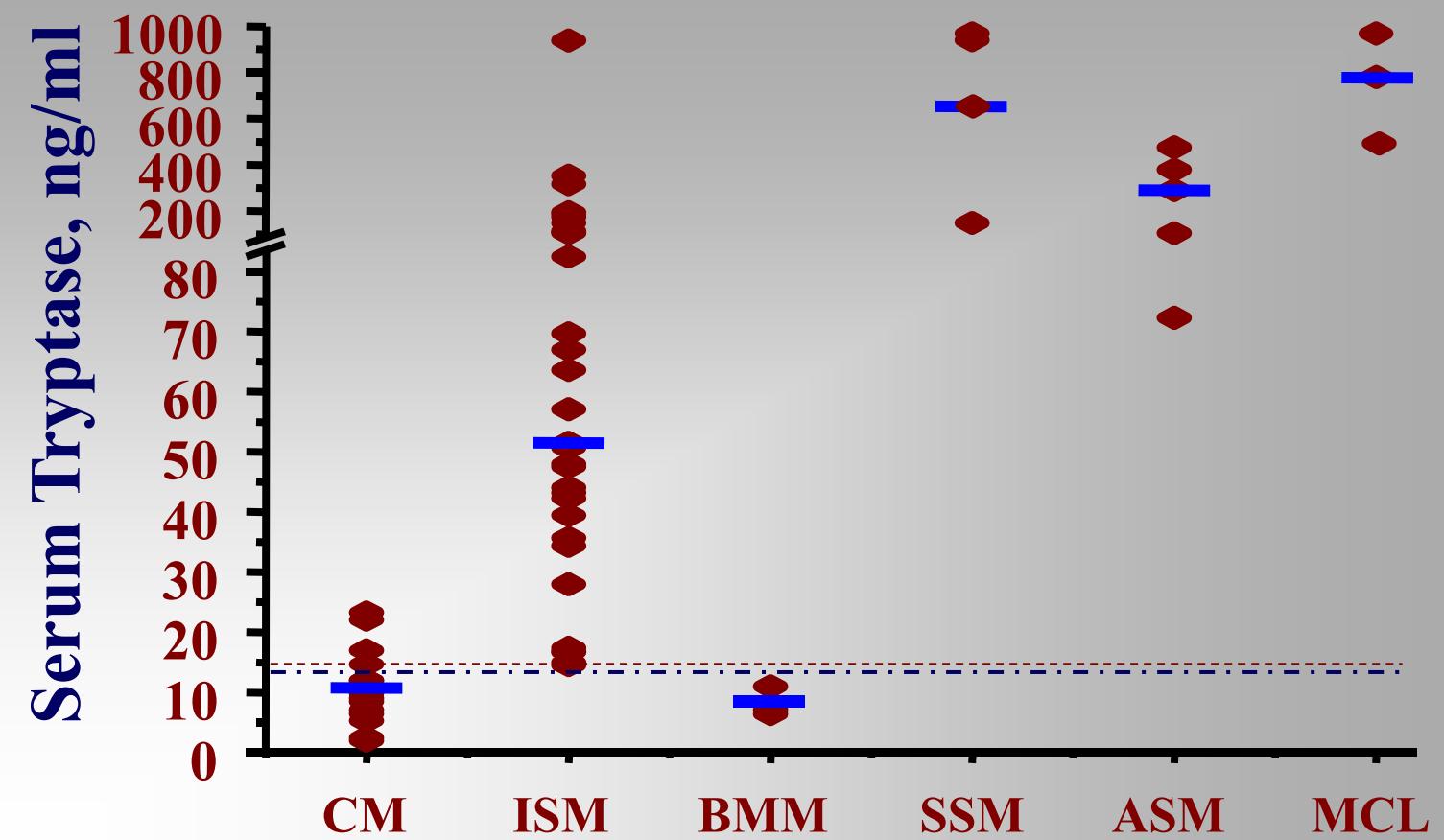
**Median:** 5.2 ng/ml

**Maximum:** 18.2 ng/ml

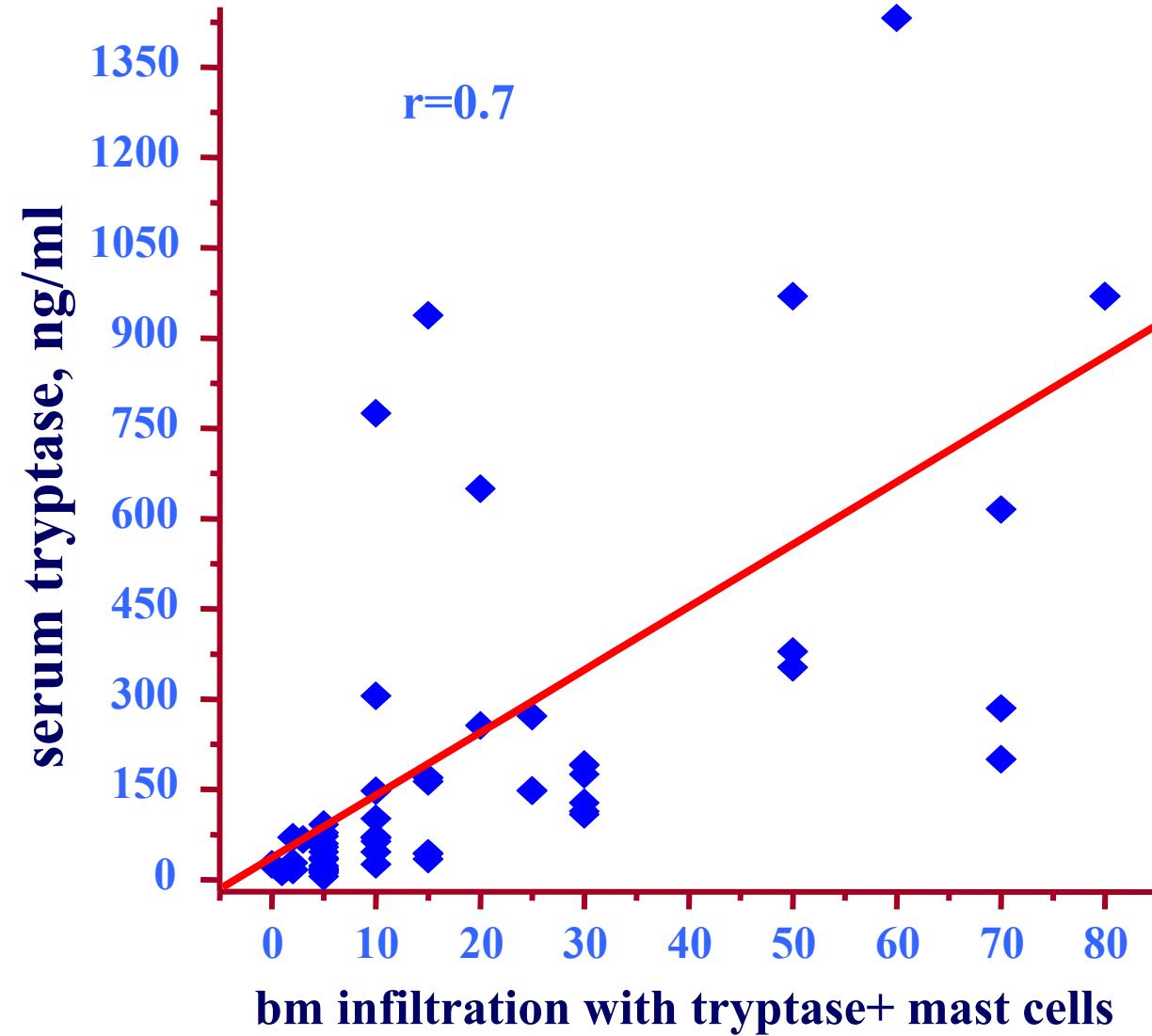
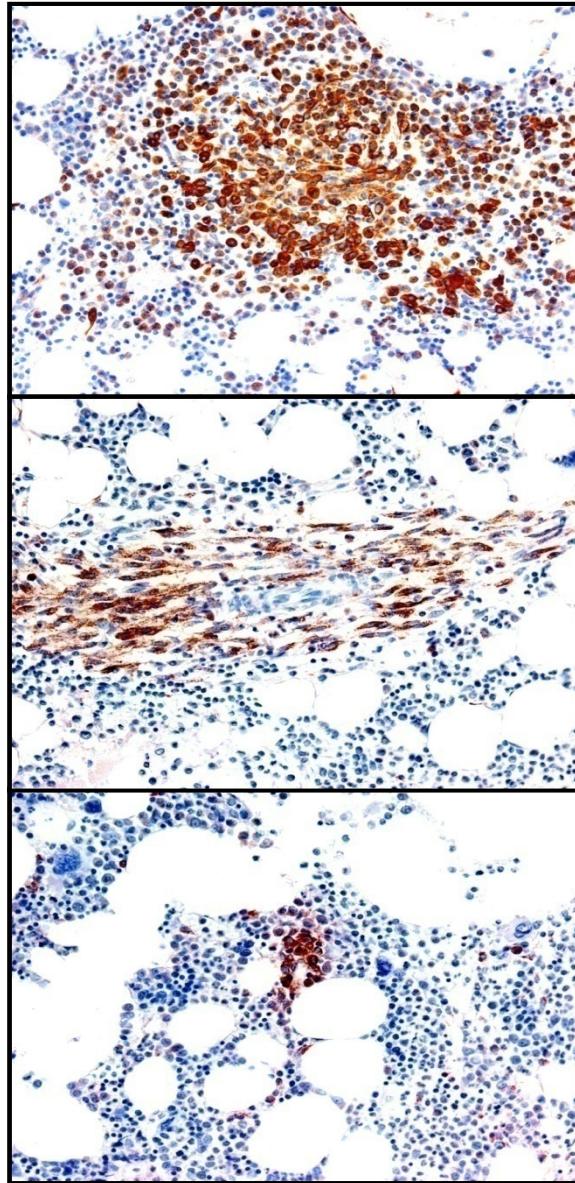




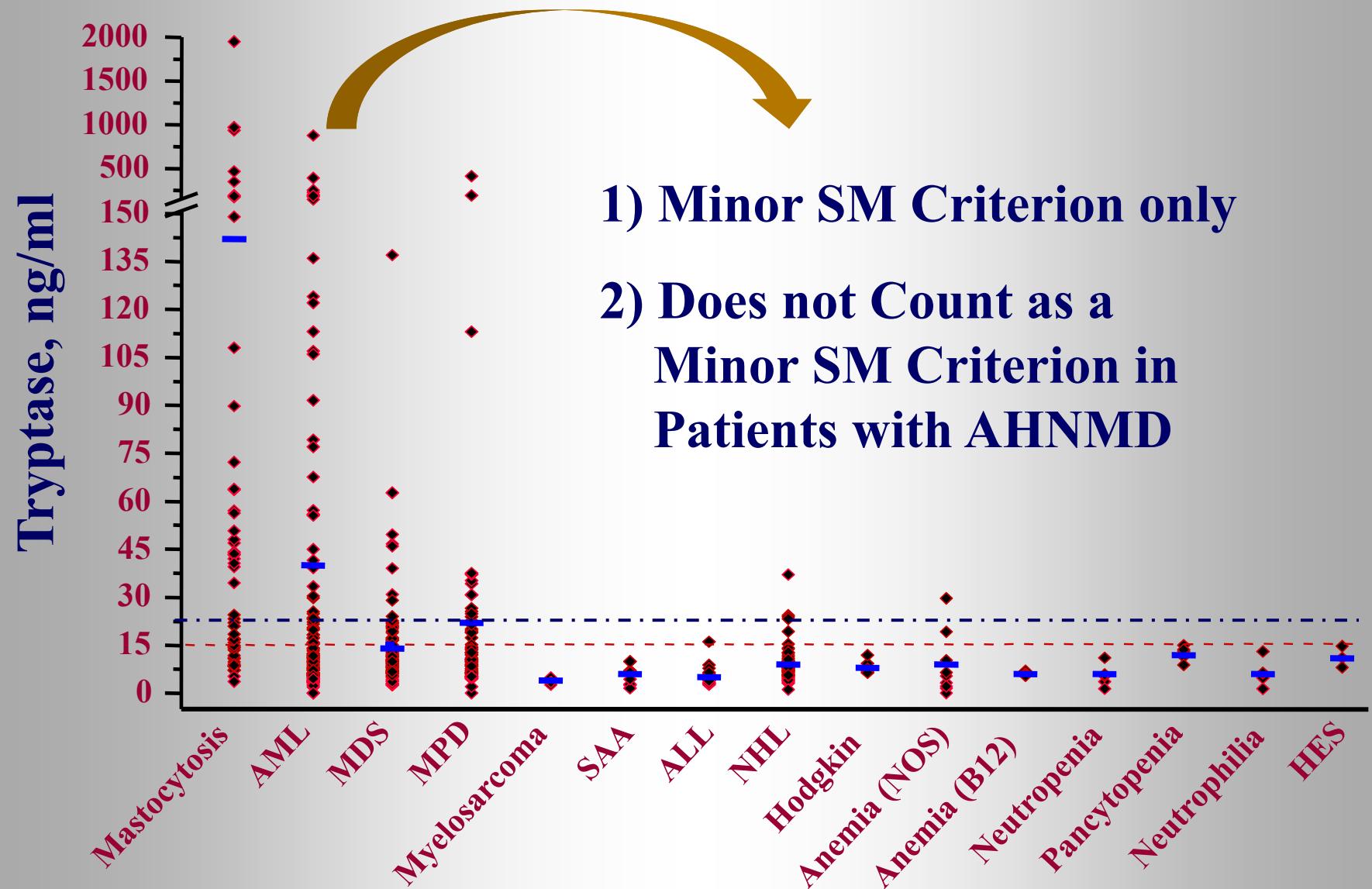
# Serum Tryptase Levels in various Groups of Patients with SM



# Correlation Between Tryptase and Infiltration (grade) of the Bone Marrow by Neoplastic Mast Cells (Dense Tryptase+ Infiltrates)



# Serum Tryptase Levels in Hematologic Disorders



# WHO Classification: Criteria for Systemic Mastocytosis (SM-Criteria)



## Major Criteria

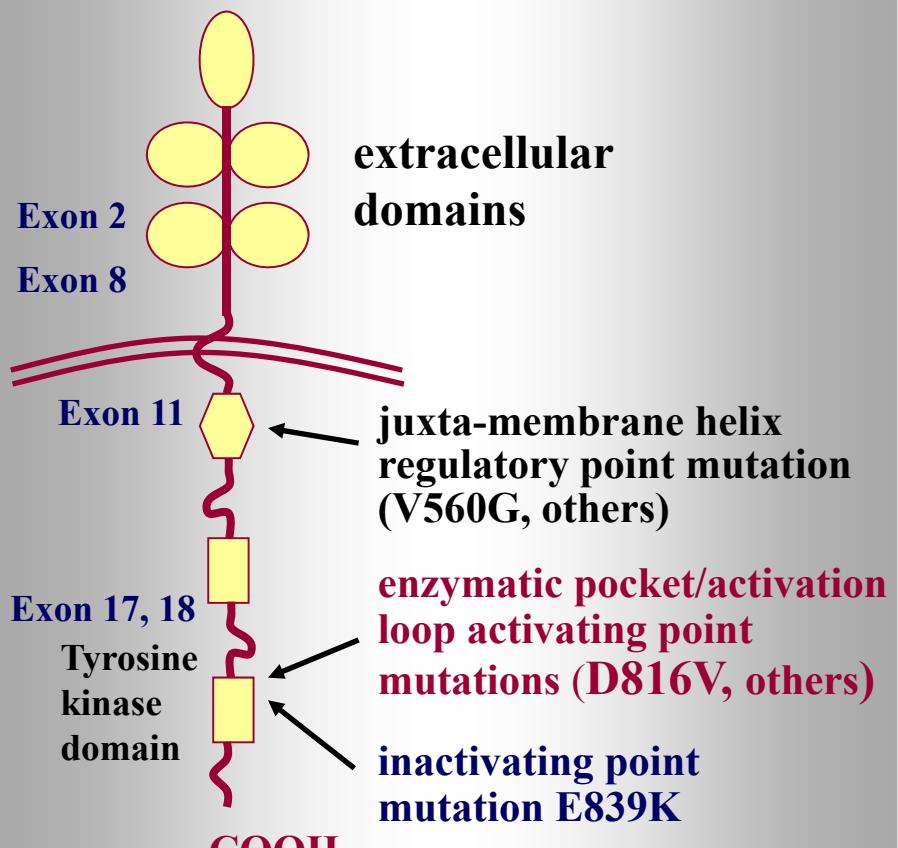
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- Expression of CD2 and/or CD25 in bone marrow MC
- Serum tryptase level  $>20$  ng/ml (does not count in cases with an AHNMD)
- **KIT point mutation at codon 816 (mostly D816V) in bone marrow or in another extracutaneous organ**

**The diagnosis Systemic Mastocytosis is established if at least 1 major and 1 minor or 3 minor criteria are fulfilled**

# KIT Point Mutations in Mastocytosis



## Proposed Standards (D816V)

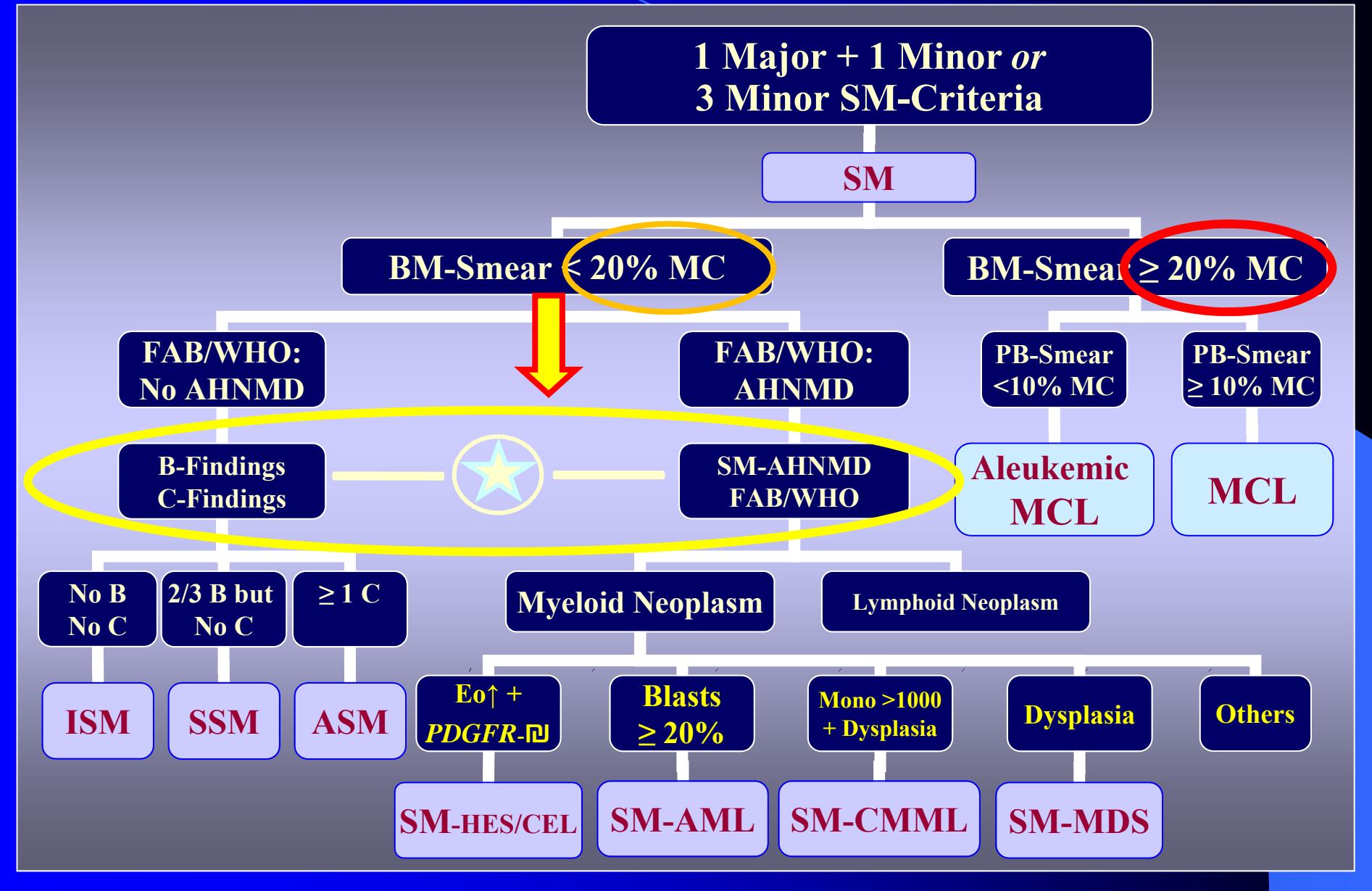
- **Bone marrow (bm) cells**
- MNC or unfractionated bm cells analyzed
- Peripheral blood (MNC) should be analyzed in early screening (e.g. in pts with elevated tryptase only)
- RT-PCR & RFLP or others  
(in D816V-negative patients  
→ sequencing of *KIT* ?)

# **KIT Point Mutations in Mastocytosis**



Mutation	Reported in	Frequency in SM
<b><i>KIT D816V</i></b>	<b><u>all variants of SM</u></b> also in cases of CM	<b>&gt;80%</b>
<i>KIT D816Y</i>	ISM, SM-AHNMD, CM ?	<5%
<i>KIT D816F</i>	ISM, CM ?	<5%
<i>KIT D816H</i>	SM-AHNMD	<5%
<i>KIT D812G</i>	SM/ASM	<5%
<i>KIT D560G</i>	SM/ISM	<5%
<i>KIT F522C</i>	SM/ISM	<5%
<i>KIT E839K</i>	CM	<5%
<i>KIT V531I</i>	SM-AHNMD	<5%
<i>KIT K509I</i>	ISM/ASM	<5%

# Stepwise Approach in Defining Subvariants of SM: Proposed Algorithm using WHO - Criteria



# B-Findings (Borderline-Benign) and C-Findings (Consider Cytoreduction)



## B-Findings:

- **Infiltration grade (MC) in BM >30% and serum tryptase  $>200$  (!) ng/ml**
- **Dysmyelopoiesis:** Hypercellular marrow with signs of myelodysplasia or myeloproliferation, but no criteria for MDS or MPN. Blood picture normal or slightly abnormal
- **Organomegaly (without impairment of organ function):** Hepatomegaly (without ascites), splenomegaly (palpable), lymphadenopathy (>2 cm in CT or US)

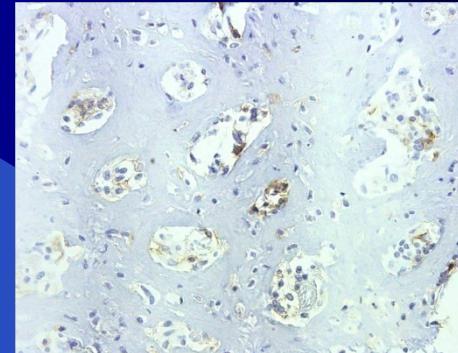
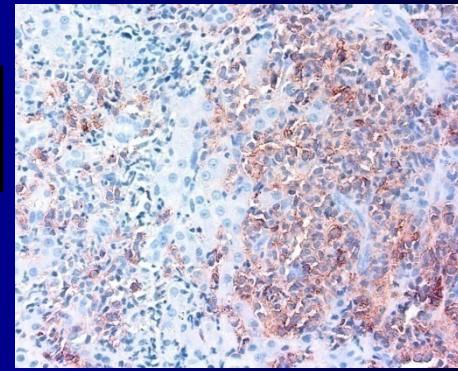
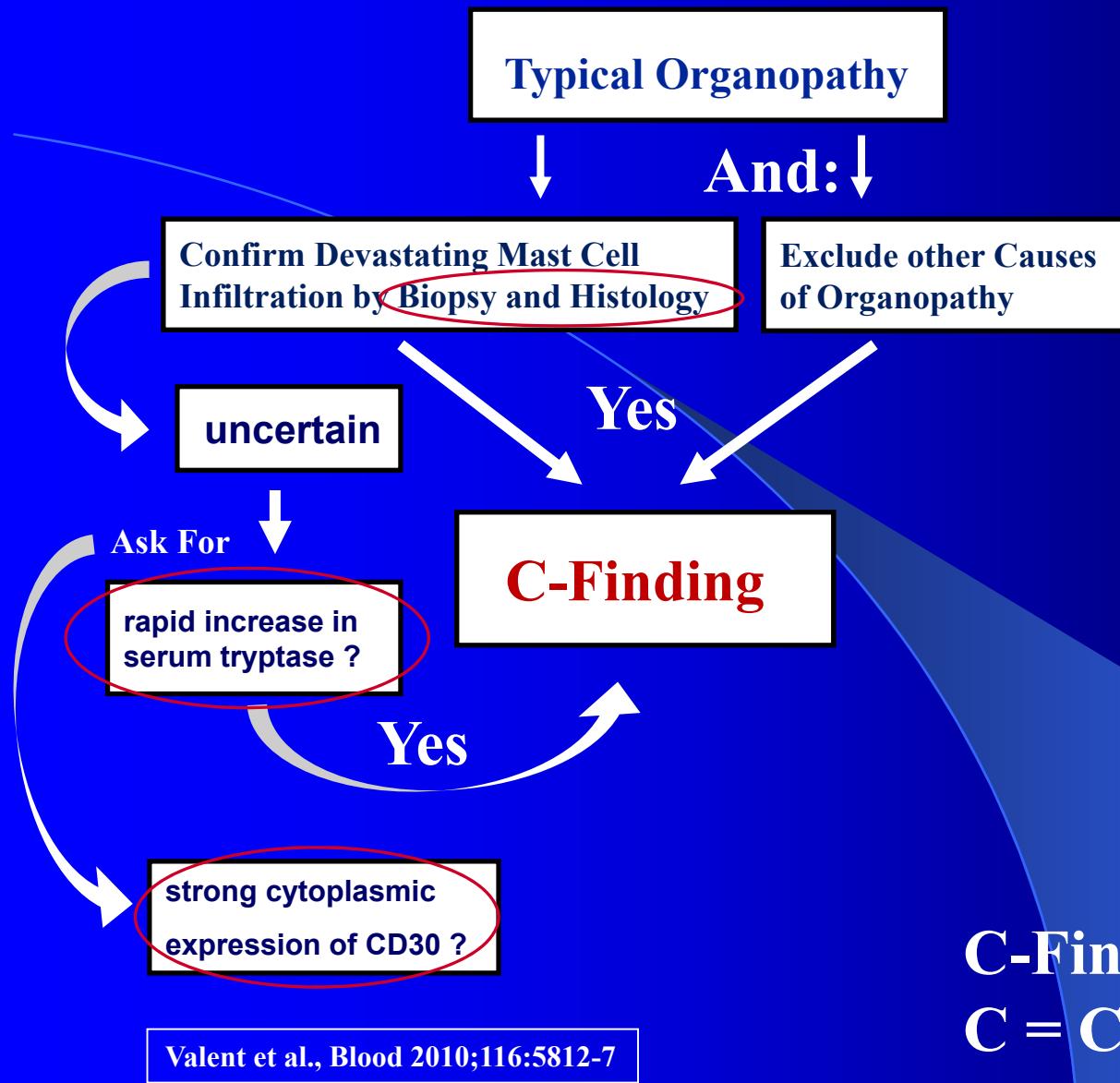
When 2 or 3 B-Findings but no C-Findings are recorded, the final diagnosis is Smouldering SM

## C-Findings:

- **One or more Cytopenias:** ANC<1000/ $\mu$ l; Hb<10 g/dl; Plt<100000/ $\mu$ l
- **Hepatopathy:** Enlarged liver with ascites, elevated liver enzymes +/- portal hypertension
- **Organopathy of Spleen:** Splenomegaly with hypersplenism
- **Malabsorption with hypalbuminemia and weight loss**
- Large **Osteolysis** and/or severe **Osteoporosis** & pathologic fractures

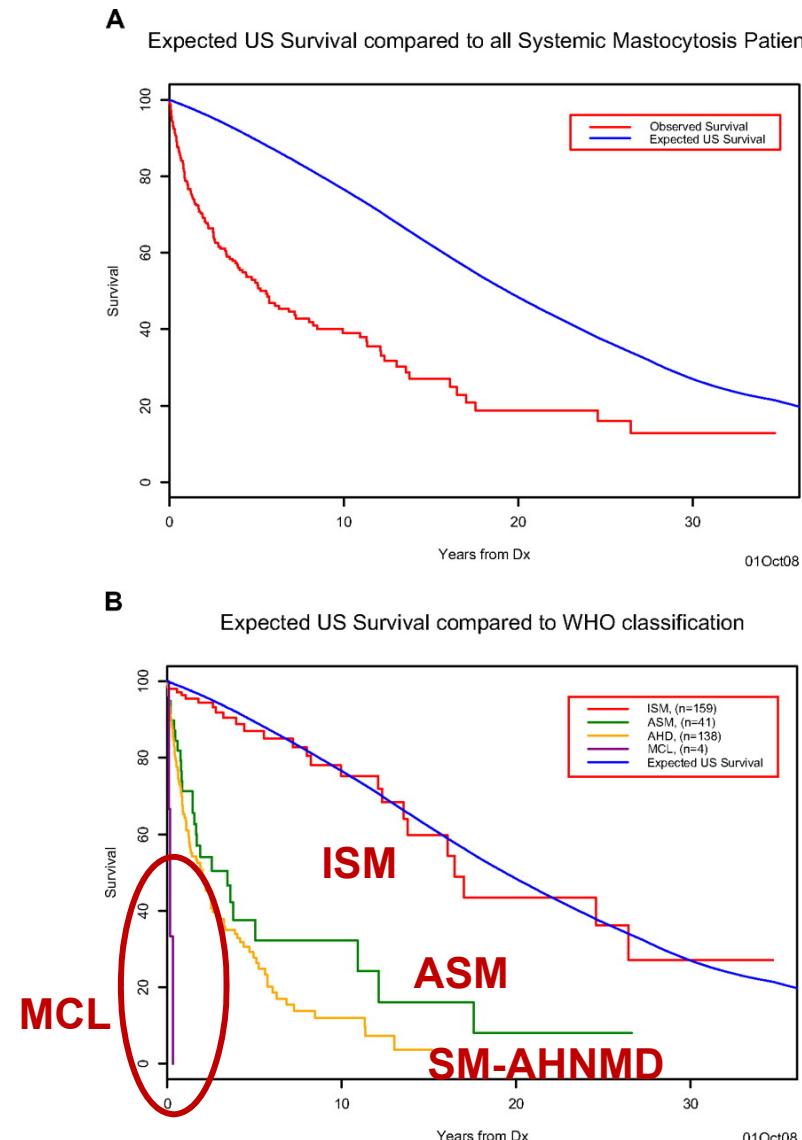


# What is a C-Finding: Guide for Daily Practice



**C-Finding:**  
**C = Consider Cytoreduction**

# Survival of Systemic Mastocytosis Patients – Mayo Experience



## Summary

- 1) Patients with Indolent SM (ISM) have a normal life expectancy
- 2) Patients with ASM and SM-AHNMD have a poor survival
- 3) In patients with Mast Cell Leukemia (MCL) survival is usually < 1 year
- 4) The WHO Classification can safely discriminate between low risk and high risk mastocytosis patients
- 5) Treatment should therefore be adjusted to the WHO variant

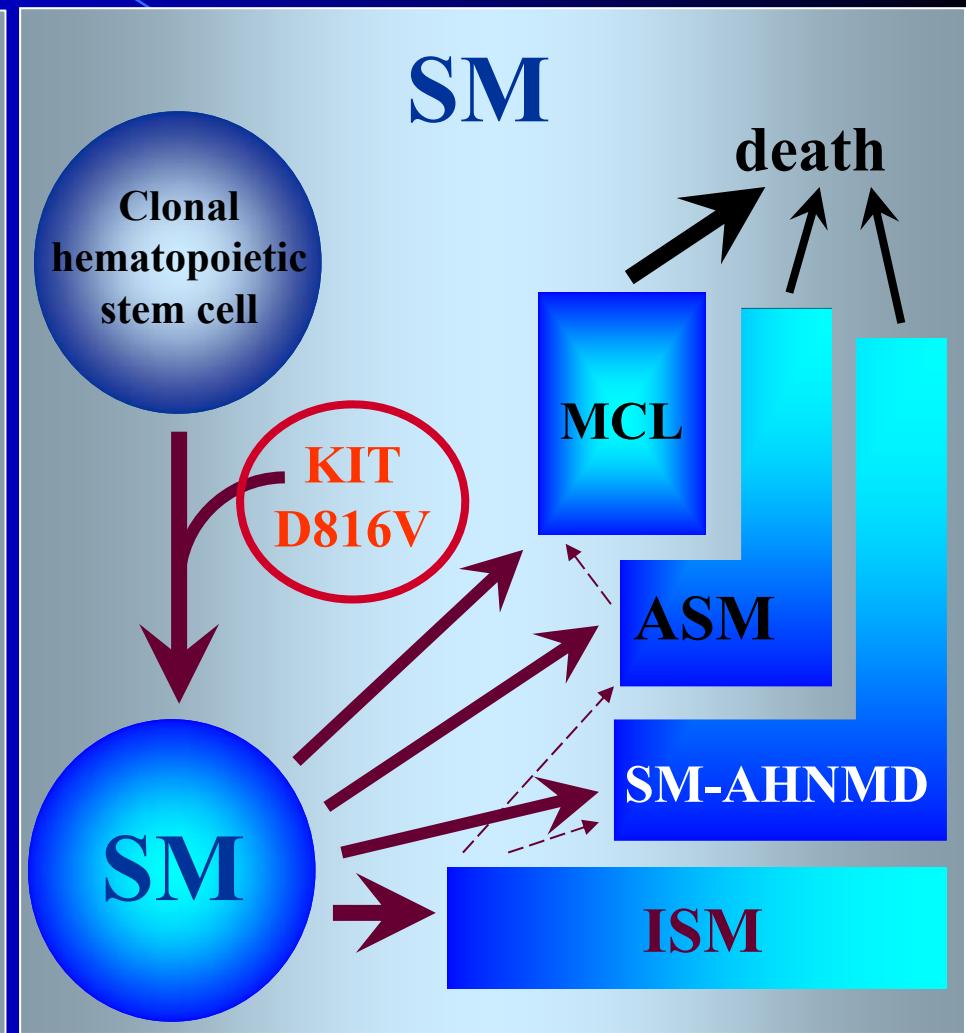


# PATHOGENETIC CONCEPT: ROLE OF OTHER DEFECTS

What factors and defects  
are responsible for SM  
and for the development  
of a high grade (mast  
cell-) disease in patients  
with *KIT D816V<sup>+</sup>* SM

?

- a) Cytokine Gene Polymorphisms
- b) KIT-independent signaling-  
pathways and molecules



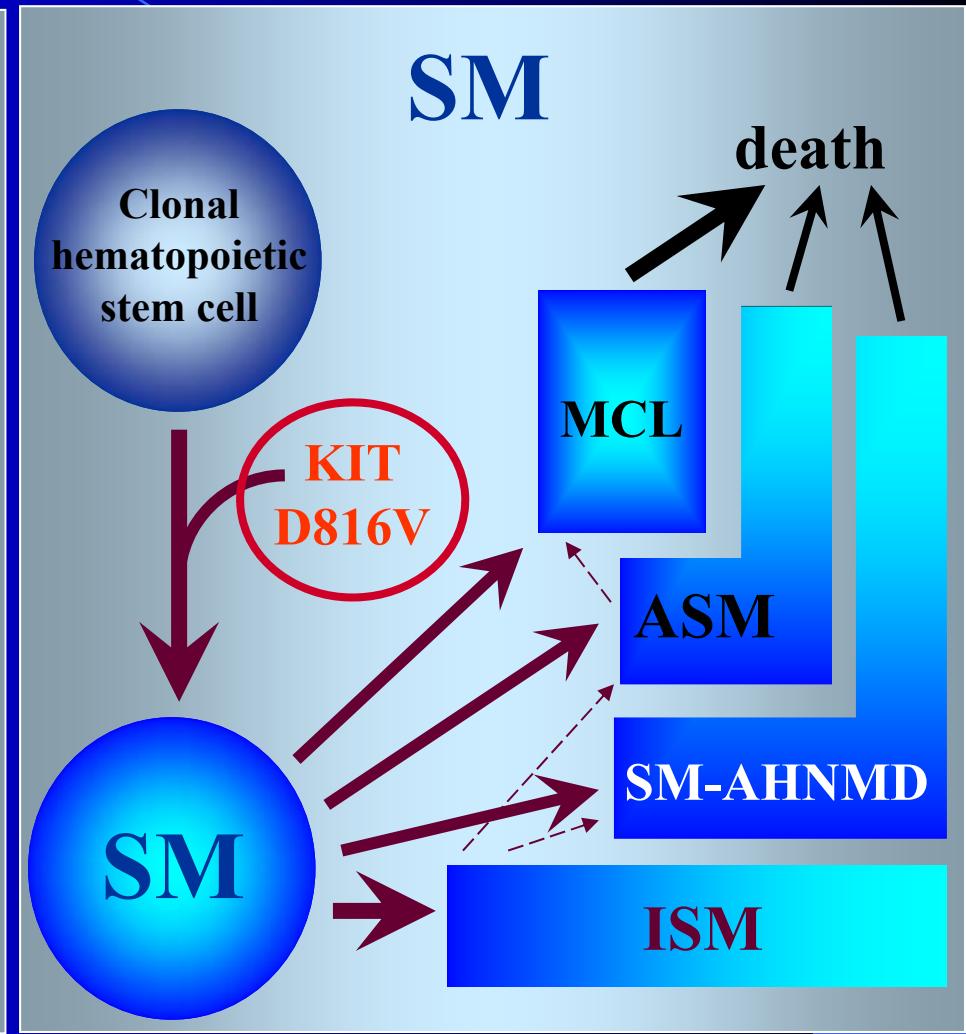


# PATHOGENETIC CONCEPT: ROLE OF OTHER DEFECTS

What factors and defects are responsible for SM and for the development of a high grade (mast cell-) disease in patients with *KIT D816V<sup>+</sup>* SM ?

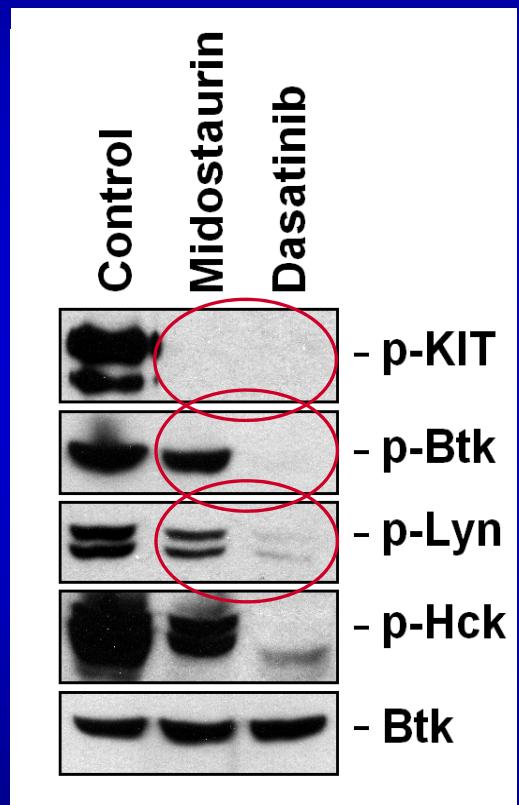
KIT-independent signaling-molecules :

- Btk ? Lyn ?
- mutated *RAS* ?
- mutated *TET2* ?
- mutated *IgERβ* ?



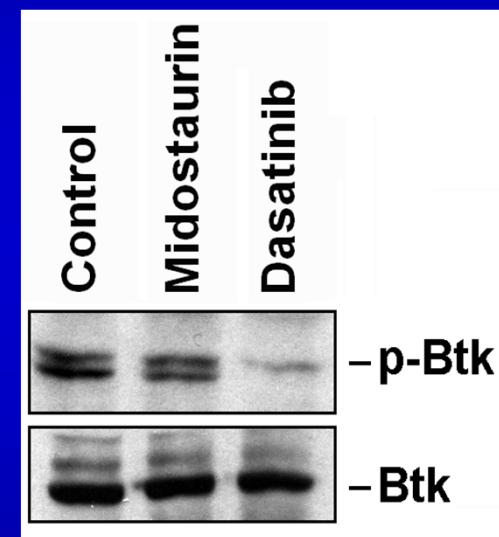


# Dasatinib counteracts phosphorylation of Btk in neoplastic mast cells



HMC-1.2

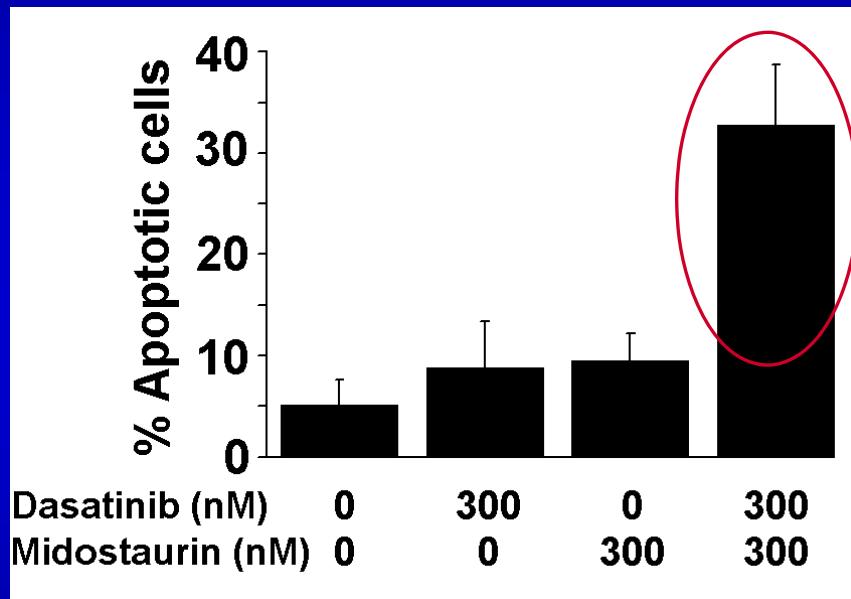
Gleixner et al., Blood 2011;118:1885-1898



Mast cell leukemia  
(BM: 75% neoplastic MC)

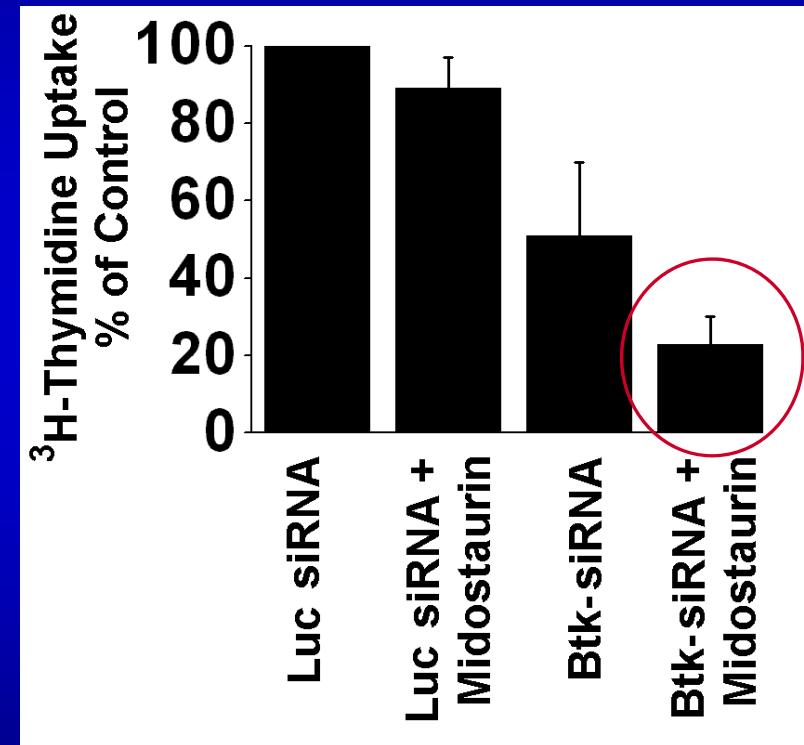


# siRNA against Btk synergizes with midostaurin in counteracting the proliferation of HMC-1 cells



Gleixner et al, *Haematologica* 2007;92:1451

**Dasatinib+PKC412**  
An Effective TKI Combination in  
KIT D816V+ Mast Cells



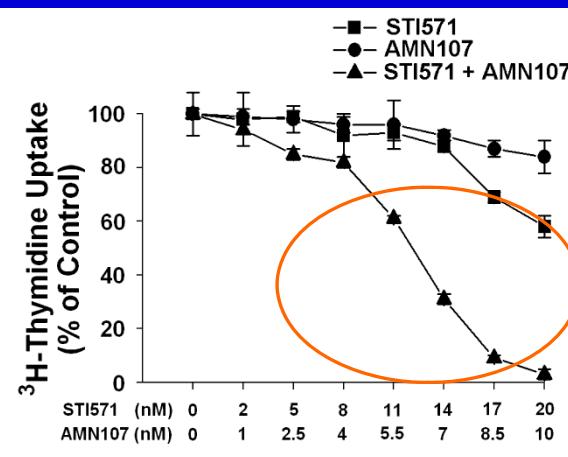
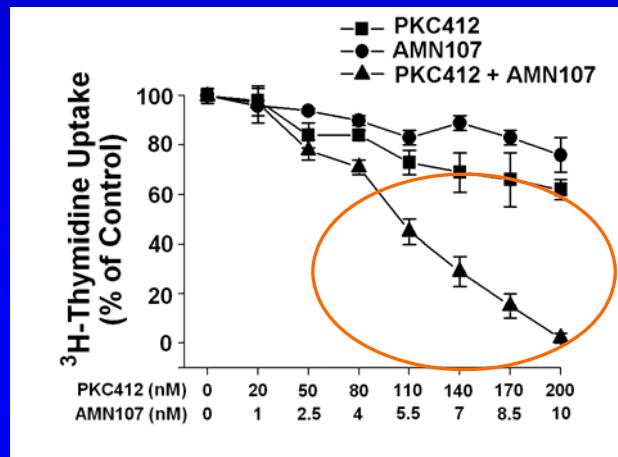
HMC-1.2

Gleixner et al., *Blood* 2011;118:1885-1898

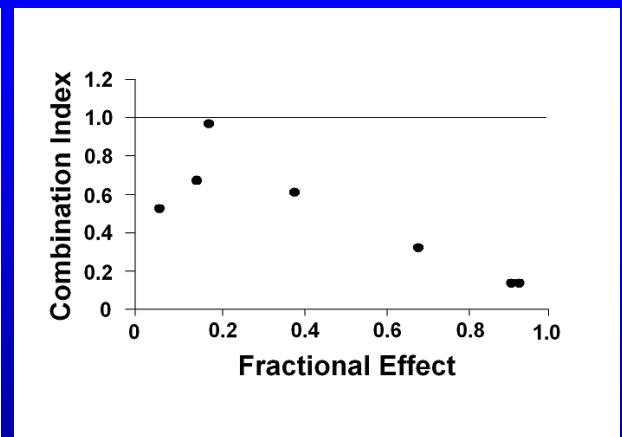
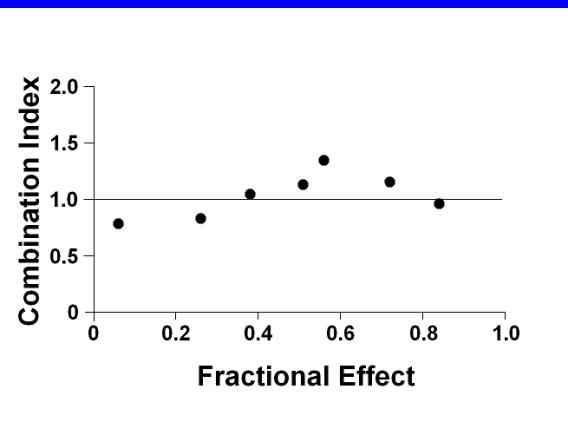
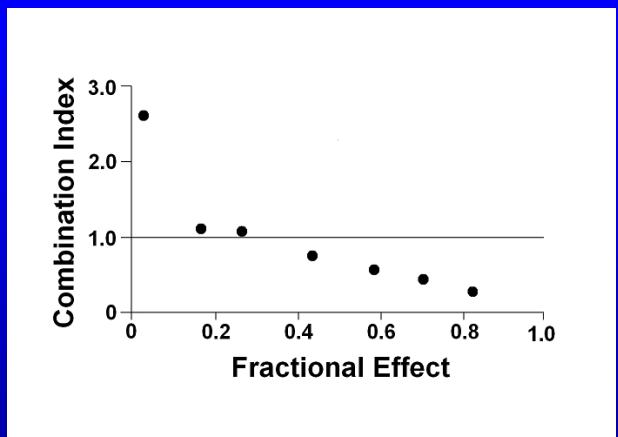
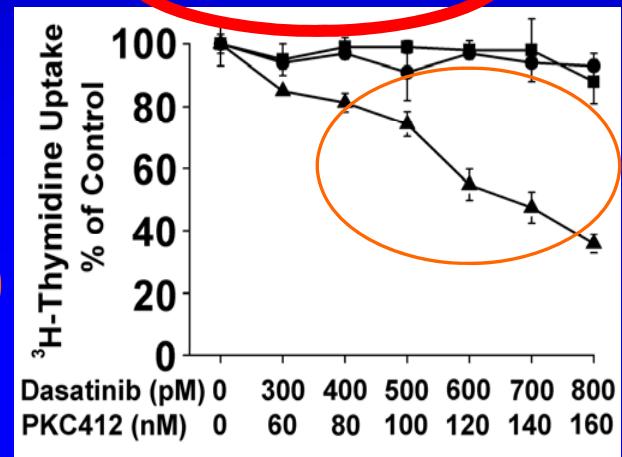
# Synergistic effects of TK inhibitors on growth of neoplastic mast cells



## KIT G560V



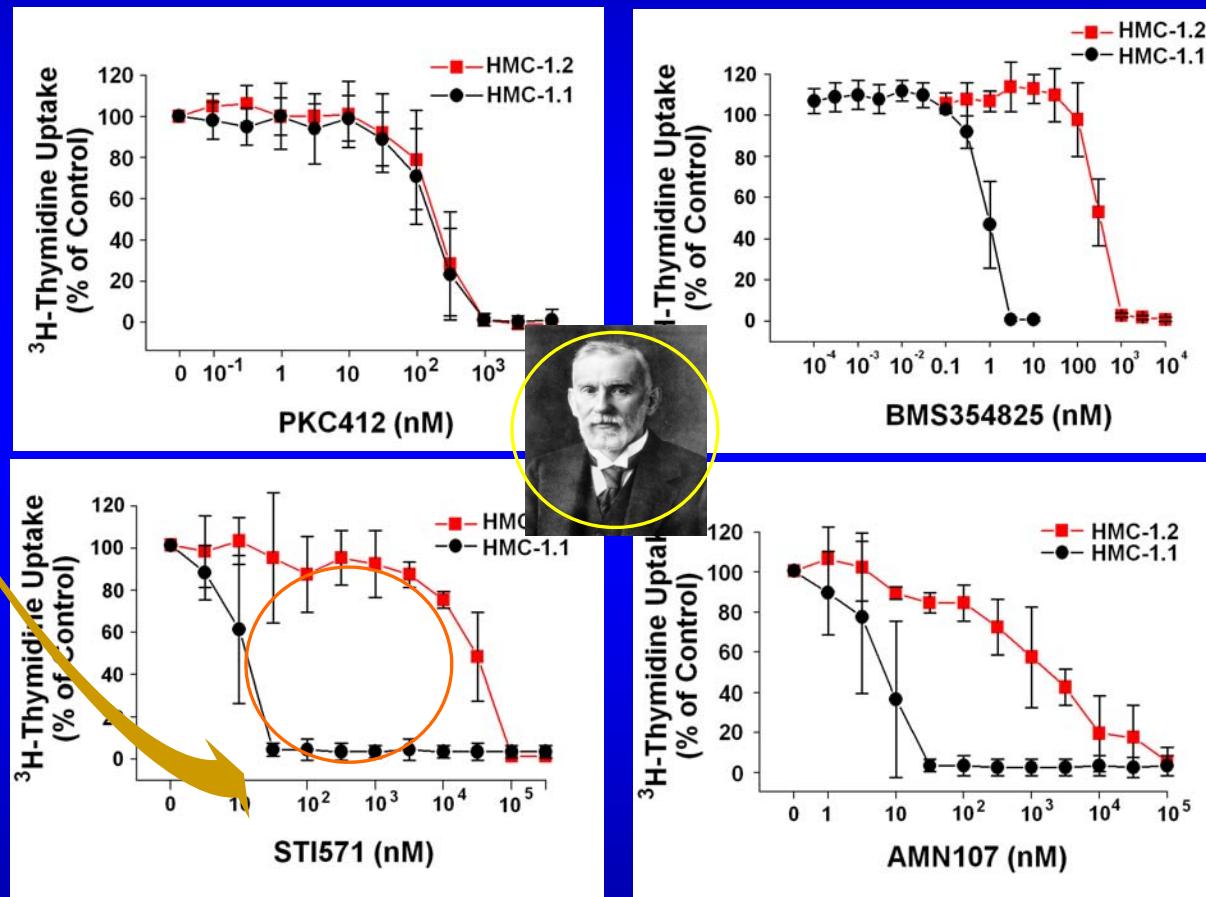
## KIT D816V



Combination Index values determined by calcusyn software

# Effects of KIT TK inhibitors on growth of neoplastic mast cells (cell lines)

KIT D816V introduces resistance against imatinib

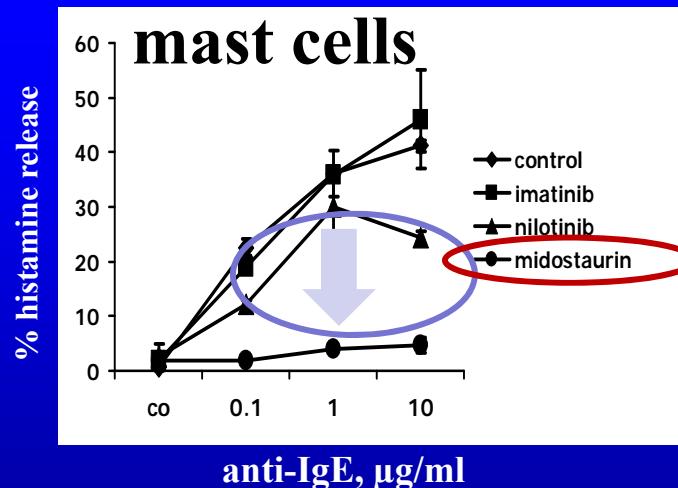
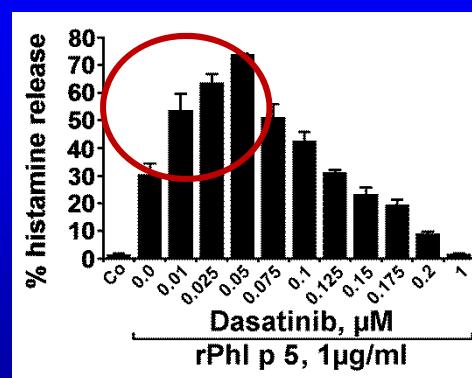
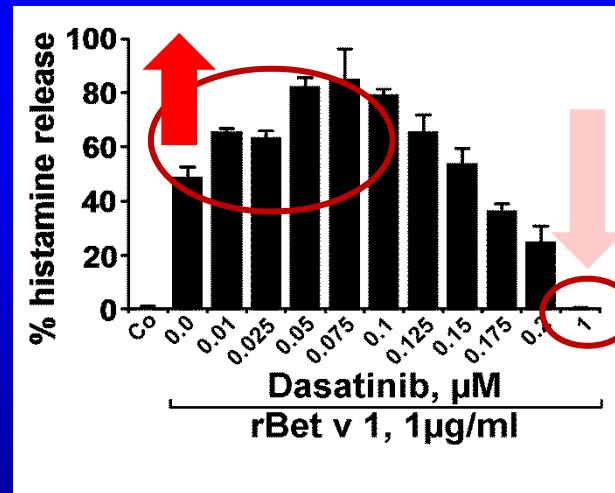
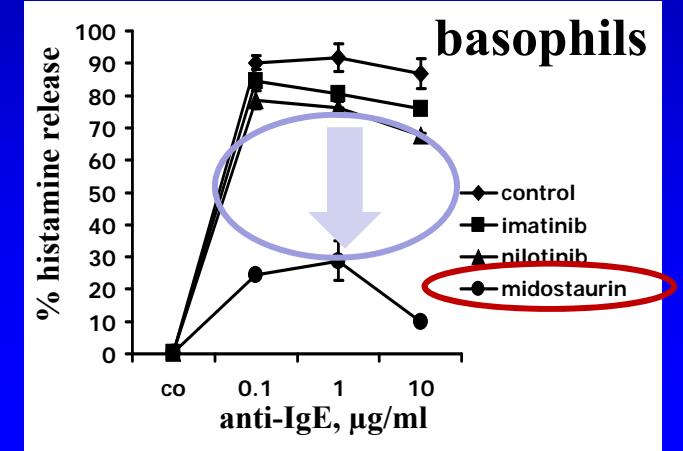
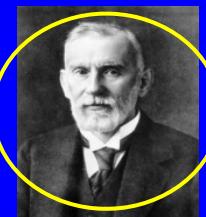
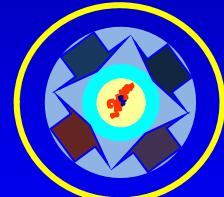
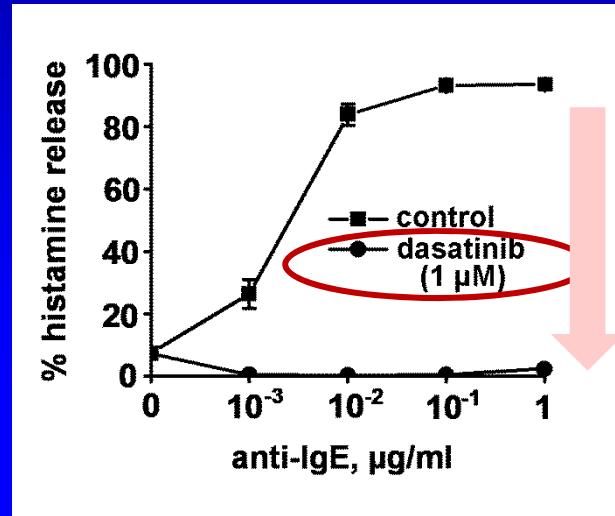


The Magic Bullets and Limitations

Gleixner et al, Blood 2006



# Effects of KIT TK inhibitors on mediator release in human mast cells and basophils

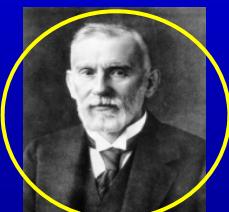


The Magic Bullets and Limitations



# Summary: TKI Effects on Mast Cells and Basophils relevant to Mastocytosis

1. **Imatinib** and most other TKI: show no relevant (beneficial) effects on KIT D816V+ Mast Cells
2. **Dasatinib:**
  - a) Half Life too short to inhibit growth of MC
  - b) Very low concentrations even promote IgE-dependent histamine release (clinically relevant?)
3. **Midostaurin (PKC412):**
  - a) Inhibits the growth of KIT D816V+ Mast Cells
  - b) Inhibits IgE-dependent histamine release !
  - c) Currently tested in clinical trials
  - d) Will hopefully be approved for use in mast cell disorders in the future

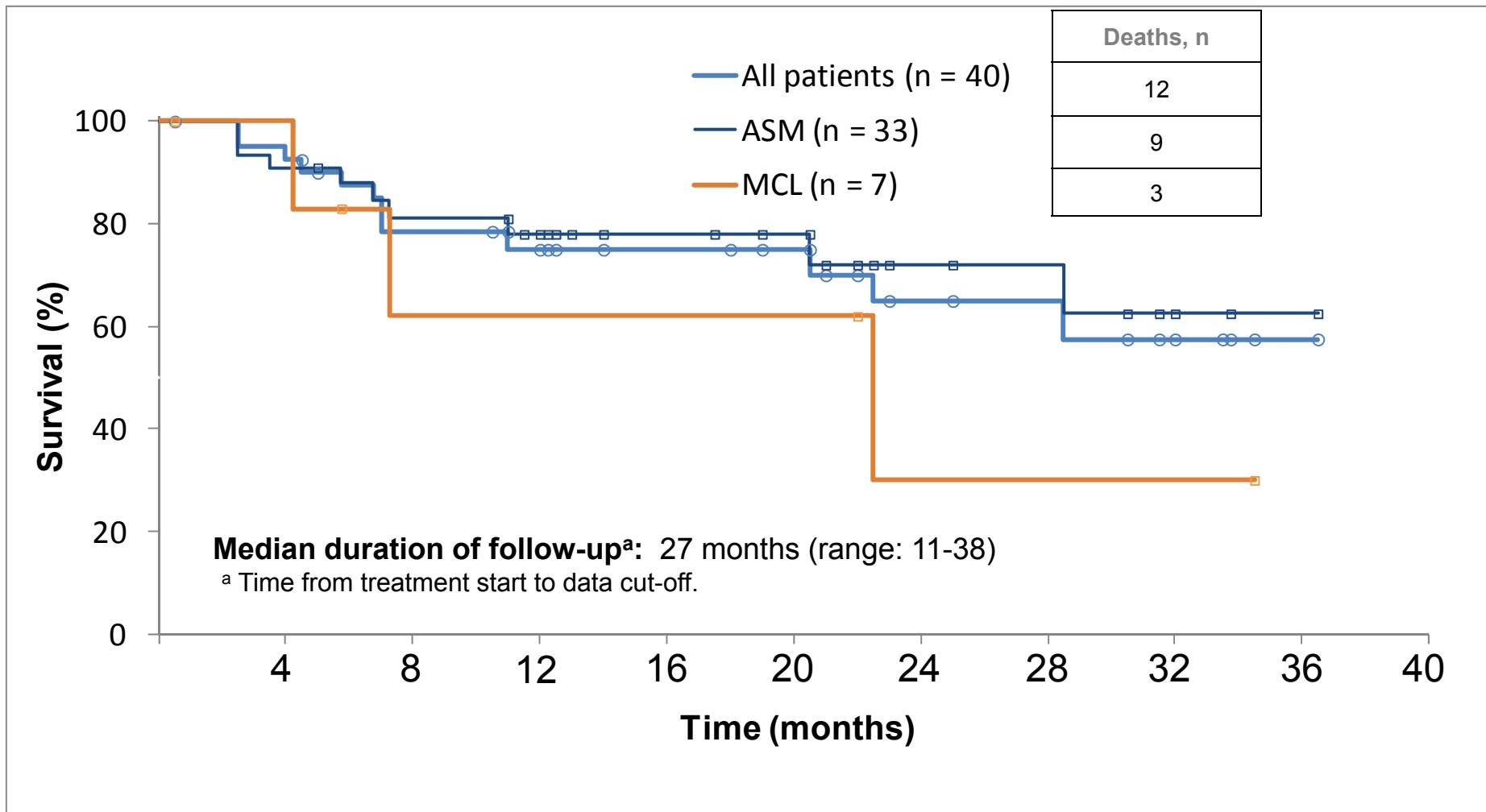




# Interim Analysis of the Global CPKC412D2201 Phase II Trial (Gotlib et al) – ASH 2012

- Midostaurin (2x100 mg per day orally) demonstrates a high rate of durable responses in advanced SM (single-arm Phase II Trial)
  - ORR 60% (> 50% of patients reached a major response)
  - ORR similar regardless of *KIT* D816V mutation status and # of prior therapies (IFN, 2CdA, imatinib, dasatinib, HU, ARA-C, others)
  - Reduction of serum tryptase levels and/or BM mast cell burden in ≈40% of patients indicates a potential for disease modification
  - > 50% response rate in MCL (historically has a dire prognosis)
- Median duration of response and median overall survival have not been reached with a median follow-up of 27 months
- Good tolerability with a safety profile consistent with prior studies
- The high response rate in Stage 1 permitted enrollment in the extension phase. Full accrual of 116 patients is now completed

# Overall Survival in ASM/MCL



Gotlib et al, ASH 2012

Kaplan-Meier Estimate for Overall Survival	Median
ASM	Not reached
MCL	22.6 months

# Treatment of Mastocytosis: Cytoreductive Drugs



**ISM (>80%)**

**NO cytoreductive treatment** (exception: severe osteopenia with risk of pathologic fracture, life threatening recurrent shock ?)

**SSM**

**Wait and watch** in most cases. In select cases (with progression) consider IFN $\alpha$ , **2CdA** or targeted drugs

**SM-AHNMD**

**Treat AHNMD as if no SM is present, and SM as if no AHNMD had been diagnosed (e.g. ASM-AHNMD !)**

**ASM with slow progression**

**IFN $\alpha$ +glucocorticoids, 2CdA**, in case of hypersplenism due to splenomegaly + MC infiltrates consider splenectomy (TKI in clinical trials, Imatinib only for rare KIT mutants)

**ASM with rapid progression**

**Polychemotherapy** with Fludarabine or 2CdA - in responding patients: **consider stem cell transplantation**

**Clinical Trials: PKC412 and other TKI**

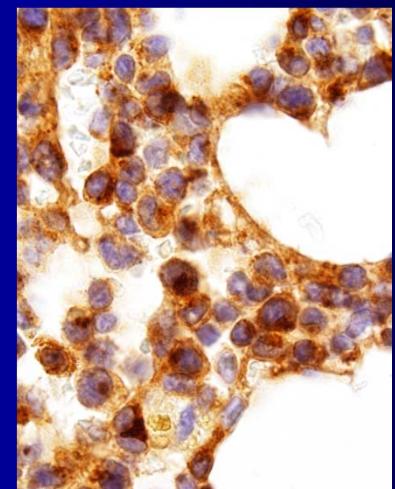
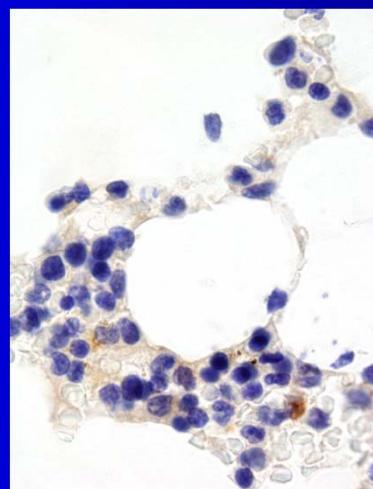
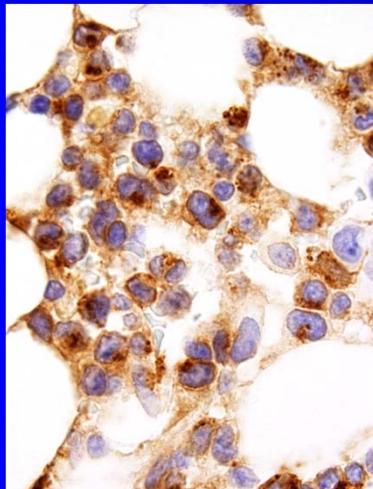
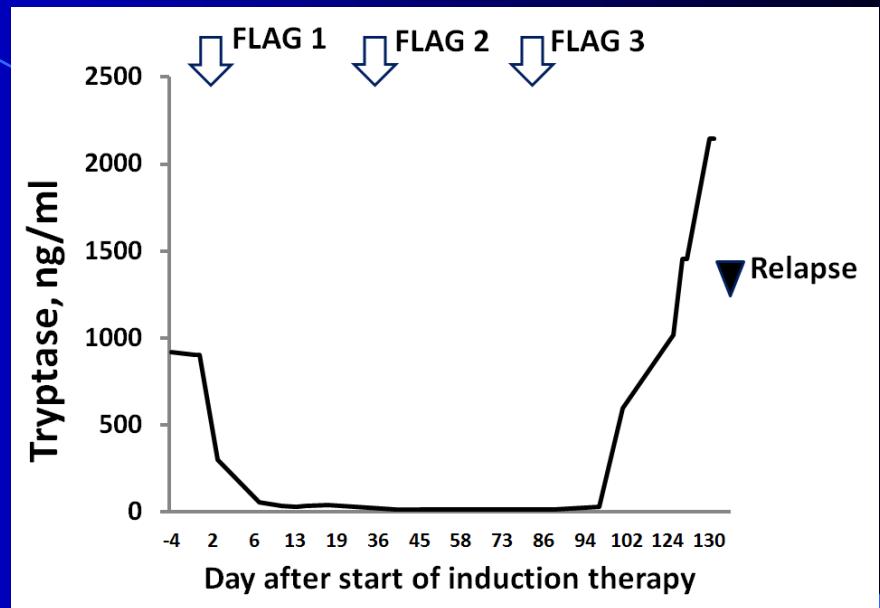
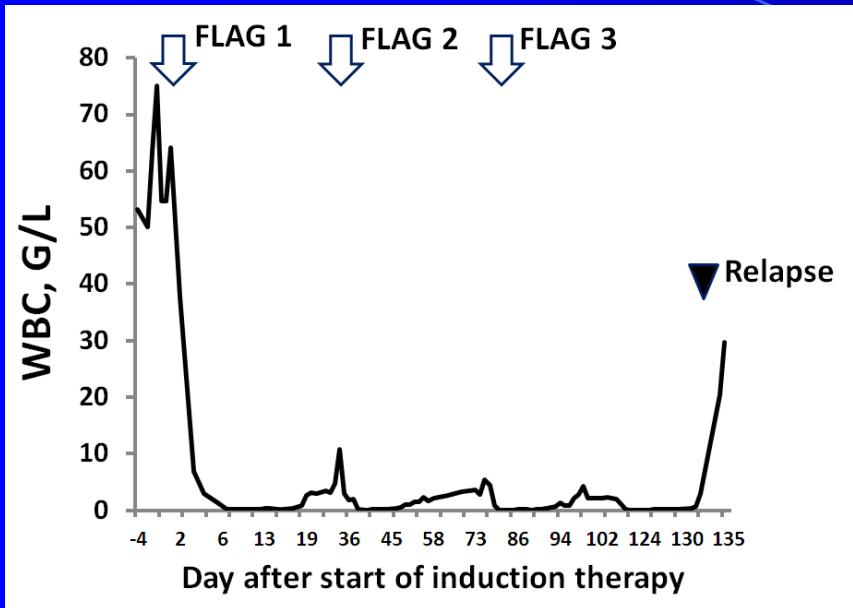
**MCL**

**Polychemotherapy** or 2CdA (IFN $\alpha$  or corticoids) - in responding patients **consider stem cell transplantation**

**Clinical Trials: PKC412 and other TKI**

In all categories, mediator-targeting drugs are given as adjunct to cytoreductive therapy

# Follow up in a Patient with Acute MCL

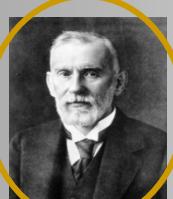


# Cytoreductive and Anti-Mediator-Type Drugs



## A: Cytoreductive Agents / Targeted Drugs

Interferon alpha



2CdA

TKI: PKC412, Dasatinib, Nilotinib

Target

progenitor cells

SCF synthesis

unknown

KIT

## B: Anti-Mediator-Type Drugs

Histamine Receptor Blockers

Glucocorticosteroids

Immunotherapy, anti-IgE, anti-IgER

Bisphosphonates

PKC412 (Dasatinib)

Target

histamine R1/R2

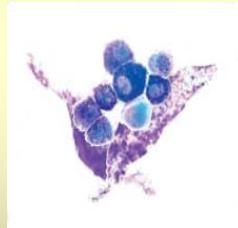
mediator release

specific IgE

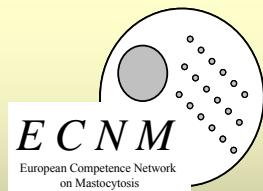
unknown

mediator release

**Thank you for  
your Attention**



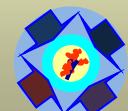
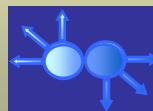
**Peter Valent and Team**



Ludwig Boltzmann Cluster  
Oncology



Der Wissenschaftsfonds.

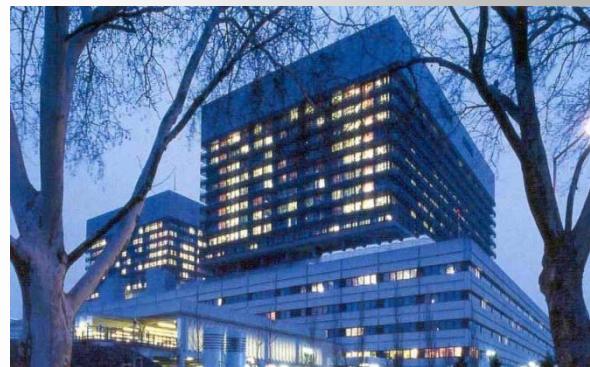


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Herrmann H.  
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Stefanzl G.  
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Hadzijusufovic E.  
Hauswirth A.W.  
Böhm A.

Herndlhofer S.  
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Shnawa P.  
Eisenwort G.  
Berger D.  
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**www.ecnm.net**



# Treatment of Patients with Mastocytosis

## A: Treatment of Mediator-Related Symptoms:

- Drugs Targeting**
  - Mediator Production
  - Mediator Release
  - Mediator Effects

## B: Cytoreductive Therapy (**SM+C-Finding/s**)

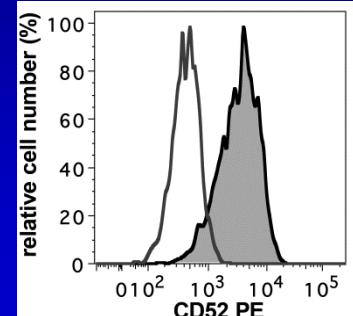
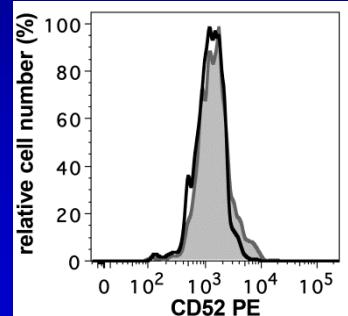
- Drugs Targeting**
  - Neoplastic Stem Cells
  - Progenitor Cells (IFN $\alpha$ )
  - Mast Cells
  - Specific Molecular Targets





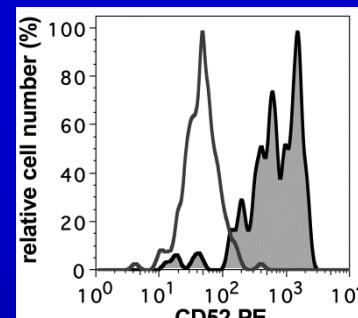
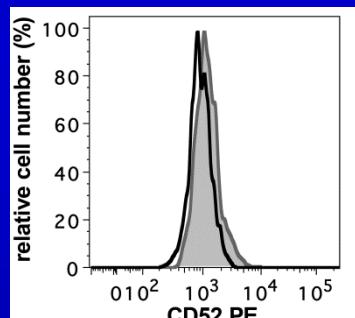
# Expression of CD52 on Neoplastic Mast Cells in Aggressive SM (ASM)

ISM



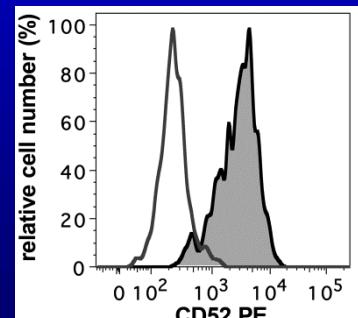
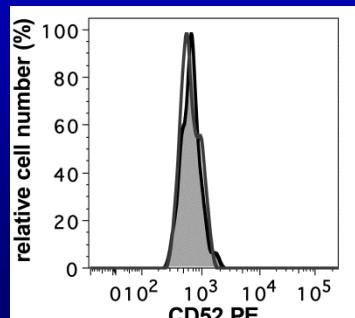
ASM

ISM



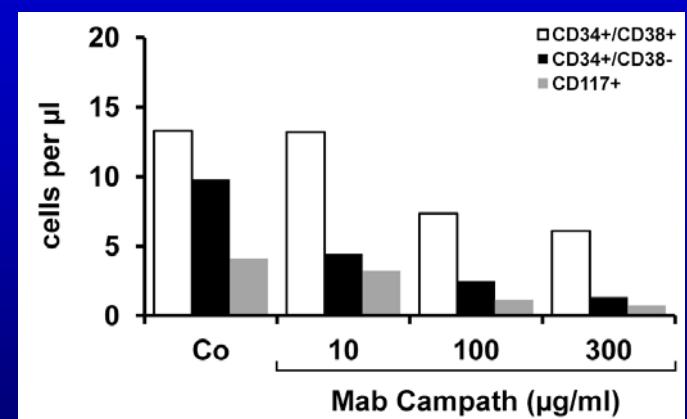
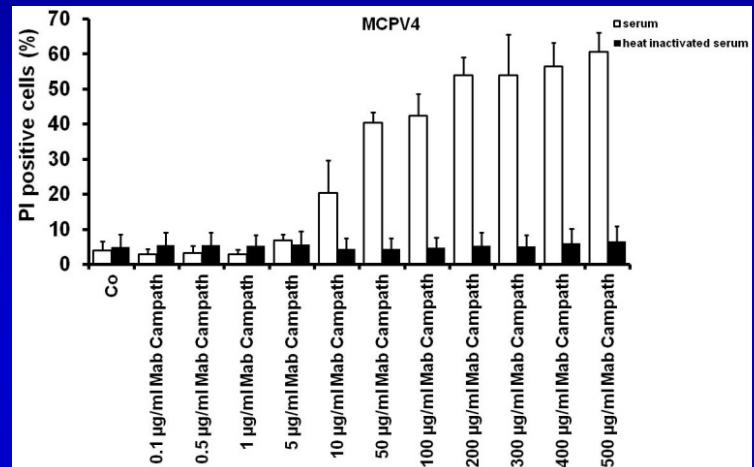
ASM

ISM



ASM

MCPV



MCL

# Established and Novel Diagnostic and Prognostic Markers in SM



## Diagnostic Markers

- Tryptase
- KIT
- Chymase
- CD2
- CD25
- CD68R
- HDC
- CD30 ?

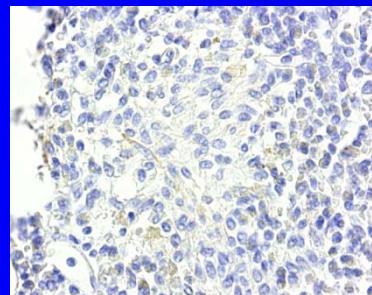
## Prognostic Markers

- CD30 ?
- Btk ?
- Lyn ?
- CD2 ? (low levels in MCL)
- CD52 ? and CD123 ?
- IL-13 SNP ?
- IL-4R SNP ?

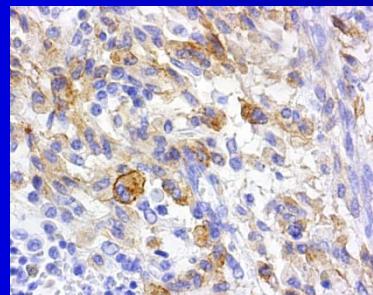


# Expression of CD30 in MC in different SM variants: A new grading marker in SM ?

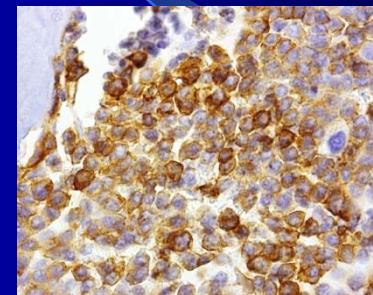
**ISM  
(CD30)**



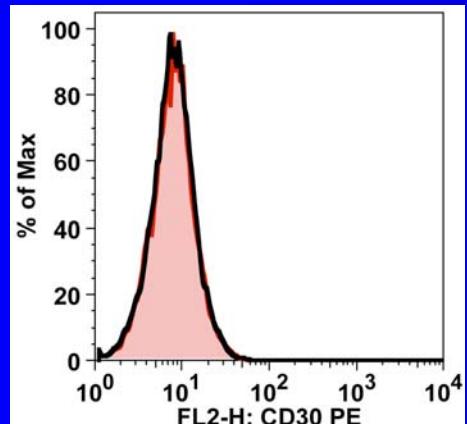
**SSM  
(CD30)**



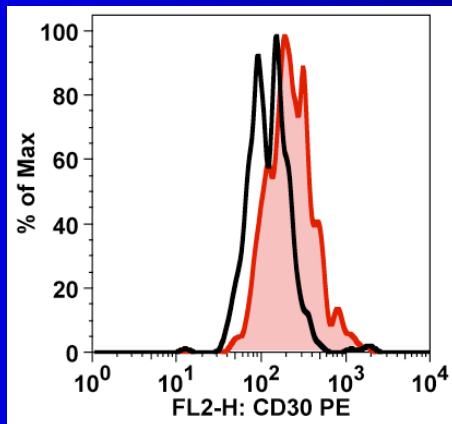
**MCL  
(CD30)**



IHC



normal BM MC



Patient with ASM

**SM, Systemic Mastocytosis**

**ISM, Indolent SM**

**SSM, Smouldering SM**

**ASM, Aggressive SM**

**MCL, Mast Cell Leukemia**

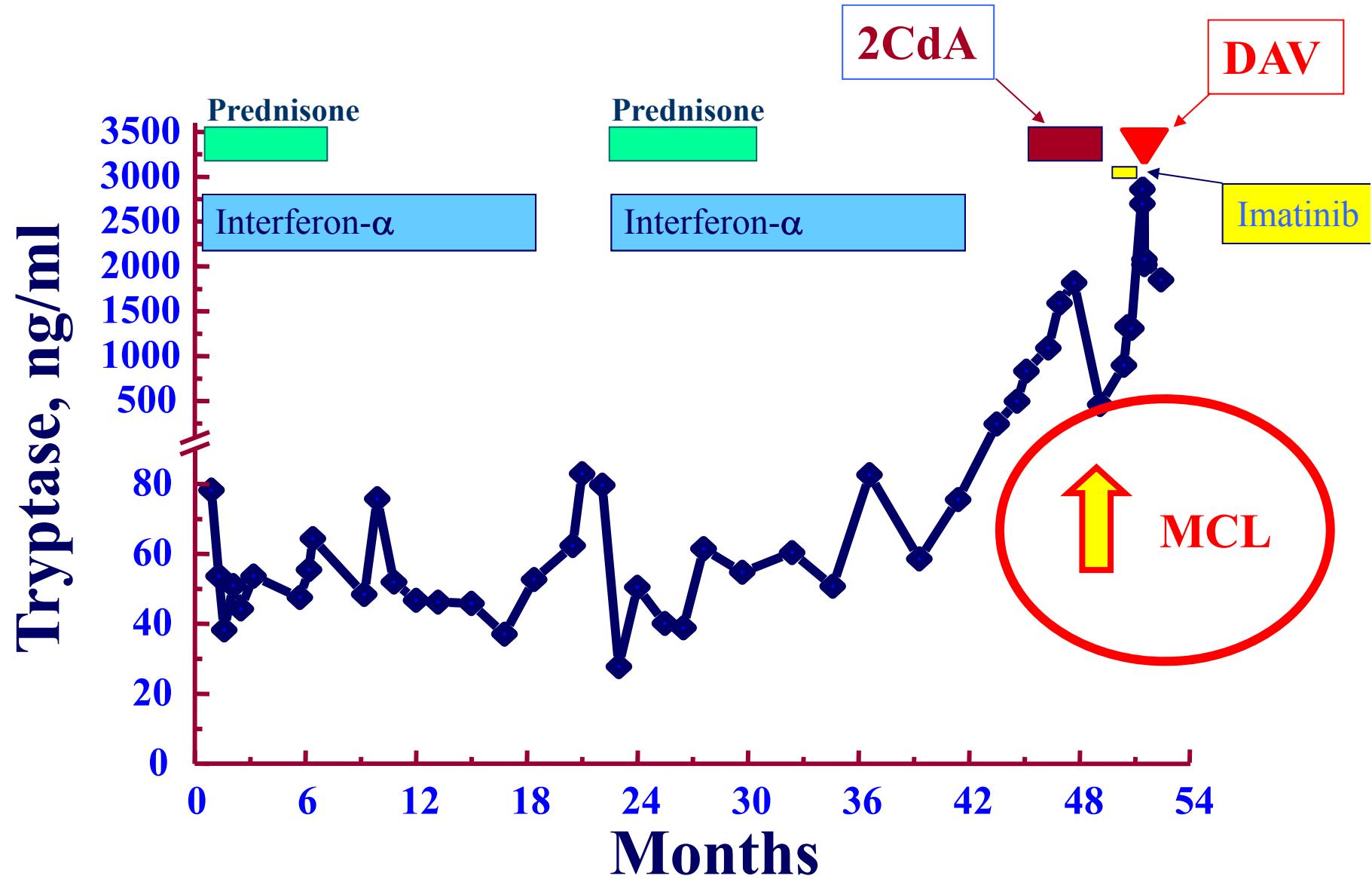
**IHC, Immunohistochemistry**

**BM, Bone Marrow**

**MC, Mast Cells**

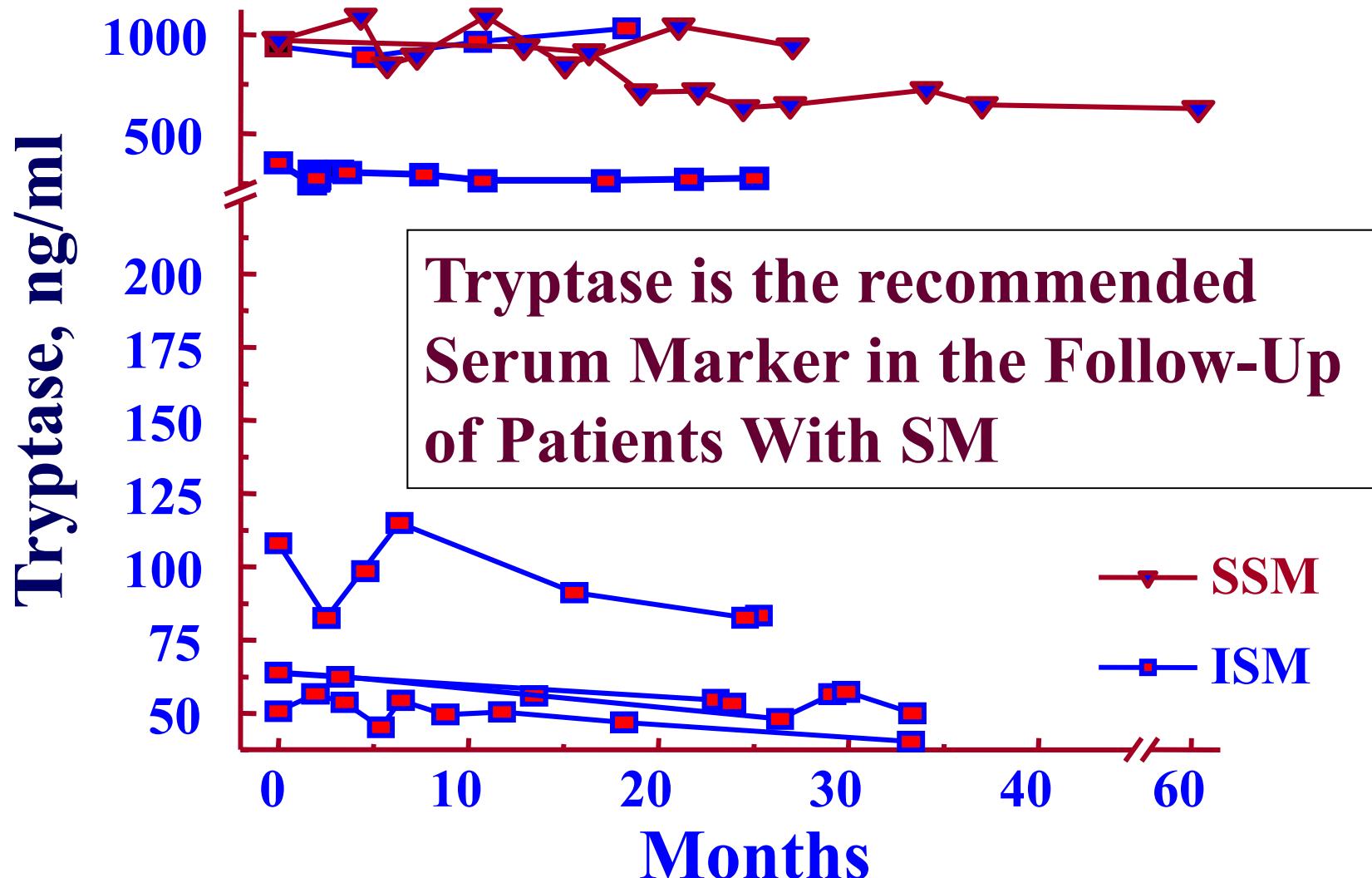


# Follow up in a Patient with ASM





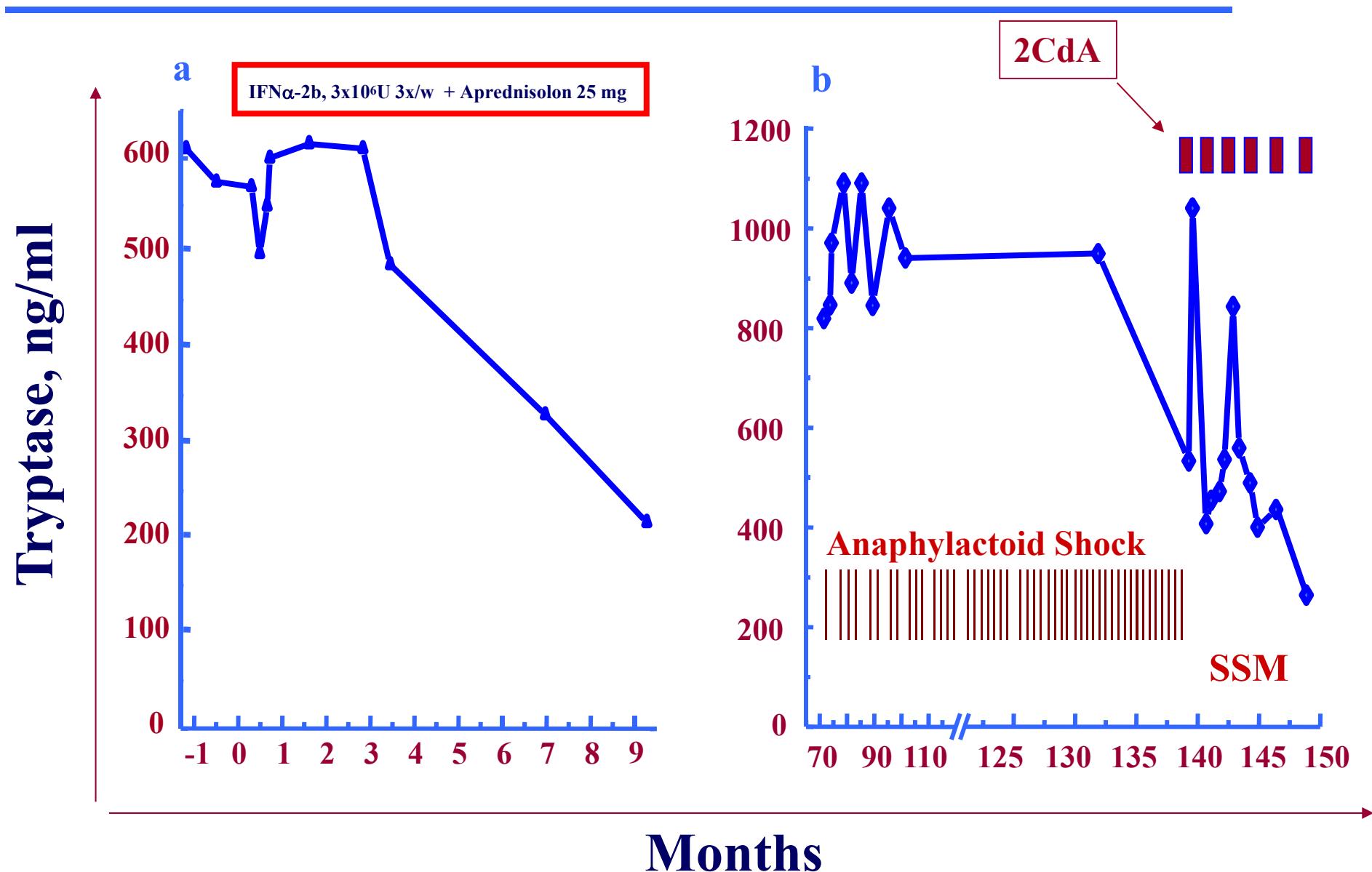
# Follow up in Patients with ISM or SSM





# Follow Up in Patients with ASM/SSM

a. ASM-CMMI treated with IFN $\alpha$ -2b; b. SSM reated with Cladribine





## Phase II Trial ASM/MCL - Stanford Group Jason Gotlib and Colleagues

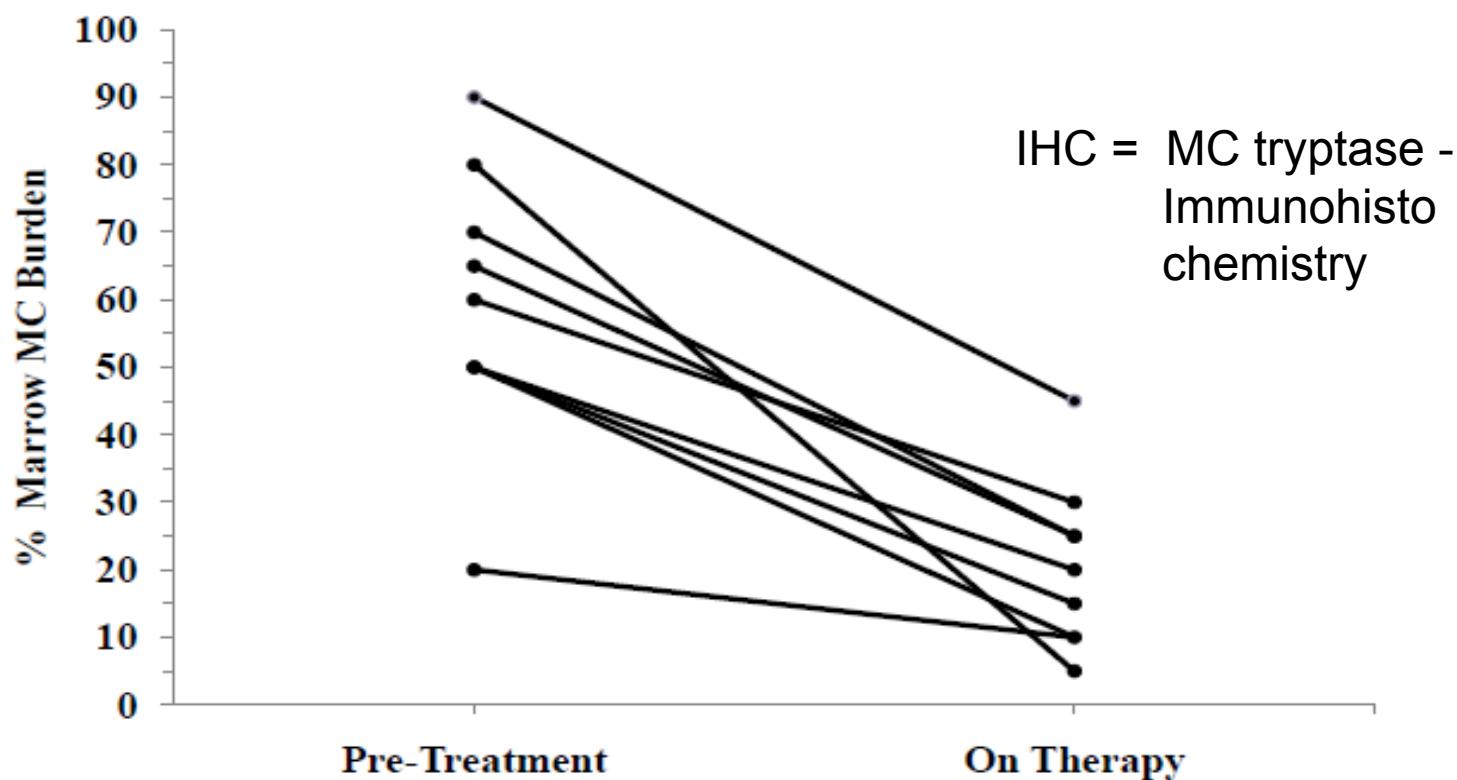
- Midostaurin 100 mg po bid on 28-day continuous cycles for up to 12 cycles
- Formal response evaluated after 2 cycles; partial or major response per consensus criteria permit ongoing treatment
- Extension treatment beyond 12 cycles for patients with response and no  $\geq$  grade 3 toxicity related to midostaurin
- Dose reduction to 50 mg bid for  $\geq$  grade 3 hematologic or non-hematologic toxicity

Gotlib et al, ASH 2010



# Histopathological Assessment

>50% Reduction in  
Marrow MC Burden by IHC (n=10)





# Efficacy (Best Response)\*

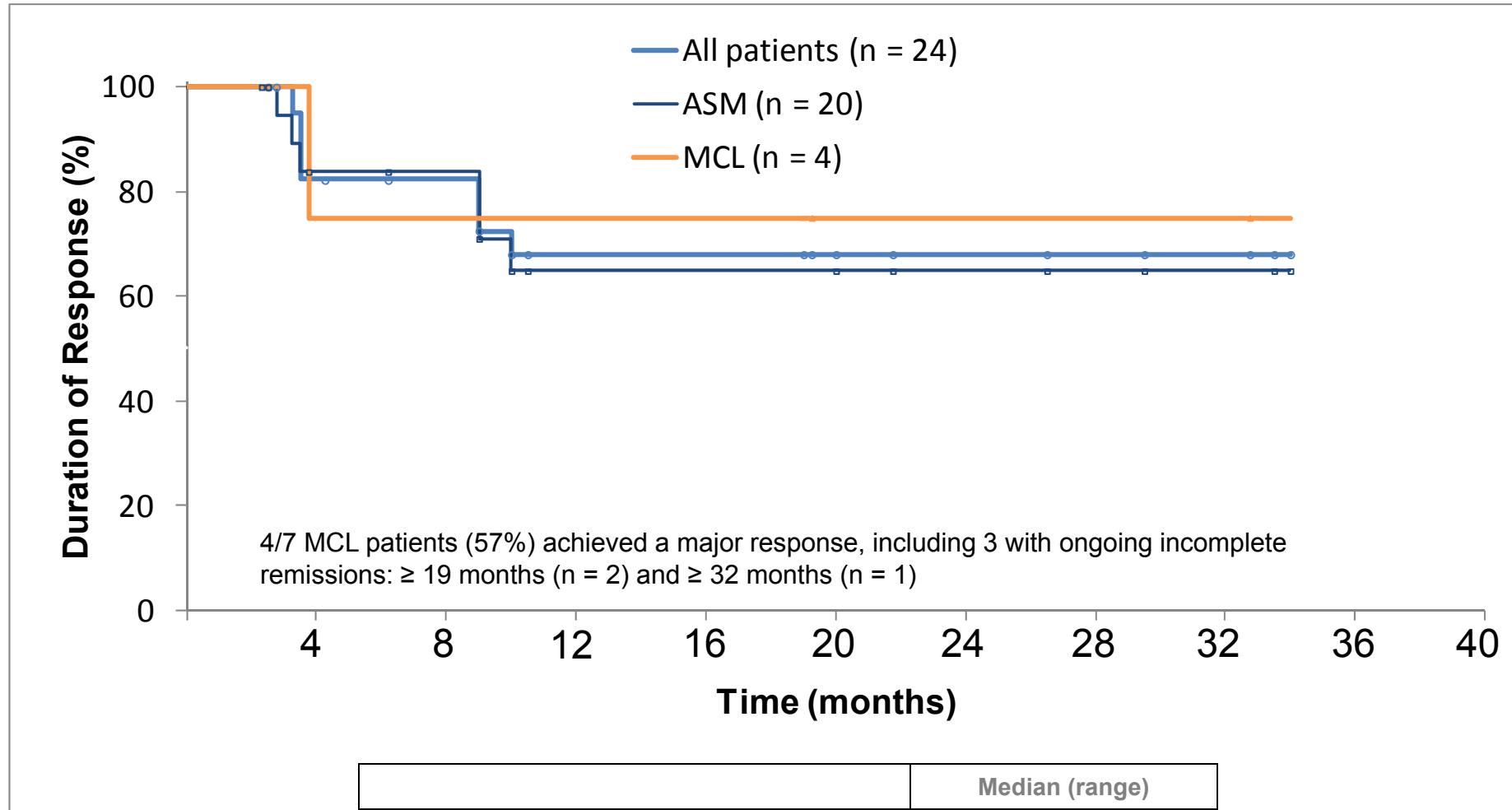
	n	%
Evaluable	26	100
<b>Major Response (MR)</b>	<b>10</b>	<b>38</b>
<i>Incomplete</i>	6	23
<i>Pure Clinical</i>	4	15
<b>Partial Response (PR)</b>	<b>8</b>	<b>31</b>
<i>Good (GPR)</i>	5	19
<i>Minor</i>	3	12
<b>Stable Disease (SD)</b>	<b>4</b>	<b>15</b>
<b>Progressive Disease (PD)</b>	<b>4</b>	<b>15</b>
<b>Overall Response Rate</b>		
MR + PR	18/26	<b>69</b>
MR + GPR	15/26	<b>57</b>

Gotlib et al, ASH 2010

\*Valent P, et al,  
Leuk Res 2003



# Duration of Hematologic Responses

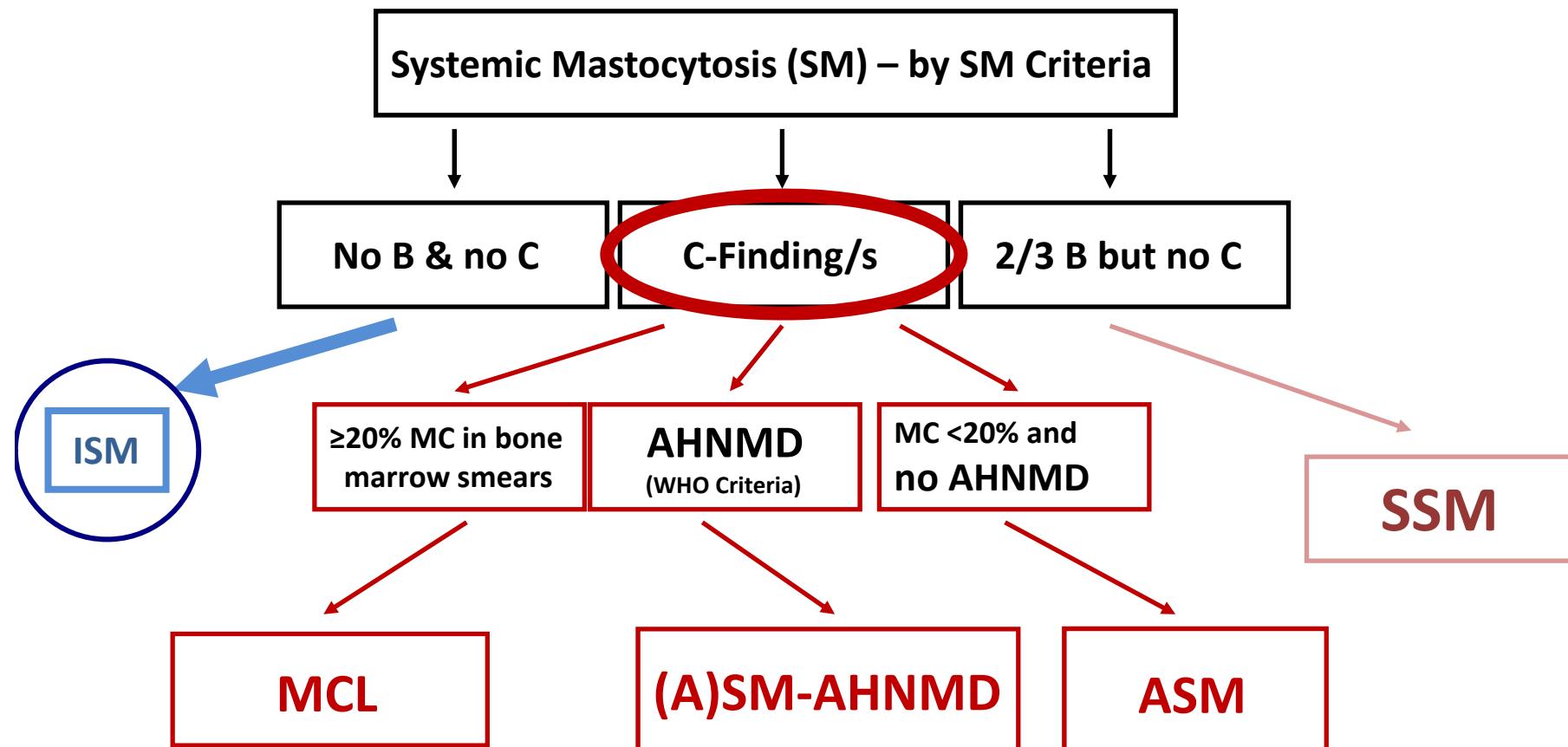


	Median (range)
Duration of exposure	12.7 months (1.9-35.7)
Duration of follow-up	26 months (12-36)
Kaplan-Meier estimate for duration of response	Not reached



# Diagnostic Algorithm in SM

(Patient Selection for Drug Therapy)



TAKE HOME MEMORIZER:

B-Finding: High Burden of Mast Cells  
C-Finding: C = Consider Cytoreduction



# C-Findings

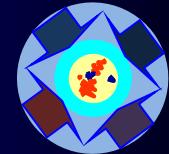
Findings resulting from organ destruction caused by local mast cell infiltration:

- Cytopenia(s)
- Liver involvement with ascites
- Huge osteolysis & pathologic fracture
- Malabsorption + hypalbuminemia
- Splenomegaly + hypersplenism

**TAKE HOME MEMORIZER:**

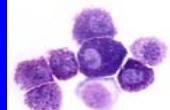
B-Finding: High Burden of Mast Cells  
C-Finding: C = Consider Cytotherapy

# Mast Cell Tryptase Levels in Healthy Subjects

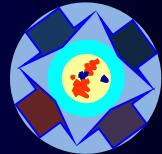


- Normal basal Serum Total Tryptase Level
- Company: Range: 0-11.4 ng/ml
- WW-ULN: 10.0 to 15.0 ng/ml depending on Lab
- Our Lab ( $n \approx 300$  healthy controls): 15.0 ng/ml
- What happens between 10.0 and 15.0 ng/ml ?

→ Case Report



# Case Report

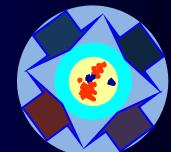


- 47 year old female patient
- Referred because of elevated tryptase from Allergy Ambulatory
- Tryptase 12.3 ng/ml, repeat: 12.9 ng/ml
- Case History: arterial hypertension; and she was told to have an allergy against penicillin ('confirmed' in the Allergy Ambulatory – but no test done)
- Allergy Tests all negative



# Case Report

- Reaction to penicillin about 12 years ago uncertain – not confirmed by lab test, no typical clinical symptoms (shortness of breath & headache, no rash/hypotension)
- Doctors at the Allergy Laboratory had based the Diagnosis Allergy on the Serum Tryptase Level & the Reaction to Penicillin
- Is it justified ? In several labs/studies such pts were excluded from 'normal population'!



# Cases 09/2009 – 06/2010 ‘Elevated’ Tryptase Levels\*

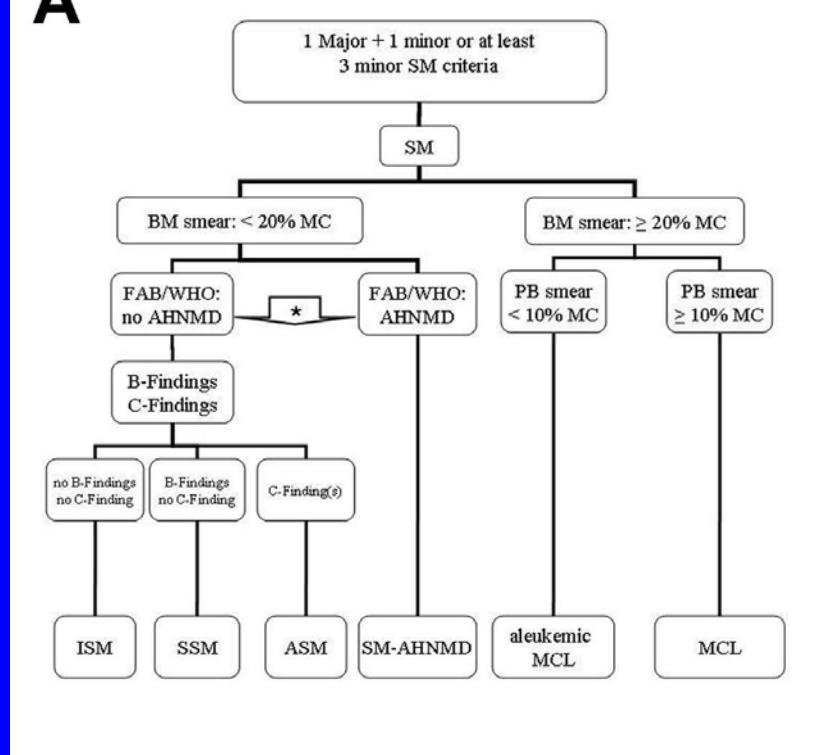
Case #	Tryptase ng/mL	Age yrs	Sex f/m	Bone Marrow BM	WBC G/L	Hb g/dL	PLT G/L	IgG/IgA IgM/IgE	LDH U/L	Crea mg/dL	Known Allergy	Lymph Nodes LN Spleen
#1	18.9	38	f	normal	7.7	12.5	275	normal	146	0.74	no	n.p.
#2	29.1	71	m	normal	5.6	13.3	196	normal	205	0.78	Clindamycin?	n.p.
#3	18.4	61	f	normal	4.3	12.2	285	normal	84	1.1	no (Cipro??)	n.p.
#4	12.9	47	f	n.y.d.	6.8	12.9	158	normal	267	0.9	Penicillin?	n.p.

\* In all 4 patients, the clinical symptoms leading to their referral to the Allergy Unit and then to our Department were atypical symptoms:

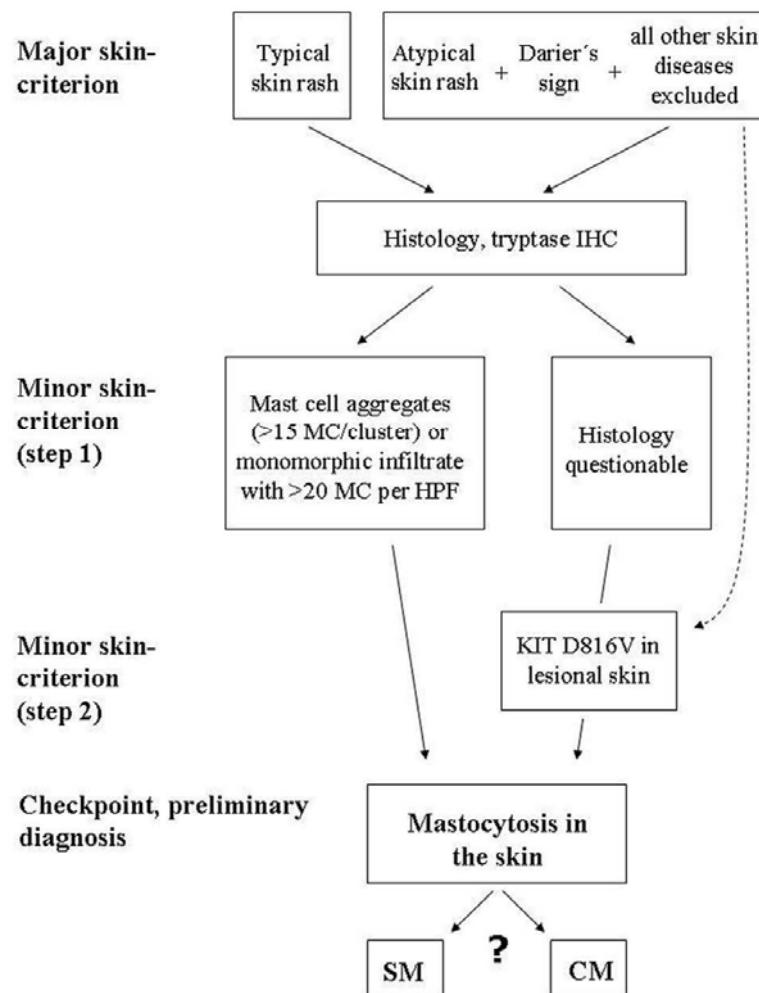
- #1: Headache + GI symptoms in case history
- #2: Exanthema after Clindamycin (allergy possible – not confirmed)
- #3: Suspected intolerance to Ciprofloxacin
- #4: Atypical non-confirmed Reaction to Penicillin

# 2005 Algorithms

**A**

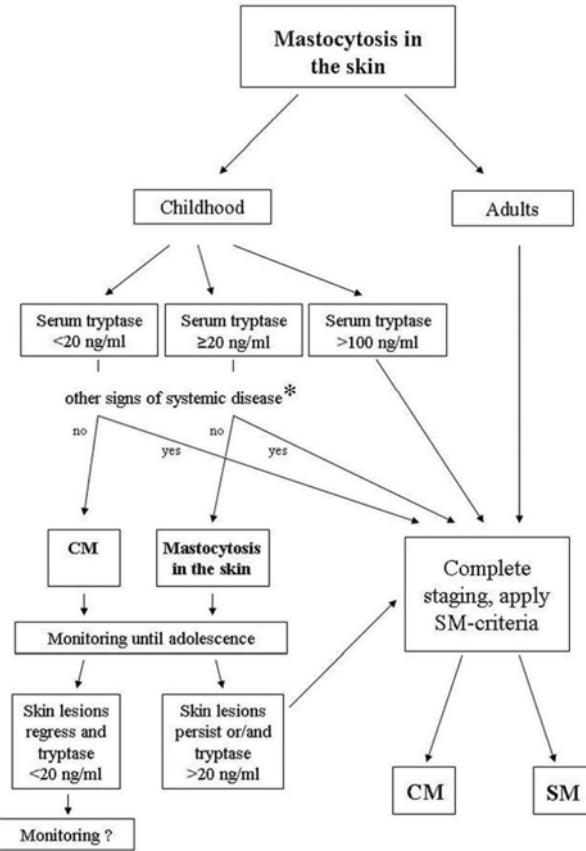


**B**

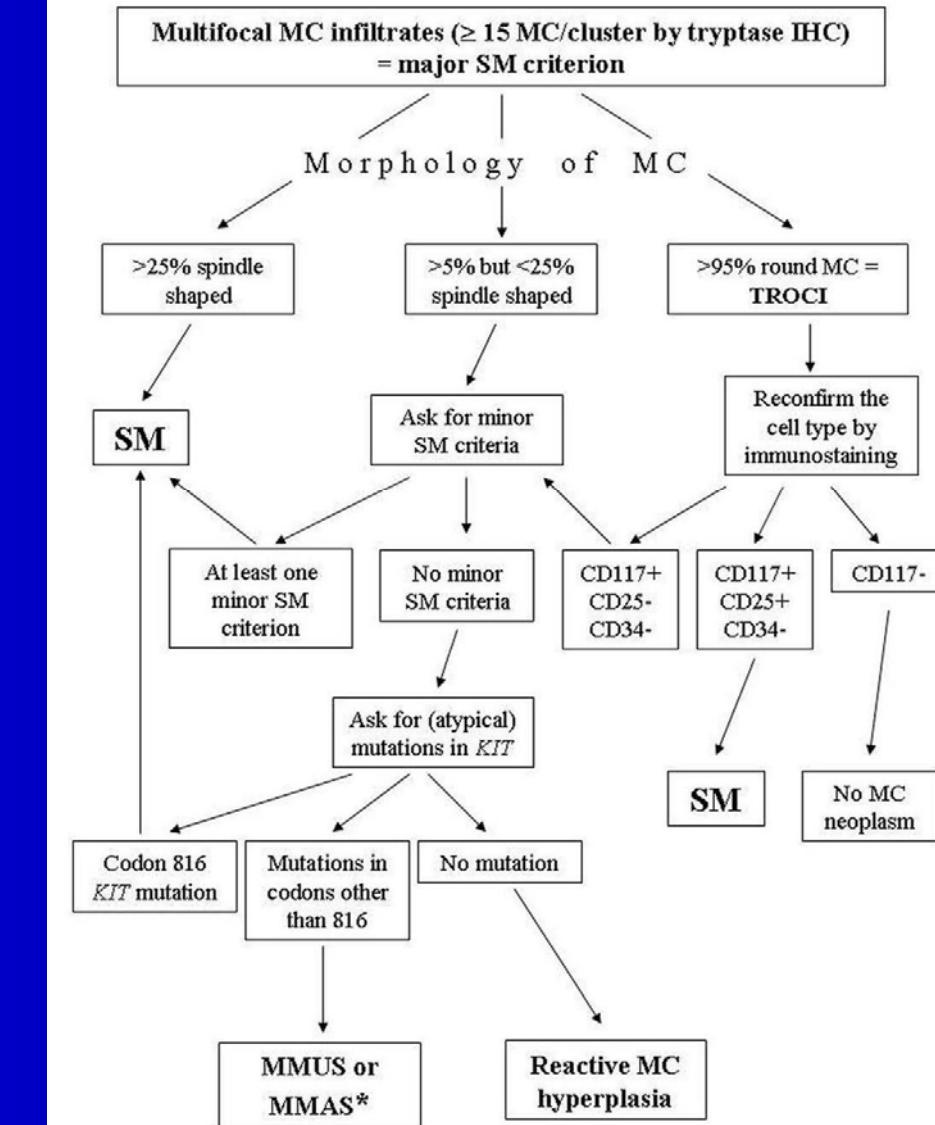


# 2005 Algorithms

**C**



**D**

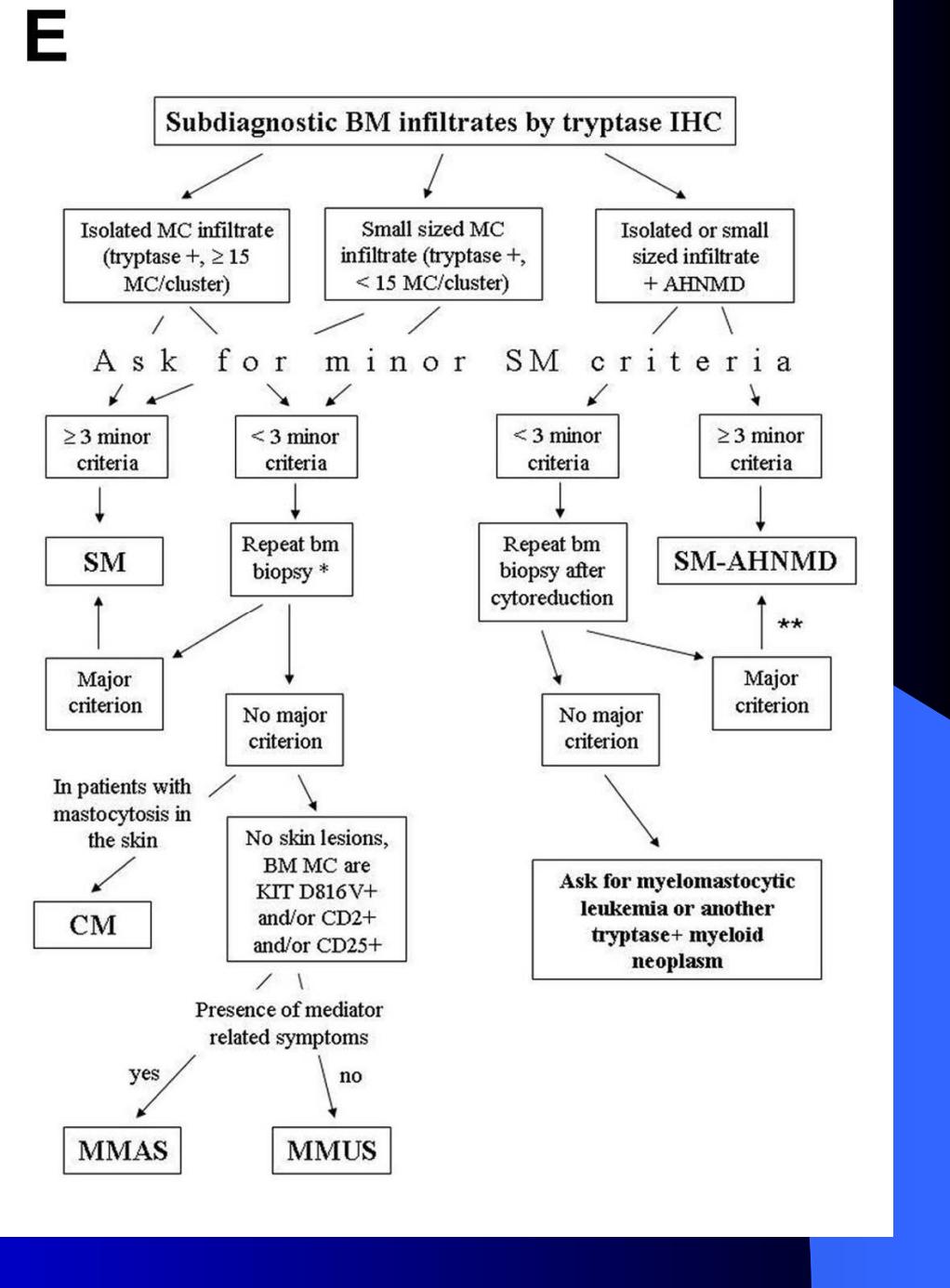


# 2005 Algorithms

## Grading of mediator-related symptoms

Grade	definition
0 = no symptoms	prophylaxis**, prophylaxis ± therapy
1 = mild, infrequent therapy	
2 = moderate	requires therapy, usually kept under control
3 = severe	suboptimal control with daily combination therapy
4 = SAE***	requires emergency therapy and hospitalization

- most frequent symptoms to be graded: headache,
- nausea, systemic hypotension / anaphylaxis.
- \*\*all patients with mastocytosis are advised to avoid precipitating factors and for most, prophylactic antihistamines (H1 and H2 antagonists)
- are recommended; \*\*\*the frequency of severe adverse events should be reported: A: <1/year; B: >1/year and <1/month; C: >1/month.





# Response Criteria in ASM/MCL

## I: Major Response:

**Complete resolution of at least one (= one or more) C-Finding(s)  
and no progression in other C-Findings**

- a) Complete remission = with disappearance of mast cell infiltrates in affected organs, decrease of serum tryptase levels to < 20 ng/ml, and disappearance of SM-associated organomegaly
- b) Incomplete remission = with decrease in mast cell infiltrates in affected organs and/or substantial decrease of serum tryptase level and/or visible regression of organomegaly
- c) Pure clinical response = without decrease in mast cell infiltrates, without decrease in tryptase levels, and without regression of organomegaly

## II: Partial Response:

**Incomplete regression of one or more C-Finding(s)\* without complete regression and without progress in other C-Findings**

- a) Good partial response: > 50% regression
- b) Minor response: ≤ 50% regression

## III: No Response:

**C-Finding(s) are persistent or are progressive\*\***

- a) Stable disease: C-Finding-parameters show constant range
- b) Progressive disease: one or more C-Finding(s) show progression

\* with or without decrease in mast cell infiltrates, serum tryptase levels, and organomegaly

\*\* in case of progressive C-Findings and documented response in other C-Finding(s),  
the final diagnosis is still: progressive disease



# Grading of constitutional and mediator-related symptoms in patients with SM (**SM<sub>SY</sub>**)

Grade	Definition
0 = no symptoms	prophylaxis**, no specific therapy required (!)
1 = mild, infrequent	prophylaxis ± as needed therapy
2 = moderate	requires therapy, can usually be kept under control
3 = severe	suboptimal or unsatisfactory control with daily and/or combination therapy
4 = severe event*	requires emergency therapy and hospitalization

**Most frequent symptoms to be graded:  
headache, nausea, systemic hypotension / anaphylaxis**

\*The frequency of severe adverse events should also be reported:

**A: <1/year; B: >1/year and <1/month; C: >1/month**



# Response Criteria for Mediator-related Symptoms in SM<sub>SY</sub>

## Response

## Definition

**Complete Regression (CR)**

**all symptoms completely resolved and not observed again during 12 months after therapy**

- **Continuous CR (CCR)**

**no further symptoms after 2 years\*\***

**Major Regression (MR)**

**improvement of symptoms by >50% or/and decrease in frequency of severe (grade 4) events from B to A or from C to B**

**Partial Regression (PR)**

**improvement to 10-50% or/and minor decrease in frequency of severe events (less than defined for the MR group – see above)**

**No Regression (NR)**

**<10% improvement and no decrease in frequency of severe events**

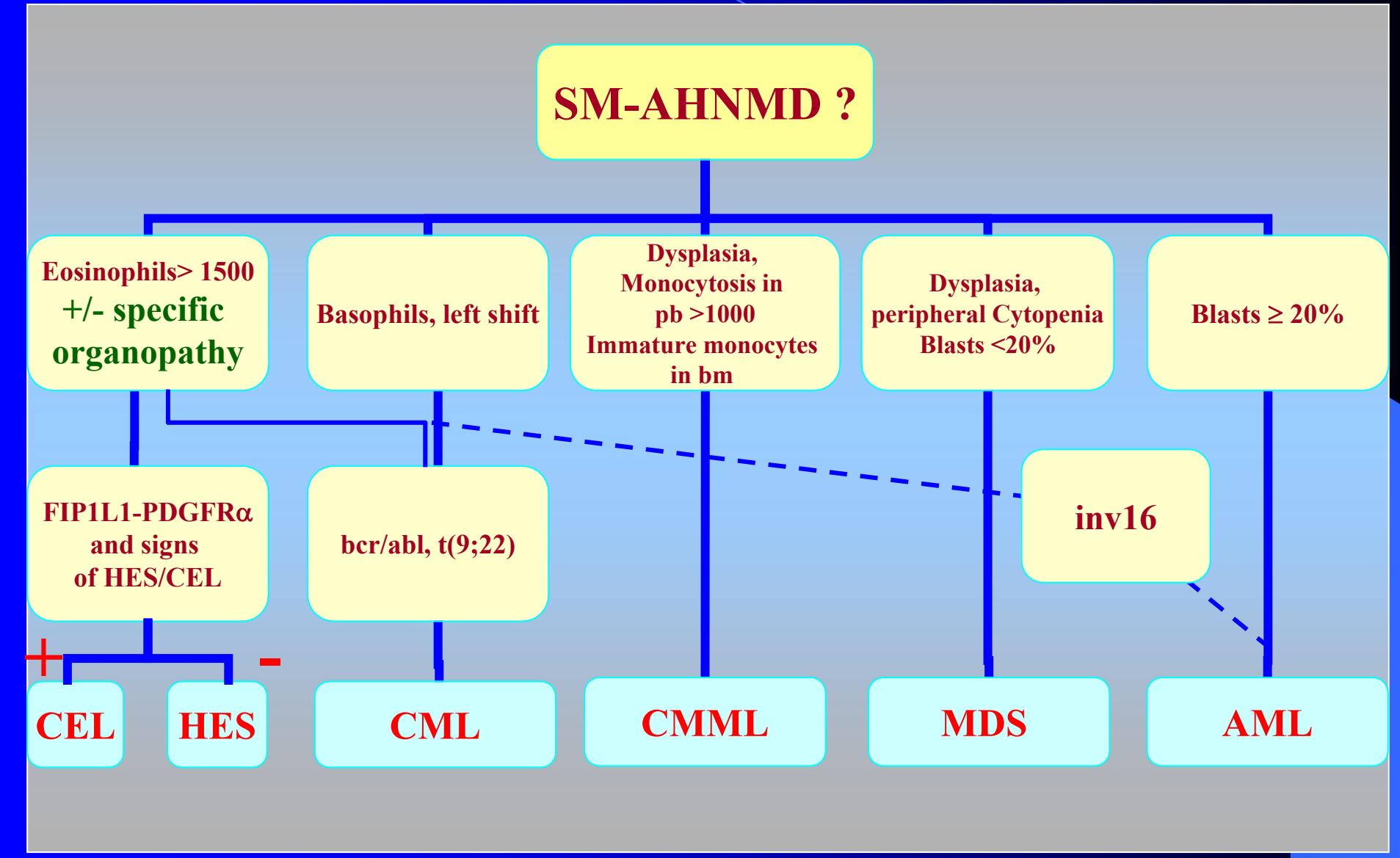


# SUSPECTED AHNMD IN SM

## RECOMMENDATIONS:

- SCREEN FOR & STAGE THE NON-MAST CELL NEOPLASM AS IF NO SM WAS DIAGNOSED
- APPLY WHO CRITERIA !
- SCREEN FOR (POTENTIAL) DRUG TARGETS
- ASK WHETHER KIT D816V IS EXPRESSED IN NEOPLASTIC (SM- AND AHNMD-) CELLS
- DETERMINE THE SUBTYPE OF THE SM-COMPONENT (e.g. ISM-AHNMD versus ASM-AHNMD)
- REFER THE PATIENT TO A HEMATOLOGY CENTER

# Recommended Diagnostic Procedures in suspected SM-AHNMD



# HES & CEL + / - SM by WHO criteria



- **A: Start → Algorithm:**
  - a) **SM (SM criteria fulfilled) + eosinophilia (eosinophils >1,500/ $\mu$ L) = **SM-eo (prediagnostic !)****
  - b) **HES or CEL (WHO criteria fulfilled) + MC  $\uparrow$**
- **B: Final Diagnosis (BY CRITERIA):**
  - **SM (eo  $\uparrow$ ) (define SM subvariant !) rare**
  - **SM-HES (define SM subvariant !) extremely rare**
  - **SM-CEL (define SM subvariant !) very rare**
  - **HES rare**
  - **CEL rare**