Mastocytosis

Olivier Hermine MD, PhD

Hematology Department, Necker Hospital

Centre National de référence des mastocytoses, Necker Hospital

INSERM U1163 CNRS ERL 8654

Institut Imagine, Necker Hospital

Paris, France

Disclosures

- AB science Co Founder, Consultant, Stock Holder, Research grants

- Novartis Research grants
- Celgene research grants

Definitions and Classifications

Mastocytosis

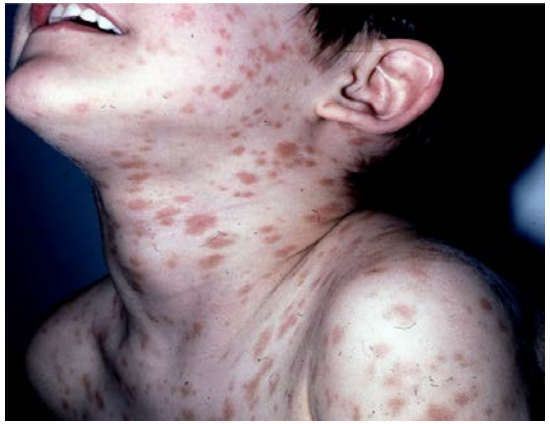
Definition

- Mast cell accumulation in various organs (Skin, GI tract, Liver, Bone and Bone Marrow, etc)

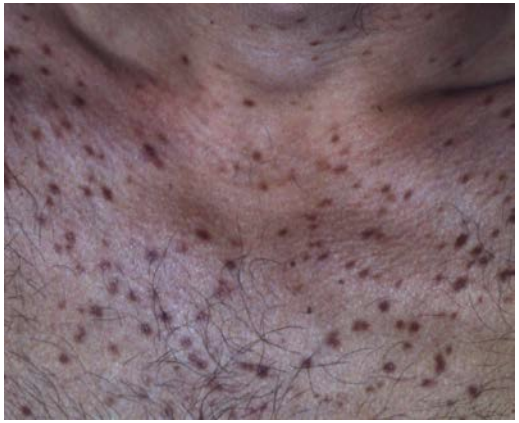
-Myeloproliferative disorder; Aggressive vs indolent disease

- Association with hematological disorders

- Clinical heterogeneity (Infiltration vs Mediators release)

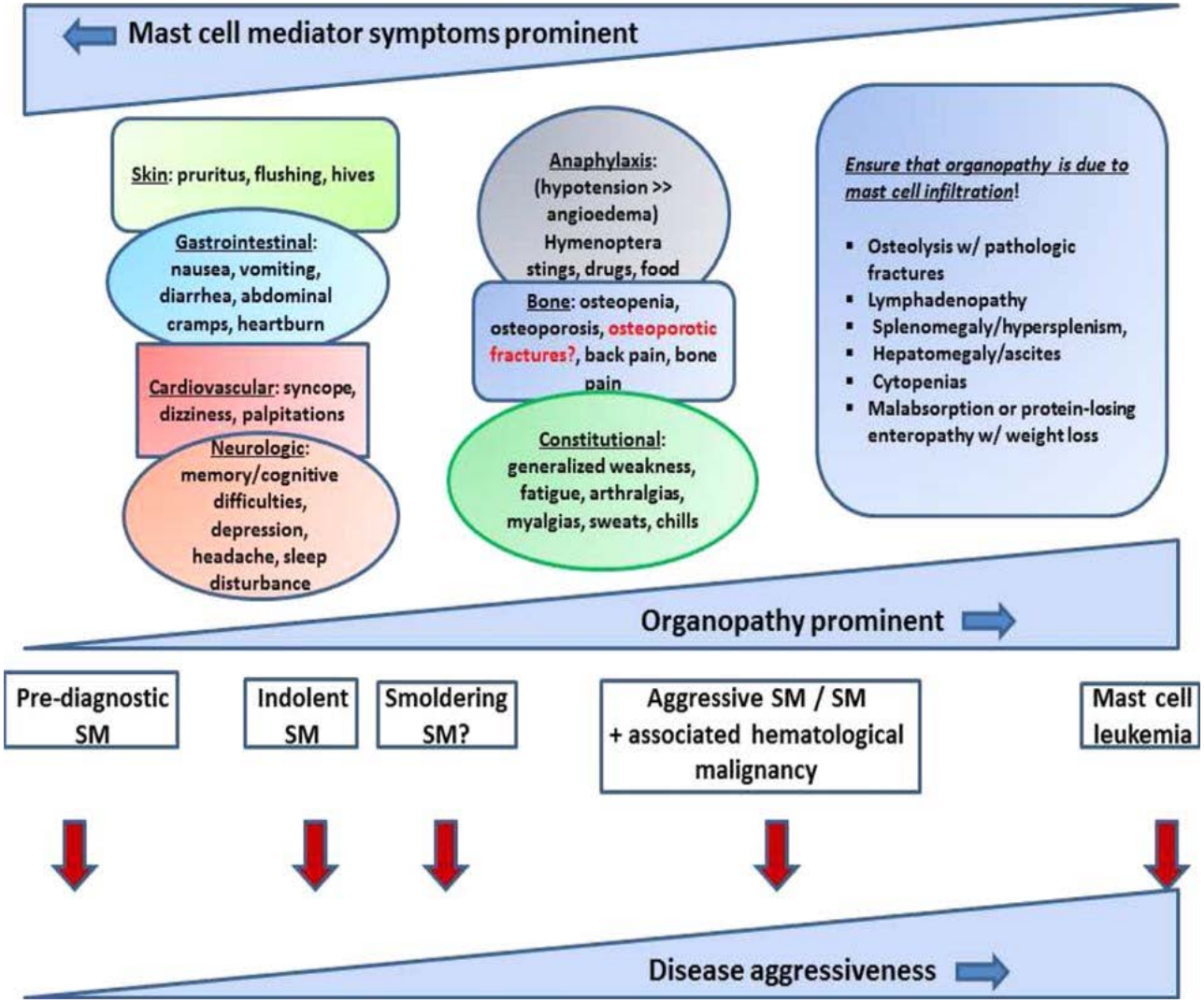


Children	**Adult Young vs Ederly**
<2 years	Adult age onset
Frequent regression	Chronic disease
Reactive disease ?	No regression
	Clonal disease



Mast cell Leukemia and Sarcoma :
Rare, Rapid Fatal outcome

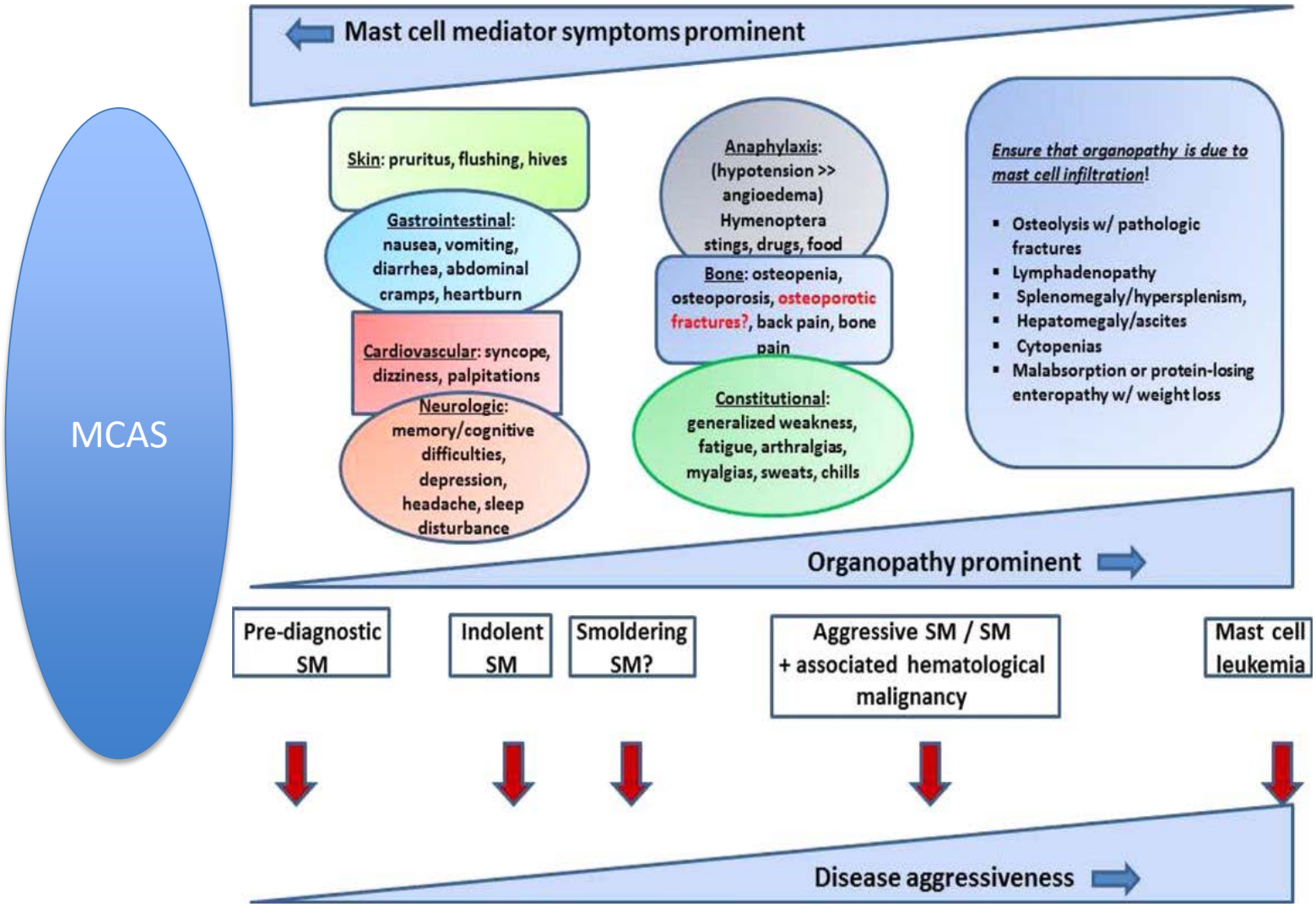
Mastocytosis : Spectrum of the disease



Systemic mastocytosis in adults: 2015 update on diagnosis, risk stratification, and management

Animesh Pardanani[1,2]*

Mastocytosis : Spectrum of the disease



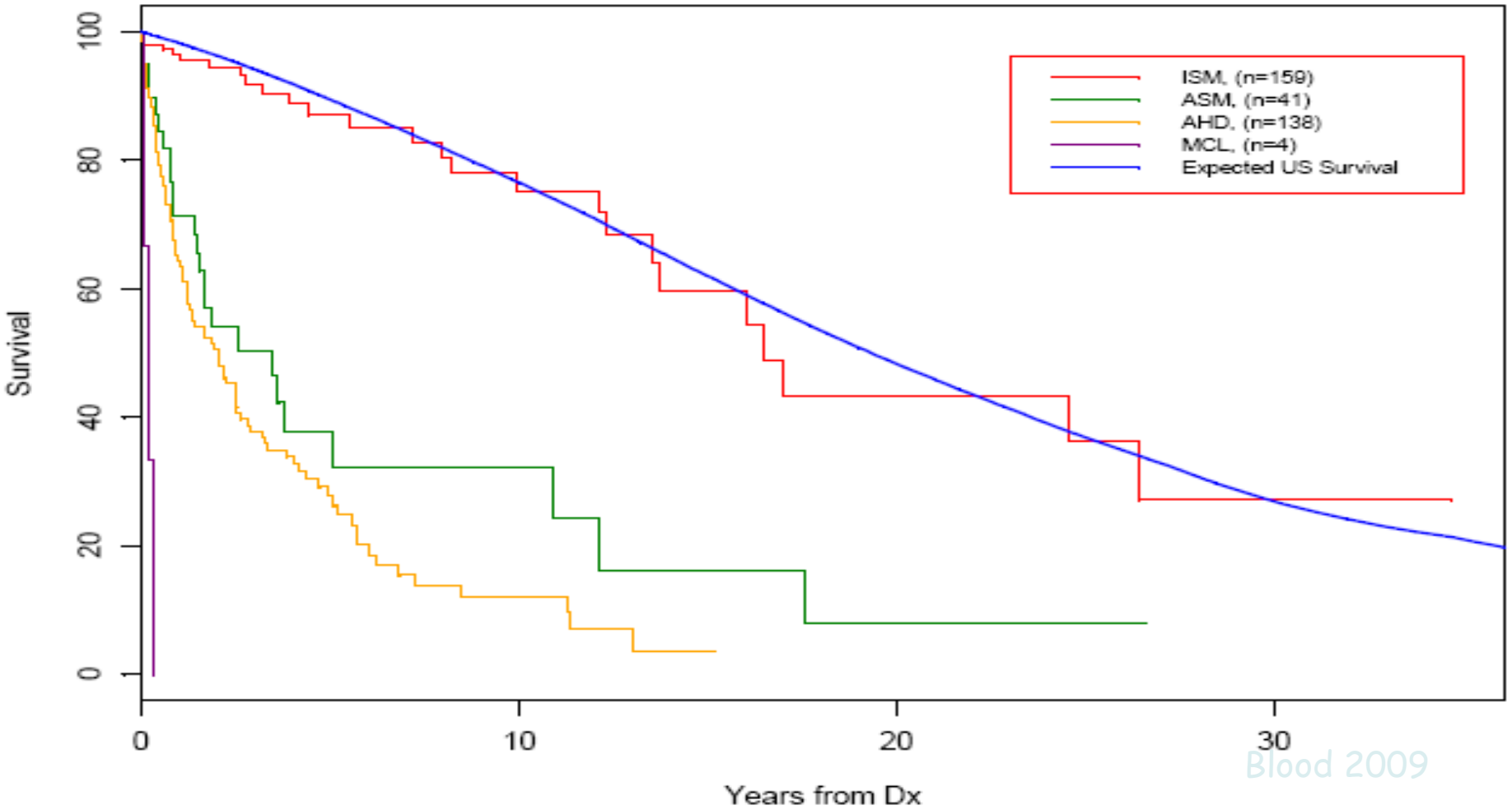
Systemic mastocytosis in adults: 2015 update on diagnosis, risk stratification, and management

Animesh Pardanani[1,2*]

Prognosis

Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors

Ken-Hong Lim, Ayalew Tefferi, Terra L. Lasho, Christy Finke, Mrinal Patnaik, Joseph H. Butterfield, Rebecca F. McClure, Chin-Yang Li and Animesh Pardanani



Blood 2009

Prognosis

Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors

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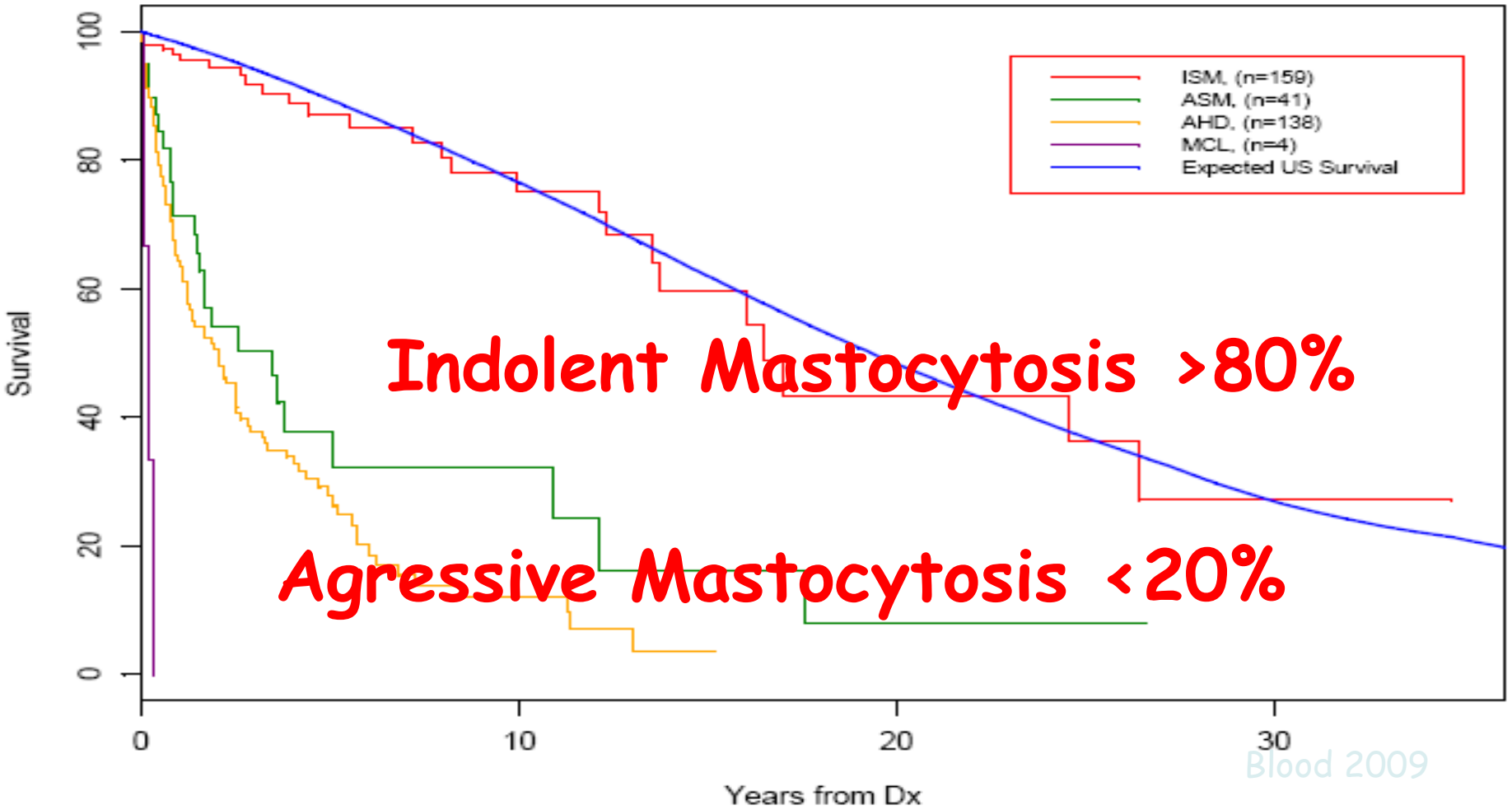
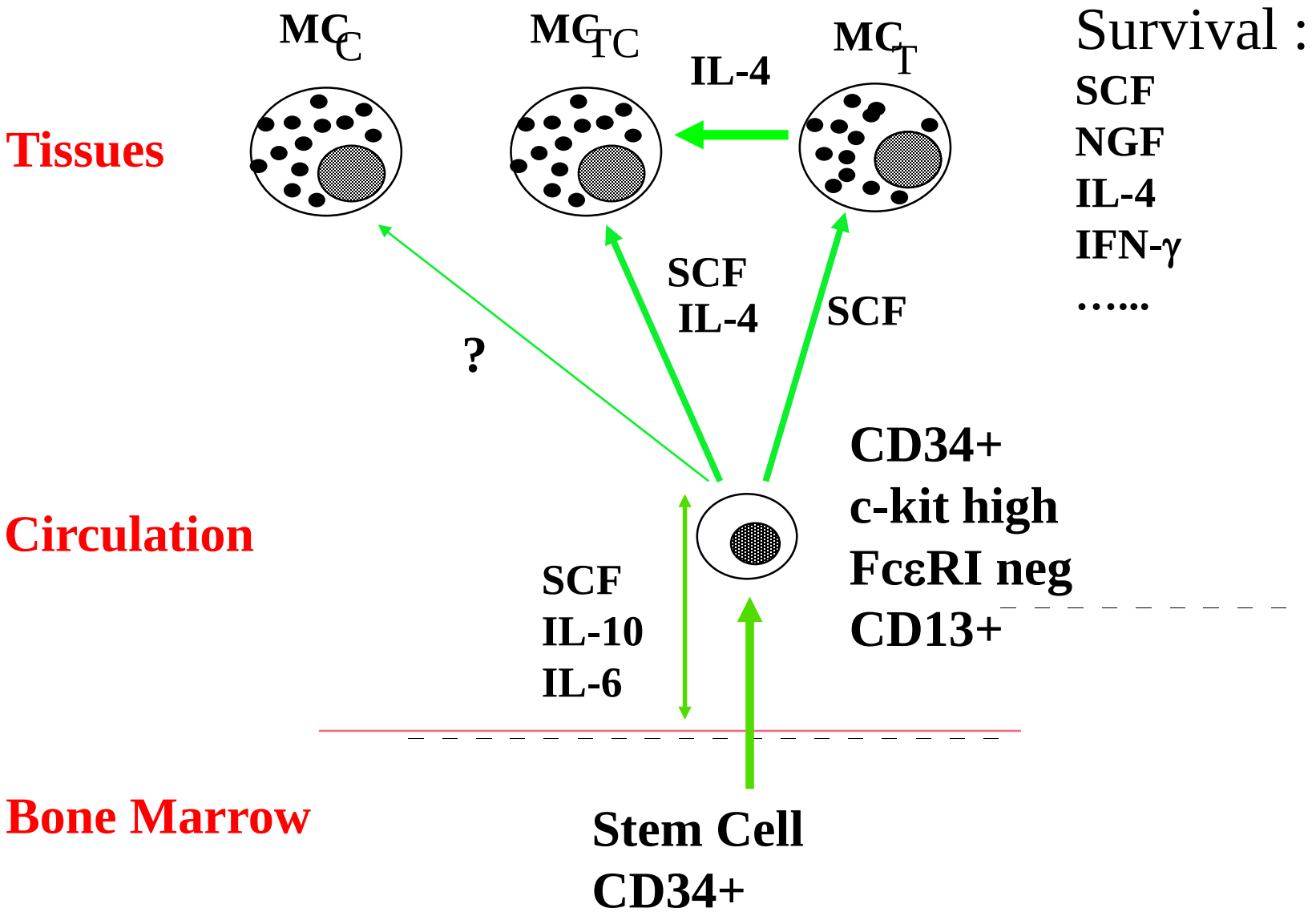
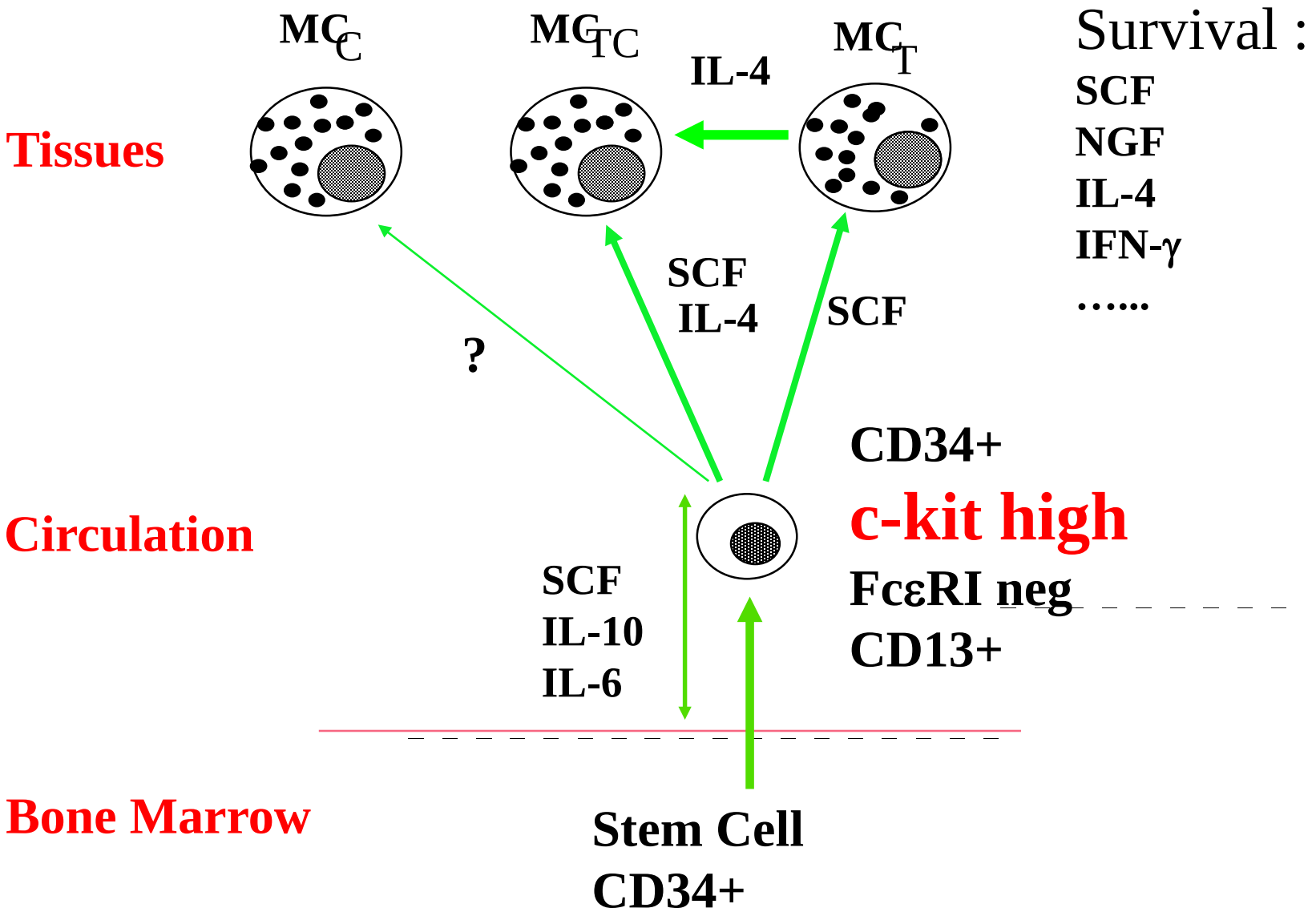


Physiopathology

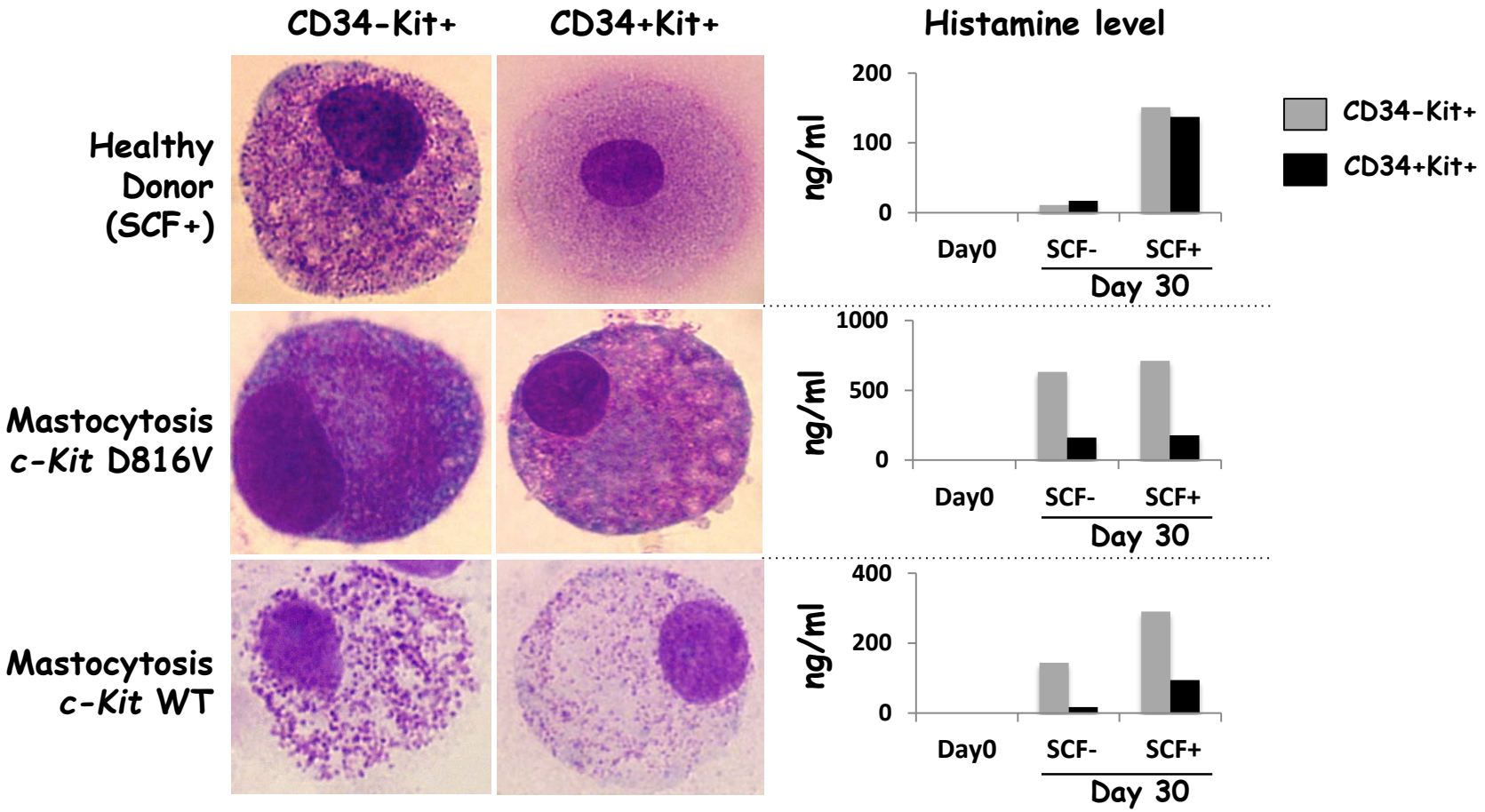
Simplified pathways of human MC differentiation



Simplified pathways of human MC differentiation

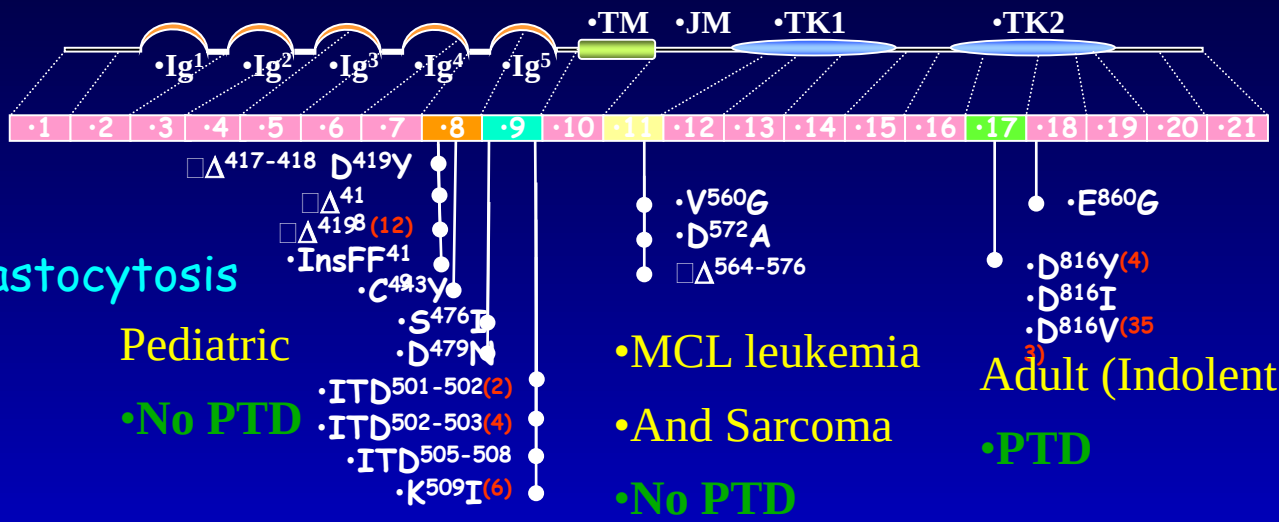


C-kit+CD34-Mast cell precursors in peripheral bloo



Sophie Georgin et al, Blood 2010

•Patrice Dubreuil, Katia Hanssen, Sébastien Leutard, Kevun Hahn, Christine Bodemer, Olivier Hermine CEREMAST



•Human mastocytosis

Pediatric

•No PTD

•MCL leukemia

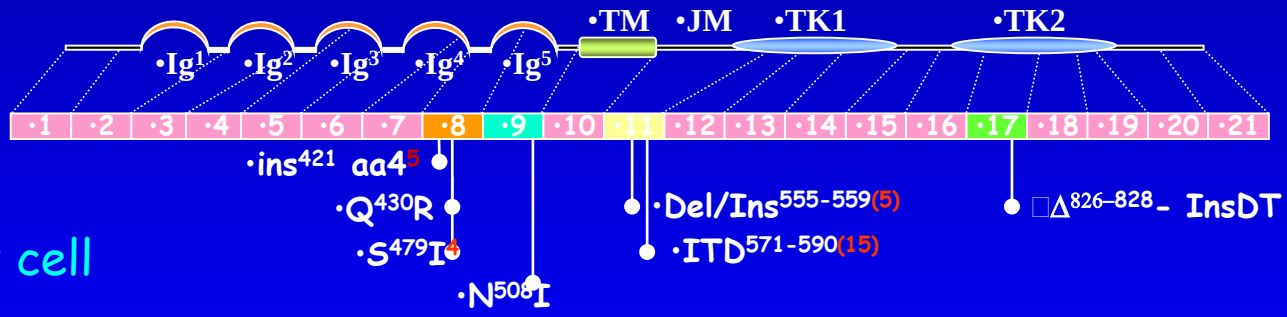
•And Sarcoma

•No PTD

Adult (Indolent and agressive)

•PTD

•n=603

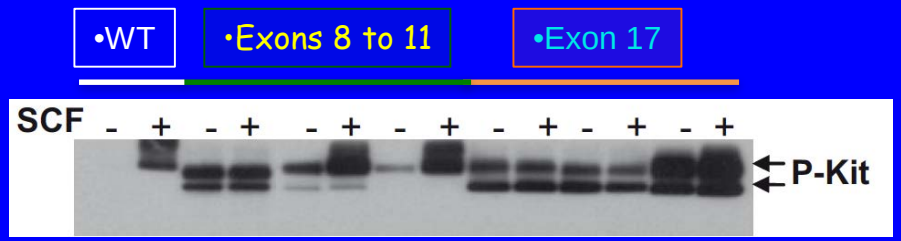


•Dog mast cell tumor

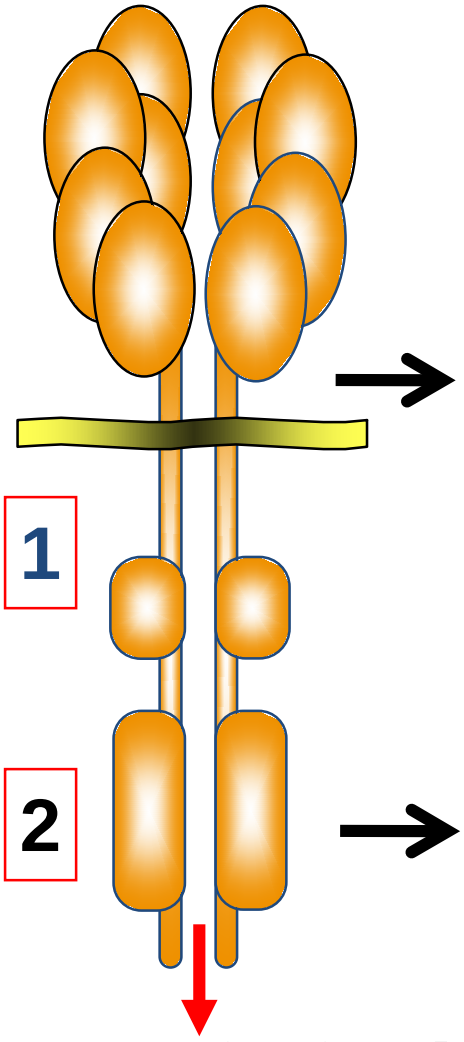
•30% of the dogs are mutated

•No PTD

•n=88



Oncogenic Mutations of c-kit in Mastocytosis

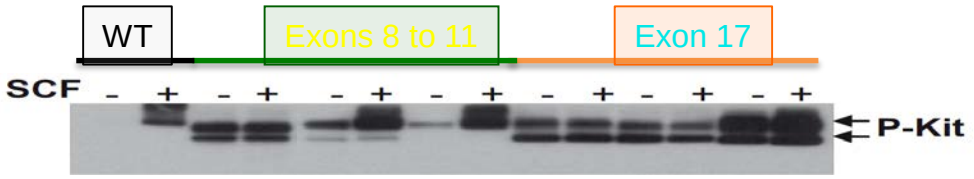


Pediatric Mutations 75%
Clonal disease +++
Regression

→ **Sarcoma**
Adult

Adult Mutations 85%
Clonal disease +++
No regression

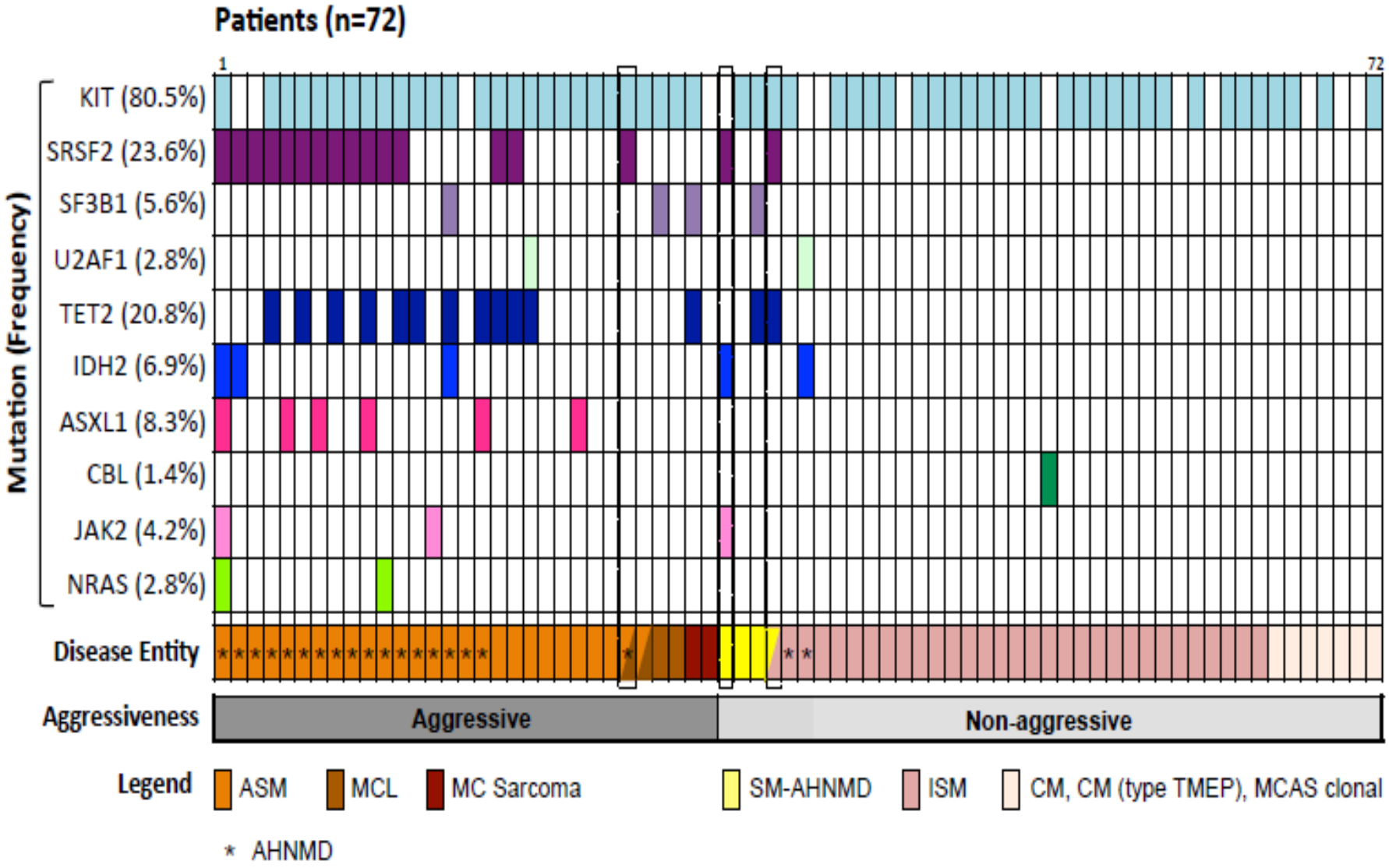
→ **Indolent**
Vs
Agressive ?
AHN
MCL



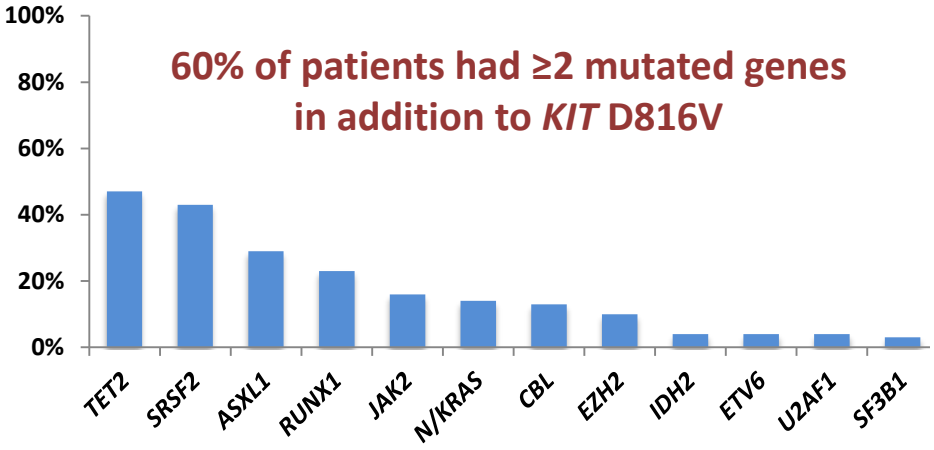
SRSF2-P95 Hotspot Mutation is Highly Associated with Aggressive Forms of Mastocytosis and Mutations in Epigenetic Regulator Genes

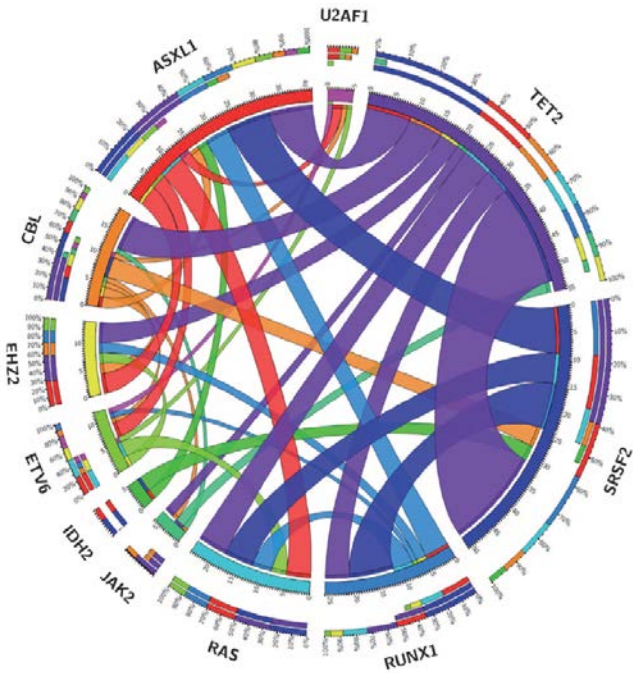
•*Katia Hanssens, Fabienne Brenet, Julie Agopian, Sophie Georgin-Lavialle, Gandhi Damaj, Laure Cabaret, Maria Olivia Chandesris, Paulo de Sepulveda, Olivier Hermine, Patrice Dubreuil * § and Erinn Soucie**

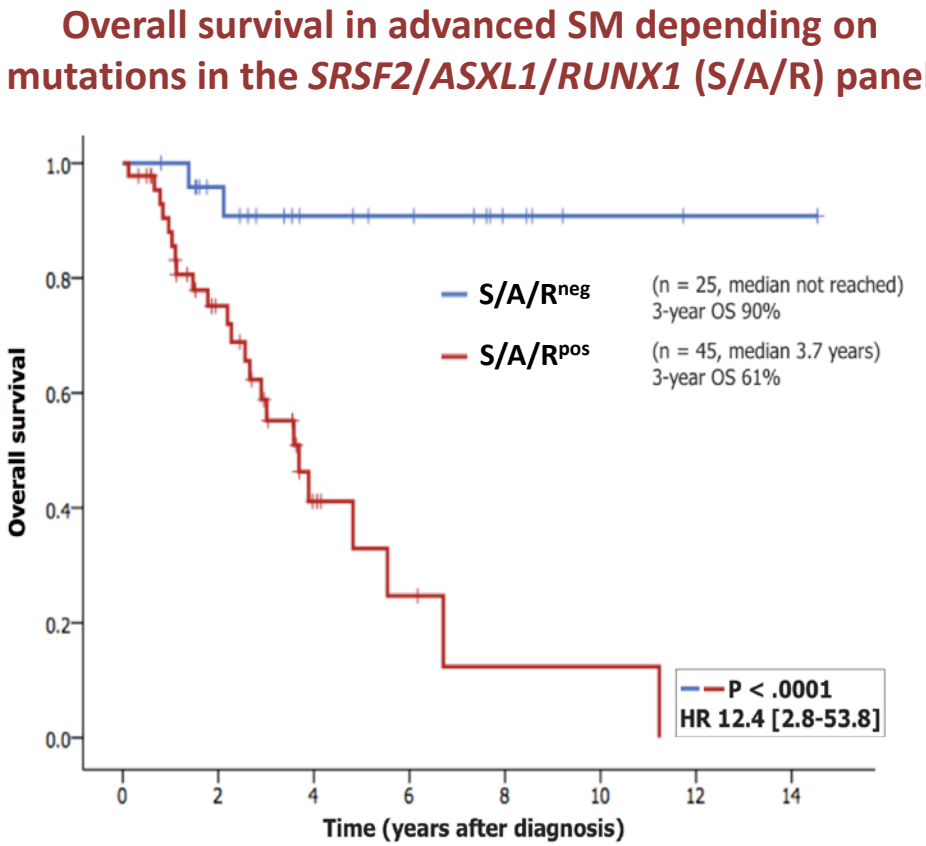
(Haematologica; in press)



Overall frequency and prognostic impact of mutated genes in 70 advanced *KIT* D816V^{+} SM patients

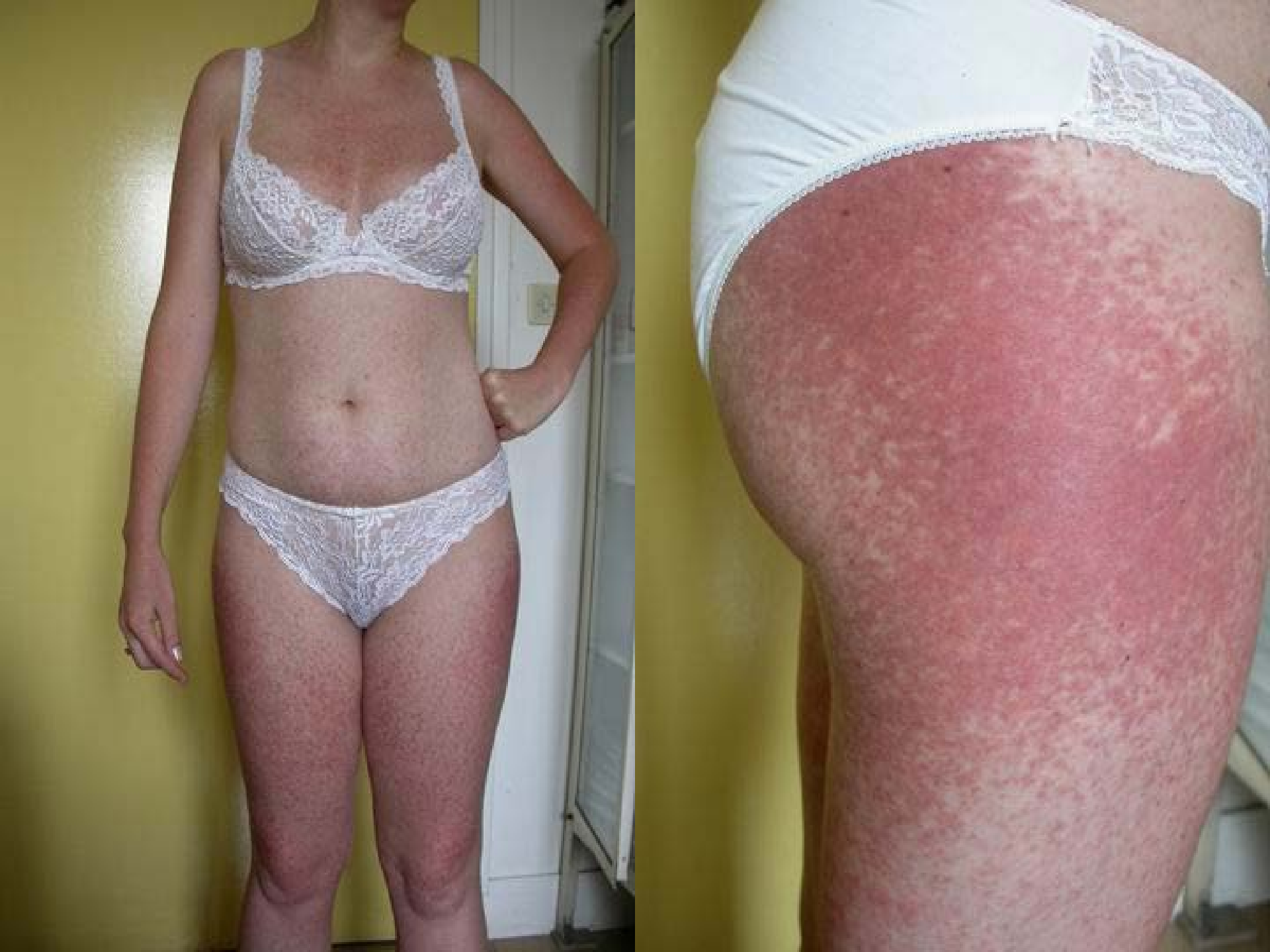


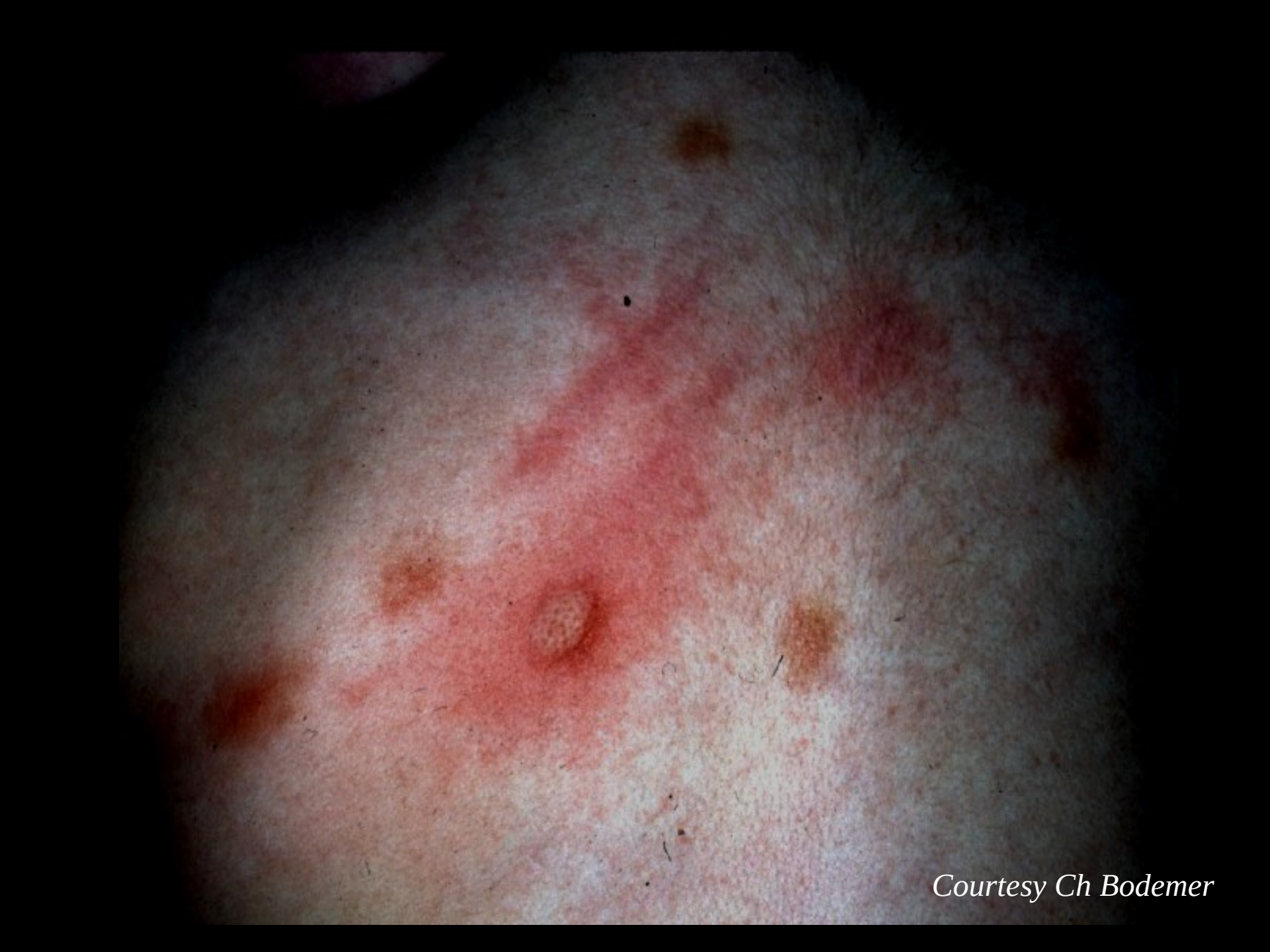


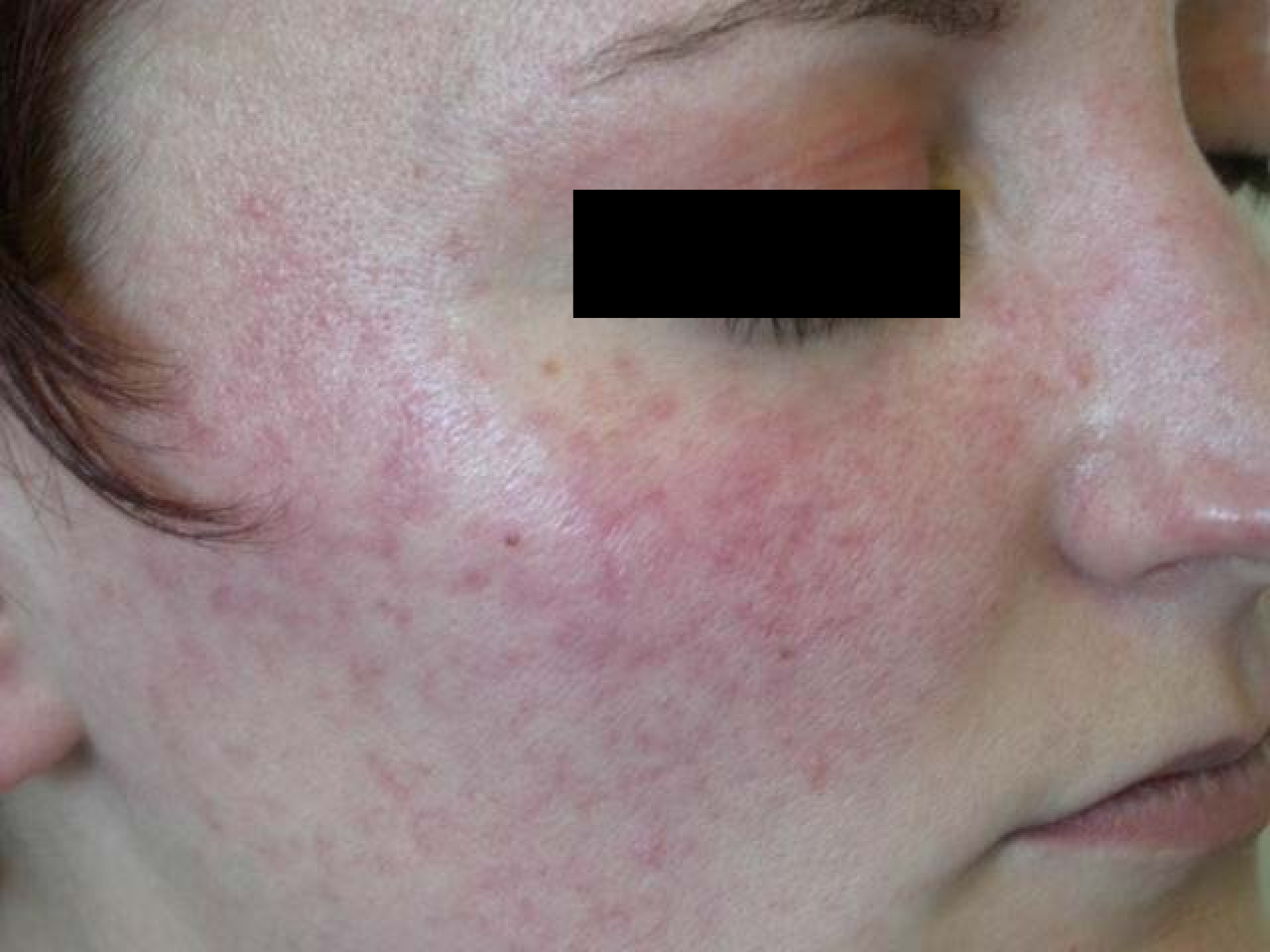


Schwaab *et al*., Blood 2013; 122:2460–2466; Jawhar *et al*., Leukemia 2016; 30:136-143

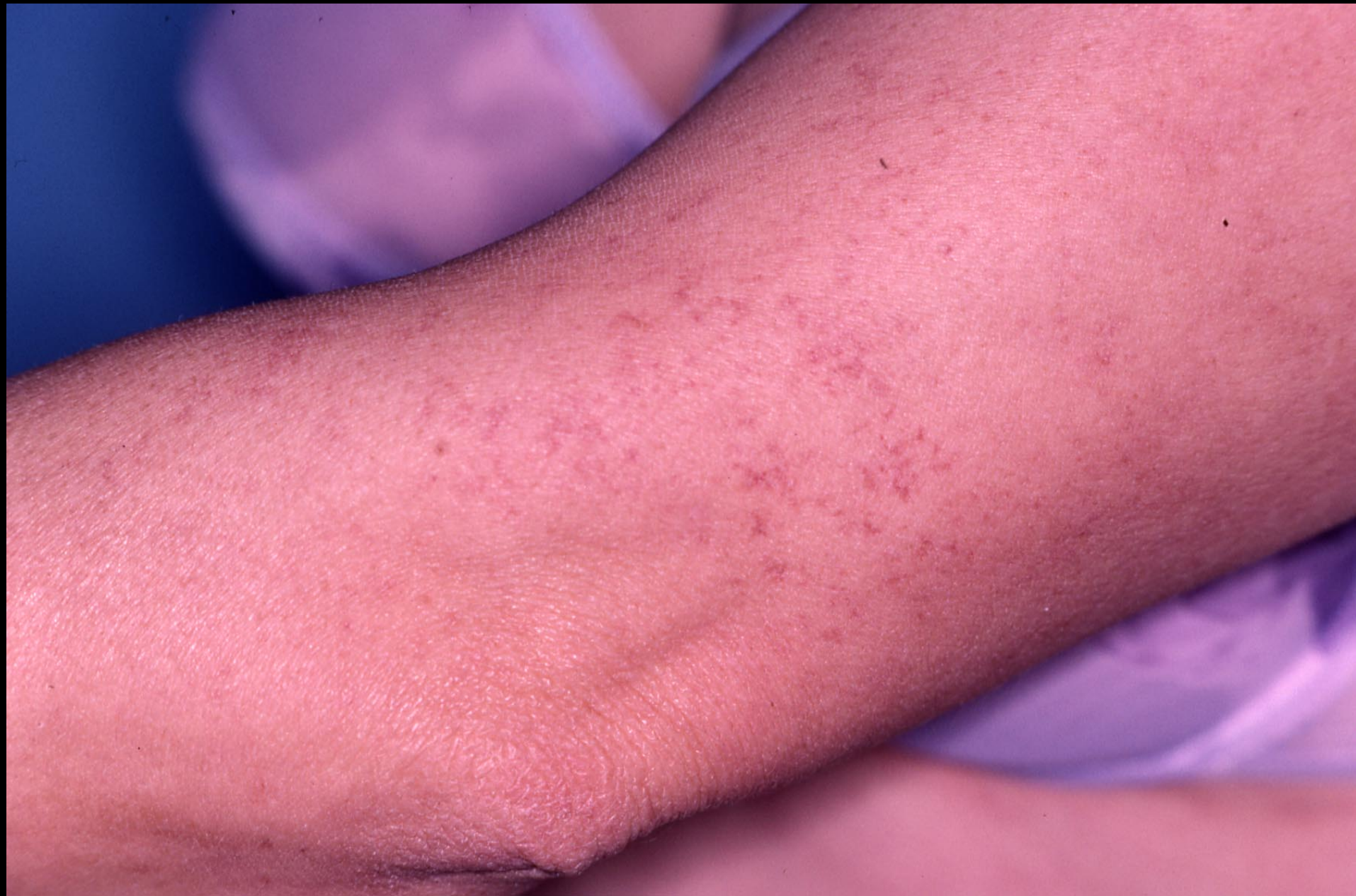
Diagnosis




Courtesy Ch Bodemer



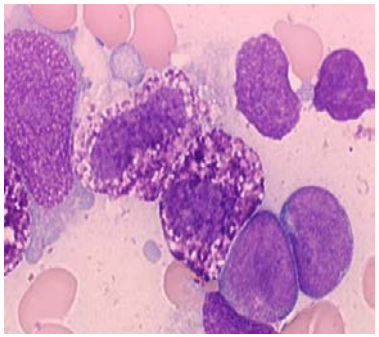
TMEP



Mastocytosis Diagnosis

1. DARIER ’S SIGN FOR CUTANEOUS MASTOCYTOSIS (Skin involvement is not required)

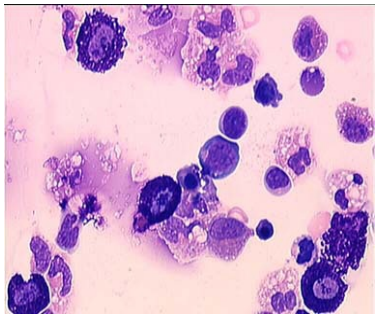
2. HISTOLOGY FOR CUTANEOUS AND/OR SYSTEMIC MASTOCYTOSIS (required)

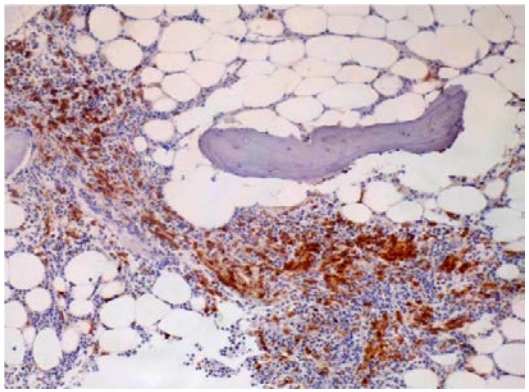


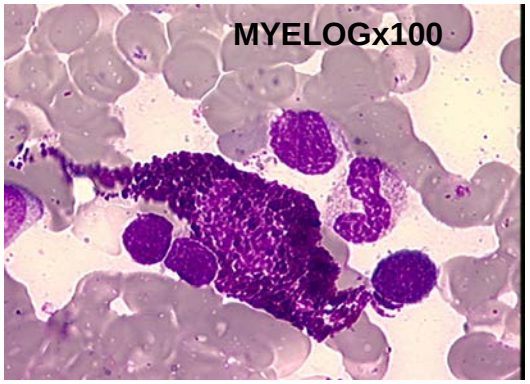
- **TOLUIDINE BLUE**
- **ANTI -TRYPTASE STAINING**
- **CD117+, CD2+ and/or CD25+, CD15-**

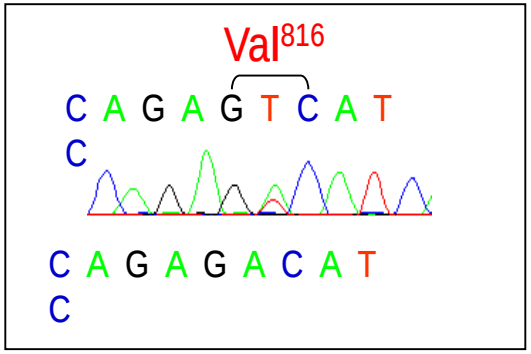
3. MAST CELL MEDIATORS

- **Total tryptase >20ng/ml**
- **Soluble C-kit level**






MYELOGx100


Val816
C A G A G T C A T
C
C A G A G A C A T
C

Clinical and Biological investigations

- Symptoms: **handicap fonctionnel**, asthenia, prurit, flush, depression, diarrhea, pollakiuria, vascular instabilities
- Clinical: Weight-nutrition, Skin, tumoral syndrome (Lymph nodes, splenomegaly, hepatomegay)
- Biology: CBC, Liver Enzymes, Albumin, tryptase, IgE, Vitamin D.
- Organ infiltration: skin biopsy, bone marrow, others (digestive tract, liver…). Bone marrow aspiration, Mast cell phenotype
- Screening of c-kit mutation (Skin, infiltrated organ, peripheral blood ?)
- Bone check up: X Ray in case of symptoms, Bone density+++.
- Associated Hematological Neoplasm

Diagnosis Criteria and Classification

A firm diagnosis of systemic mastocytosis is established when at least 1 major and 1 minor or at least 3 minor criteria are present	
Major	Multifocal dense infiltrates of MCs in bone marrow sections or other extracutaneous organs (>15 MCs in aggregate).
Minor	a. MCs in bone marrow or other extracutaneous organs show an abnormal (spindle-shaped) morphology (>25%). b. Mutation at codon 816 of the *KIT* gene in extracutaneous organs. In most cases the mutation is D816V. c. MCs in bone marrow express CD2 and/or CD25. d. Serum tryptase >20 ng/mL (not in patients with AHNMD-type disease).
B findings	a. Bone marrow biopsy showing >30% infiltration by MCs (focal, dense aggregates) and/or serum tryptase level >200 ng/mL. b. Signs of dysplasia or myeloproliferation in non-MC lineages, but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts. c. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.
C findings	a. Bone marrow dysfunction manifesting as cytopenia (ANC <1.0 x 10^9/L, Hb <10 g/dL, or platelets <100 x 10^9/L), but no obvious non-MC hematopoietic malignancy. b. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension. c. Skeletal involvement with large osteolytic lesions and/or pathological fractures. d. Palpable splenomegaly with hypersplenism. e. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.

Updated WHO Classification of Mastocytosis 2016

Cutaneous mastocytosis (CM)

- Maculopapular CM (MPCM) = urticaria pigmentosa (UP)
- Diffuse CM (DCM)
- Mastocytoma of skin

Systemic mastocytosis (SM)

- Indolent SM (ISM)
- Smoldering SM (SSM)
- SM with associated hematologic neoplasm (AHN)*
- Aggressive SM (ASM)
- Mast cell leukemia (MCL)

Mast cell sarcoma

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*The previous term SM-AHNMD (SM with clonal hematologic non-mast cell-lineage disease) and the new term AHN can be used synonymously.

Treatment

Therapeutic Decision

- Agressive disease : Reduction of life expectancy and organ failure

- Indolent disease : No life expectancy reduction, no organ failure , Handicap associated with symptoms (patient vs physician)

Treatment of Indolent Diseases

Identification of all systemic manifestations in patients suffering from mastocytosis

- From 2004, 363 mastocytosis patients and 90 controls in France were asked to rate their overall disability (OPA score) and the severity of 38 individual symptoms.
- A specific questionnaire (AFIRMM V1), encompassing these 38 symptoms, has been created and validated.

PLoS ONE. 2008 May 28;3(5):e2266

OPEN ACCESS Freely available online

PLoS one

Case-Control Cohort Study of Patients' Perceptions of Disability in Mastocytosis

Olivier Hermine[1,2,3*], Olivier Lortholary[3,4], Phillip S. Leventhal[3], Adeline Catteau[3], Frédérique Soppelsa[3], Cedric Baude[3], Annick Cohen-Akenine[3], Fabienne Palmérini[3,4,6], Katia Hanssens[3,4,6], Ying Yang[4], Hagay Sobol[6], Sylvie Fraytag[5], David Ghez[1,2], Felipe Suarez[2], Stéphane Barete[1,7], Philippe Casassus[3,8], Beatrice Sans[9], Michel Arock[10], Jean Pierre Kinet[3], Patrice Dubreuil[3,4,6], Alain Moussy[3]

Identification of all systemic manifestations in patients suffering from mastocytosis

Table 3. Disability by symptom: patients vs. controls.

Symptom	Rank[a]	Controls			Patients			*P*-value[b]	
		n	Any disability[c]	Severe or intolerable disability[d]	*n*	Any disability[c]	Severe or intolerable disability[d]	Any disability[c]	Severe or intolerable disability[d]
Psychological impact	1	90	9 (10%)	1 (1%)	363	261 (72%)	120 (33%)	*<0.0001*	*<0.0001*
Asthenia	2	90	34 (38%)	3 (3%)	362	296 (82%)	102 (28%)	*<0.0001*	*<0.0001*
Pruritus	3	90	25 (28%)	3 (3%)	363	299 (82%)	82 (23%)	*<0.0001*	*<0.0001*
Food allergy/intolerance	4	90	9 (10%)	0 (0%)	363	222 (61%)	97 (27%)	*<0.0001*	*<0.0001*
Erythemateous crisis	5	90	17 (19%)	1 (1%)	363	293 (81%)	69 (19%)	*<0.0001*	*<0.0001*
Muscle and joint pain, cramps	6	90	36 (40%)	3 (3%)	363	276 (76%)	71 (20%)	*<0.0001*	*0.0002*
Pollakiuria	7	90	58 (64%)	6 (7%)	362	263 (73%)	64 (18%)	0.12	*0.0098*
Drug allergy	8	90	16 (18%)	0 (0%)	363	205 (56%)	70 (19%)	*<0.0001*	*<0.0001*
Aerophagia/eructation	9	90	43 (48%)	1 (1%)	363	229 (63%)	62 (17%)	*0.0080*	*<0.0001*
Dyspnea/bronchoreactivity	10	90	15 (17%)	3 (3%)	362	154 (43%)	94 (26%)	*<0.0001*	*<0.0001*
Headache	11	90	34 (38%)	4 (4%)	362	250 (69%)	48 (13%)	*<0.0001*	*0.0190*
Bone pain	12	90	16 (18%)	0 (0%)	363	196 (54%)	65 (18%)	*<0.0001*	*<0.0001*
Reduced sexual relations	13	90	11 (12%)	4 (4%)	362	132 (36%)	65 (18%)	*<0.0001*	*0.0014*
Epigastric pain	14	90	35 (39%)	2 (2%)	362	249 (69%)	40 (11%)	*<0.0001*	*0.0100*
Ocular discomfort	15	90	43 (48%)	1 (1%)	363	219 (60%)	55 (15%)	*0.0309*	*0.0003*
Memory loss	16	90	32 (36%)	0 (0%)	362	240 (66%)	34 (9%)	*<0.0001*	*0.0025*
Tinnitus	17	90	29 (32%)	1 (1%)	363	166 (46%)	47 (13%)	*0.0205*	*0.0011*

Tinnitus 17 90 29 (32%) 1 (1%) 363 166 (46%) 47 (13%) 0.0205 0.0011

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Evidence for Cognitive Impairment in Mastocytosis: Prevalence, Features and Correlations to Depression

Daniela Silva Moura[1,2*], Serge Sultan[7,8], Sophie Georgin-Lavialle[1,3,4], Stéphane Barete[1,3,5], Olivier Lortholary[1,6], Raphael Gaillard[9,10], Olivier Hermine[1,3,11,12*]

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Depression in Patients with Mastocytosis: Prevalence, Features and Effects of Masitinib Therapy

Daniela Silva Moura[1,2], Serge Sultan[2,3], Sophie Georgin-Lavialle[1,4], Nathalie Pillet[5], François Montestruc[5], Paul Gineste[5], Stéphane Barete[6], Gandhi Damaj[7], Alain Moussy[5,8], Olivier Lortholary[9], Olivier Hermine[1,4,5,8*]

Mastocytosis and psychological stress

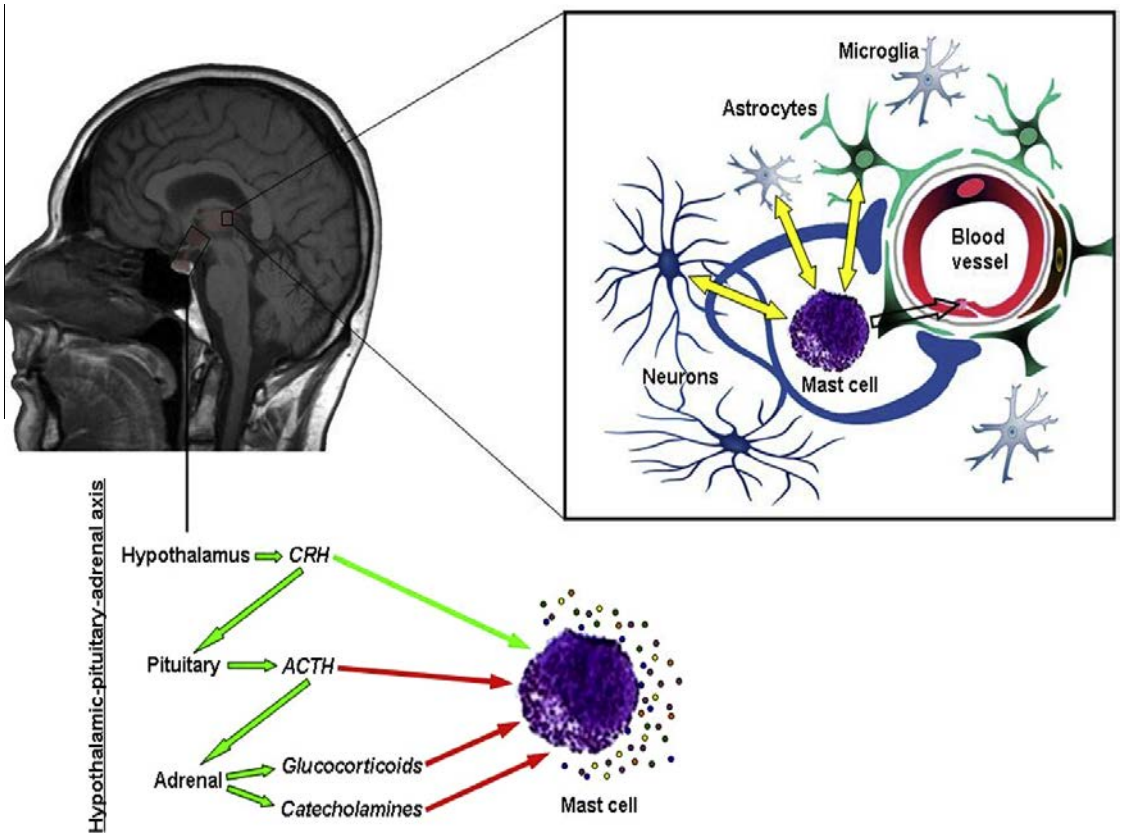
Alexythymia ++++

Cognitive functions impairement

Depression

Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases

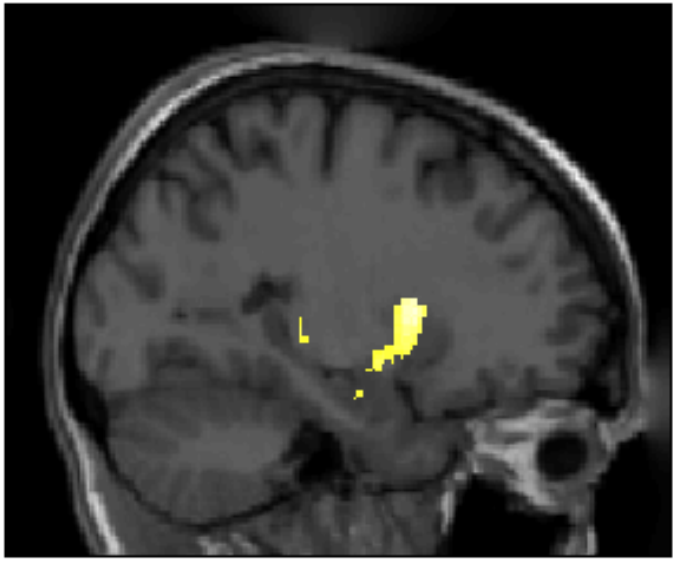
Lawrence B. Afrin [a], Dieter Pöhlau [b], Martin Raithel [c], Britta Haenisch [d,e], Franz L. Dumoulin [f], Juergen Homann [f], Uwe M. Mauer [g], Sabrina Harzer [h], Gerhard J. Molderings [h,*]

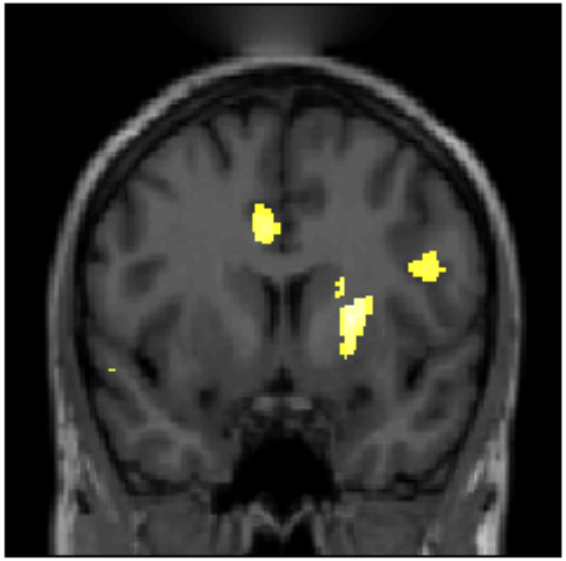


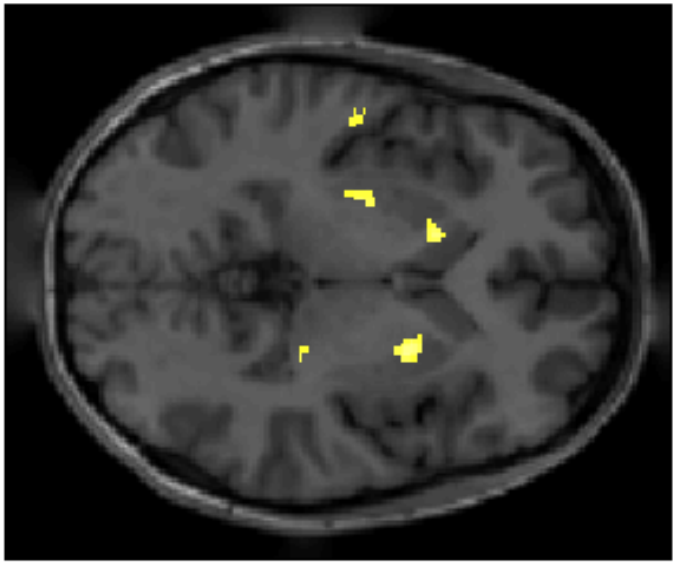
Hyperperfusion of central grey nuclei :

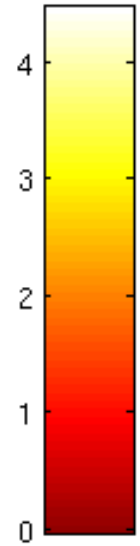
11 patients with cognitive imapirement vs 33 controls

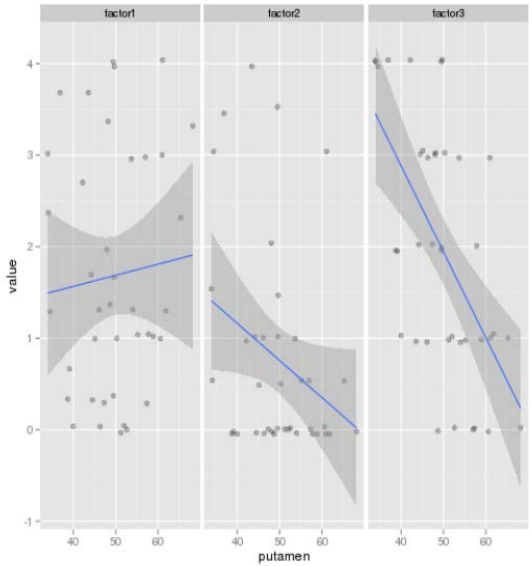
Corelation with cognitive dysfunctions





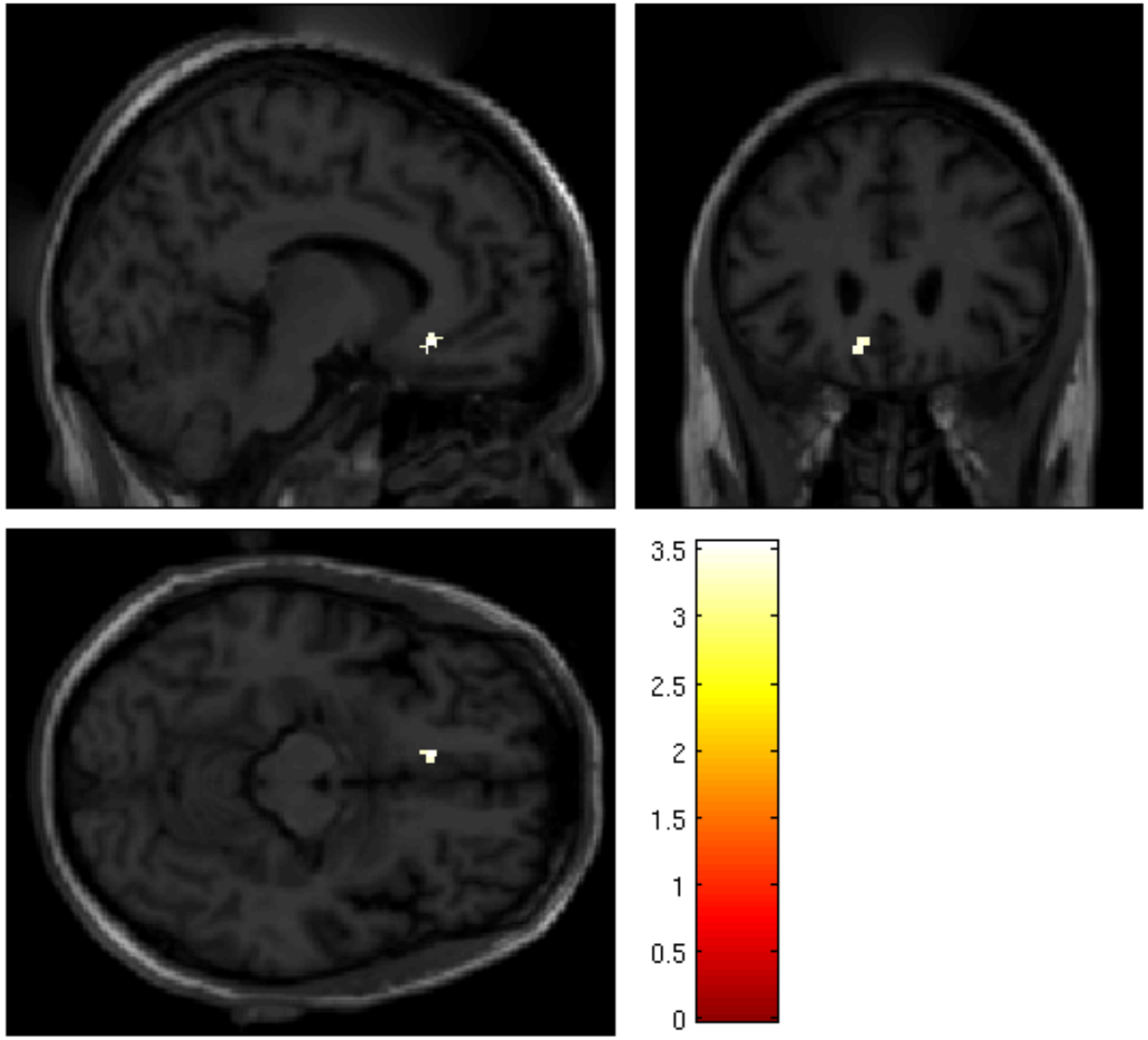






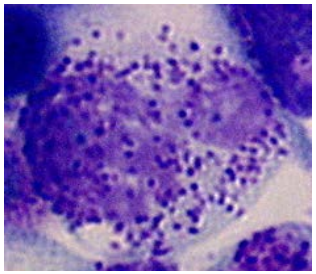
Hypoperfusion of the anterior Cingulum antérieur

10 patients with depression and mastocytosis Vs. 18 patients with Mastocytosis but not depressed

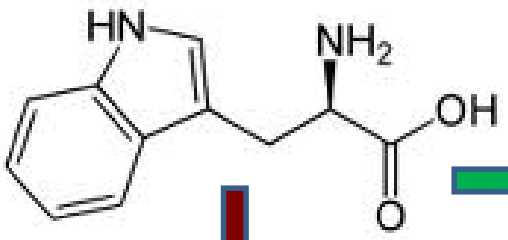


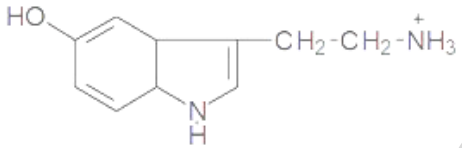
Trypytophan metabolism and Mastocytosis

Georgin Lavialle et al, Molecular Psychiatry, 2016



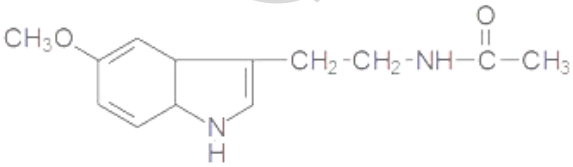
Tryptophane





Serotonin
(5-hydroxytryptamine)

serotonin



Melatonin

Histamine
Others

ASL
abnormalities

TNFα

\+

IDO

Kynurenine

Acid
xanthurenic

Acid
quinolenic

Low serotonin

Depression ?

Proteases

Neurotoxicity
Oxidative stress
apoptosis

Cognition (?)

Symptomatic Therapies of Mastocytosis

Eviction of mast cells stimulants: depend on the patient history, Desensitization in anaphylaxis

Aim at inhibiting mediator release by mast cell or mediators effects.

- **Anti-H1 :** pruritus, flush and sometimes GI pains.

- **Anti-H2 :** essentially GI pains.

- **Aspirin :** for flushing, tachycardia, but may cause vascular collapse!!!

- **Corticoids :** for local treatment of cutaneous lesions, ascite, malabsorption, GI cramps (budesonide: corticoïde à délitement entéral)

- **Cromoglycate disodium :** non specific mediator release symptoms

- **Anti-leucotriènes** (montelukast-singulair): for respiratory manifestations

- **Epinephrin :** Hypotension

- **Biphosphonates :** bone pain and bone loss

- **Psychiatric** : SSRI, Ketamine, EMEND,

ITK for indolent diseases

- New ITK
- Inhibiton of Mast cell activation (c-kit, Lyn, Fyn, etc)
- Cytoreductive on Mast cells (optional ++)
- Not cytoreductive on other cells
- Not toxic (short term and long term)
  - Genotoxic, carcinogenic
  - Cardiotoxic (Abl++, Src, VEGF, Herg chanel, etc)

OPEN ACCESS Freely available online

PLoS one

Masitinib (AB1010), a Potent and Selective Tyrosine Kinase Inhibitor Targeting KIT

Patrice Dubreuil[1,2,3,4]*, Sébastien Letard[1,2,3,4], Marco Ciufolini[4,5], Laurent Gros[4], Martine Humbert[4], Nathalie Castéran[4], Laurence Borge[1,2,3], Bérengère Hajem[4], Anne Lermet[4], Wolfgang Sippl[6], Edwige Voisset[1,2,3], Michel Arock[7], Christian Auclair[4,7], Phillip S. Leventhal[4], Colin D. Mansfield[4], Alain Moussy[4], Olivier Hermine[4,8]*

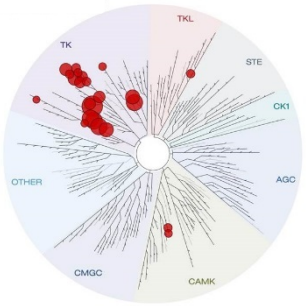
Masitinib – Kinase inhibitory activity profile

Masitinib is a tyrosine kinase inhibitor that target mast cells and macrophages.

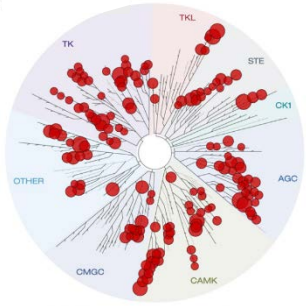
Kinase Inhibition Profile of Masitinib

Target	IC_{50} [nM]	Kd [µM]
KIT wild-type (WT)	200	0.008
FYN	240	0.14
LYN	225	0.061
D816V KIT (exon 11)	5,000	
KIT mutation (exon 17)	0.3	
MCSFR-1	90	0.0076
PDGFRb	300	0.0084
PDGFRα	50	0.0025

Masitinib (AB1010)



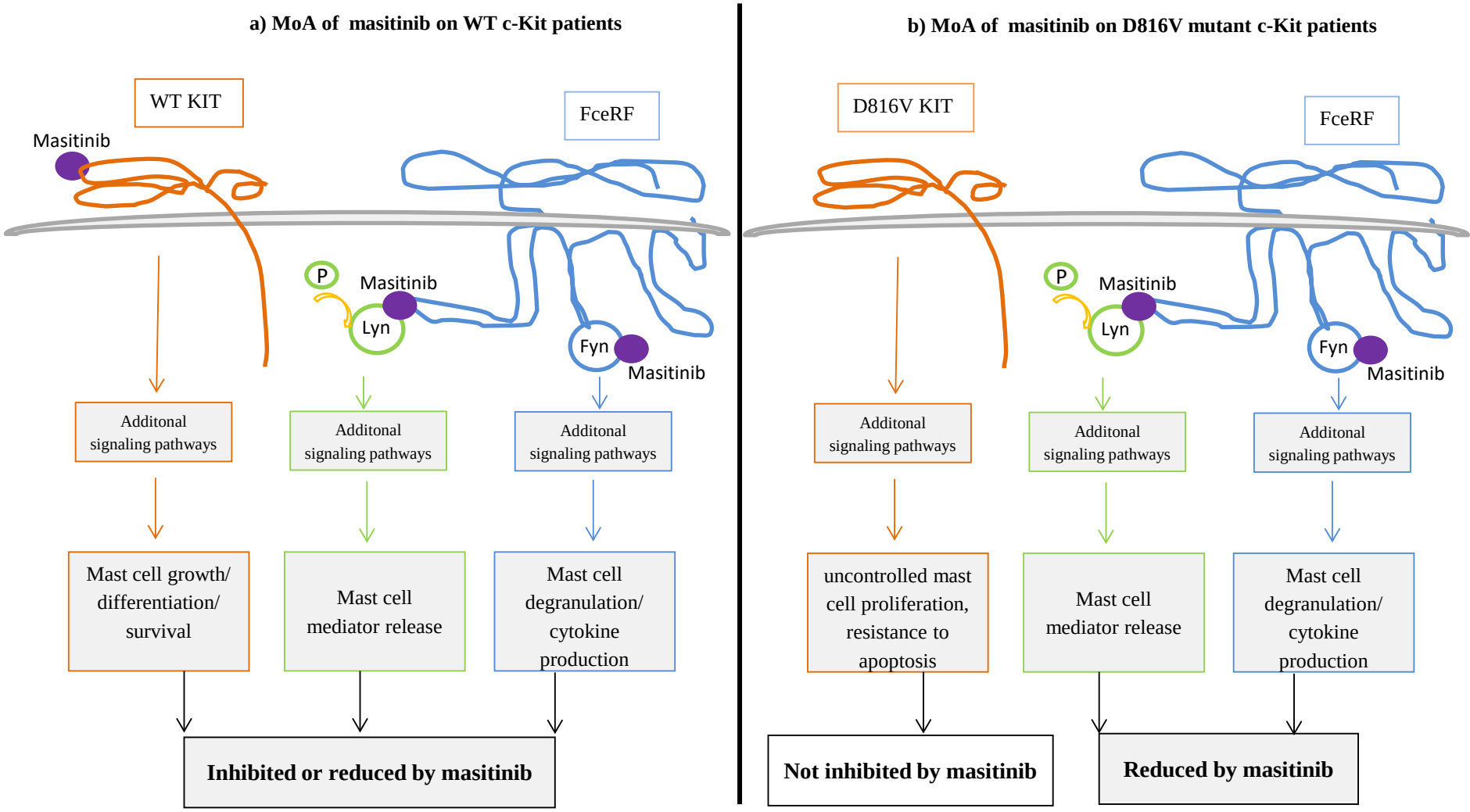
Midostaurin (PKC412)



[1] Dubreuil 2009, PLoSONE.4(9):e7258 ; AB Science. [2] Davis 2011, Nat Biotechnol;29(11):1046

Masitinib activity on mast cells expressing D861V Kit mutation seems to come from Lyn and Fyn

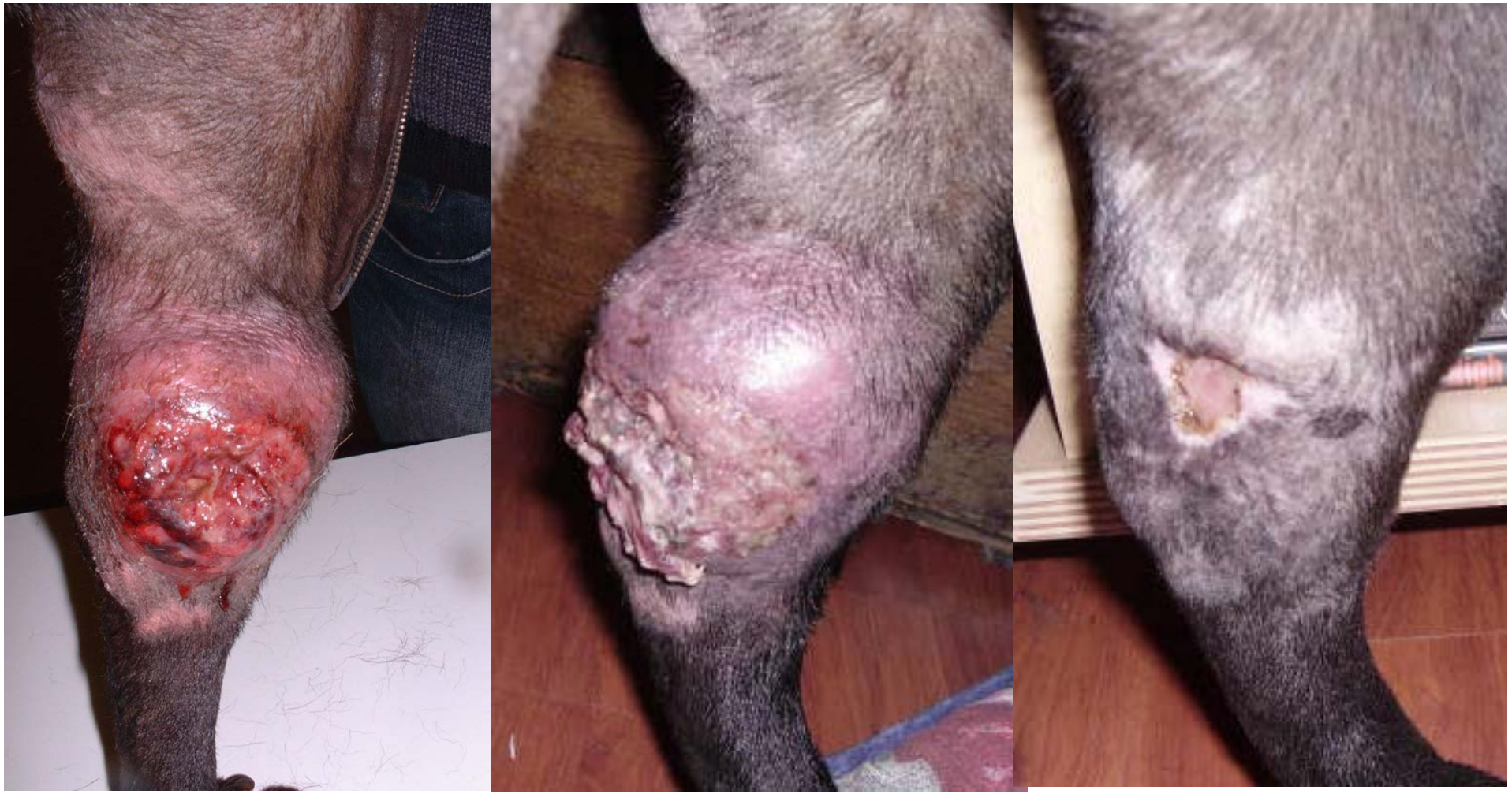
Theoretical model for the MoA of masitinib in mastocytosis



The c-Kit receptor is primarily responsible for mast cell growth/differentiation/survival with mast cell mediator release being initiated through the integration of downstream signaling pathways of c-Kit and FcεRI. D816V mutant c-Kit receptors result in uncontrolled mast cell proliferation and resistance to apoptosis. Masitinib blocks WT c-Kit, Lyn and Fyn. In WT c-Kit mast cells (panel a) masitinib directly inhibits mast cell activation via inhibition of WT c-Kit, while mast cell mediator release and cytokine production is inhibited through targeting of Lyn and Fyn. In D816V mutant c-Kit mast cells (panel b) masitinib inhibits mast cell degranulation and cytokine production via Lyn and Fyn inhibition.

Human : A model for Dog and "vice versa"

Case Report in Mast Cell Tumor.



DAY 0 DAY 3 DAY 18

Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study

Olivier Lortholary, Marie Olivia Chandesris, Cristina Bulai Livideanu, Carle Paul, Gérard Guillet, Ewa Jassem, Marek Niedoszytko, Stéphane Barete, Srdan Verstovsek, Clive Grattan, Gandhi Damaj, Danielle Canioni, Sylvie Fraitag, Ludovic Lhermitte, Sophie Georgin Lavialle, Laurent Frenzel, Lawrence B Afrin, Katia Hanssens, Julie Agopian, Raphael Gaillard, Jean-Pierre Kinet, Christian Auclair, Colin Mansfield, Alain Moussy, Patrice Dubreuil, Olivier Hermine

www.thelancet.com **Published online January 6, 2017 http://dx.doi.org/10.1016/S0140-6736(16)31403-9**

Patients Characteristics

	Masitinib (n=67)	Placebo (n=62)
Demographic		
Age (years)	45·3 (11·1; 19–69)	49·2 (12·7; 27–86)
Sex		
Female	50/67 (75%)	41/62 (66%)
Male	17/67 (25%)	21/62 (34%)
c-KIT status		
Clonal (KIT Asp816Val)	63/67 (94%)	53/62 (86%)
KIT wild-type	1/67 (2%)	7/62 (11%)
Unknown	3/67 (5%)	2/62 (3%)
Disease type		
Indolent systemic mastocytosis*	54/67 (81%)	49/62 (79%)
Smouldering systemic mastocytosis*	6/67 (9%)	7/62 (11%)
Unclassified	7/67 (10%)	6/62 (10%)
Severe symptoms at baseline		
Pruritus		
Cases (%)	45/67 (67%)	42/62 (68%)
Mean score (SD)	9·0 (3·0)	9·1 (3·6)
Flushes		
Cases (%)	18/66 (27%)	17/62 (27%)
Mean (SD)	8·0 (9·6)	6·4 (7·4)
Depression (HAMD-17)		
Cases (%)	23/67 (34%)	27/62 (44%)
Mean score (SD)	16·0 (7·4)	17·3 (8·1)
Asthenia (FIS)		
Cases (%)	50/66 (76%)	46/61 (75%)
Mean score (SD)	90·2 (37·1)	89·4 (34·3)
Objective marker of mast cell activation		
Tryptase level (>20 µg/L)		
Number of cases (%)	46/60 (77%)	44/62 (80%)
Mean (SD)	75·8 (120)	72·2 (75·6)
BSA urticaria pigmentosa†	87·8 (48·0)	101·0 (46·3)
Darier's sign	21/25 (84%)	19/27 (70%)

The result is clinically relevant because it is supported by patient response analysis.

- **Patient response on at least one handicap is positive**

Patient response rate 4H: Number of patients having response (≥75%) on at least 1 handicap

Overall W8-W24 – Pearson Chi-Square				Overall W8-W24- GEE			
M (n=67)	P (n=62)	**Diff.**	p-value*	M (n=333)	P (n=305)	**Diff.**	p-value
40.3%	24.2%	**16.1%**	0.0062	26.7%	12.8%	**13.9%**	0.0212

- **Patient response on each handicap is positive**

Patient response rate 4H: Number of patients having response (≥75%) on all their baseline handicaps

Overall W8-W24 – Pearson Chi-Square			
M (n=67)	P (n=62)	**Diff.**	p-value*
16.4%	1.6%	**14.8%**	0.0038

- **Patient response regardless of the number of baseline handicaps is positive**

Response rate 4H: Number of patients having response (≥75%) for each handicap

	Overall W8-W24		
	M	P	**Diff.**
Patient having 2 handicaps at baseline	21.0% (n=19)	0.0% (n=25)	**21.0%**
Patient having 3 handicaps at baseline	12.5% (n=16)	0.0% (n=18)	**12.5%**
Patient having 4 handicaps at baseline	16.7% (n=6)	0.0% (n=3)	**16.7%**

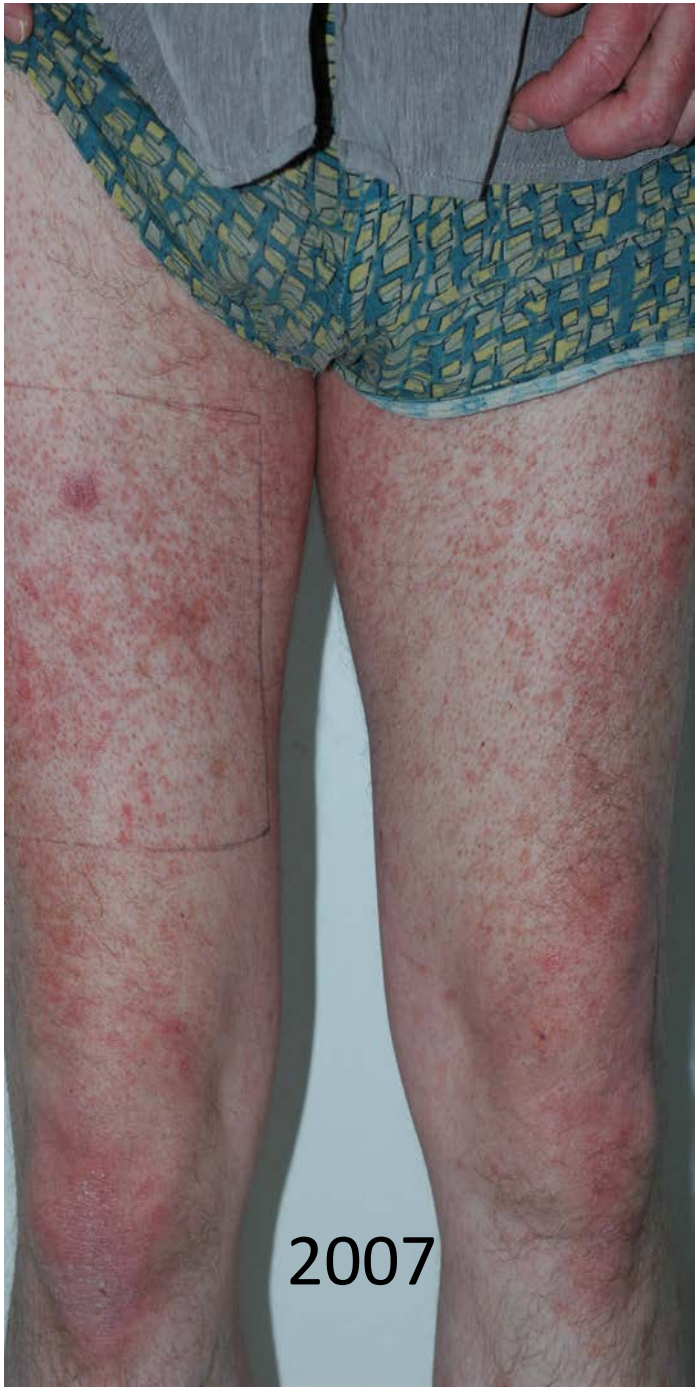
Population: mITT. Missing Data Method: MDF. * Rerandomization.

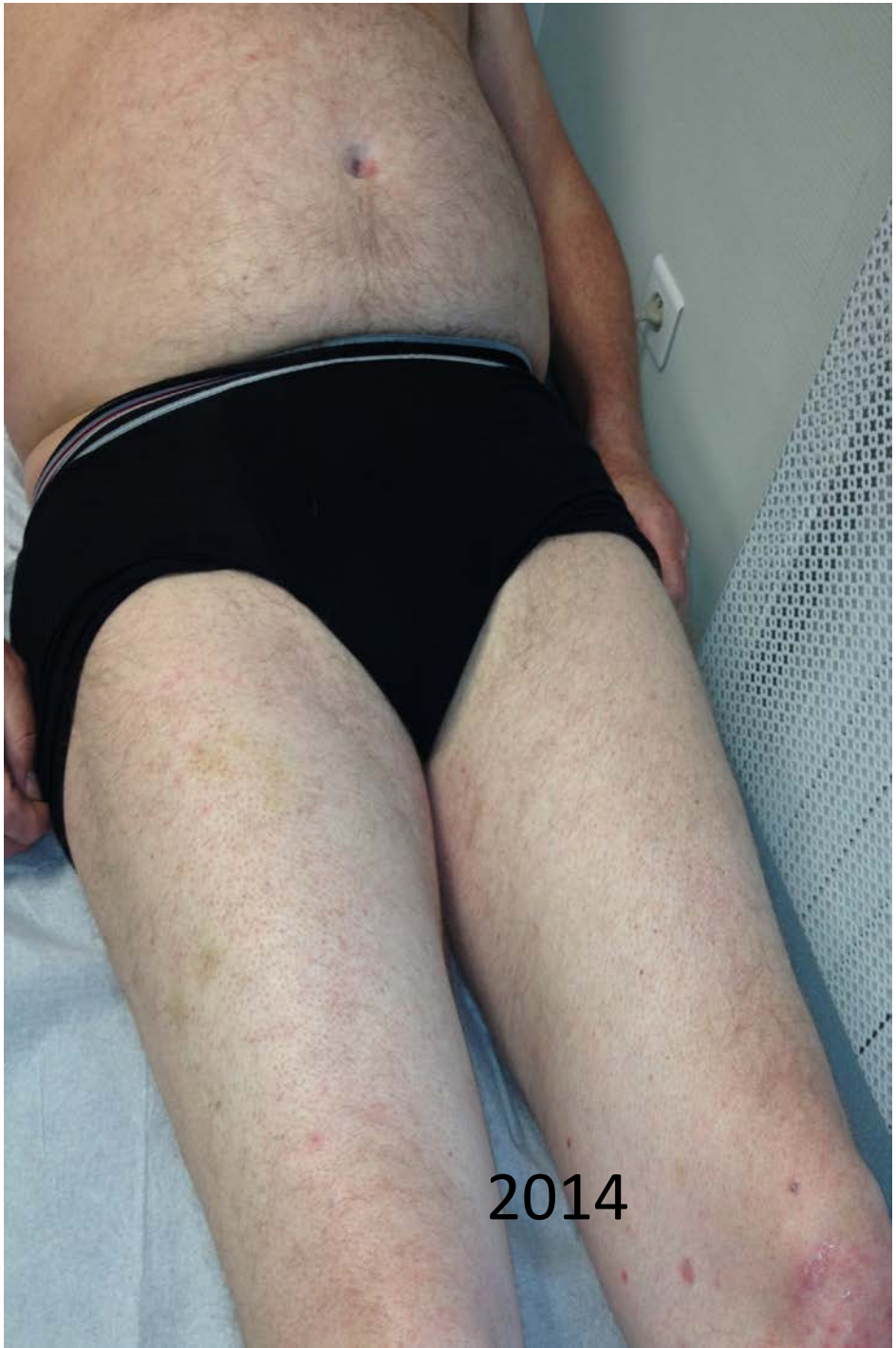
Phase 3 AB06006 – Objective Markers of Mast Cell Activity Results

Masitinib demonstrated activity on objective markers of mast cell activation and burden

AB06006 – Efficacy analyses based on objective endpoints – [W8-W96] timeframe

	Masitinib	Placebo	p-value
Tryptase - Patients with baseline tryptase ≥20 µg/L	46	44	0.0001
Average relative change from baseline Mean±SD	-18.0 ± 21.4	2.2 ± 26.9	
Urticaria Pigmentosa (UP) - Patients with baseline UP	33	36	0.0210
Average relative change from baseline in the Body Surface Area (BSA) covered by UP (Wallace correction)	-12.34 ± 26.41	15.91 ± 59.79	
Darier's sign – Number of patients (baseline)	37	37	0.0187
Response rate for Darier's sign disappearance (Yes/No) in patients with "Darier's sign" at baseline	18.92%	2.70%	


2007


2014

Summary of AE with masitinib in the pivotal AB06006 study – protocol period.

AB06006 - Summary of AEs – [W0-W24]– Safety + Other population

Number (%) of patients with at least one	**Data in CSR v1.0**			**Updated Data within new system**		
	Masitinib (N=110)	*Placebo (N=110)*	*Delta (M-P)*	*Masitinib (N=110)*	*Placebo (N=110)*	*Delta (M-P*
AE	**109 (99.1%)**	**109 (99.1%)**	**0.0%**	**109 (99.1%)**	**109 (99.1%)**	**0.0%**
- Suspected/Not assessable				106 (96.4%)	90 (81.8%)	14.5%
SAE (non fatal)	**32 (29.1%)**	**15 (13.6%)**	**15.5%**	**32 (29.1%)**	**17 (15.5%)**	**13.6%**
- Suspected/Not assessable				23 (20.9%)	5 (4.5%)	16.4%
Death	**0 (0.0%)**	**1 (0.9%)**	**-0.9%**	**0 (0.0%)**	**1 (0.9%)**	**-0.9%**
- Suspected/Not assessable				0 (0.0%)	0 (0.0%)	0.0%
AE leading to study termination	**26 (23.6%)**	**6 (5.5%)**	**18.2%**	**26 (23.6%)**	**6 (5.5%)**	**18.2%**
- Per protocol	21 (19.1%)	5 (4.5%)	14.5%	21 (19.1%)	5 (4.5%)	14.5%
- As per safety rules	12 (10.9%)	4 (3.6%)	7.3%	12 (10.9%)	4 (3.6%)	7.3%
Severe AE	**55 (50.0%)**	**33 (30.0%)**	**20.0%**	**55 (50.0%)**	**34 (30.9%)**	**19.1%**
- Suspected/Not assessable				48 (43.6%)	15 (13.6%)	30.0%
AE leading to dose reduction	**24 (21.8%)**	**2 (1.8%)**	**20.0%**	**24 (21.8%)**	**2 (1.8%)**	**20.0%**
- Suspected/Not assessable				24 (21.8%)	2 (1.8%)	20.0%

Treatment of Aggressisve Diseases

Cytoreductive Treatment

- High dose steroids
- Alpha Interferon (?)
- Cladribine
- Kinases Inhibitors
- Thalidomide
- mTOR inhibitors (Rapamycine, Temsirolimus)
- Bone marrow transplantation
- Treatment of AHNMD

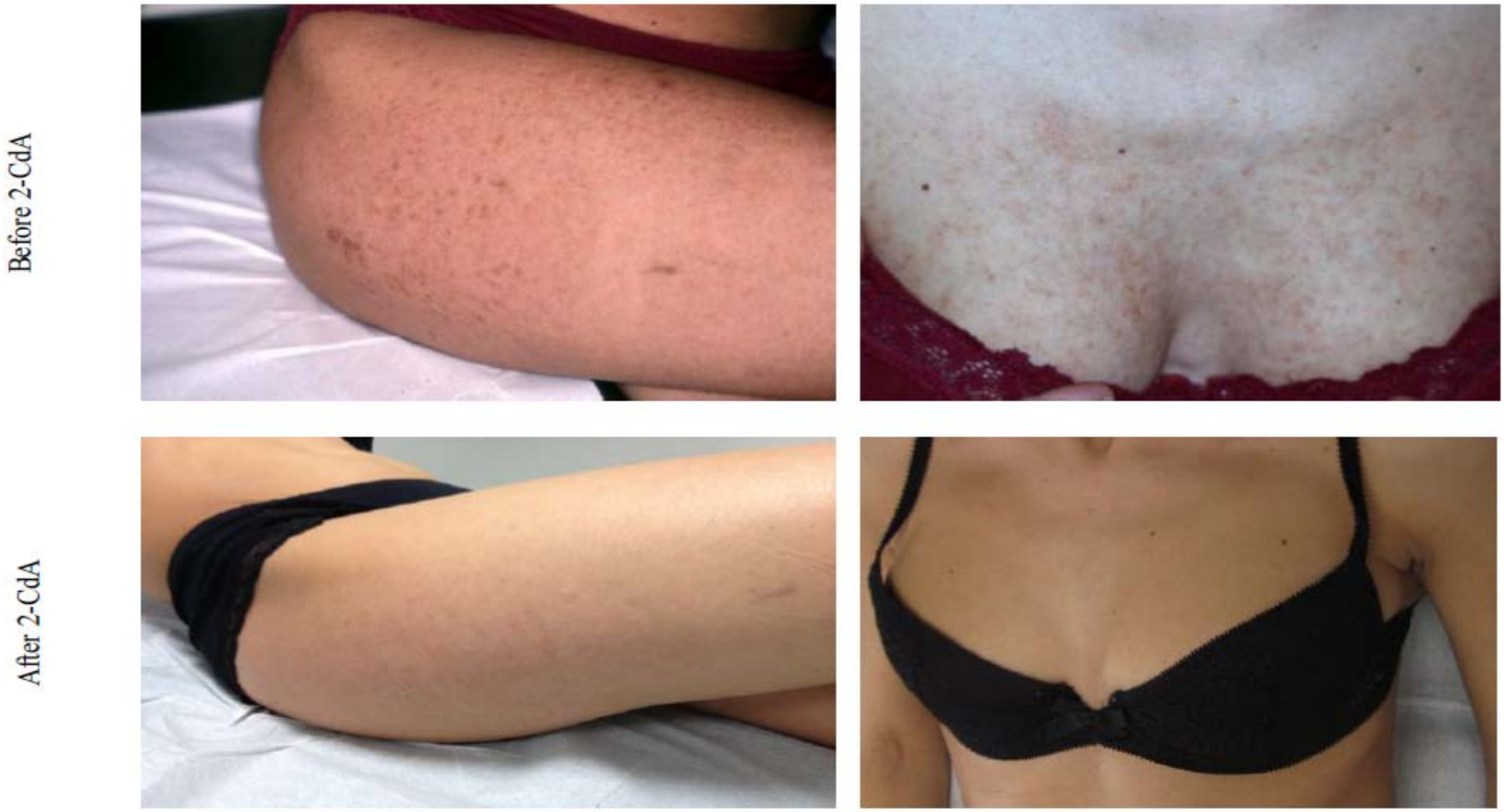
Clinical Response

Clinical data responses	No. of patients before treatment (%)	No. of patients after treatment (%)	P
Mediators release symptoms			
Fatigue	53 (79)	22 (33)	<.0001
Flush	34 (52)	11 (17)	<.0001
Pruritus	33 (51)	16 (25)	<.0001
Diarrhea	37 (55)	9 (13)	<.0001
Abdominal pain	33 (49)	12 (18)	<.0001
Neuropsychiatric symptoms	24 (37)	13 (20)	.0009
Headache/pain	23 (34)	15 (22)	.0046
Nausea, vomiting	22 (33)	8 (12)	.0001
Dyspnea	14 (21)	5 (7)	.007
Anaphylaxis	7 (10)	0 (0)	.02
Pollakiuria	9 (14)	5 (8)	.13
Mast cell infiltration-related symptoms			
Urticaria pigmentosa	48 (73)	10 (15)	<.0001
Hepatomegaly	34 (51)	24 (36) (+1)*	.006
Splenomegaly	32 (48)	24 (36)	.013
Weight loss, fever, chills, night sweats (B-signs)	25 (37)	9 (13)	<.0001
Lymphadenopathy	18 (27)	15 (22) (+2)*	.44
Ascites	15 (22)	8 (12)	.023
Biological parameters			
Hemoglobin, g/dL			
Hb <10	18 (27)	13 (19)	.07
Absolute eosinophil count, $\times 10^9$/L			
AEC >.5	14 (24)	12 (21)	.5
Platelet count, $\times 10^9$/L			
Platelet <100	14 (22)	13 (19)	.24
Liver parameters (total bilirubin, SAP, AST, ALT > UNL)	9 (13)	7 (10) (+1)*	.47
Serum tryptase, ng/mL			
Mean value	172	97	.01
Median value	79	53	

Clinical improvement for

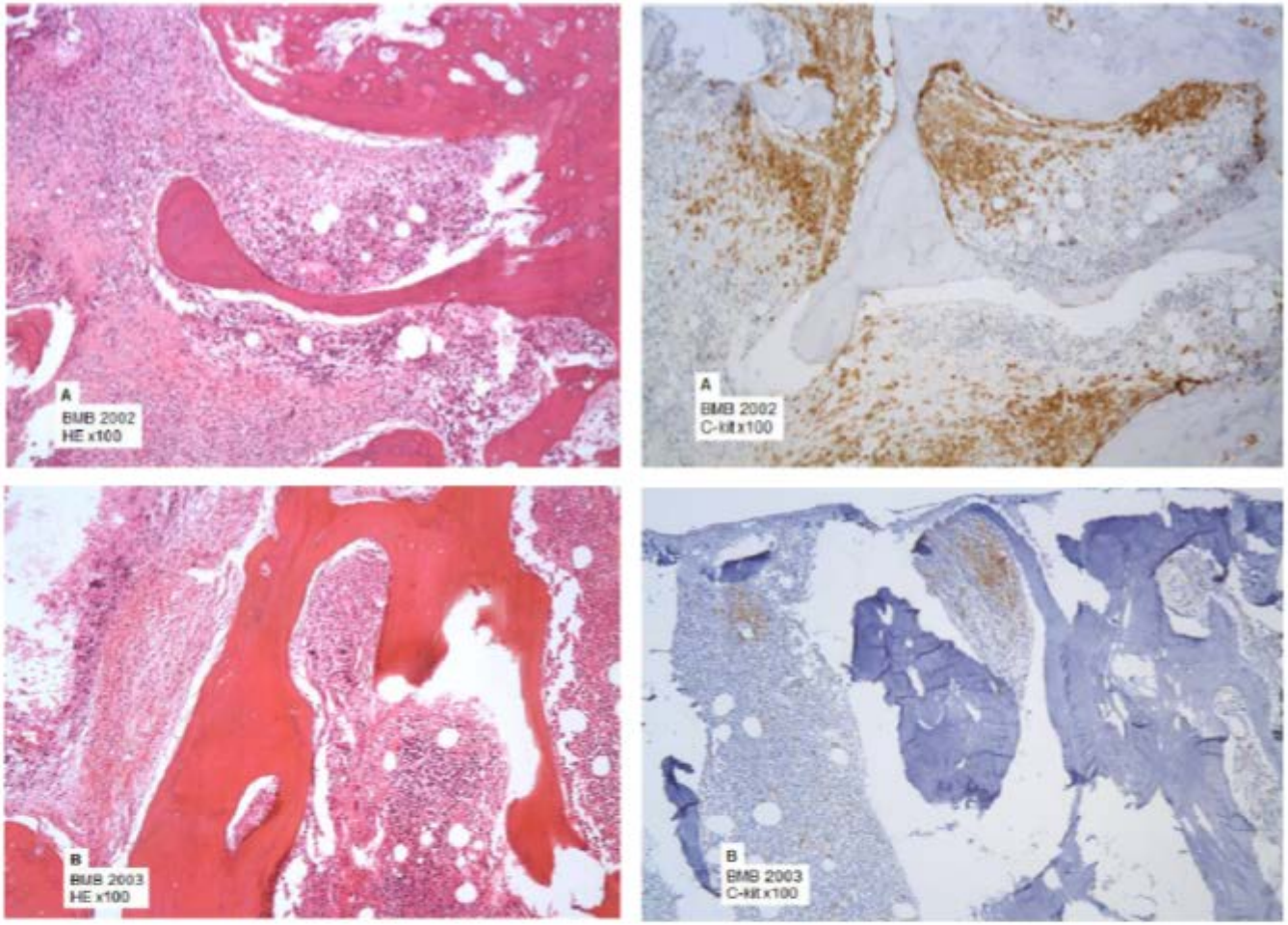
- 10/11 mediator release symptoms including anaphylaxis
- 5/6 mast cell infiltration-related symptoms including urticaria pigmentosa, and organomegaly (P<.02)
- Serum tryptase levels decreased (P= .01).

Complete clinical response of urticaria pigmentosa with 2-CdA treatment



38 patients (80%) comprising 11 CR, 17 MR and 10 PR.

ASM Patient

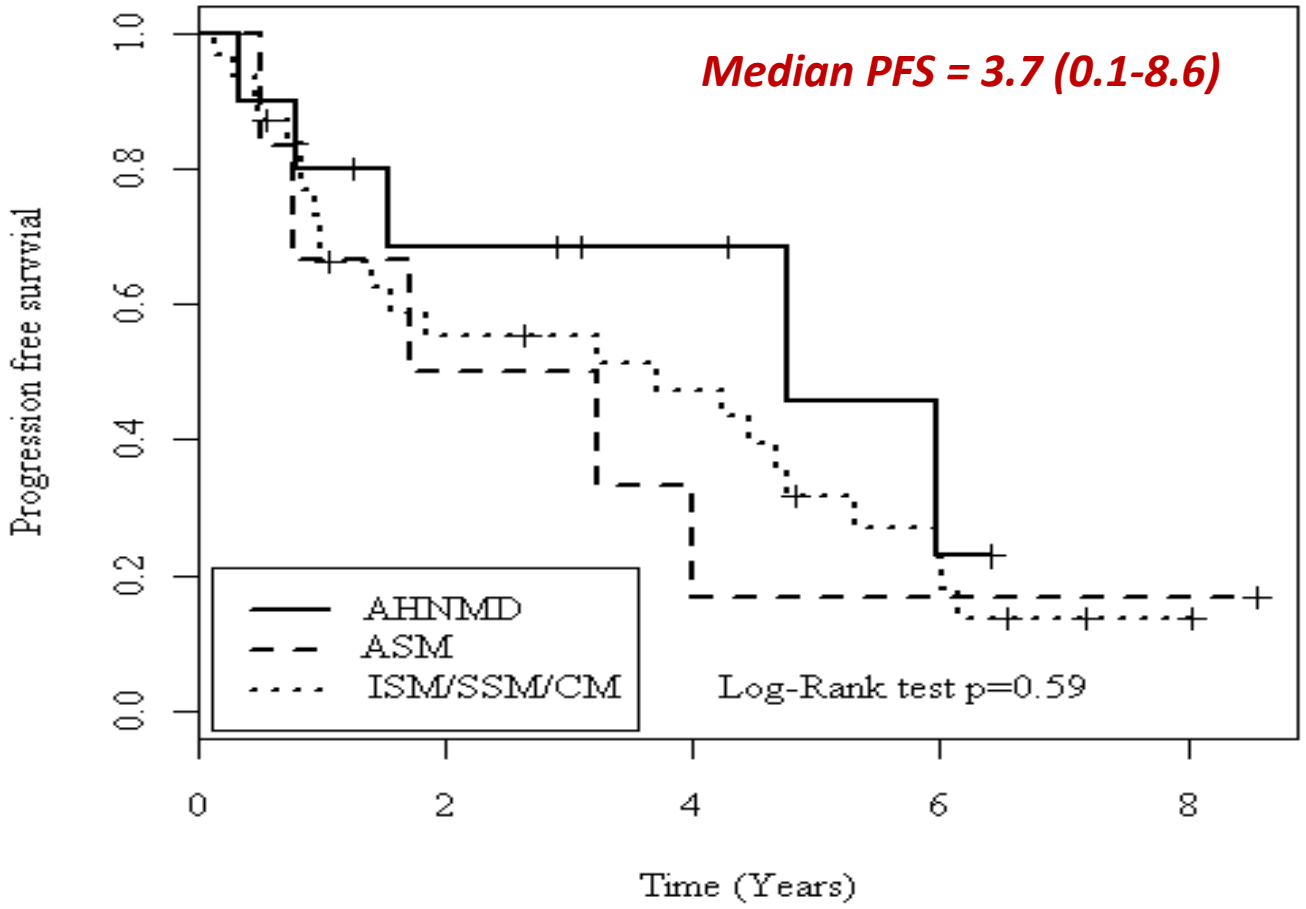


before

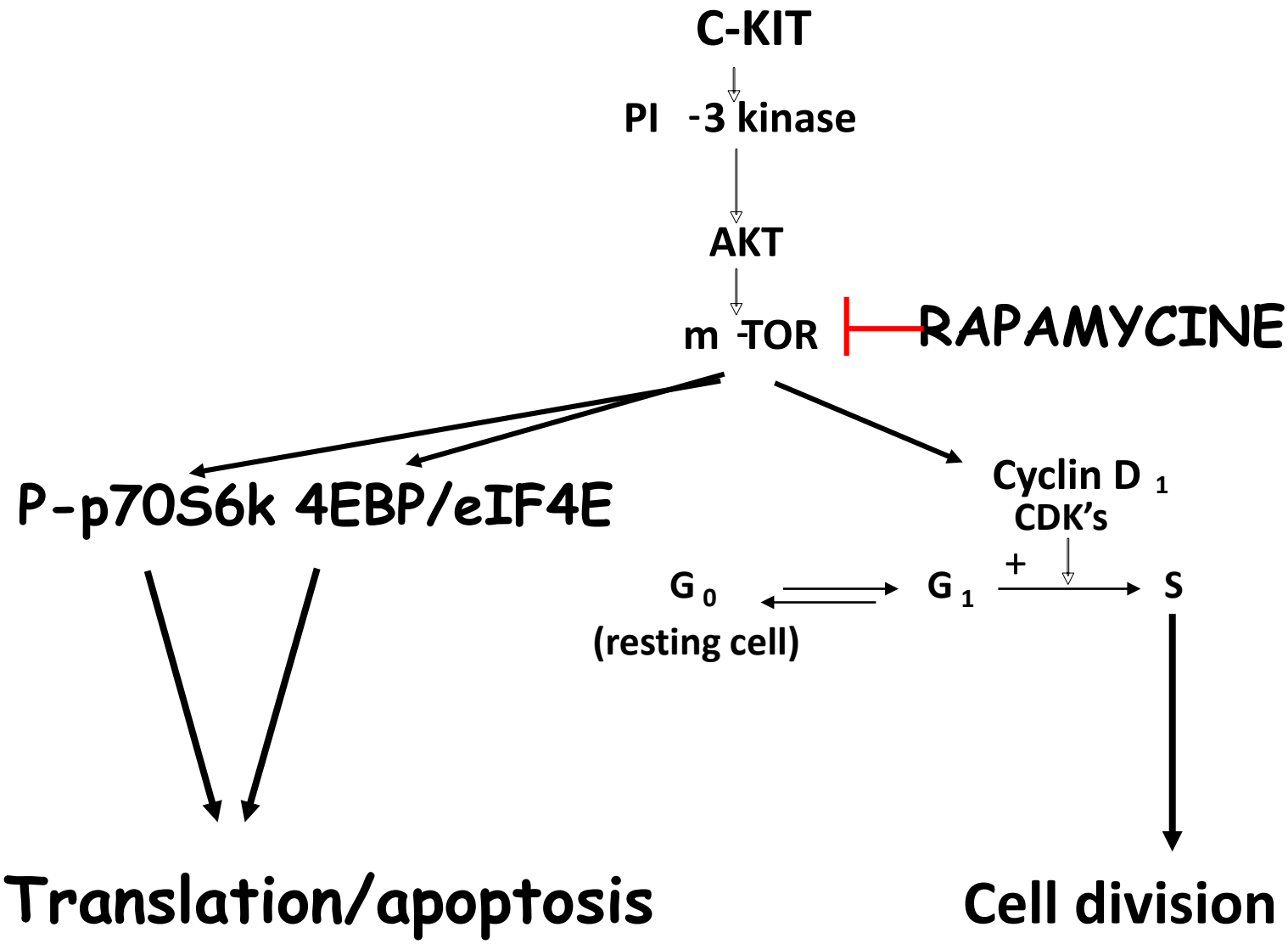
After

Bone marrow biopsy before 2-CdA in 2002 (A) showing 40% of mast cells infiltration (H&E and c-kit staining HPF x100)
Bone marrow biopsy after treatment (2003) (B) revealing a decrease of the mast cells infiltration (10%) (H&E and c-kit staining HPF x100)

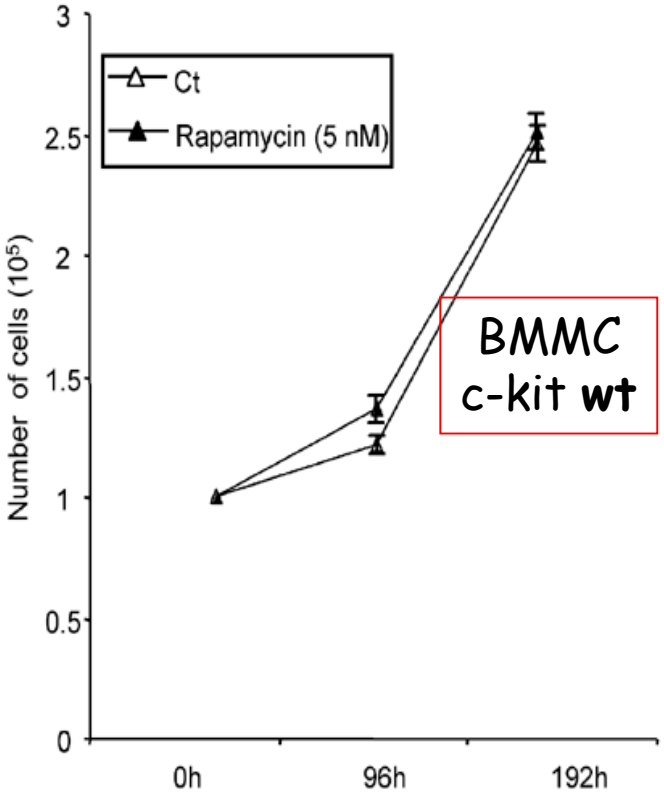
Progression free survival

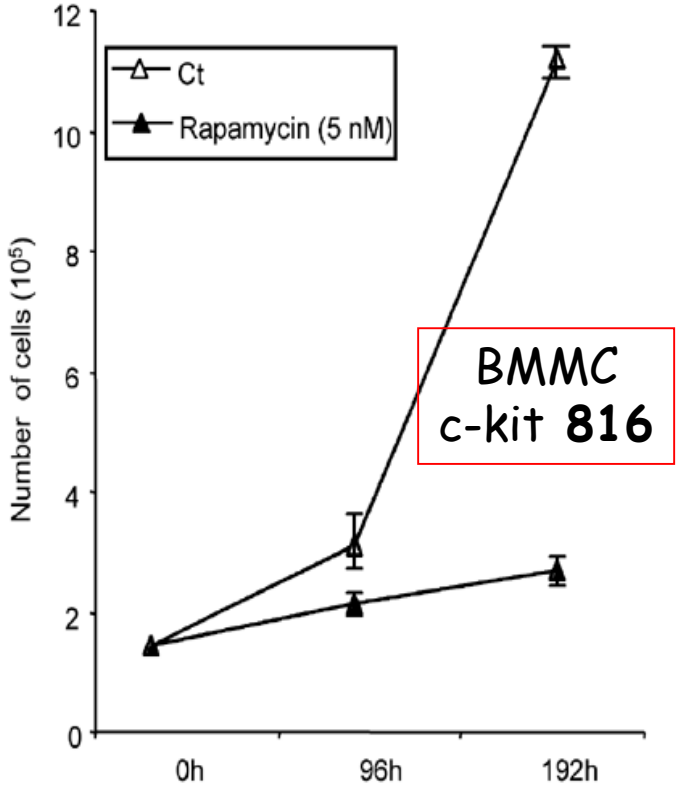


Signaling of PI-3k/Akt/mTOR

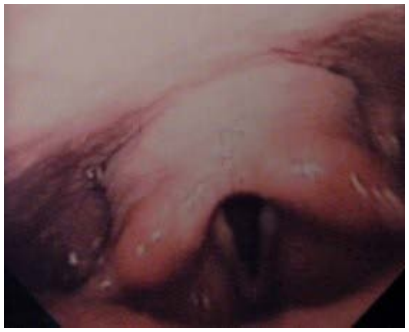


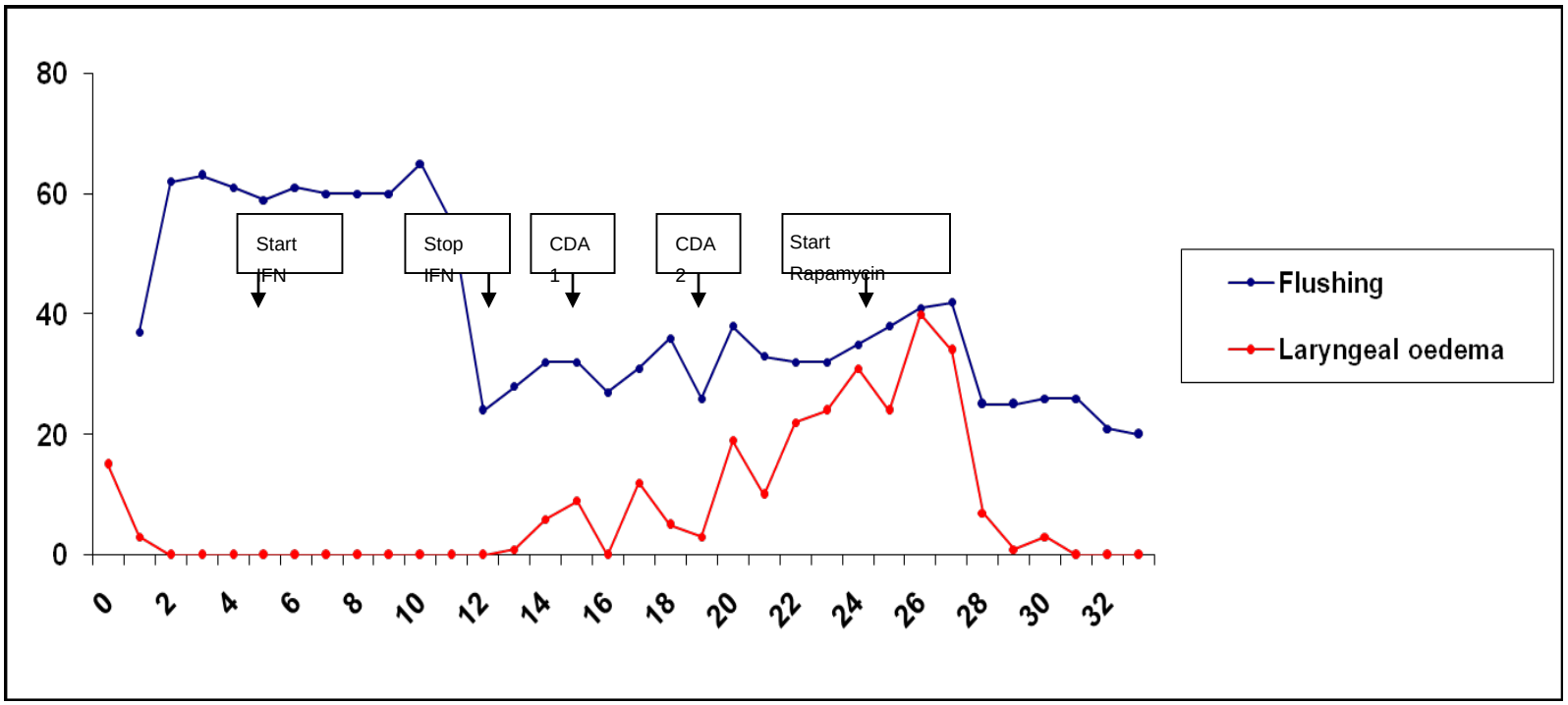
Rapamycin inhibits cell growth of C-KIT D816V Mast cells





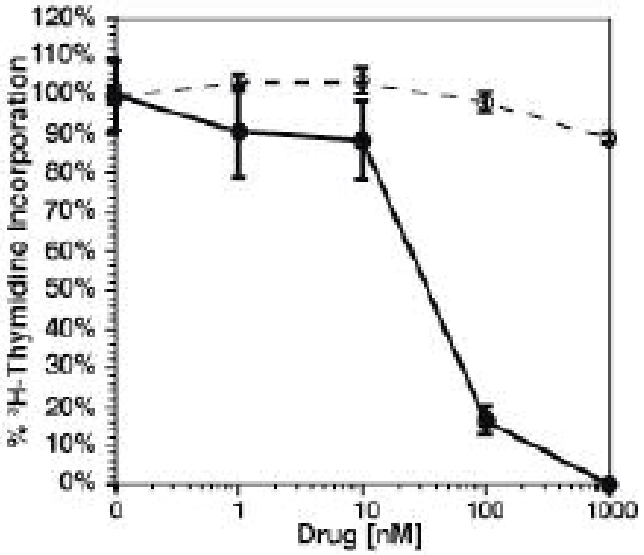
Rapamycin and MS





PKC412 (N-benzyl staurosporine)

- Inhibits PKC, VEGFR, Kit, PDGFR, flt3
- Phase I/II trials in hematologic and solid tumors
  - Nausea, vomiting, diarrhea, fatigue
- Inhibits D816V c-kit



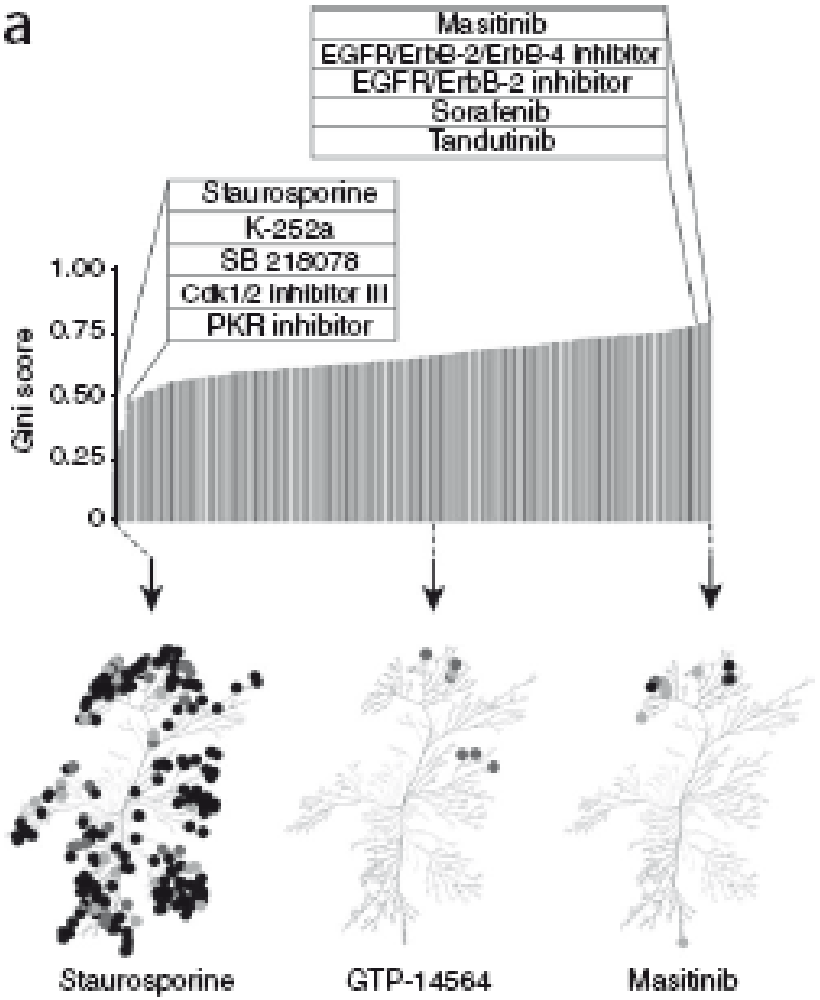
BAF3 D816V cells

Gotlib et al. Blood, in press, 2005

Comprehensive assay of kinase catalytic activity reveals features of kinase inhibitor selectivity

nature biotechnology

Theonie Anastassiadis[1], Sean W Deacon[2], Karthik Devarajan[1], Haiching Ma[2] & Jeffrey R Peterson[1]



ORIGINAL ARTICLE

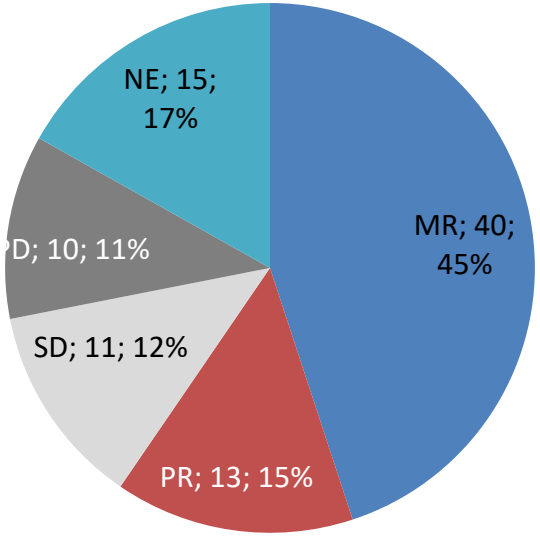
Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis

Jason Gotlib, M.D., Hanneke C. Kluin-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 Labed, 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.

Efficacy

Response

- Largest prospective trial in advanced SM; 65% of patients presented with > 1 C-finding
- A study steering committee adjudicated the eligibility and response
  - Of 116 enrolled patients, 89 were eligible for efficacy assessment

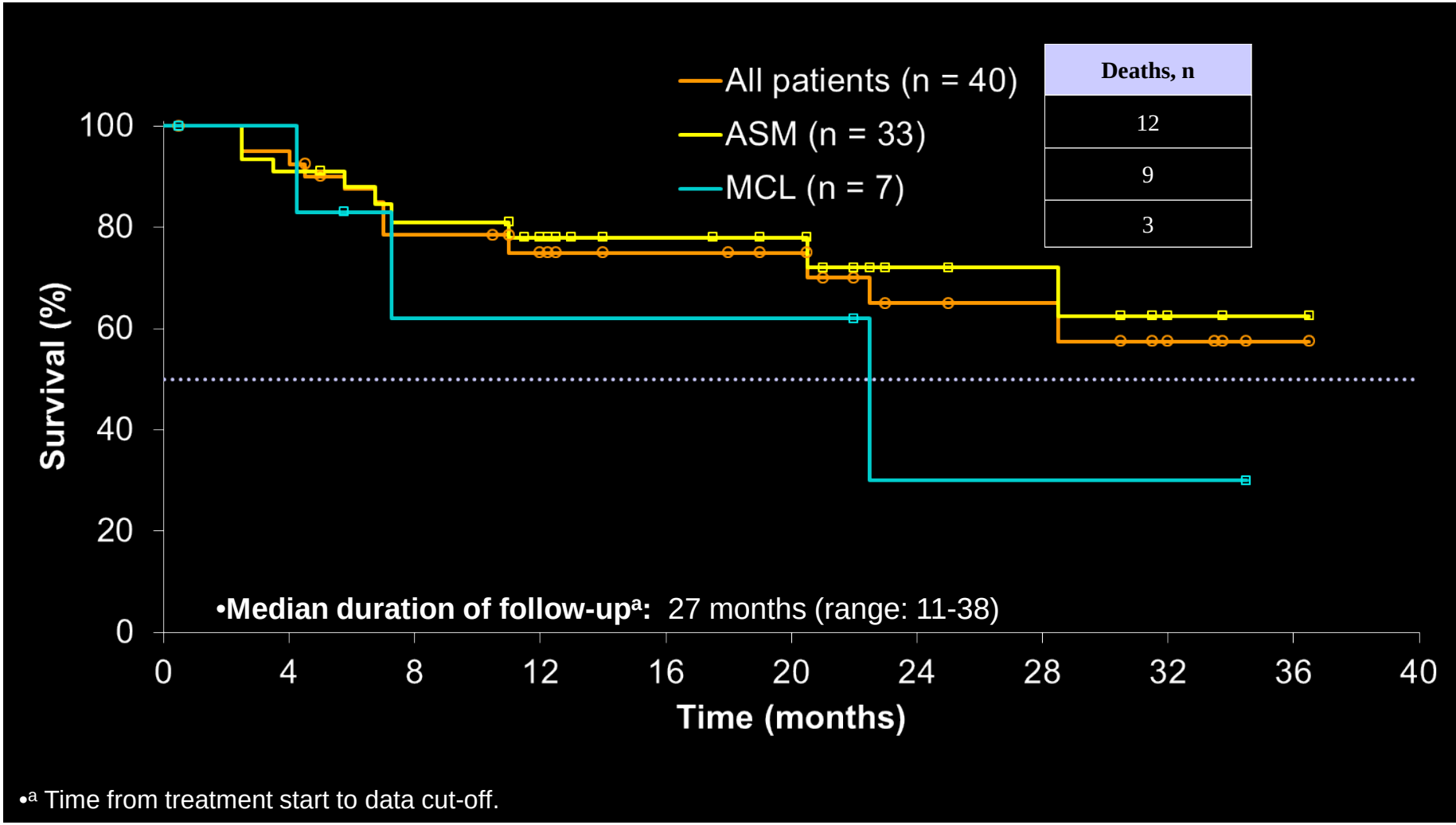


ORR (MR + PR) = 53 (60% [95% CI, 49-71])

MR, major response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Gotlib J, et al. *N Engl J Med*. 2016;374:2530-2541.

Overall Survival

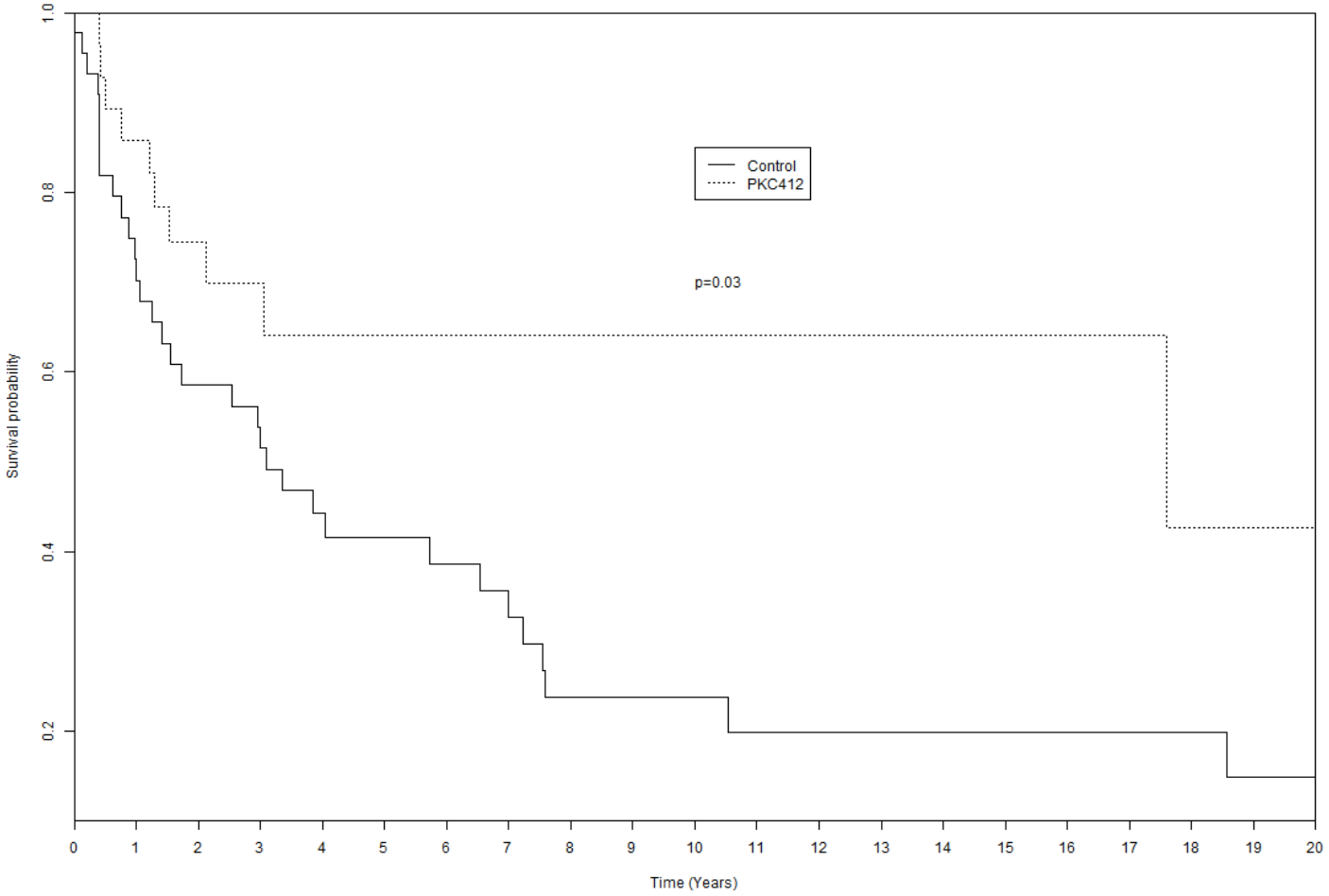


•[a] Time from treatment start to data cut-off.

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

Prospective survey of PKC412 compassionate use for adult patients suffering from AdSM in France. Survival curves in PKC412 treated and control groups

MO Chandesris et al



The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 374;26 NEJM.ORG JUNE 30, 2016

Safety

Nonhematologic AEs (ITT; n = 116)

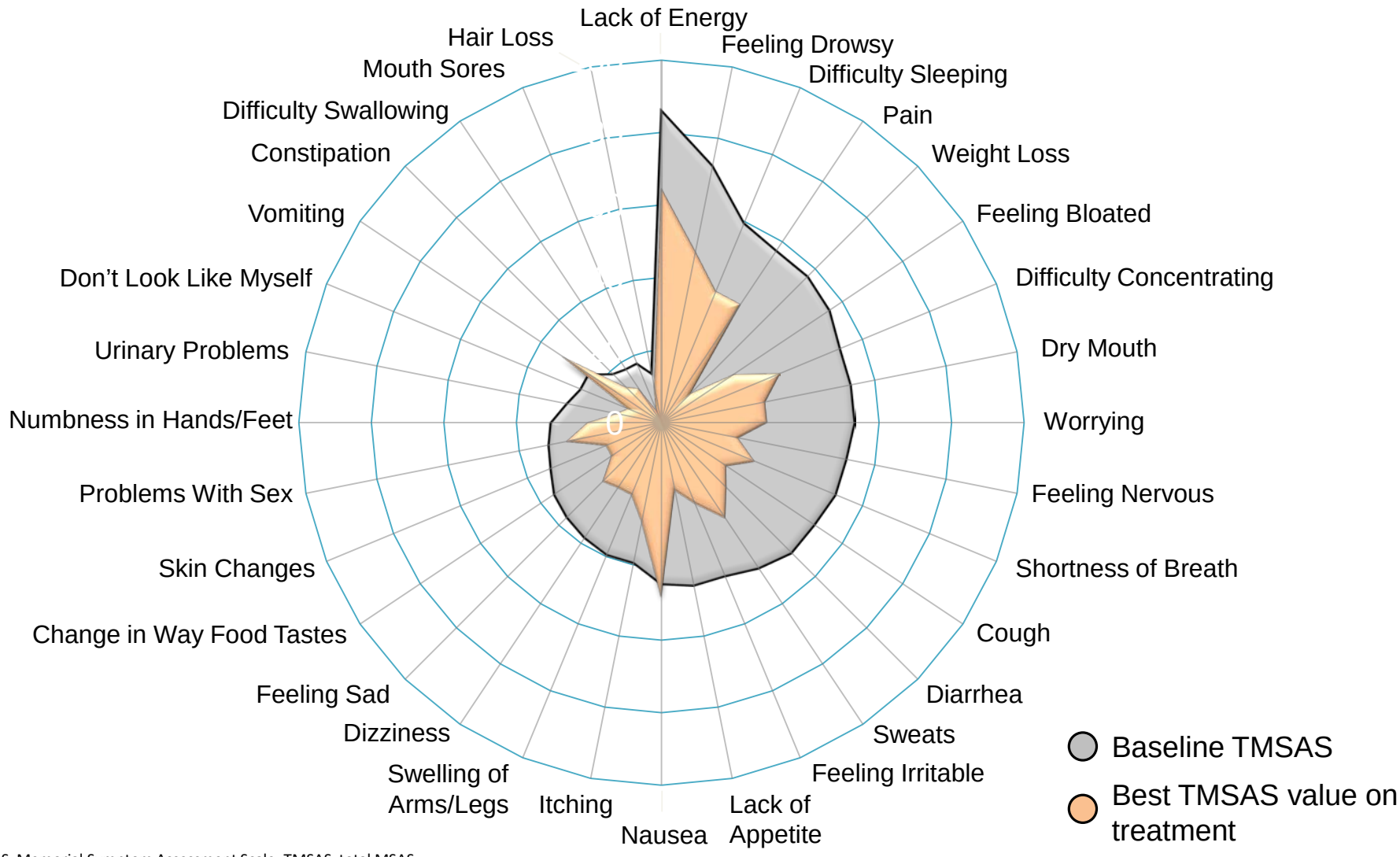
Most Common Nonhematologic AEs (> 20% of patients)	Regardless of Study Drug Relationship, n (%)		Suspected Related to Study Drug, n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nausea	92 (79)	7 (6)	84 (72)	7 (6)
Vomiting	77 (66)	7 (6)	71 (61)	7 (6)
Diarrhea	63 (54)	9 (8)	32 (28)	3 (3)
Peripheral edema	40 (34)	5 (4)	3 (3)	0
Abdominal pain	33 (28)	4 (3)	6 (5)	0
Fatigue	32 (28)	11 (9)	9 (8)	0
Pyrexia	31 (27)	7 (6)	4 (3)	1 (1)
Constipation	28 (24)	1 (1)	4 (3)	0
Headache	27 (23)	2 (2)	7 (6)	0

ITT, intent-to-treat.

Gotlib J, et al. *N Engl J Med*. 2016;374:2530-2541.

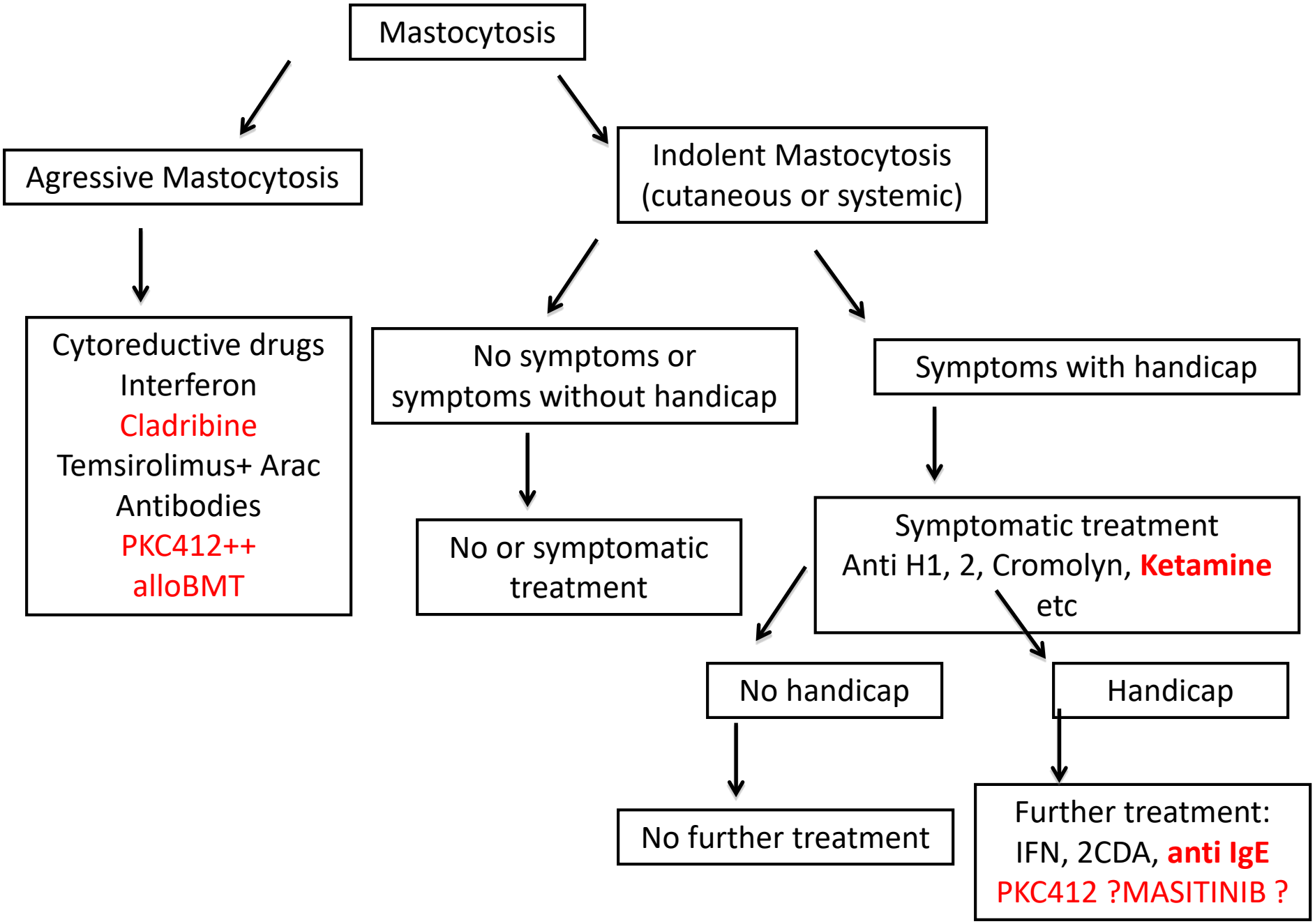
Exploratory Endpoints

Symptom burden – MSAS



MSAS, Memorial Symptom Assessment Scale; TMSAS, total MSAS.

Gotlib J, et al. *N Engl J Med*. 2016;374:2530-2541.


Mastocytosis
Agressive Mastocytosis
Indolent Mastocytosis
(cutaneous or systemic)
Cytoreductive drugs
Interferon
Cladribine
Temsirolimus+ Arac
Antibodies
PKC412++
alloBMT
No symptoms or
symptoms without handicap
Symptoms with handicap
No or symptomatic
treatment
Symptomatic treatment
Anti H1, 2, Cromolyn, Ketamine
etc
No handicap
Handicap
No further treatment
Further treatment:
IFN, 2CDA, anti IgE
PKC412 ?MASITINIB ?

Mast Cell Activation Syndrome Definitions

- Signs of symptoms
- Primary, secondary or idiopathic
- Mast cell release syndrome
- Decrease in the frequency severity and resolution of symptoms with
  - anti-mediator therapy
  - mast cell stabilizers
- Biology increase of mast cell mediators above the basal value during acute episodes

Symptoms of MCAS

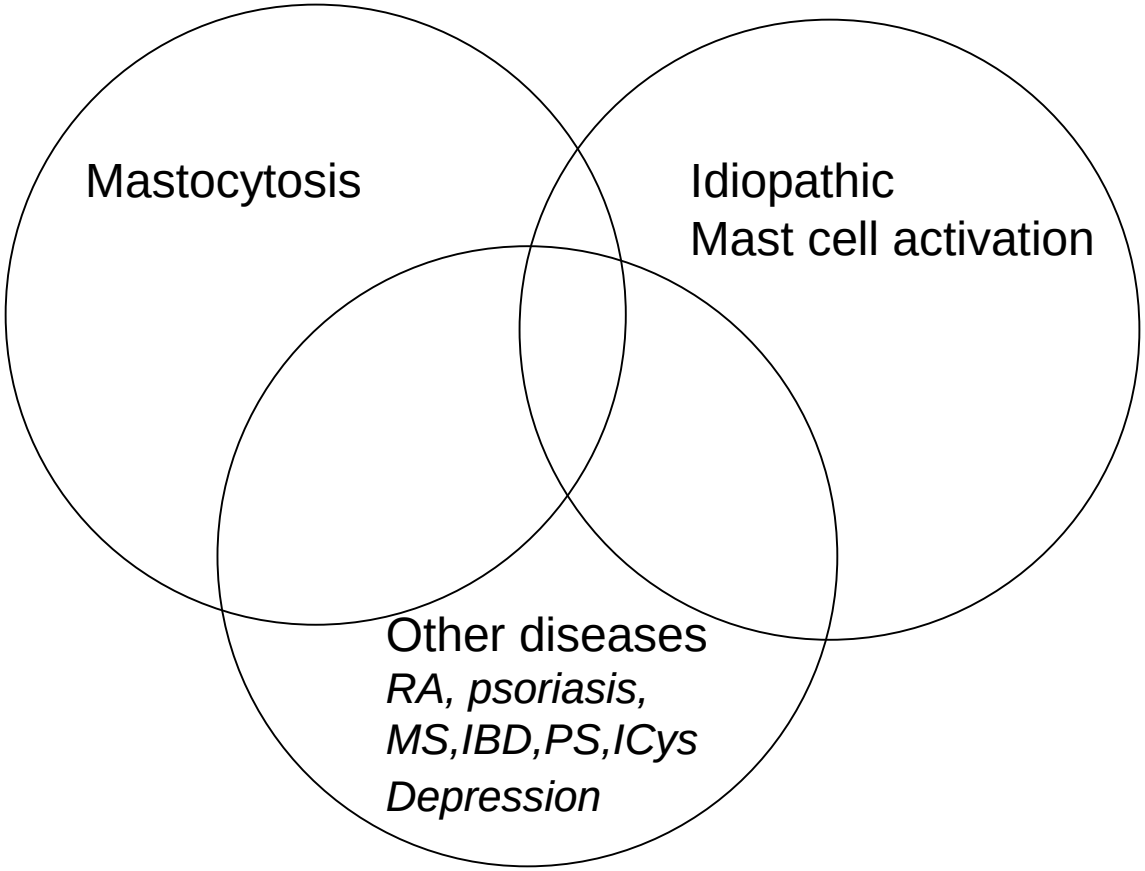
Table 1 Clinical symptoms typically found in patients suffering from mast cell activation (MCA)* and their impact in the evaluation of MCA syndromes (MCAS)

Symptom(s)*	Diagnostic impact in the evaluation of severe MCA (= suspected MCA syndrome = MCAS)
Hypotension ± shock	Pathognomonic key finding in MCAS (other underlying diseases that could explain hypotension need to be excluded)
Tachycardia	Tachycardia usually accompanies hypotension in MCAS
Diarrhea	Usually accompanied by systemic symptoms of MCAS; in the absence of these, the diagnosis remains uncertain
Abdominal cramping	Usually accompanied by systemic symptoms of MCAS; in the absence of these, the diagnosis remains uncertain
Nausea	Usually accompanied by systemic symptoms of MCAS; in the absence of these, the diagnosis remains uncertain
Flushing	Severe flushing may be an indicator of MCAS; in these cases; flushing is often accompanied by systemic symptoms
Pruritus	Severe pruritus may be an indicator of MCAS; in these cases; flushing is often accompanied by systemic symptoms
Acute urticaria	Severe acute urticaria may be an indicator of MCAS; in these cases, systemic symptoms are usually found
Angioedema	Severe angioedema may be an indicator of MCAS and then is usually accompanied by systemic symptoms
Nasal congestion	Diagnostic only in the context of other MCAS-related symptoms and the presence of other MCAS criteria
Wheezing	Diagnostic only in the context of other MCAS-related symptoms and the presence of other MCAS criteria
Headache	Diagnostic only in the context of other MCAS-related symptoms and the presence of other MCAS criteria
Neurologic symptoms	Diagnostic only in the context of other MCAS-related symptoms and the presence of other MCAS criteria
Fatigue	Diagnostic only in the context of other MCAS-related symptoms and the presence of other MCAS criteria

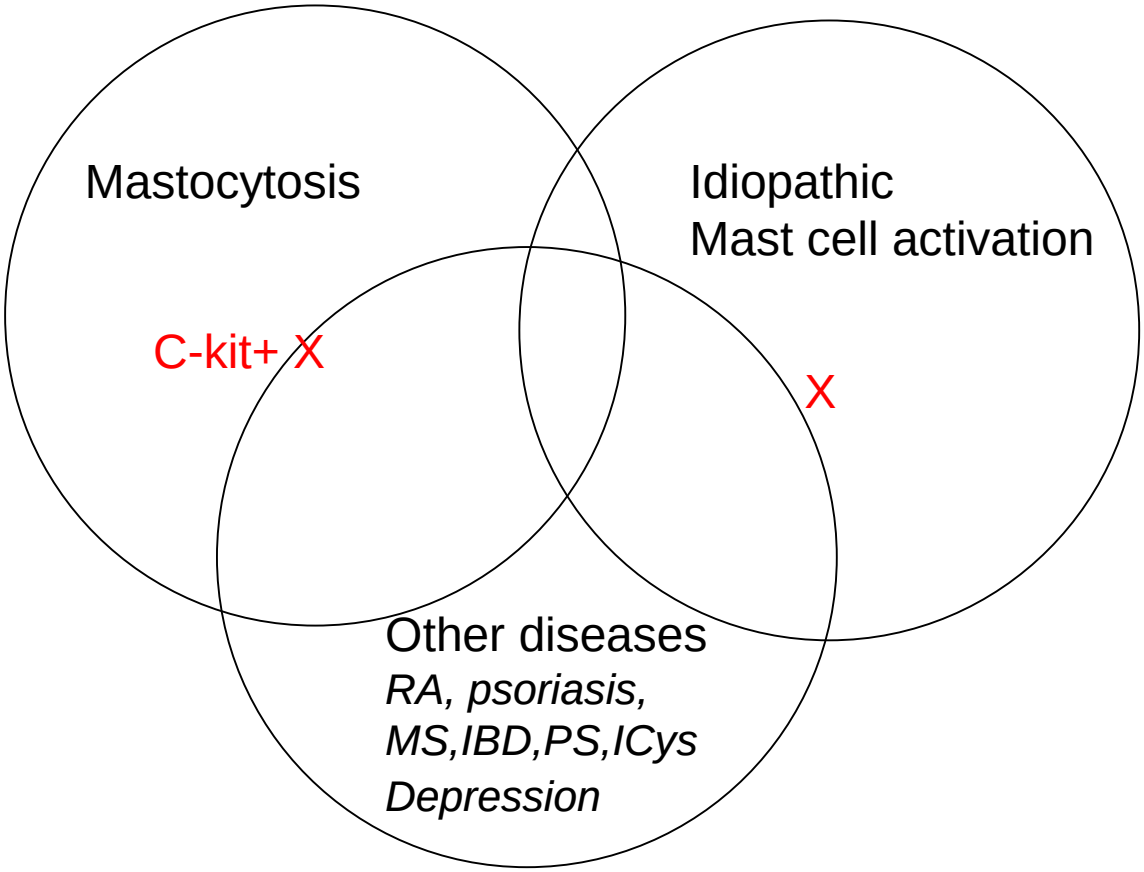
*All these symptoms can be triggered by mast cell-derived compounds. Therefore, an isolated symptom is not a typical finding in MCAS patients. Rather, the likelihood of MCA, and thus MCAS, increases when two or more of these symptoms have been recorded and the symptoms improve in response to therapy with antimediator-type drugs or mast cell-stabilizing agents.

Pain, Psychiatric, Bone and joints, Urinary ?

Spectrum of MCAS



Spectrum of MCAS

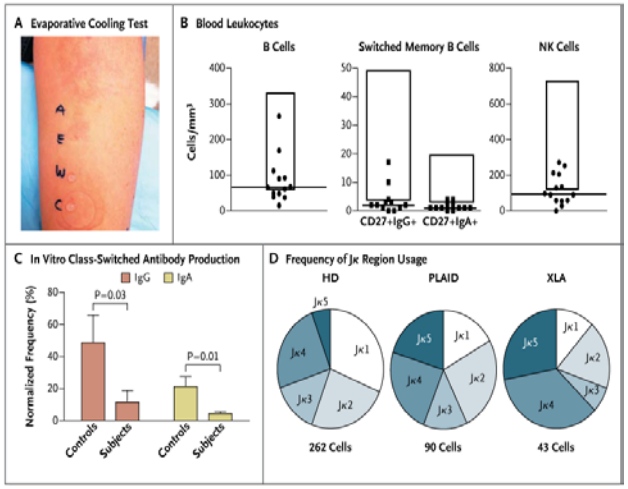


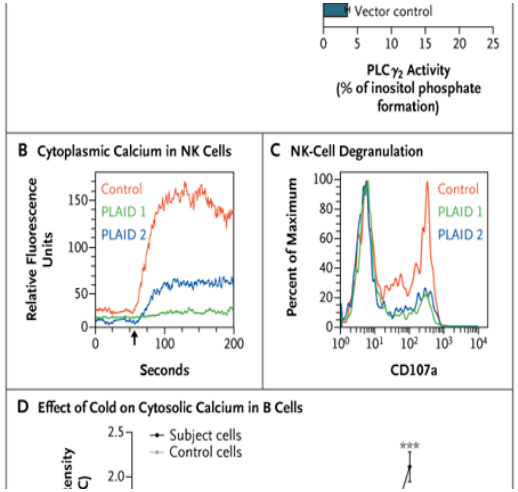
X =kinase inhibited by Masitinib

Cold Urticaria, Immunodeficiency, and Autoimmunity Related to *PLCG2* Deletions

30–338. doi:10.1056/NEJMoa1102140.

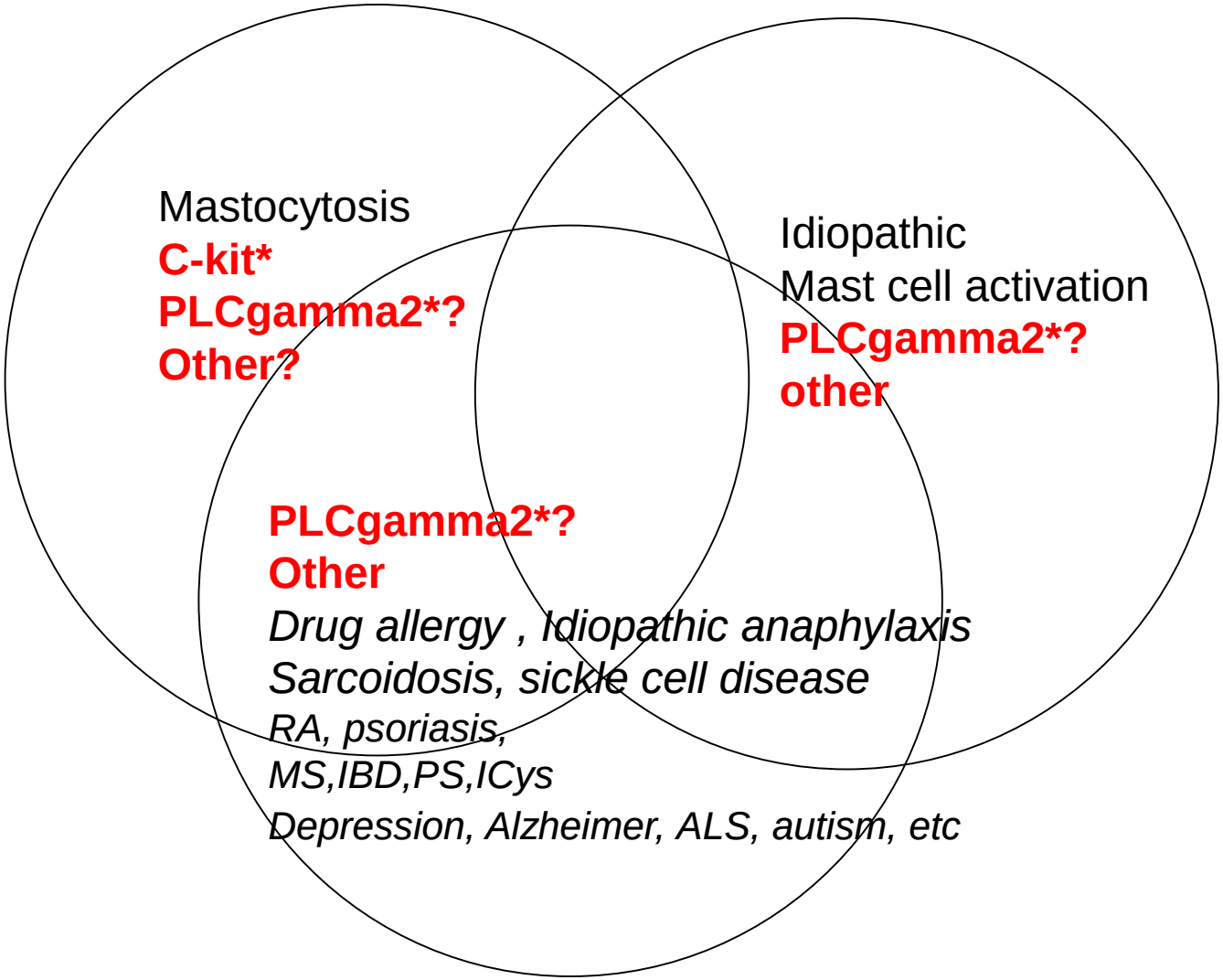
Clinical Manifestation	Frequency *no./total no. (%)*
Cold urticaria	27/27 (100)
Recurrent sinopulmonary infection	12/27 (44)
Antibody deficiency*	15/20 (75)
Common variable immunodeficiency	3/27 (11)
Symptomatic autoimmune disease†	7/27 (26)
Positive test for antinuclear antibodies‡	13/21 (62)
Symptomatic allergic disease	15/27 (56)





Spectrum of MCAS

Other =Inhibited by Masitinib



Insect sting allergy in adults

- MCAS and mastocytosis are at higher risk to develop higher reaction++
- Pt with high Tryptase are at higher risk
- Always look for MCAS and Mastocytosis because higher risk of anaphylaxis++
- Higher Tryptase in ederly patient and cardiovascular diseases++
- History, Tryptase (15min-3h), Few hours after (Basal tryptase)

Score of MCAS (REMA score) >2 Clonal Mast cells

Variable		Score
Gender	Male Female	+1 –1
Clinical symptoms	Absence of urticaria and angioedema Urticaria and/or angioedema Presyncope and/or syncope	+1 –2 +3
Serum tryptase	<15 ng/mL >25 ng/mL	–1 +2

Sensitivity 92% Specificity 81%

Diagnostic Procedure for Mastocytosis

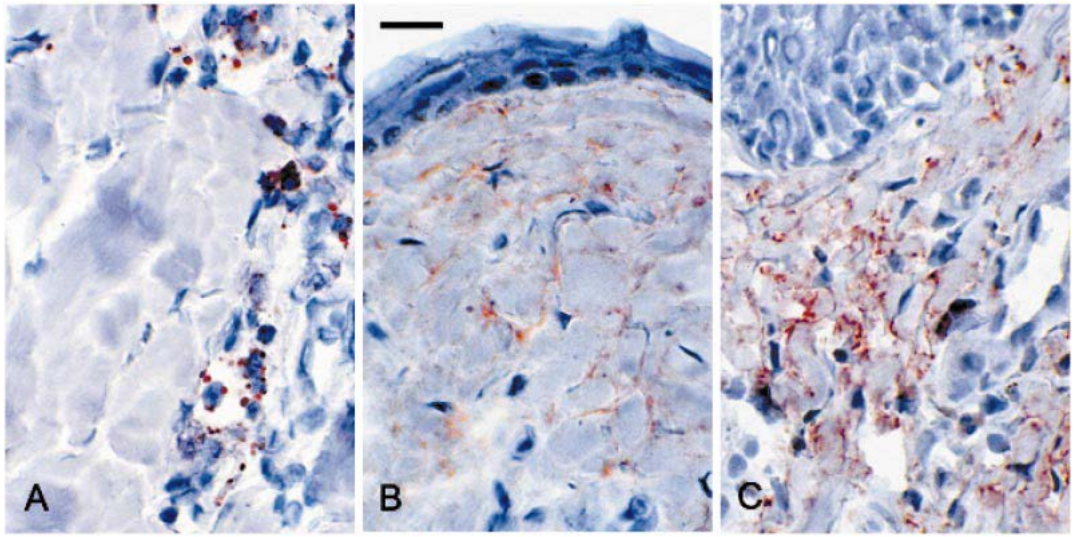
- Personnal and famillial history of MCAS/mastocytosis
- Clinical examination (UP, Dermographism, other)
- Tryptase level
- Bone marrow biopsy
- Bone marrow aspiration and cytometry
- c-kit analysis
- Basophil activation
- IgE against venoms (skin tests, Serum specific IgE); 3 To 6 weeks after
- In vitro basophil activation test (CCR3+:CD3-, CD123+, HLA-DR-, RIgE+, CD203+C63 after activation
- Osteodensitometry (30% of osteopenia in Venom reaction)

Venom (no IgE) and Idiopathic Anaphylaxis?

Atopic dermatitis

Skin mast cell histamine release following stem cell factor and high-affinity immunoglobulin E receptor cross-linking in dogs with atopic dermatitis

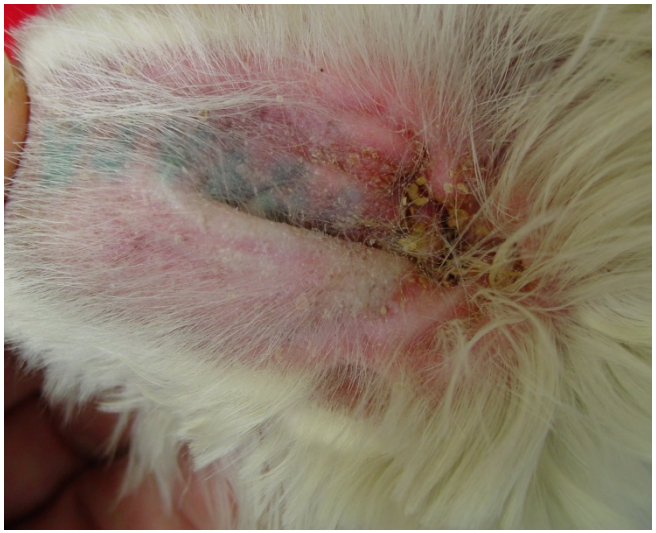
BRUCE HAMMERBERG,* THIERRY OLIVRY† and SUSAN M. ORTON*

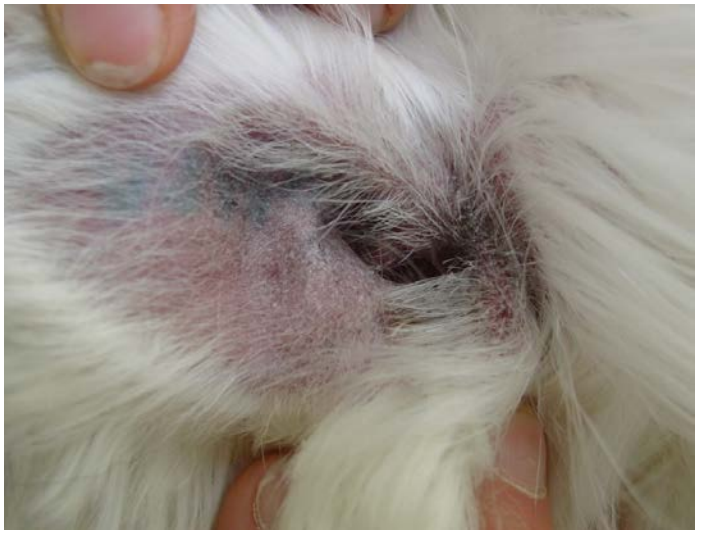


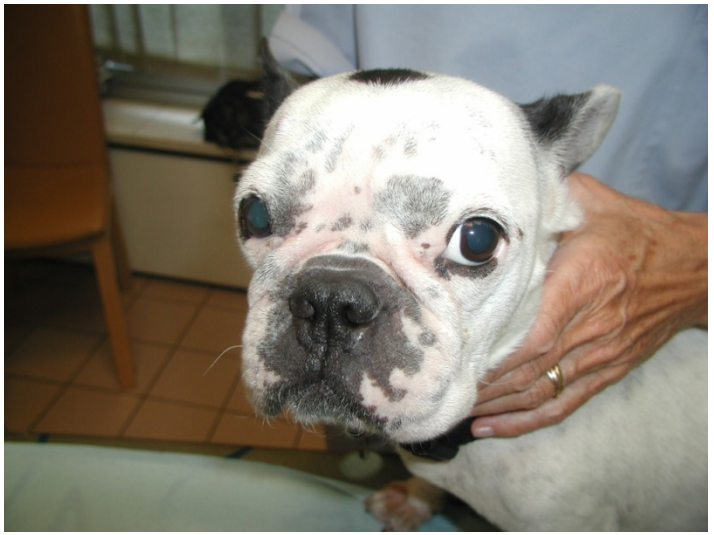
SCF expression in normal skin and DA

By blocking c-kit Kinavet might reduced IgE hypersensitivity

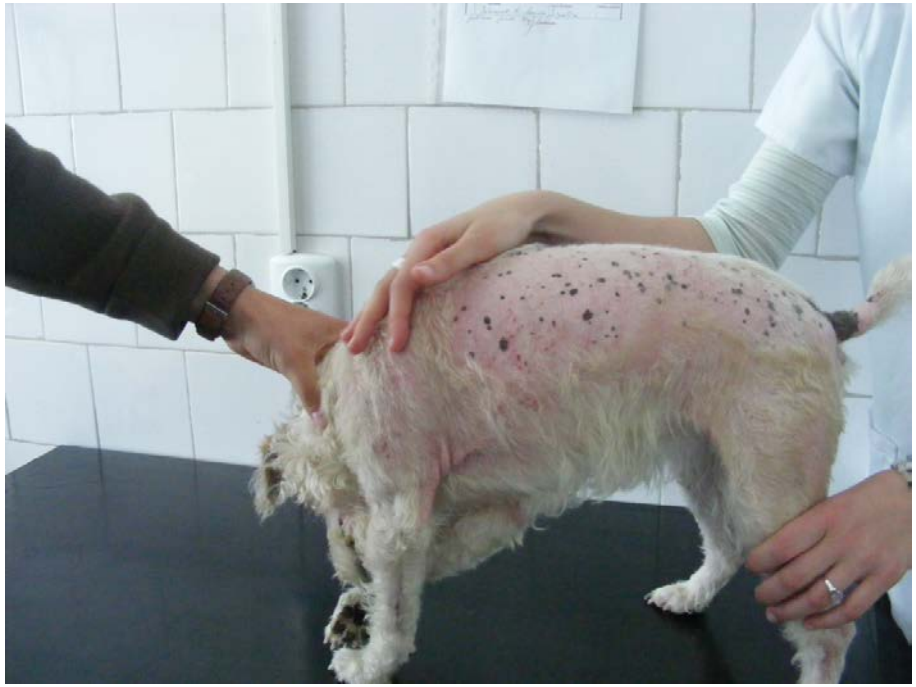
Results of Efficacy (5)

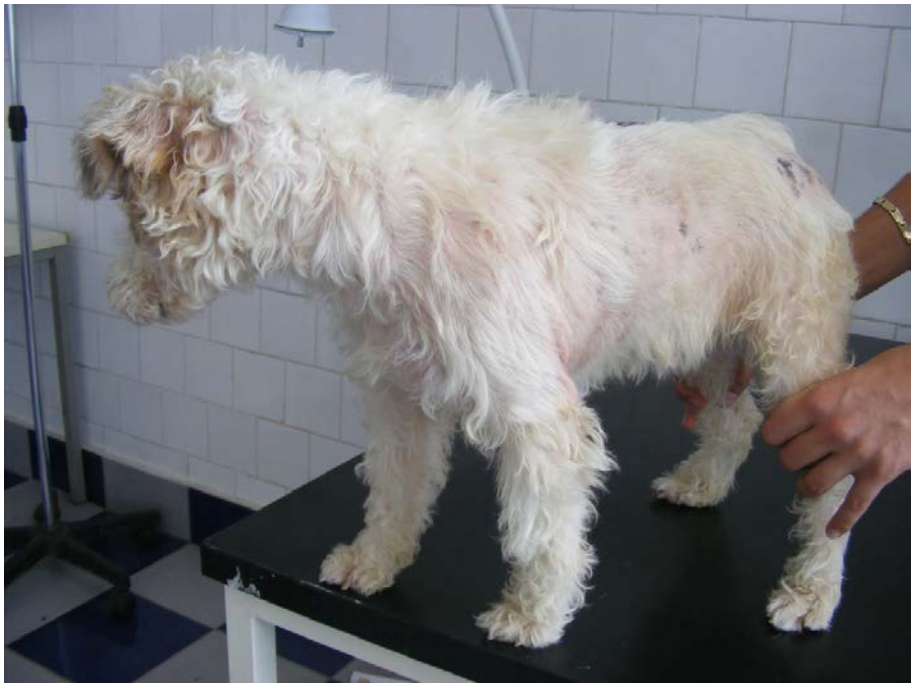






AB SCIENCE

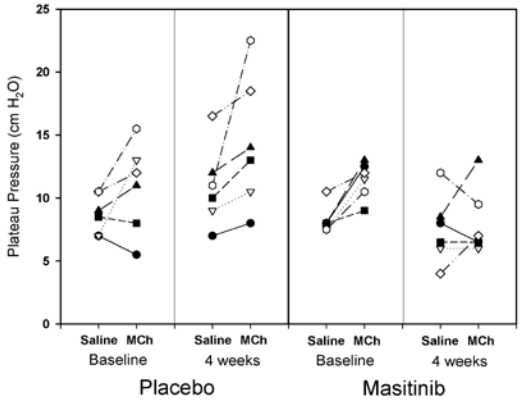


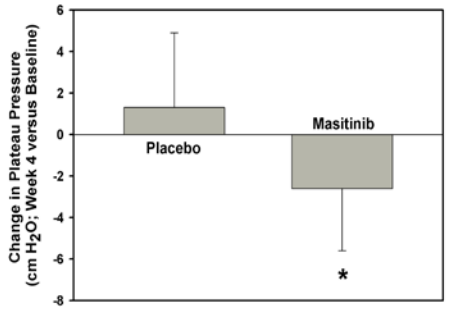


Results

	Before treatment	After treatement
Placebo	44%	30%
Masitinib	46%	7%

Eosinophil count





Bronchial pressure

In a human clinical phase II trial in asthma, masitinib demonstrated preliminary efficacy

Exacerbation

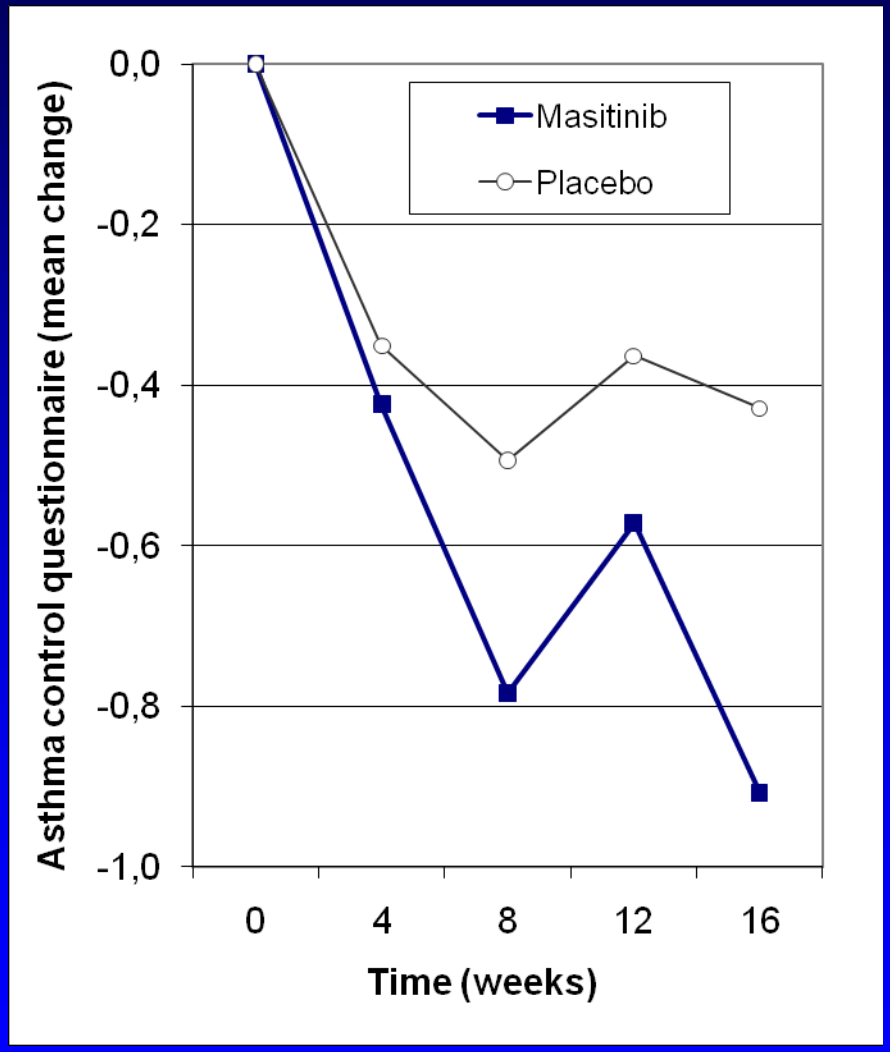
	Masitinib (N=33)	Placebo (N=11)
Number (%) of patients	14 (42.4 %)	6 (54.5 %)
	- 22%	
Number per month	0.5 ± 0.7	0.9 ± 1.0
	-44%	
Number per patient	0.22 ± 0.59	0.37 ± 0.53
	-40%	

Corticoisteroids Reduction

	Masitinib (N=19)	Placebo (N=6)
Absolute change between W4 and W16 (mg)		
Mean ± Std Median	-14 mg ± 14 -15 mg	-7 mg ± 16 -8 mg
% change between W4 and W16		
Mean ± Std Median	-52% ± 53 -65%	-28% ± 47 -38%
Number (%) of weaned patients	6 (31.6 %)	0 (0.0 %)

Patients initially treated with more than 15 mg of prednisone

Asthma Control



Julie Bru
Sophie Georg
Zakia Belaid

Geneviève Courtois
Marie Bouillié
Francine Côté
Pascal Amireault
Flavia Guillem
David Sibon
Yves Lepelletier

Inserm U891 - Marseille
Patrice Dubreuil
Sébastien Letard

Plateforme d'imagerie cellulaire - Imagine
phaëlle Devaux Nicolas Goudin
Meriem Garfa-Traore

stocytoses - NEM
ne Bodemer
Olivier Lortholary

Laboratoire d'hématologie - NEM
Vahid Asnafi Ludovic Lhermitte
Patrick Villarese

Laboratoire de cytogénétique - NEM
Serge Romana Isabelle Radford-Weiss
Gwendoline Soler

Service de pathologie - HMN
Philippe Gaulard Nicolas Ortonne
Nadine Martin

Laboratoire Télomères - Institut Curie
Arturo Londono-Vallejo
Irena Draskovic

Inserm U768 - NEM
Patrick Revy
Tangui Le Guen

Service de pathologie - NEM
Nicole Brousse Danielle Canioni
Sylvie Fraitag Stéphanie Leclerc-Mercier
Gisèle, Martine, Annie, Stéphanie, Marie-Aimée…

Merci