Prima Giornata Fiorentina dedicata ai pazienti con malattie mieloproliferative croniche

Venerdì 15 aprile 2011

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Nuovi farmaci per le ipereosinofilie e per le mastocitosi

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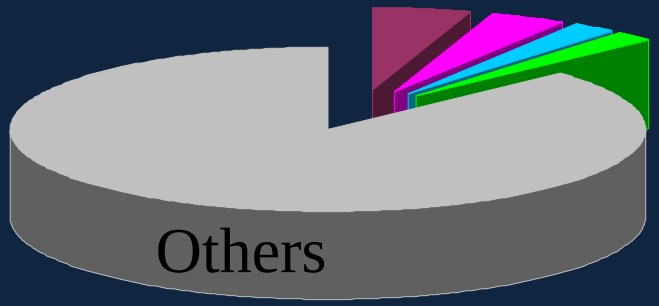
MPN with associated eosinophilia



5q31 PDGFRβ

WDR48–PDGFRB	t(1;3;5)(p36;p21;q33)
GPIAP1–PDGFRB	der(1)t(1;5)(p34;q33), der(5)t(1;5)(p34;q15), der(11)ins(11;5)(p12;q15q33)
TPM3–PDGFRB	t(1;5)(q21;q33)
PDE4DIP–PDGFRB	t(1;5)(q23;q33)
PRKG2–PDGFRB	t(4;5;5)(q23;q31;q33)
GOLGA4–PDGFRB	t(3;5)(p21–25;q31–35)
HIP1–PDGFRB	t(5;7)(q33;q11.2)
CCDC6–PDGFRB	t(5;10)(q33;q21)
GIT2–PDGFRB	t(5;12)(q31–33;q24)
NIN–PDGFRB	t(5;14)(q33;q24)
KIAA1509–PDGFRB	t(5;14)(q33;q32)
CEV14–PDGFRB	t(5;14)(q33;q32)
TP53BP1–PDGFRB	t(5;15)(q33;q22)
NDE1–PDGFRB	t(5;16)(q33;p13)
RABEP1–PDGFRB	t(5;17)(q33;p13)
SPECC1–PDGFRB	t(5;17)(q33;p11.2)

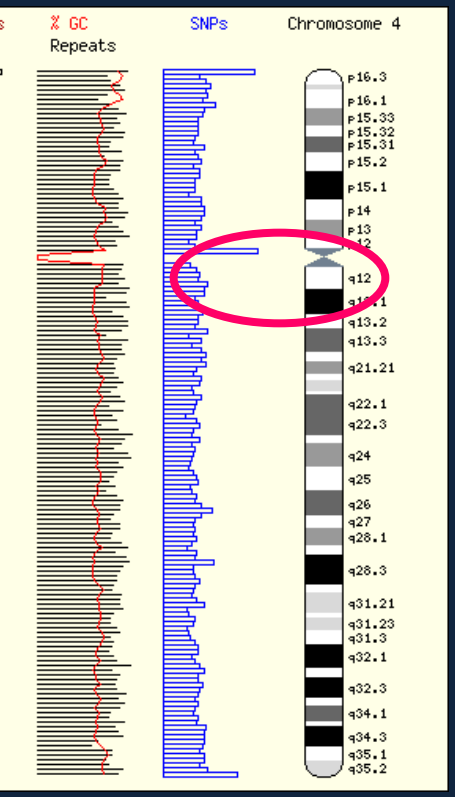
FIP1L1–PDGFRA	del(4)(q12q12)
BCR–PDGFRA	t(4;22)(q12;q11)
KIF5B–PDGFRA	Complex karyotyp

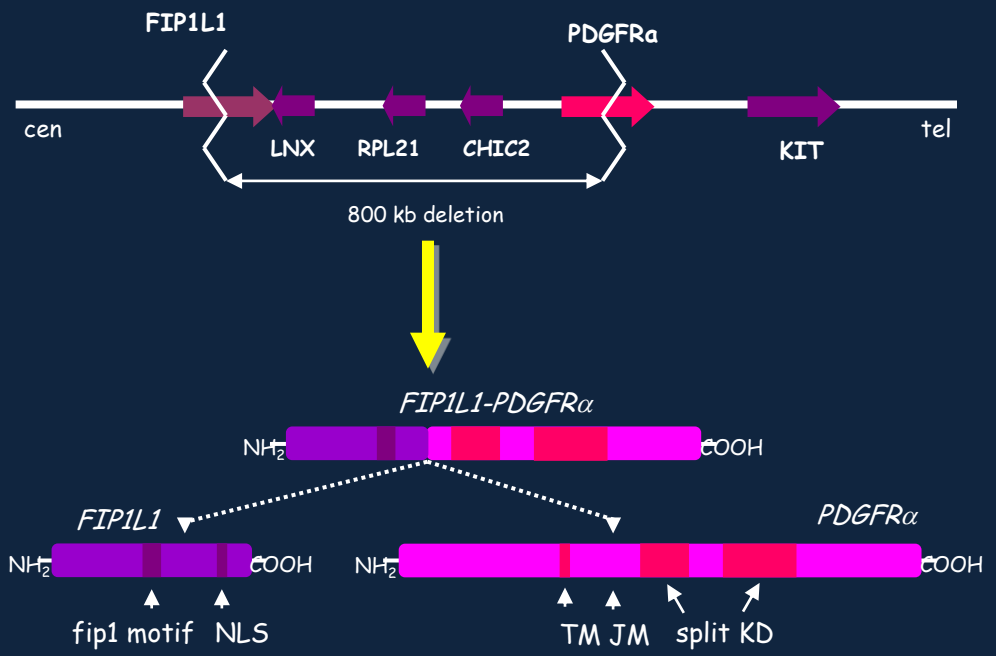
8p11 FGFR1

ZNF198–FGFR1	t(8;13)(p11;q12)
CEP110–FGFR1	t(8;9)(p11;q33)
FGFR1OP1–FGFR1	t(6;8)(q27;p11–12)
BCR–FGFR1	t(8;22)(p11;q11)
TRIM24–FGFR1	t(7;8)(q34;p11)
MYO18A–FGFR1	t(8;17)(p11;q23)
HERVK–FGFR1	t(8;19)(p12;q13.3)
FGFR1OP2–FGFR1	ins(12;8)(p11;p11p22)

4q12 PDGFRα

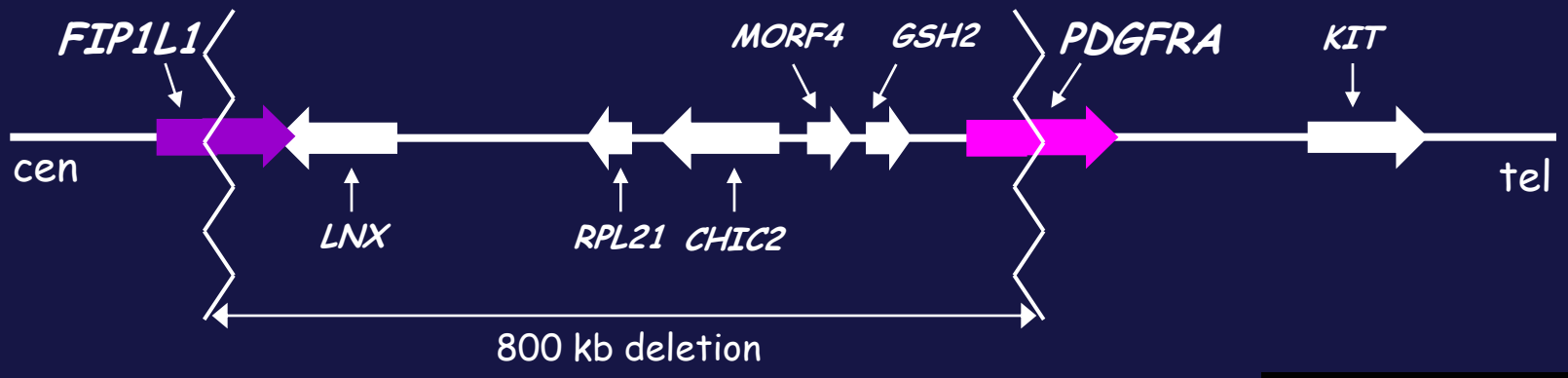
FIP1L1-PDGFRA rearrangement

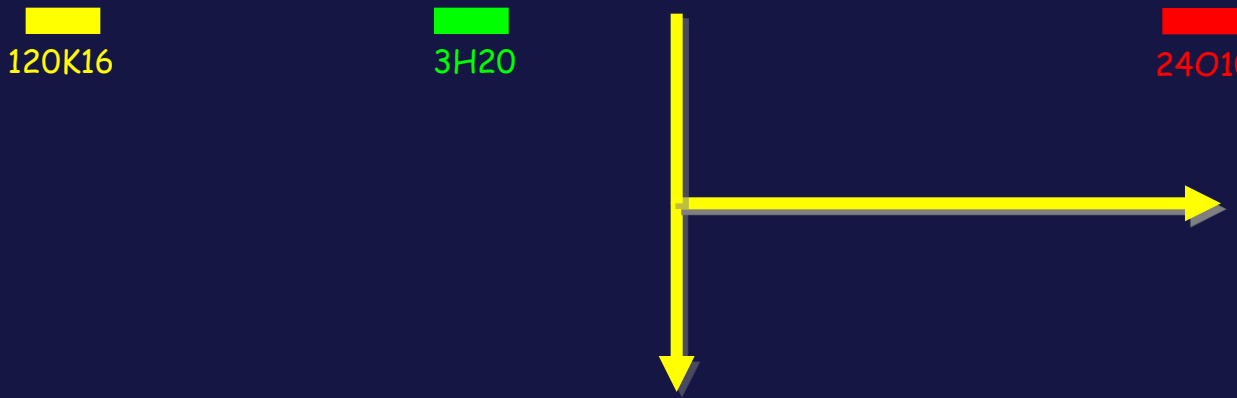


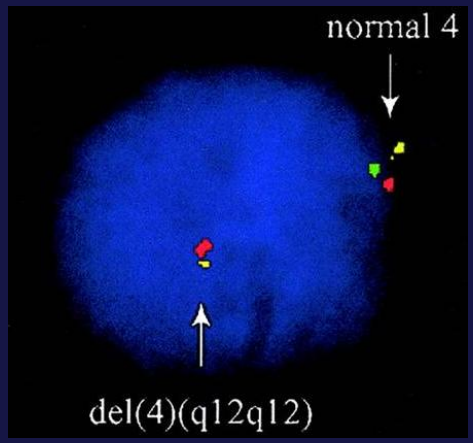


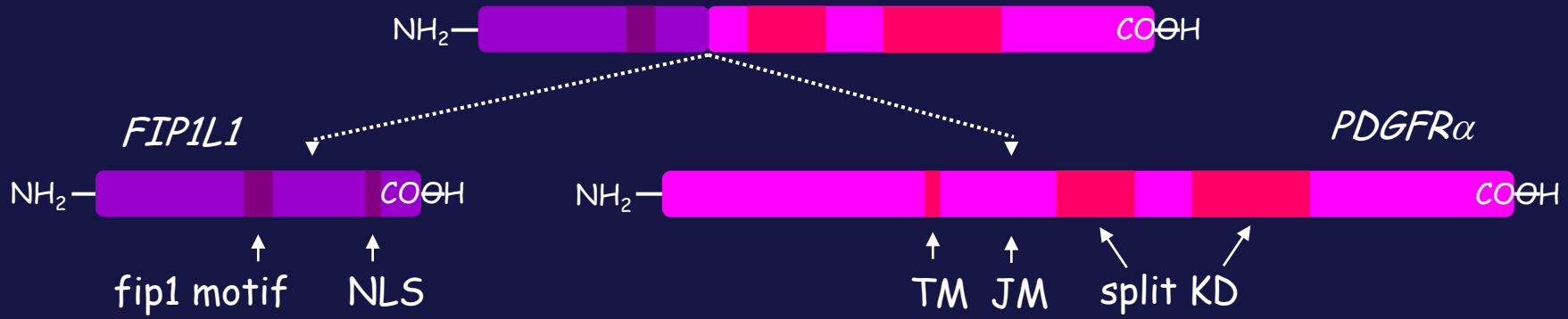
- Most common fusion
- Criptic deletion
- Exquisite sensibility to imatinib
- Extreme variability of breakpoint on FIP1L1 (exon 9 to 18)

FIP1L1-PDGFRα: a novel target of imatinib









Cools et al, NEJM 2003

Valutati clinicamente e biologicamente
199 pts

126 pts
eosinofilie secondarie

73 pts
eosinofilie primitive

41 FIP1L1-PDGFR –
(7/38 altre anomalie citogenetiche clonali)

32 FIP1L1-PDGFR +

Terapia con Imatinib

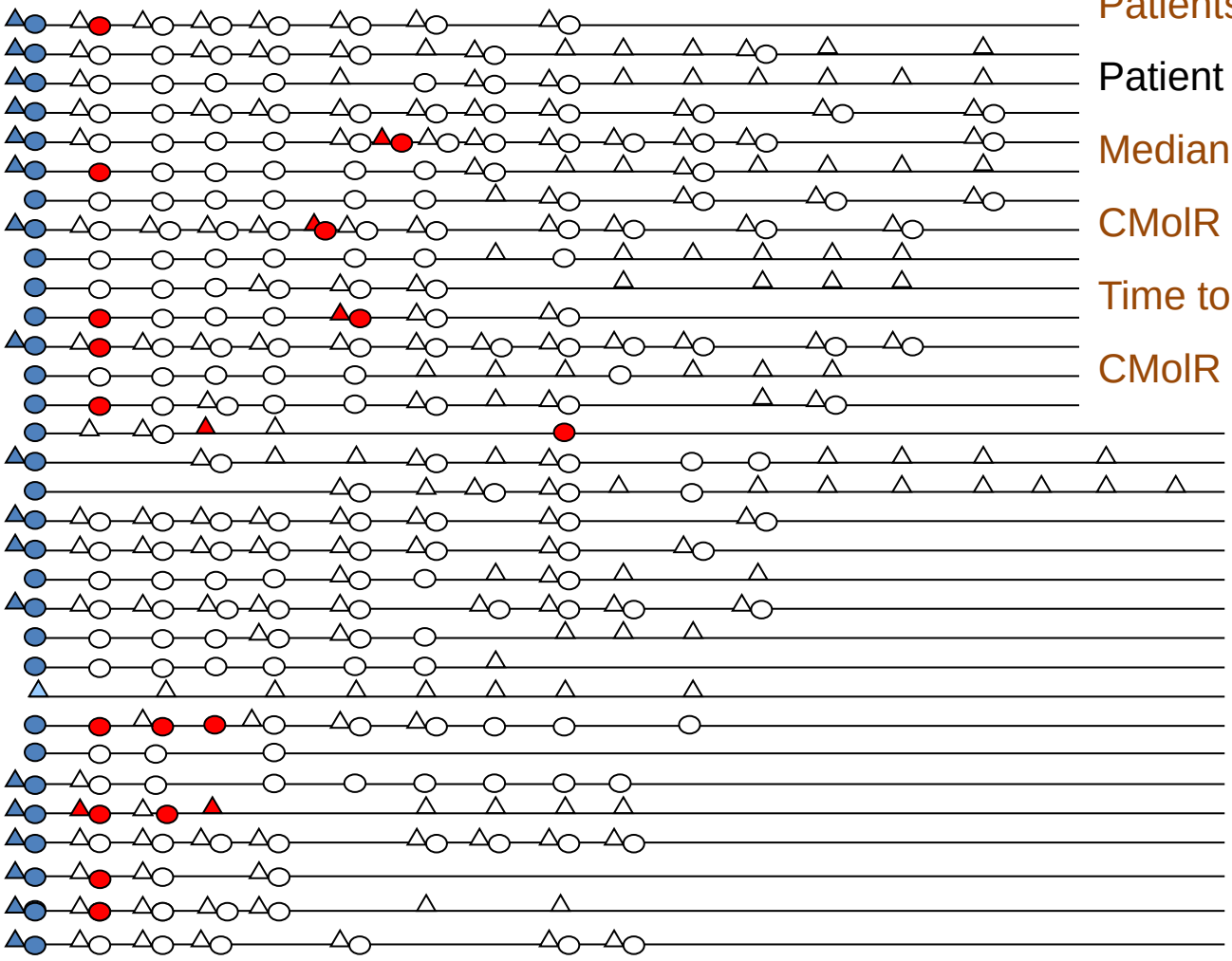
WP on HES

OPEN LABEL, PILOT PHASE II STUDY OF STI571 IN THE TREATMENT OF PATIENTS WITH IDIOPATHIC HYPEREOSINOPHILIC SYNDROME (HES)

Protocol No. NCT 00276929

	FIP1L1-PDGFRα rearranged	FIP1L1-PDGFRα non-rearranged
N° of cases	32	41
Male/female	31/1	27/14
Age,ys, median and range	48 (17-75)	60 (18-81)
Median time from diagnosis, months (range)	16 (6-125)	23 (6-209)
Eo x10^9/L, m-r	4.8 (1.6-28.8)	3,4 (1,5-39,9)
Organ localization	14 (44%)	20 (49%)
Hematologic Response	100%	14%

HES0203: molecular follow-up



Patients on FU :30

Patient on IMA :28/30

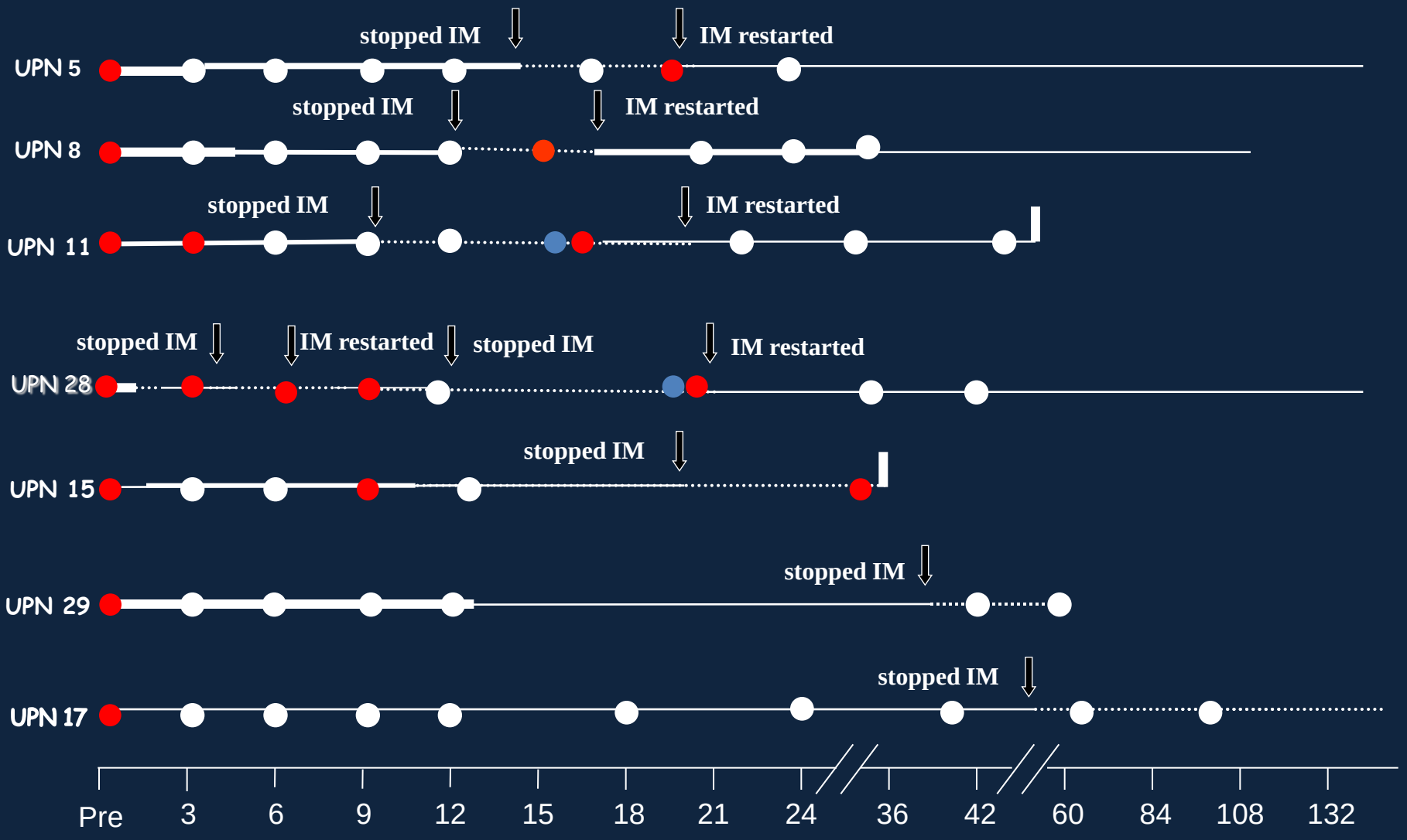
Median FU: 60 months

CMolR rate: 100%

Time to CMolR : 3 months

CMolR duration : 52 months

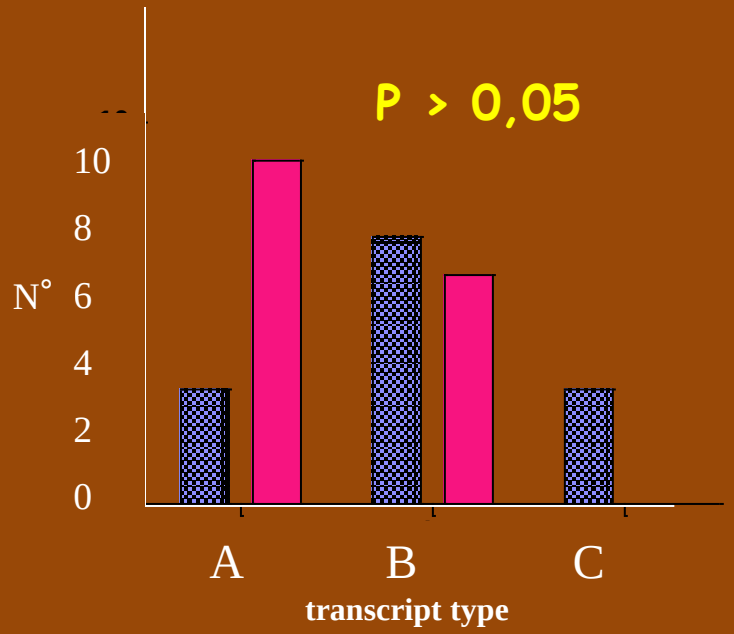
Imatinib discontinuation and molecular response



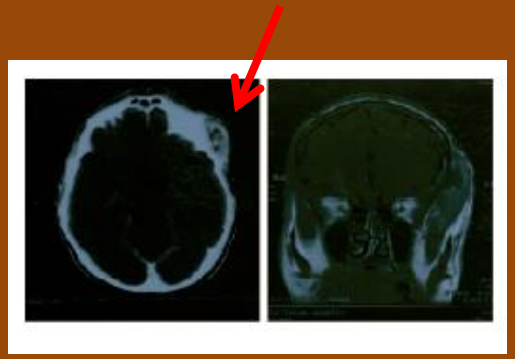
Months on imatinib therapy

Median time to molecular relapse: 5 months (4-9). Second Molecular response is obtained

Clinical correlation

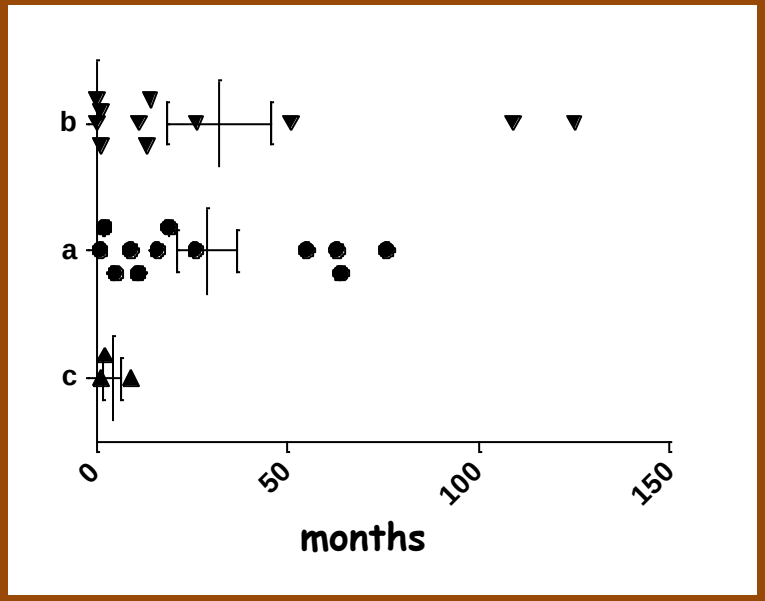


- Organ involvment **44%**
- Time to diagnosis **16 m (6-125)**
- Eo/mmc, time to HR/CMR **no difference**

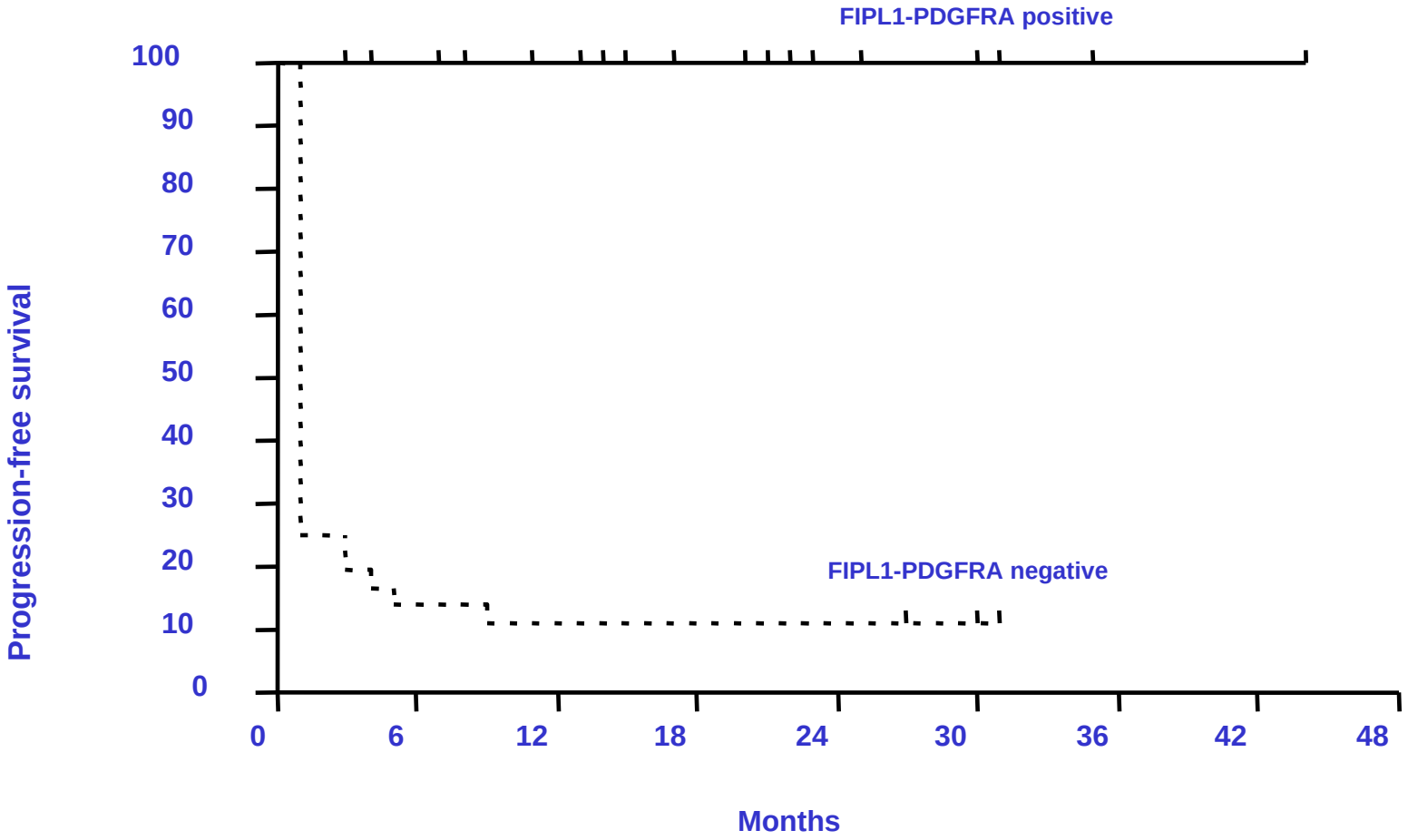


UPN 7,

Type C



Rates of progression-free survival according with FIP1L1-PDGFRalpha rearrangement status before imatinib therapy



Conclusions HES 1

- **Imatinib is the front-line therapy for HES FIP1L1-PDGFRa positive with Molecular Complete Remission rate of 100%**

- **Resistance to Imatinib therapy is extremely rare.**

WHO Classification of Systemic Mastocytosis (SM)

• Indolent SM (ISM)	>80%	no B/C/AHNMD*
• SM with AHNMD*		AHNMD
• Smouldering SM (SSM)		B-Findings
• Aggressive SM (ASM)		**C-Finding/s**
• Mast Cell Leukemia (MCL)		**MC ≥20% in BM Smear and C-Findings**

*AHNMD: associated clonal hematological non-mast cell lineage disease

- KIT D816V found in >80% of all SM cases
- Additional Oncogenic Molecules – not yet identified!

Valent et al., Leuk Res 2001;25:595, Valent et al., WHO Book 2001; Horny et al., WHO Book 2008

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

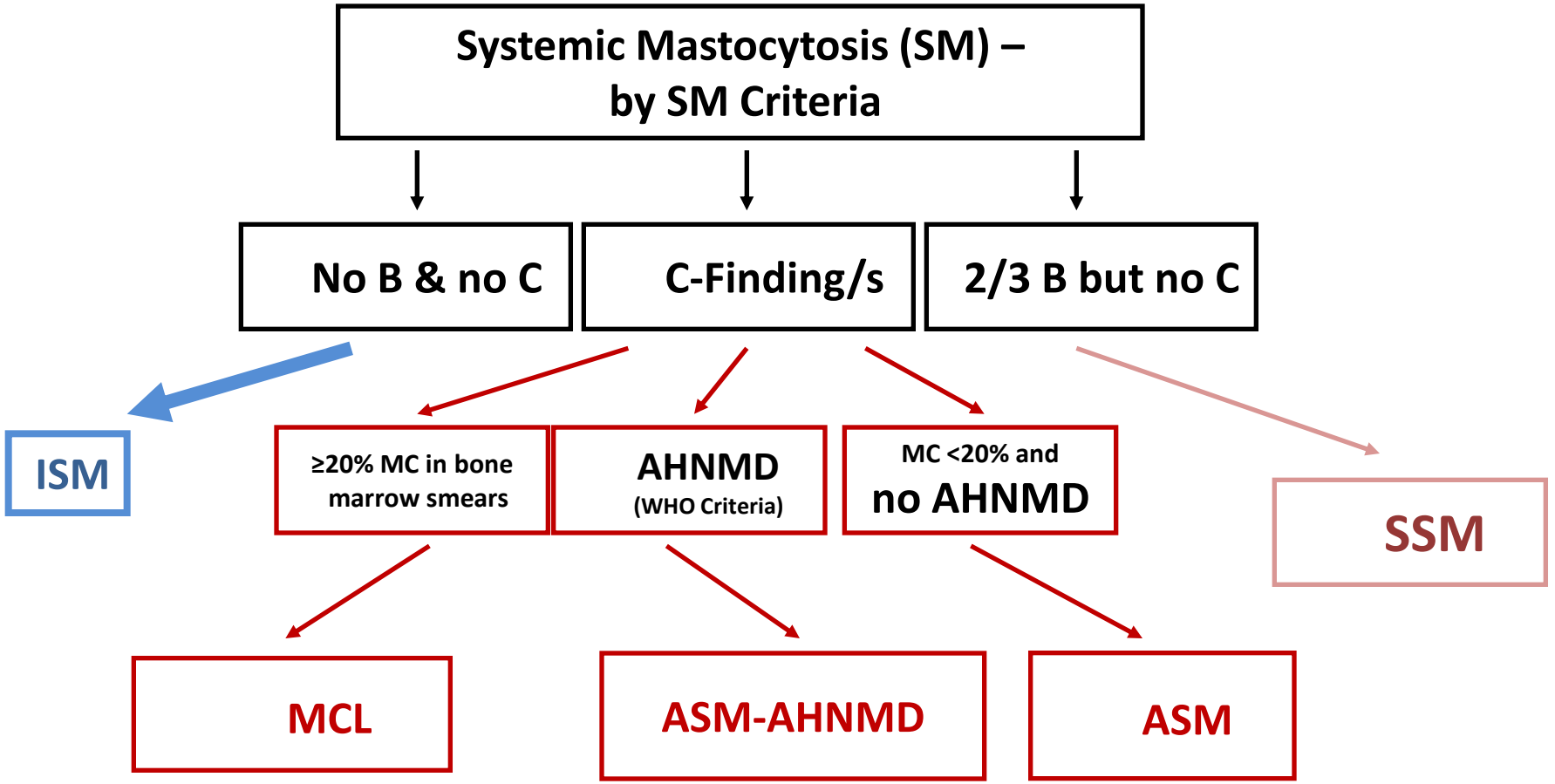
- Cytopenia
- Liver involvement with ascites
- Osteolysis plus pathologic fracture
- Malabsorption + hypalbuminemia
- Splenomegaly + hypersplenism

TAKE HOME MEMORIZER:

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

Diagnostic Algorithm in SM

(Patient Selection for Drug Therapy)

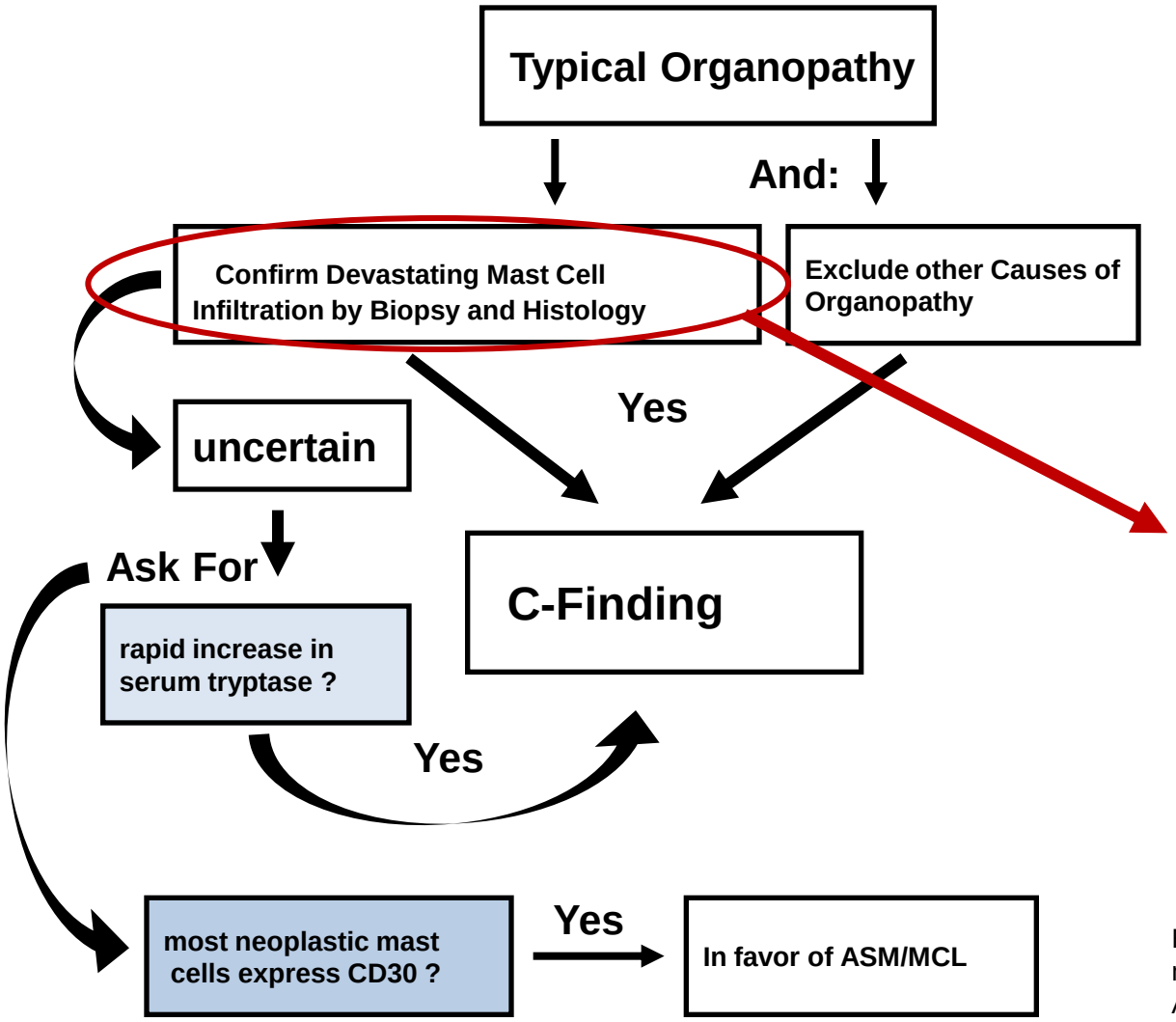


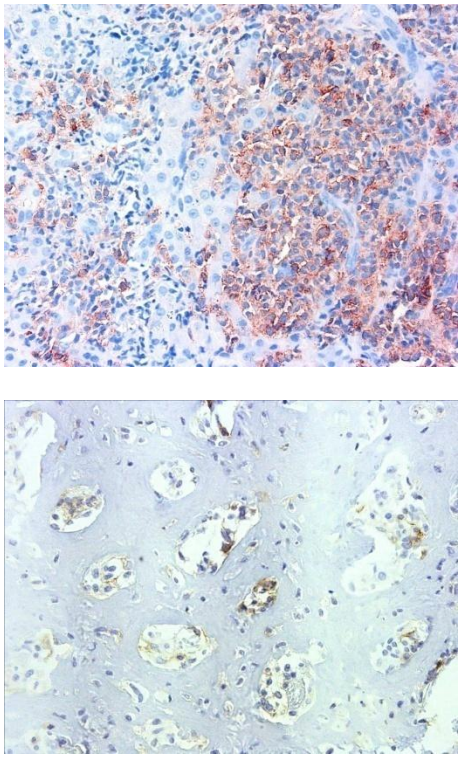
TAKE HOME MEMORIZER:

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

Valent et al., Blood, in press

Diagnostic Algorithm in SM





Biopsy of liver (upper panel) and bone marrow (lower panel) in a patient with ASM: tryptase IHC.

Valent et al., Leuk Res 2001;25:595; Valent et al., Blood, in press; Sotlar et al, Modern Pathology, in press.

Therapy of Patients with SM

- In >90% of all pts: symptomatic therapy only (BSC) +/- bisphosphonates (T score < -2)
- These **ISM** patients have a normal or near normal life-expectancy !
- The Burden of MC alone (B-Findings) is not an indication for cytoreductive therapy
- **Only C-Findings are indicative of the fact that the patient is a candidate for Cytoreduction**

Memorizer: C = Consider Cytoreduction

Valent et al., Leuk Res 2001;25:595; Valent et al., Eur J Clin Invest 2007;37:435; Valent et al., Blood, in press

Therapy of Advanced SM

• Glucocorticosteroids	Adjunct to IFNα or 2CdA
• **Interferon-alpha (IFNα)**	ASM with Slow Progression
• **Cladribine (2CdA)**	ASM or MCL
• **PKC412 (Midostaurin)**	**Trials ongoing**
• Imatinib	Rare Cases (KIT D816V-)
• Polychemotherapy	MCL, Prior to SCT
• Stem Cell Transplantation	In young patients
• Hydroxyurea	Palliative drug
• Splenectomy	Prior to CT (thrombopenia)

- Basis: HR1+HR2 blockers
- Osteopathy: Bisphosphonates (T Score < -2)
- Allergy: Immunotherapy (venom allergy!)

Valent et al., Leuk Res 2001;25:595; Valent et al., Eur J Clin Invest 2007;37:435; Valent et al., Blood, in press

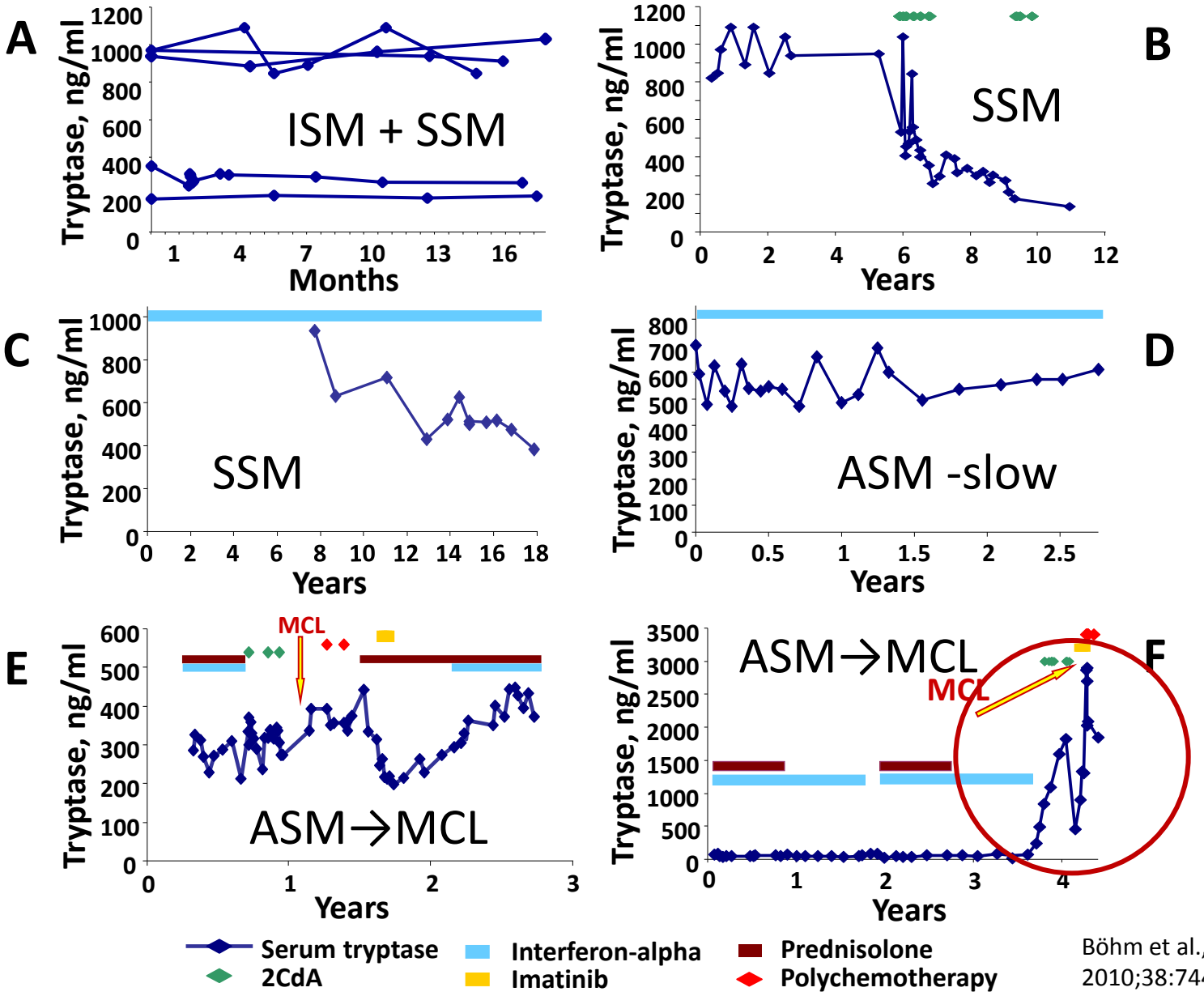
FU and Response Evaluation

- **C-Findings** (improve/resolve, etc)
- Serum Tryptase Levels
- B Findings
- KIT D816V burden
- Mediator Symptoms (also after IT)
- Osteodensitometry (T-Score)
- Quality of Life

For detailed Information and Response Criteria in SM see:
1) Leuk Res 2003;27:635
2) Eur J Clin Invest 2007;37:435

Valent et al., Leuk Res 2003; 27:635; Valent et al., Eur J Clin Invest 2007;37:435; Valent et al., Blood, in press

Tryptase-Monitoring in SM: Examples



Böhm et al., Exp Hematol 2010;38:744.

Summary and Statements

- Therapy of SM is a multi-disciplinary approach
- All patients should be referred to a specialized center, preferably to a Center of Excellence of the ECNM or an associated center
- There is no cure for patients with advanced SM
- However, several effective drugs are now available and are tested in clinical trials
- Patients with advanced SM should be treated in clinical trials if possible

New drugs in Mastocytosis

1. Dasatinib
2. SU11248
3. PKC412

Dasatinib has “in vitro” activity in all SM patients

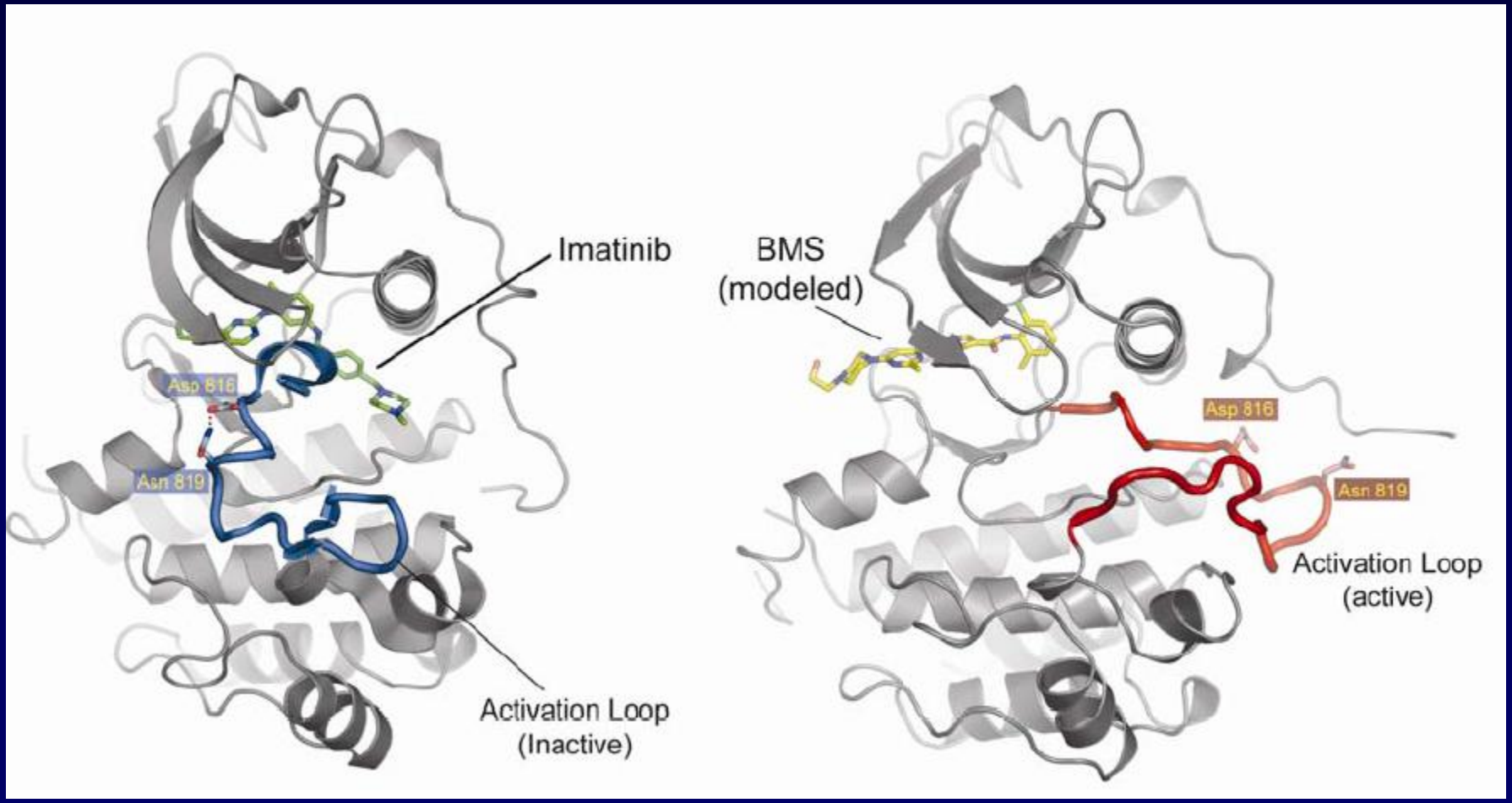
Compound	Kinase	IC50 (nM)
Dasatinib	cKIT(WT)	79
	cKIT(D816V)	37
Imatinib	cKIT(WT)	1550
	cKIT(D816V)	> 10000

Blood First Edition Paper, prepublished online January 24, 2006; DOI 10.1182/blood-2005-10-3969

Dasatinib (BMS-354825) inhibits KIT^{D816V}, an imatinib-resistant activating mutation that triggers neoplastic growth in the majority of patients with systemic mastocytosis

Neil P. Shah[1], Francis Y. Lee[2], Roger Luo[2], Yibin Jiang[3], Marjolein Donker[3,4], and Cem Akin[3]

Dasatinib binds mutated D816V c-kit receptor



ADVANCED SYSTEMIC MASTOCYTOSIS: An Italian Multicentric experience

Number of patients (1995-2006)	24
Median age (years; range)	59(36-75)
Gender (male/female; ratio)	13/11
KIT D816V mut	13/18 (72%)
Disease type	
Aggressive systemic mastocytosis	12 (50%)
Mast cell leukemia	8 (33%)
AHNMD-SM*	4 (17%)

OS @ 5 yrs 64% median 24 months (6-60)

19 pts still alive with active disease

Pagano et al, Int J Hemat,2008

Nilotinib in ASM

A Study of Oral AMN107 in Adults With Chronic Myelogenous Leukemia (CML) or Other Blood Related Cancers(NCT00109707) sponsored Novartis

Study Start Date: May 2004

60 pts, (34M, 26F), median age 53 ys

30/36 D816V pos (83%)

37% stopped therapy

Response: tryptase, BM MCs counts, improvement of clinical symptoms

12 patients (20%) clinical response

2 (3%) CR, 5(8%) ICR, 4(7%) miCR, 1 PR

G3/4 AE: diarrhea, thrombocytopenia, haedache

Long term results: unknown

Hochhaus, ASH poster presentation 2006

Midostaurine (PKC412) in ASM

A Single Arm, Phase II, Open-Label Study to Determine the Efficacy of Twice Daily Oral Dosing of PKC412 Administered to Patients With Aggressive Systemic **Mastocytosis** (ASM) and Mast Cell Leukemia (MCL) **(**NCT00233454) sponsored Stanford University

Study Start Date: March 2005

15 pts, median age 62 ys

9/15 D816V pos (60%)

30% stopped therapy

Response: tryptase, BM MCs counts, improvement of clinical symptoms

11/15 patients (73%) clinical response 5(33%) MR, 6(39%) PR

G3/4 AE: nausea/vomiting, thrombocytopenia

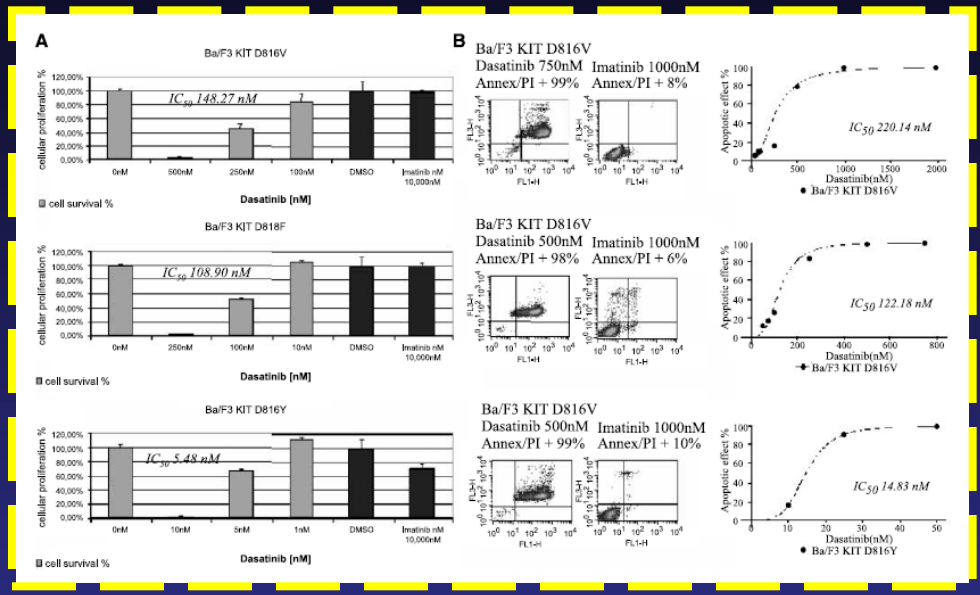
Gotlib, ASH poster presentation 2007

Efficacy and Safety of Midostaurin in Patients With ASM or Mast Cell Leukemia (NCT00782067) Novartis sponsored

Study Start Date: October 2008

Dasatinib in ASM

- Razionale:



Cancer Res 2006; 66: (1). January 1, 2006

- Esperienza clinica limitata

Verstorvsek, CCR, 2008 (9 ASM, 18 ISM, 6 SM-AHNMD) OR 33%

Purtil, Eur J M, 2008 (2 ASM, 1 ISM, 1 SM-AHNMD) OR 50%

Ustun, Leuk Res, 2009 (1 ASM)

Dasatinib therapy in ASM

- **6 pts ASM on compassionate use**
- **3 pts (1 ASM, 1 SSN, 1 ISM) as off-label therapy**
- **70 mg BID**
- **Evaluation of response on C and B findings and tryptase level**

EOSINOFILIA SENZA RIARRANGIAMENTI

Human IL-5

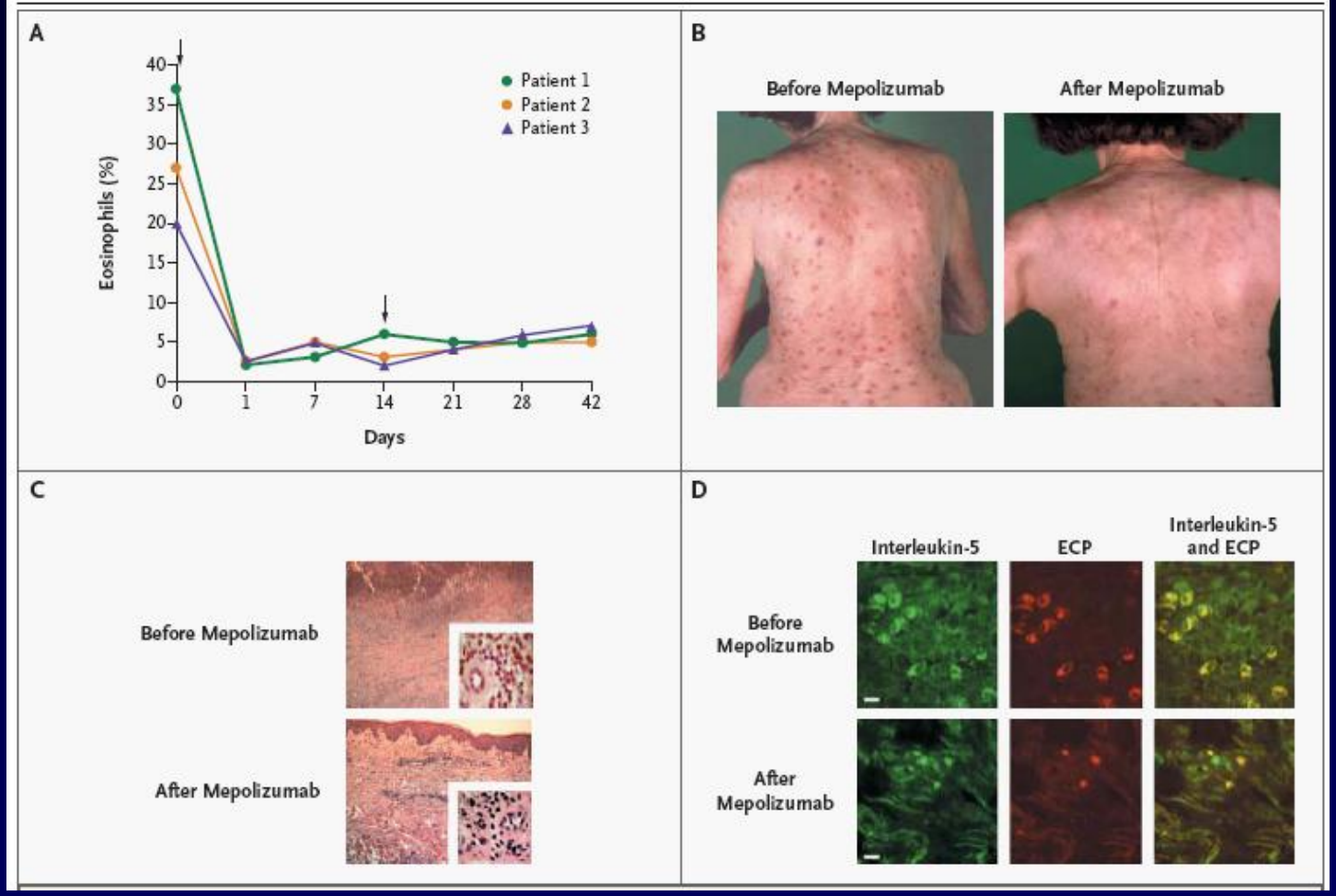
•Human IL-5 is the major hematopoietin responsible for the growth and differentation, recruitment, activation and survival of eosinophils.

•Mepolizumab blocks binding of hIL-5 to the alpha chain of the hIL-5 receptor complex expressed on the eosinophil cell surface.

•It was anticipate that it would have an effect in asthma, allergic rhinitis and atopic dermatitis by reducing the accumulation and activation of eosinophils in the target tissue, reducing the activation of infiltrated cells as well as reducing blood eosinophil numbers.

•While studies assessing acute treatment of asthma and atopic dermatitis have generated results of minimal clinical significance, the results of experience with HES subjects has been far more promising.

Mepolizumab is a fully humanized monoclonal antibody which is specific for hIL-5



The Effects of Mepolizumab Treatment.

Panel A shows the effect of mepolizumab infusions (arrows) on the percentage of peripheral-blood eosinophils in each of the three patients.

Panel B shows the clinical response on day 21, after two mepolizumab infusions, in Patient 2. Panels C and D show the reduction in the number of eosinophils in the skin before and on day 21 after the start of mepolizumab therapy in Patient 2. Before therapy with mepolizumab, hematoxylin-and-eosin–stained skin-biopsy specimens (Panel C, ¬100) contained inflammatory-cell infiltrates largely consisting of eosinophils and lymphocytes. After therapy, the number of inflammatory cells had decreased, and no eosinophils were detected. The insets show the same specimens at a higher magnification (¬1000). Double immunofluorescence staining with anti–interleukin-5 and anti–eosinophil cationic protein (ECP) antibodies (Panel D) showed that most of the infiltrating eosinophils expressed interleukin-5 before therapy with mepolizumab. After therapy, fewer eosinophils were detected, although they did contain interleukin-5. The scale bars represent 10 µm.

Skin-Infiltrating Eosinophils and Lymphocytes before (Day 1) and 21 Days after the Initiation of Mepolizumab Treatment.

Method and Finding	Patient 1		Patient 2		Patient 3	
	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21
Hematoxylin and eosin						
Eosinophils (per 1000 skin cells)	245	0	136	0	238	3
Immunofluorescence						
Positive for eosinophil cationic protein (cells/mm²)	70	34	140	19	80	10
Positive for eosinophil cationic protein and interleukin-5 (%)	50	88	85	100	75	100
CD4+ cells (per mm²)	40	40	30	10	24	5
CD4+ and positive for interleukin-5 (%)	25	0	25	100	42	60
CD8+ cells (per mm²)	20	8	25	10	20	10
CD8+ and positive for interleukin-5 (%)	50	0	40	100	50	0

The clinical experience with mepolizumab shows promise in both men and women with HES.

In these small studies, most subjects have received repeat doses of mepolizumab at a 750mg-dose level with a maximum of 8 doses of 750mg doses in approximately a 10 month period.

Mepolizumab has been well tolerated by all the subjects with no reports of related serious or non-serious adverse events, thus it has demonstrated a safety profile comparable to the previous experience in atopic disease.

Among the 15 subjects with a clinical status update, 13 have shown significant reduction in blood eosinophils; 12 subjects have shown partial or significant clinical response.

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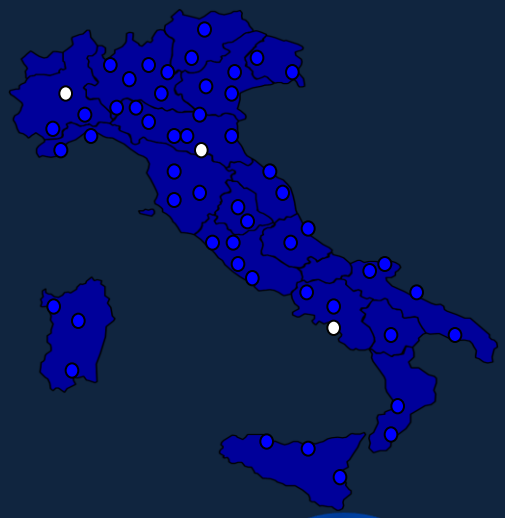

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