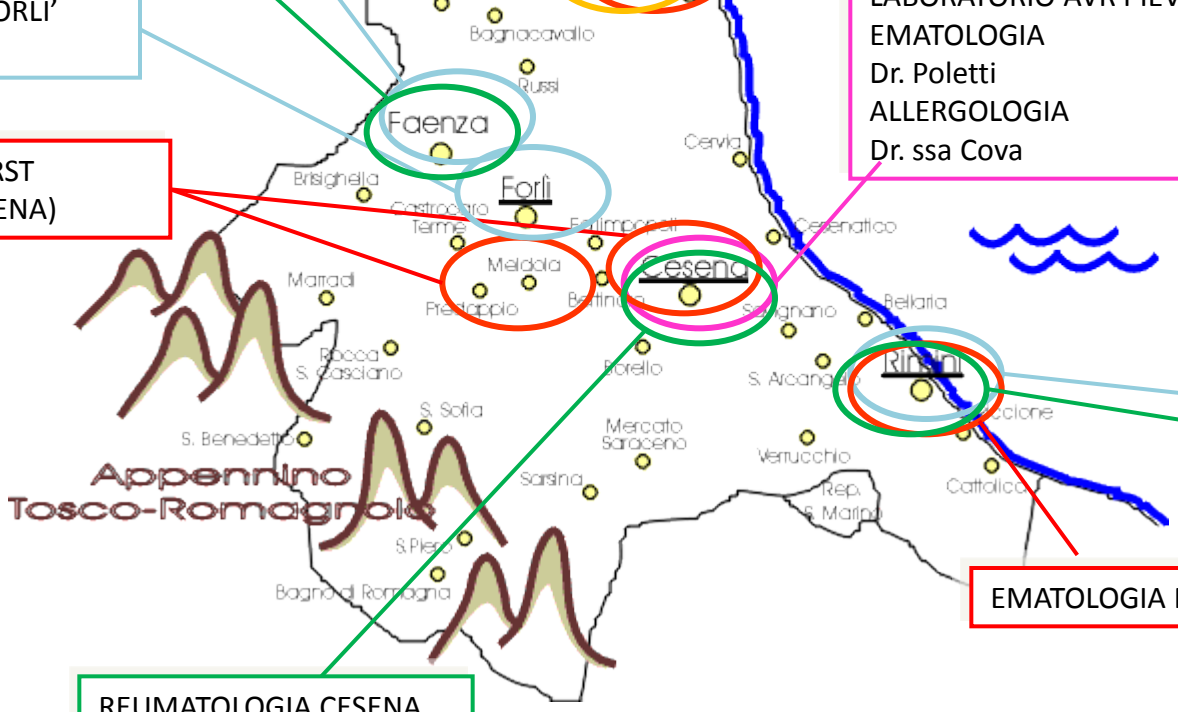
Attività dell' Ambulatorio Mastocitosi in Romagna

Dr. ssa Michela Rondoni
U.O.C. Ematologia Ravenna

Faenza, 07.06.2018

Sviluppo Gruppo Interdisciplinare sulla Mastocitosi di AVR (giugno 2013)



DERMATOLOGIA RA
Dr. ssa M. Tabanelli

ALLERGOLOGIA FAENZA
Dr. Oliviero Quercia

EMATOLOGIA RAVENNA

REUMATOLOGIA FAENZA
(Dr. R. Giannini)

PNEUMOLOGIA FORLI'
(Dr. E. Cortesi)

LABORATORIO AVR PIEVESESTINA
EMATOLOGIA
Dr. Poletti
ALLERGOLOGIA
Dr. ssa Cova

EMATOLOGIA IRST
(MELDOLA-CESENA)

MEDICINA INTERNA
RIMINI
ALLERGOLOGIA
Dr. Gabriele Cortellini
REUMATOLOGIA
Dr. Taroni

EMATOLOGIA RIMINI

REUMATOLOGIA CESENA
(Dr. M. Bruschi)

Perché?

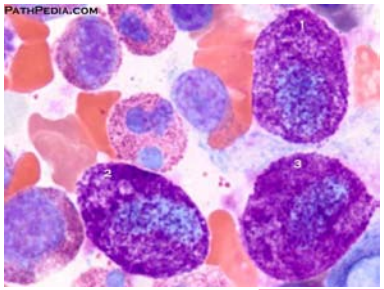
Associazione Italiana Mastocitosi costituita nel 2008

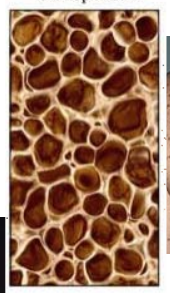
- attività di collaborazione con i centri di riferimento sulla Mastocitosi attraverso l'organizzazione di eventi culturali per raccogliere fondi da destinare alla ricerca

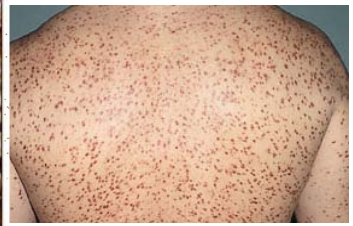
- Obiettivo: l' inserimento della mastocitosi nell'elenco delle malattie rare esenti da ticket (codice RD0081) inserita nei nuovi LEA 2015

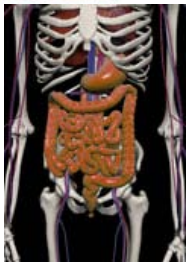
Malattia rara e con sintomatologia eterogenea, per cui è sempre necessario un approccio multidisciplinare

- Ematologo
- Pediatra
- Allergologo
- Gastroenterologo
- Reumatologo









HISTORY

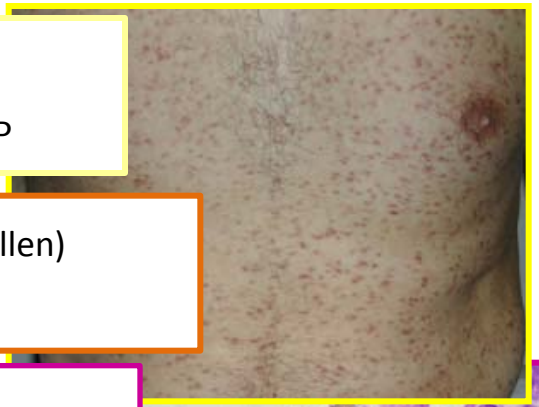
1869- Nettelship	Rare form of urticaria
1878- Sangster	Urticaria Pigmentosa UP

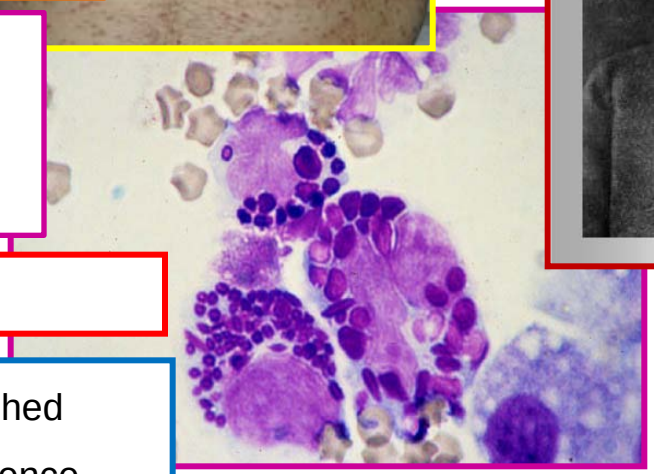
1879- Ehrlich	Mast cells (Mastzellen)
1887- Unna	Mast cells in UP

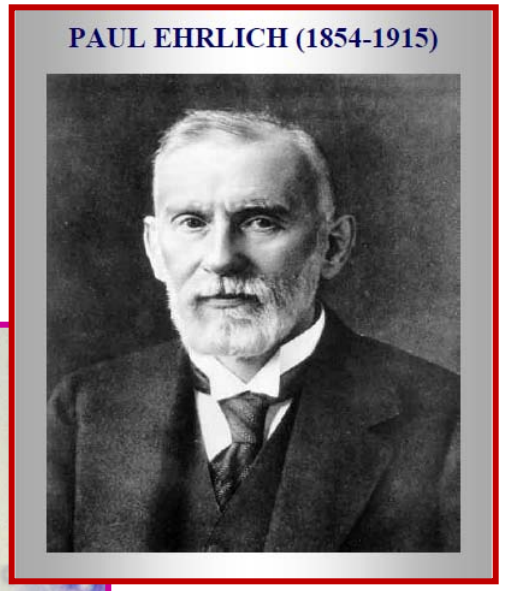
1949- Ellis	Systemic Mastocytosis
1979- Lennert	Kiel Classification
1991- Metcalfe	Consensus Classification

1996- Longley	c-kit D816V in SM

1990-2000	Criteria Established
2000- Valent	Working Conference







Diagnostic criteria and classification of mastocytosis: a consensus proposal

Peter Valent [a,*], Hans-P. Horny [b], Luis Escribano [c], B. Jack Longley [d], Chin Y. Li [e], Lawrence B. Schwartz [f], Gianni Marone [g], Rosa Nuñez [c], Cem Akin [h], Karl Sotlar [i], Wolfgang R. Sperr [a], Klaus Wolff [j], Richard D. Brunning [k], Reza M. Parwaresch [l], K. Frank Austen [m], Karl Lennert [l], Dean D. Metcalfe [h], James W. Vardiman [n], John M. Bennett [o]

Leukemia Research 25 (2001) 603–625

Diagnostic criteria and classification of mastocytosis: a consensus proposal

Peter Valent [a,*], Hans-P. Horny [b], Luis Escribano [c], B. Jack Longley [d], Chin Y. Li [e], Lawrence B. Schwartz [f], Gianni Marone [g], Rosa Nuñez [c], Cem Akin [h], Karl Sotlar [i], Wolfgang R. Sperr [a], Klaus Wolff [j], Richard D. Brunning [k], Reza M. Parwaresch [l], K. Frank Austen [m], Karl Lennert [l], Dean D. Metcalfe [h], James W. Vardiman [n], John M. Bennett [o]

- **CRITERIO MAGGIORE**
  - Infiltrati mastocitari multifocali densi (>15 mastociti aggregati) in sezioni istologiche di midollo osseo e/o di altri organi extracutanei
- **CRITERI MINORI**
  - Presenza di: > 25% di mastociti di forma fusata o morfologia atipica in infiltrati mastocitari rilevati in sezioni istologiche di midollo osseo od altro organi extracutanei oppure > 25% di mastociti immaturi o atipici negli strisci di midollo osseo
  - Positività della mutazione puntiforme del codone 816 del KIT (Asp816→Val) nel midollo osseo, nel sangue o in altri organi extracutanei
  - Positività per CD2 e/o CD25 , oltre che per gli altri markers mastocitari, in mastociti del midollo osseo, del sangue o di altri organi extracutanei
  - Concentrazioni sieriche di triptasi persistentemente > 20 ng/ml (purchè non ci sia un altro disordine mieloide associato, in questo caso questo parametro non è valido)

La diagnosi può essere posta in presenza di:- criterio maggiore + 1 minore oppure - 3 criteri minori

EMATOLOGO→DIAGNOSI!!

B- FINDINGS (HIGH BURDEN OF MAST CELLS)

- Tryptase > 200 µg/L and BM (Isto) MCs < 30%
- Dismyelopoiesis
- asymptomatic organomegaly
- osteopenia (T score < -2)
- Recurrent anaphylactic shock

C-FINDINGS (ORGAN DESTRUCTION caused by MC infiltration)

- Cytopenia
- Liver involvement with ascite
- Splenomegaly with hypersplenism
- Large Osteolysis plus pathologic fracture
- Malabsorption + hypoalbuminemia
- Life-threating organ damage due to MCs infiltrates

TKI in SM

Research letters

THE LANCET • Vol 362 • August 16 2003 •

Imatinib for systemic mast-cell disease

A Pardanani, M Elliott, T Reeder, C-Y Li, E J Baxter, N C P Cross, A Tefferi

Imatinib Mesylate in the Treatment of Systemic Mastocytosis

A Phase II Trial

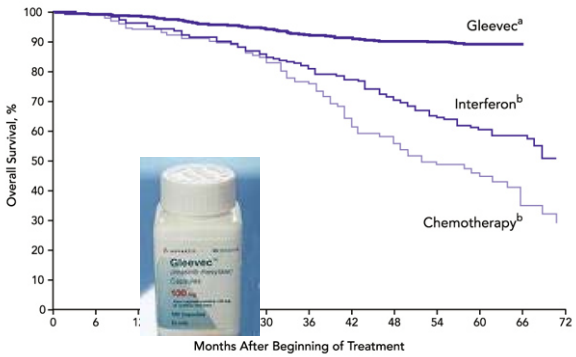
CANCER July 15, 2006 / Volume 107 / Number 2

Cancer Therapy: Clinical

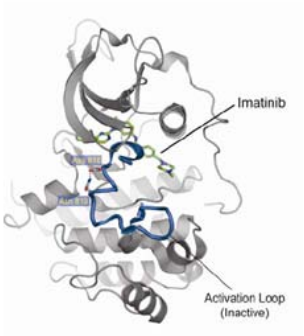
Phase II Study of Dasatinib in Philadelphia Chromosome–Negative Acute and Chronic Myeloid Diseases, Including Systemic Mastocytosis

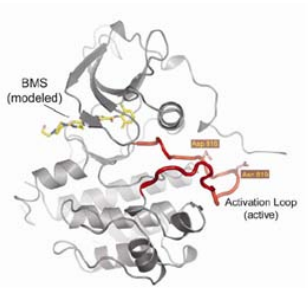
Srdan Verstovsek,[1] Ayalew Tefferi,[2] Jorge Cortes,[1] Susan O'Brien,[1] Guillermo Garcia-Manero,[1] Animesh Pardanani,[2] Cem Akin,[3] Stefan Faderl,[1] Taghi Manshouri,[1] Deborah Thomas,[1] and Hagop Kantarjian[1]

Clin Cancer Res 2008;14(12) June 15, 2008



[a] From Druker BJ, Guilhot F, O'Brien SG *et al. N Engl J Med.* (2006) **355**:2408-2417.
[b] From The Italian Cooperative Study Group On Chronic Myeloid Leukemia. *N Engl J Med.* (1994) **330**:820-825.





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.

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

TKI in SM

Research letters

THE LANCET • Vol 362 • August 16 2003 •

Imatinib for systemic mast-cell disease

A Pardanani, M Elliott, T Reeder, C-Y Li, E J Baxter, N C P Cross, A Tefferi

IMATINIB: indicato solo nelle forme con KIT WT o varianti mutate di KIT (D560G, F522C, K509I) o riarrangiamento FIP1L1/PDGFRA
Negli altri casi riportate risposte nel 5% dei casi

Imatinib Mesylate in the Treatment of Systemic Mastocytosis

A Phase II Trial

CANCER July 15, 2006 / Volume 107 / Number 2

Cancer Therapy: Clinical

Phase II Study of Dasatinib in Philadelphia Chromosome–Negative Acute and Chronic Myeloid Diseases, Including Systemic Mastocytosis

Srdan Verstovsek,[1] Ayalew Tefferi,[2] Jorge Cortes,[1] Susan O'Brien,[1] Guillermo Garcia-Manero,[1] Animesh Pardanani,[2] Cem Akin,[3] Stefan Faderl,[1] Taghi Manshouri,[1] Deborah Thomas,[1] and Hagop Kantarjian[1]

Clin Cancer Res 2008;14(12) June 15, 2008

DASATINIB: efficace nel ridurre i sintomi da infiltrazione d' organo (USO TERAPEUTICO)
33 patients with SM (18 ISM, 9 ASM, 6 AHNMSD)
2 patients (both D816V negative) achieved CR
9 patients improved G3 AE: 19 patients (58%)

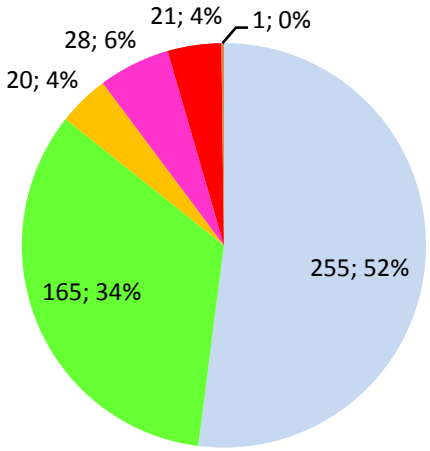
Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis

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.

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

MIDOSTAURINA: risultati promettenti nei pazienti con ASM (89 pts, ORR 60%).
Efficace nel miglioramento dei sintomi e della qualità di vita.
Approvato FDA e EMA 2018.

Clinical presentation and management practice of systemic mastocytosis. A survey on 460 Italian patients.



75% dg 2008-2014 – 25% antecedenti

ISM 86%
SSM 4%
ASM 6%
SM-AHD 4%
MCL 1%

Pieri L, et al. Am J Hematol. 2016 Jul;91(7):692-9.

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

Ken-Hong Lim,[1,2] Ayalew Tefferi,[1] Terra L. Lasho,[1] Christy Finke,[1] Mrinal Patnaik,[1] Joseph H. Butterfield,[3] Rebecca F. McClure,[4] Chin-Yang Li,[4] and Animesh Pardanani[1]

Total no. of SM patients	342	
ISM	159 (46)	
Isolated bone marrow mastocytosis	36 (23)	
Smoldering systemic mastocytosis	22 (14)	
ASM	41 (12)	
SM-AHNMD	138 (40)	
MCL	4 (1)	
Male	188 (55)	
Age, y		57 (19-87)

Retrospective study Mayo Clinic 1976-2007

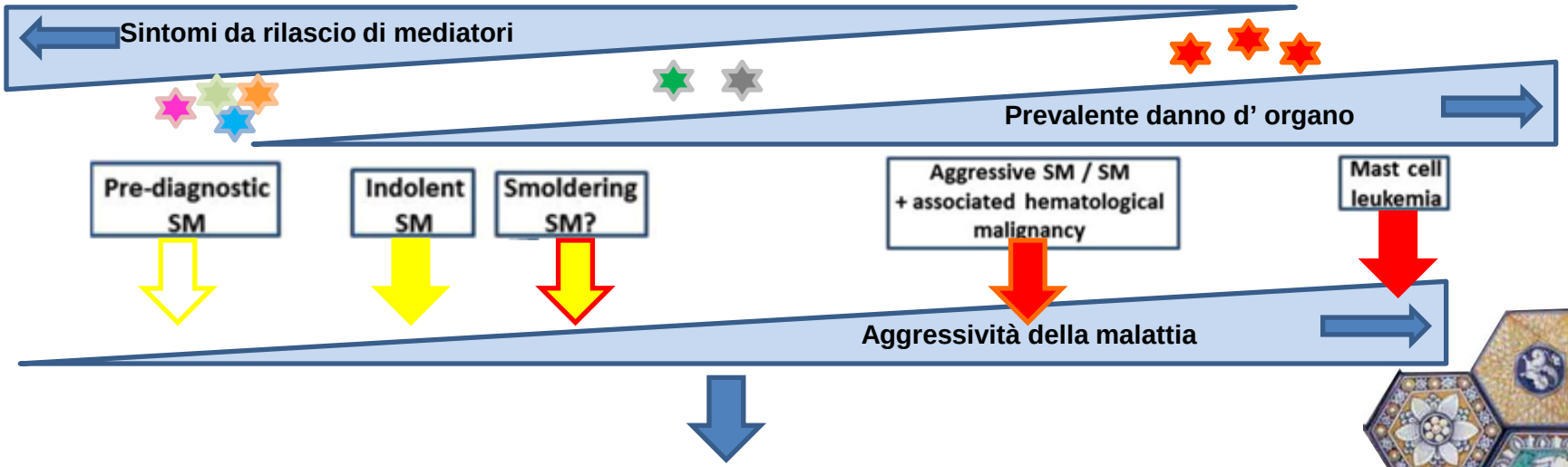
Attività Ambulatorio 2013-oggi

- ✓ 73 1° Visite
- ✓ Modalità di accesso all' Ambulatorio → 51 riferiti da specialisti
  - 21 EMATOLOGO (5 casi già diagnosticati altrove)
  - 4 DERMATOLOGO
  - 22 ALLERGOLOGO
  - 4 REUMATOLOGO
- → 21 AUTONOMAMENTE 1 MMG, altri via mail o telefono, 11 per problema cute, 6/11 con Bx CUTE pos masto)

✓ Sintomi di esordio→	LESIONI CUTANEE O PRURITO	25/73	34%
	ANAFILASSI	21/73	29%
	SINTOMI DA MEDIATORI	1/73	1.4%
	OSTEOPOROSI	4/73	5.5%
	SINTOMI NEUROLOGICI	1/73	1.4%
	TRIPTASI ELEVATA	4/73	5.5%
	ORGANOMEGALIA O ALTERAZIONI EMATOLOGICHE	9/73	12.3%

Attività Ambulatorio 2013-oggi

- ✓ Prima visita → ANAMNESI ACCURATA
  - MdC iodato/ Anestesie generali
  - Episodi ipertensivi/Ipotensione
  - Farmaci (ASA-FANS-morfina)
  - Punture di VESPE
  - Flushing
  - Fratture
  - Sintomi gastroenterici/gastrite
- → OBIETTIVITA'
  - Cute
  - Organomegalia-Linfonodi
  - Tensione addominale



BIOPSIA MIDOLLARE

Attività Ambulatorio 2013-oggi

73 pazienti

20 ISM (Rimini)

49 SM

24 no diagnosis

56ISM (81%)
5 SSM (7.2 %)
2 ASM (2.9%)
6 MCL (8.7 %)

13 pz

6 BM non indicato → ALTRO
7 BM negativo
5 rifiuto BM (B. Mol. Sp neg.)
4 B. Mol s.p negativa
2 bambini

Amb. Dedicato (BO)

82 Follow-up specifico

Ambulatorio mastocitosi : approccio e follow-up

VALUTAZIONE OSTEOPOROSI 1° LIVELLO

- Anamnesi
- Calcemia, fosforemia, calciuria e fosfaturia 24 ore, 25OH vitamina D, PTH, CTX, ALP ossea
- Densitometria ossea (DXA) lombare e femorale
- RX scheletro assiale + eventuali altri siti in base a sospetti

VALUTAZIONE OSTEOPOROSI 2° LIVELLO

Solo per necessità/sintomi

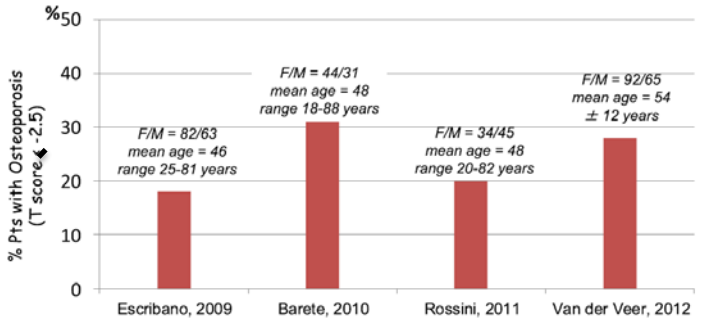
VALUTAZIONE ALLERGOLOGICA 2° LIVELLO

Solo per necessità/sintomi/anamnesi positiva

VALUTAZIONE GASTRO/DERMATO 2° LIVELLO

Solo per necessità (rara)

- Dosaggio triptasi 12-18 mesi (6 mesi SSM)
- Visita 12-18 mesi (6 mesi SSM) (valutazione insorgenza nuovi sintomi)
- Valutazione osteoporosi 2-4 anni (o se necessità)
- Ecografia addominale 12 mesi (neoplasie secondarie)
- Aggiustamento terapia anti-mediatori
- Valutazione pre-chirurgia generale o altra necessità particolare



Oral Communications

Myeloproliferative Disorders 1

C016

SECONDARY NON HEMATOLOGICAL MALIGNANCIES IN ADULT PATIENTS WITH MASTOCYTOSIS: AN ITALIAN MULTICENTRIC SURVEY

M. Bonifacio[1], P. Bonadonna[2], C. Elena[3], L. Pieri[4], F. Grifoni[5], C. Papayannidis[6], M. Rondoni[7], L. Scaffidi[1], F. Resci[1], L. Malcovati[3], E. Bono[3], F. Mannelli[4], M. Sciumè[5], G. Martinelli[6], A. Cortelezzi[5], A.M. Vannucchi[4], M. Cazzola[3], M. Krampera[1], A. Ambrosetti[1], R. Zanotti[1]

Ambulatorio mastocitosi : MCL

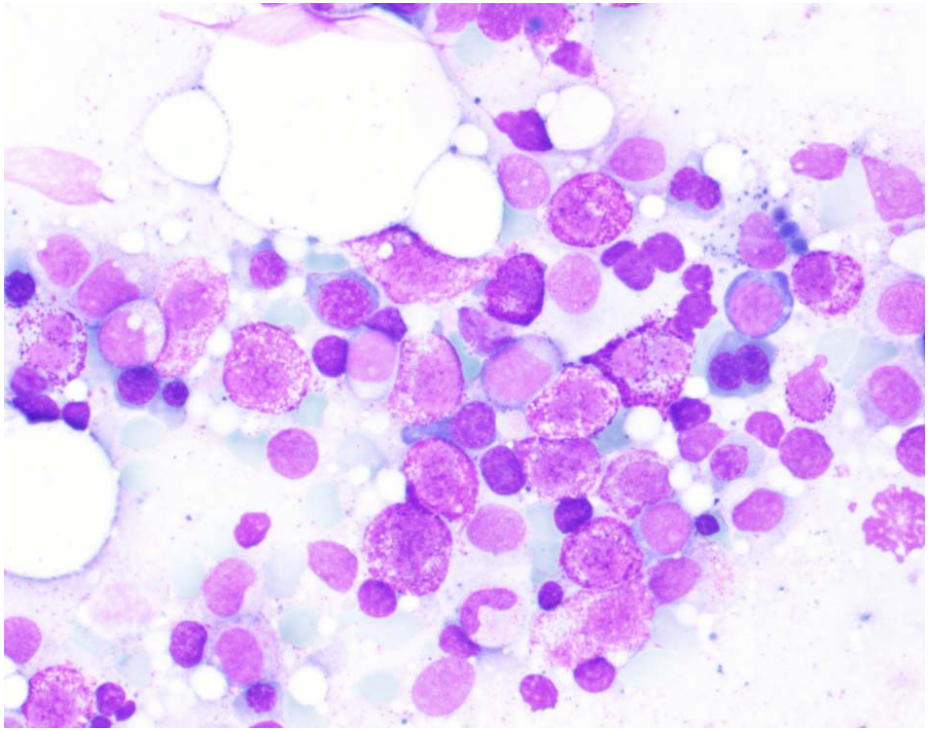
- MCL 8.7% in AVR
- Diagnosi citologica (BOM indistinguibile da ASM)

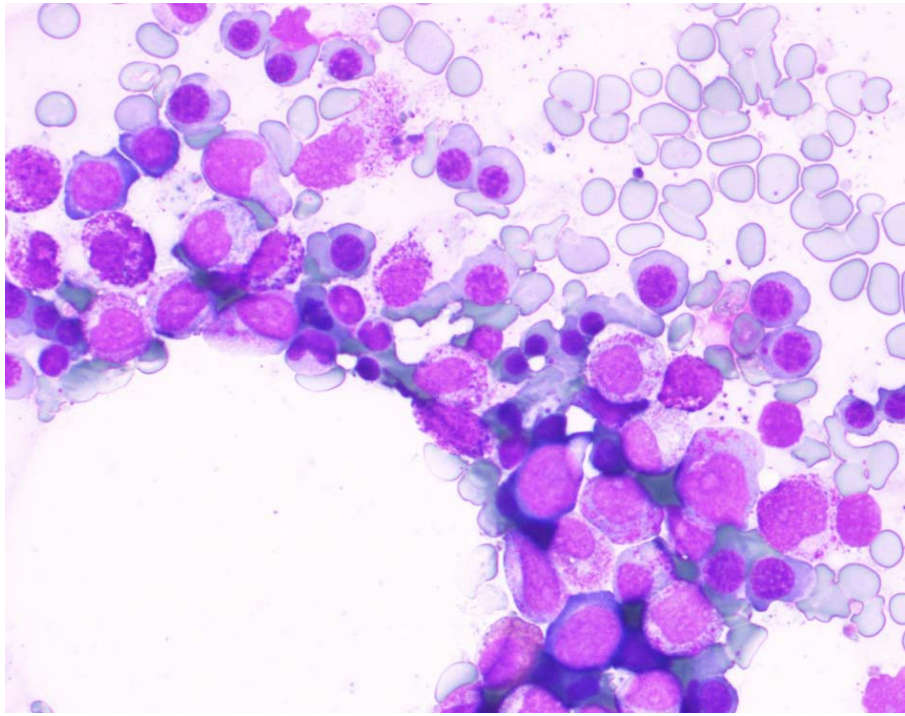
- ≥20% mastocytes in bone marrow smears (atipycal?)
- Variante leucemica/aleucemica (< 10% dei GB)

- WHO 2016 classifica forme “croniche” (nel 2009 OS 3 mesi!) oltre che “acute”
- WHO 2016 classifica ASM-t (MCs > 5%, < 20%)

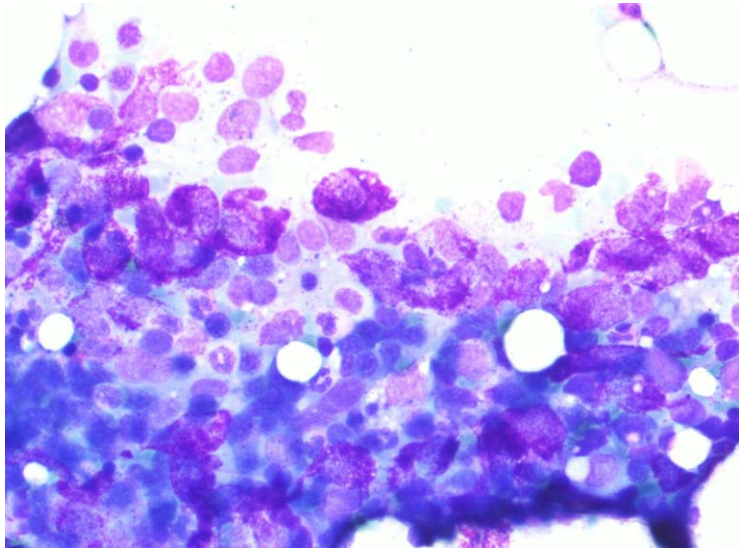
68 aa,
Dg: dicembre 2014 MCL-MDS (47, XY, +8) . Triptasi 47 ug/L
Tp: 2-CdA 6 cicli- Res
MIDOSTAURINA 3 cicli –Res (stop Nov 2017)
06.06.18 : Hb 10.8 g/dL, PMN 1640/mmc, PLT 83.000 (aggregati)

No sintomi
Mastociti immaturi 30-60%- triptasi 68 ug/L OS: 42 mesi

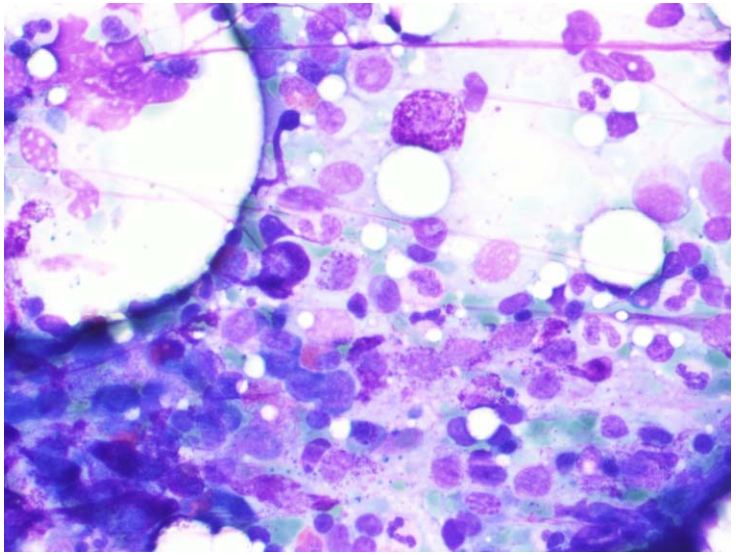




Maschio, 66 aa
Dg CM 1989 (29 anni) – anti-H1 per prurito
2012 studio midollare completo →ISM/SSM
Hb 15,7; PLT 179.000/mmc;WBC 8.320/mmc; Triptasi 100 ug/L
epatomegalia→BX solo cirrosi
Obeso..iperteso…
Cesena 2015:
Hb 12.3 (carenza Fe-VARICI), triptasi 141 ug/L, RSO -/+
Aprile 2017 Hb 14,3 -----Ottobre 2017 Hb 11.2
Marzo 2018 BM MCs 20-30%→ MCL



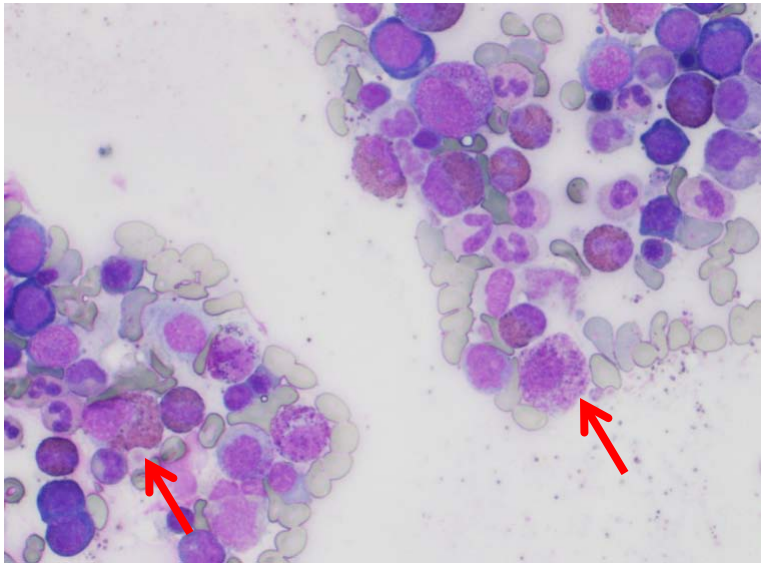
?



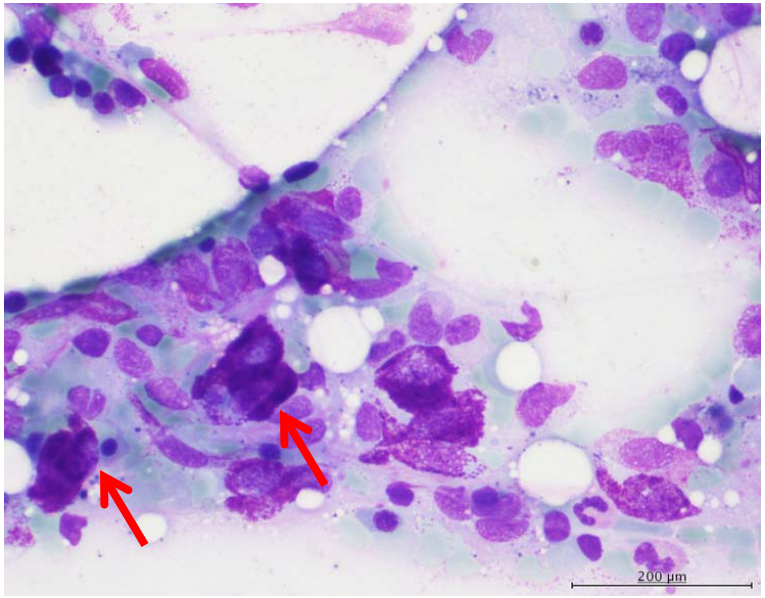
Revisione BM 2012 : MCs 16% !!

MCL??
ASM-t??

2011



2018



67 aa,
Dg: 2011 (per linfonodi addominali 4 cm). Triptasi 52 ug/L.

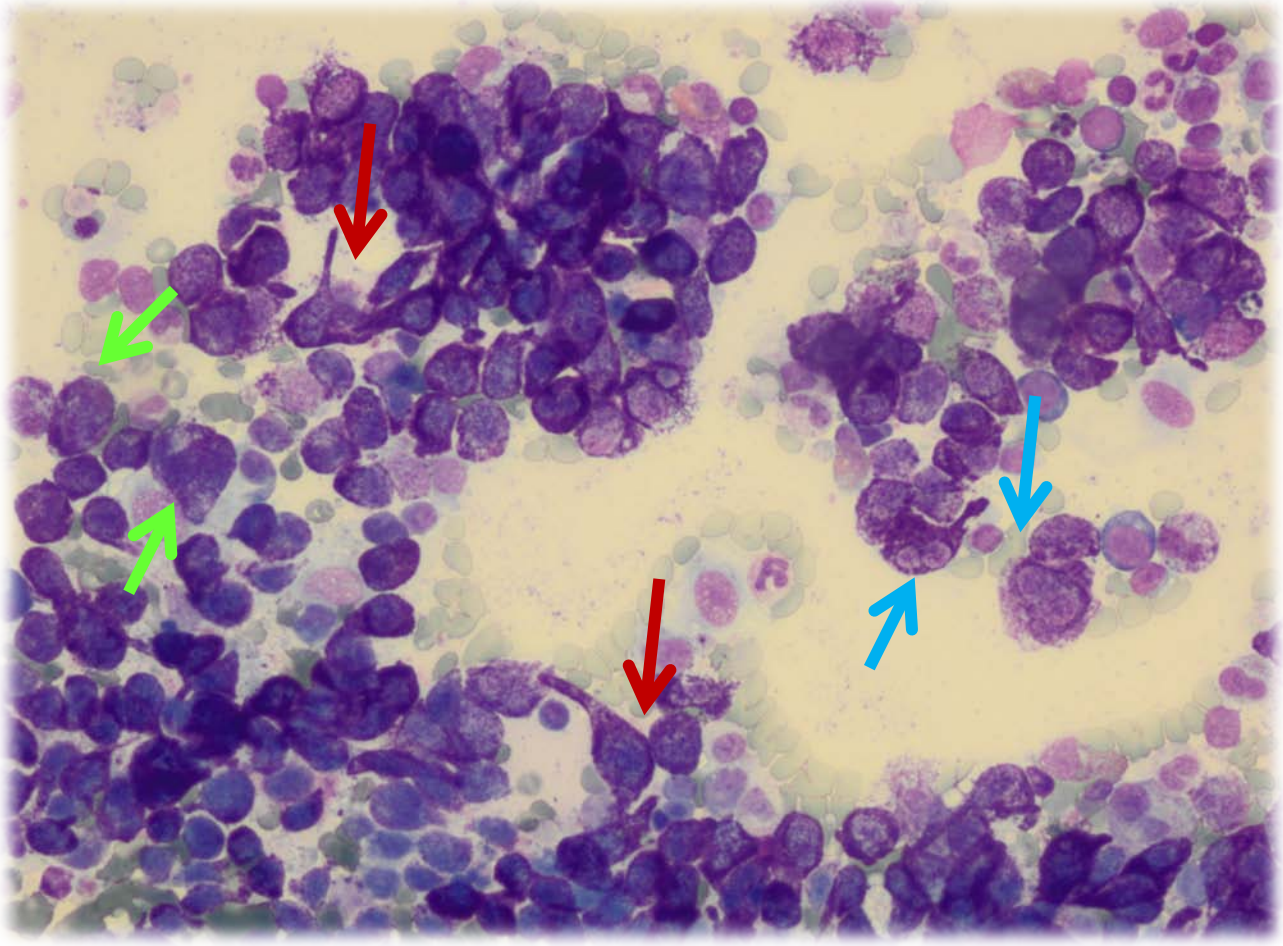
MIDOSTAURINA 15 mesi
2-CdA 18 cicli (0.14 mg/m^2 5 gg/mese)

Sintomi: crisi da rilascio mediatori 1-2/ anno.

OS: 84 mesi

STOP TERAPIA

MCL: Bone Marrow smear



G. Poletti, Laboratorio Unico AVR Pievesestina-Cesena

MC > 20%

Atypical MC type I

Atypical MC type II

Metachromatic blasts

Femmina, 63 aa
Dg: crisi rilascio mediatori e triptasi 2.250 ug/L
D816V negativa→ IMA

OS:

OPEN

Leukemia (2018) 32, 139–148
www.nature.com/leu

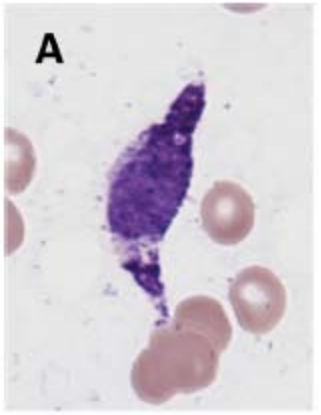
ORIGINAL ARTICLE

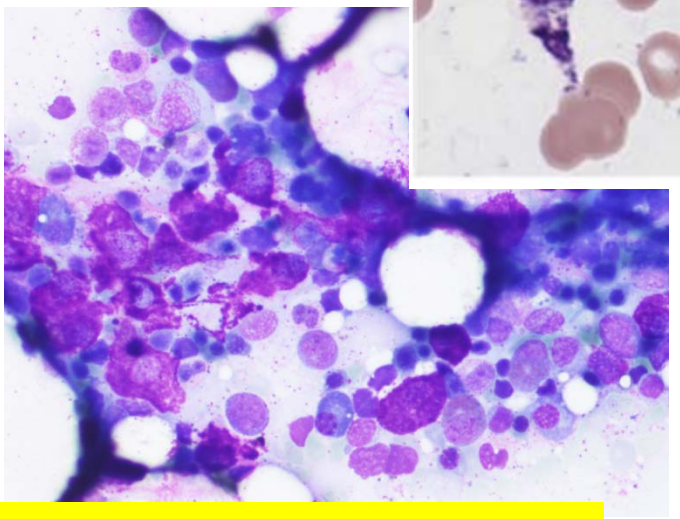
SETD2 and histone H3 lysine 36 methylation deficiency in advanced systemic mastocytosis

G Martinelli[1,20], M Mancini[1,20], C De Benedittis[1,21], M Rondoni[2,21], C Papayannidis[1], M Manfrini[1], M Meggendorfer[3], R Calogero[4], V Guadagnuolo[1], MC Fontana[1], L Bavaro[1], A Padella[1], E Zago[5,6], L Pagano[7], R Zanotti[8,9], L Scaffidi[8,9], G Specchia[10], F Albano[10], S Merante[11], C Elena[11], P Savini[12], D Gangemi[13], P Tosi[14], F Ciceri[15,16], G Poletti[17], L Riccioni[18], F Morigi[18], M Delledonne[5,6], T Haferlach[3], M Cavo[1], P Valent[19] and S Soverini[1]

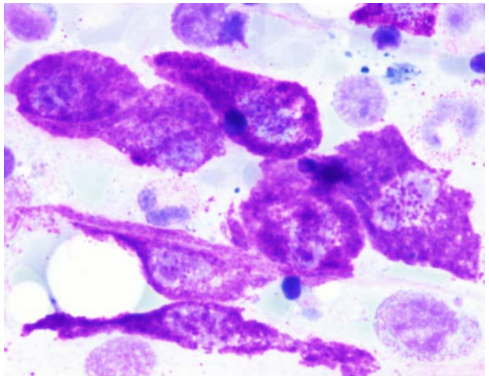
The molecular basis of advanced systemic mastocytosis (SM) is not fully understood and despite novel therapies the prognosis remains dismal. Exome sequencing of an index-patient with mast cell leukemia (MCL) uncovered biallelic loss-of-function mutations in the *SETD2* histone methyltransferase gene. Copy-neutral loss-of-heterozygosity at 3p21.3 (where *SETD2* maps) was subsequently found in SM patients and prompted us to undertake an in-depth analysis of *SETD2* copy number, mutation status, transcript expression and methylation levels, as well as functional studies in the HMC-1 cell line and in a validation cohort of 57 additional cases with SM, including MCL, aggressive SM and indolent SM. Reduced or no SETD2 protein expression—and consequently, H3K36 trimethylation—was found in all cases and inversely correlated with disease aggressiveness. Proteasome inhibition rescued SETD2 expression and H3K36 trimethylation and resulted in marked accumulation of ubiquitinated SETD2 in SETD2-deficient patients but not in patients with near-normal SETD2 expression. Bortezomib and, to a lesser extent, AZD1775 alone or in combination with midostaurin induced apoptosis and reduced clonogenic growth of HMC-1 cells and of neoplastic mast cells from advanced SM patients. Our findings may have implications for prognostication of SM patients and for the development of improved treatment approaches in advanced SM.

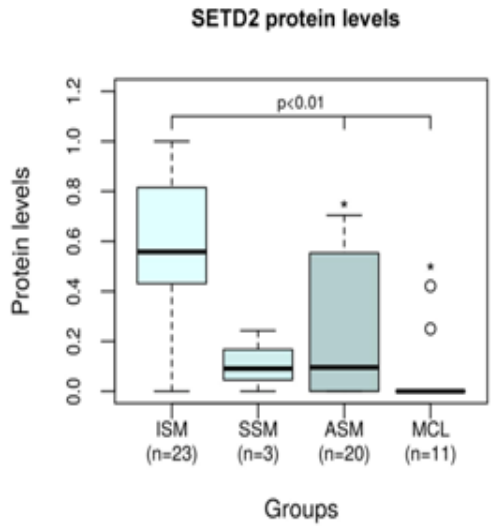
Leukemia (2018) **32**, 139–148; doi:10.1038/leu.2017.183

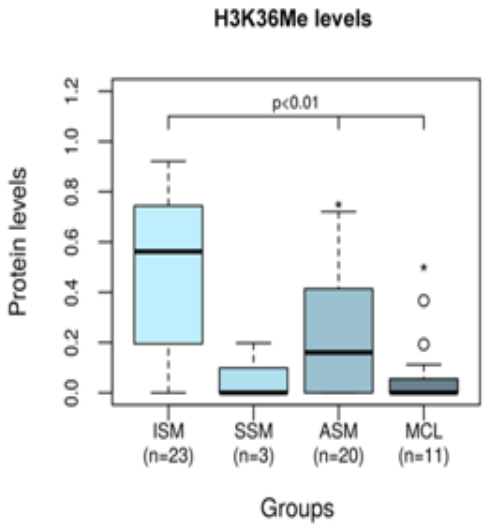




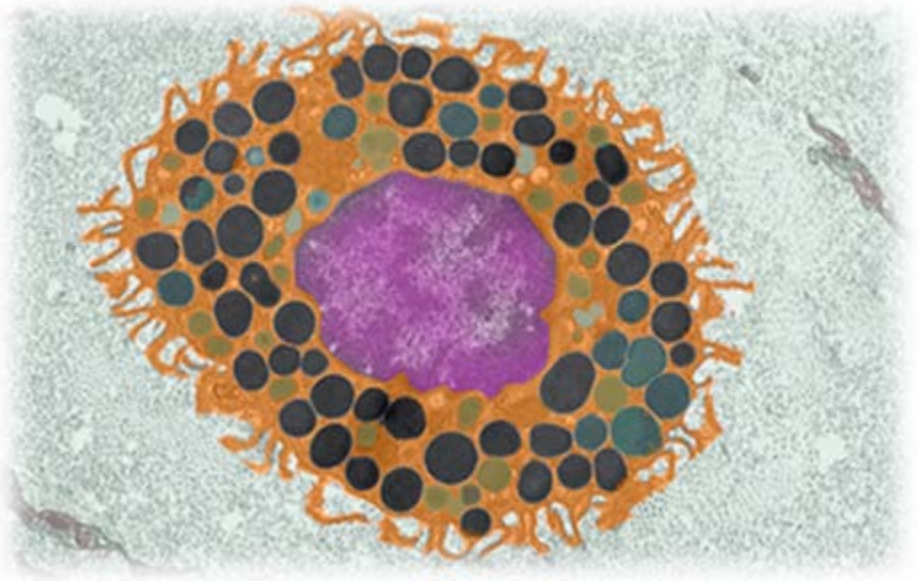
Necessario studiare marcatori di maturazione delle MCs con citometria…







Grazie per l' attenzione!



Luis Escribano
(Salamanca)
Roberta Zanotti
(Verona)
Federica Grifoni
(Policlinico Milano)

Giovanni Poletti

U.O.C. Ematologia Ravenna

Simona Soverini
Luana Bavaro
Cristina Papayannidis
Giovanni Martinelli

Hematology/Oncology University of Bologna: