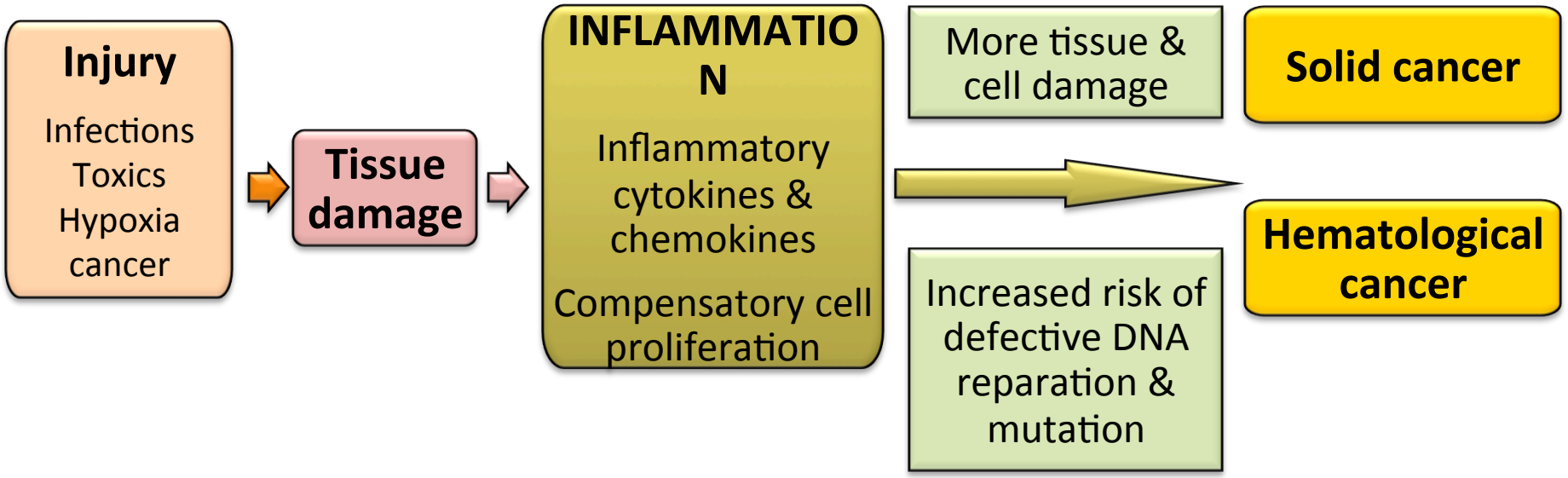
Progetto Ematologia Romagna

Ruolo dei farmaci anti-infiammatori in oncoematologia

Francesca Palandri

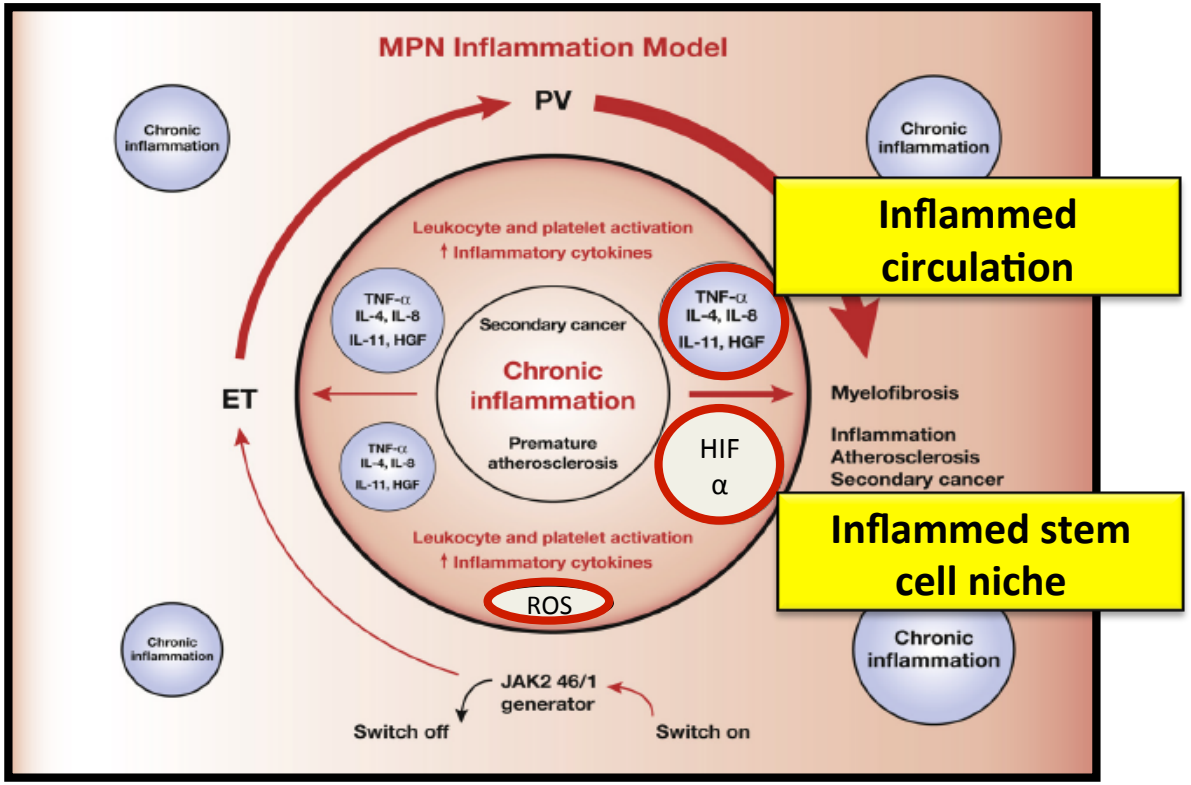
From chronic inflammation to cancer



- A physical, chemical, or infectious injury leads to tissue damage which results in the autocrine/paracrine production of prosurvival, inflammatory cytokines, as well as chemokines, to attract immune cells to the site of injury.
- Chronic inflammation overstimulates the production of hematopoietic cells and induces more tissue damage, with increased risk of DNA mutations in cells from affected tissues (increased risk of solid cancer) and in cells participating in the immune/ inflammatory response (increased risk of hematological malignancy).

Todoric J, Cancer Prev Res 2016; 9(12); 895–905; Hermouet S eta l. Mediators Inflamm. 2015;2015:964613. Hermouet S et al. Mediators Inflamm. 2015;2015:145293; Musolino C et al. Mediators Inflamm. 2017;2017:1852517; Lussana F, Rambaldi A. Journal of Autoimmunity 85 (2017) 58e63

MPN are a Model of Inflammation

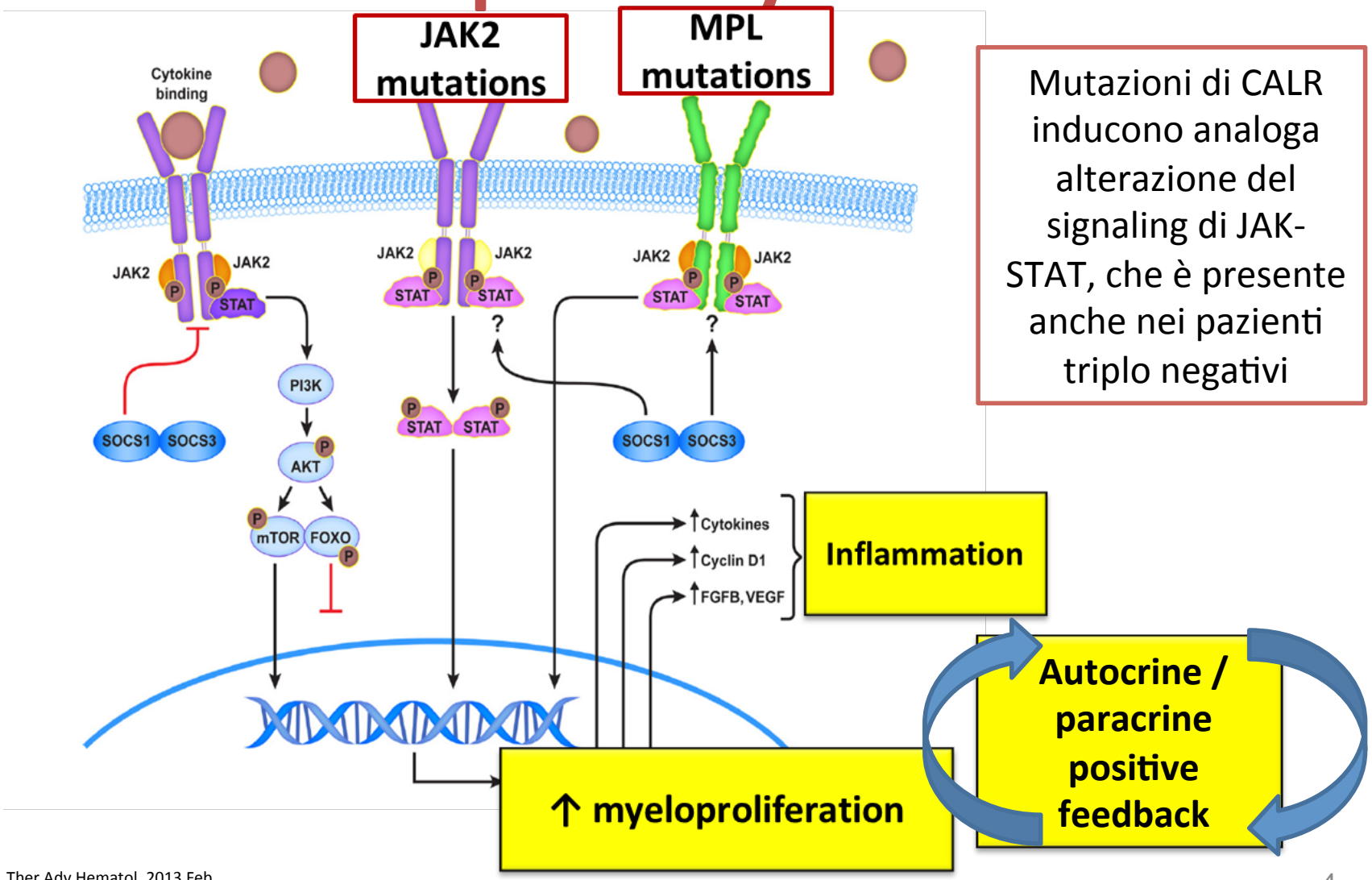


MPN are characterized by a state of chronic inflammation due to the continuous release of proinflammatory cytokines from leukocytes, platelets and endothelial cells (**inflamed circulation**).

Also, cancer stem cells contribute to the state of chronic inflammation (**inflamed stem cell niche**) by producing: 1) TNF-alpha → clonal espansion; 2) ROS → DNA damage; 3) HIF-alpha → angiogenesis and disease progression

Mughal et al. International Journal of General Medicine, 2014 – Hasselbalch . Cytokine & Growth Factor Reviews, 2013

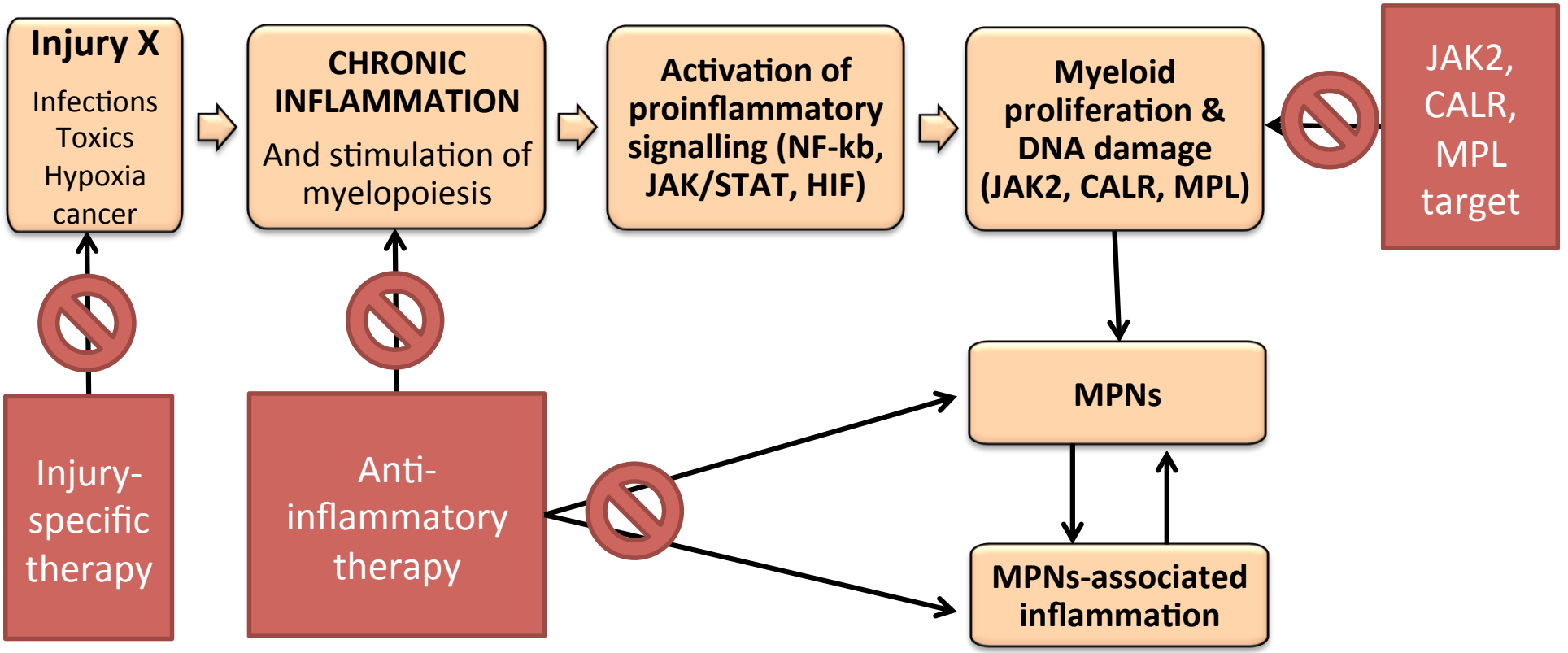
The trigger of inflammation is the dysregulation of the JAK-STAT pathway



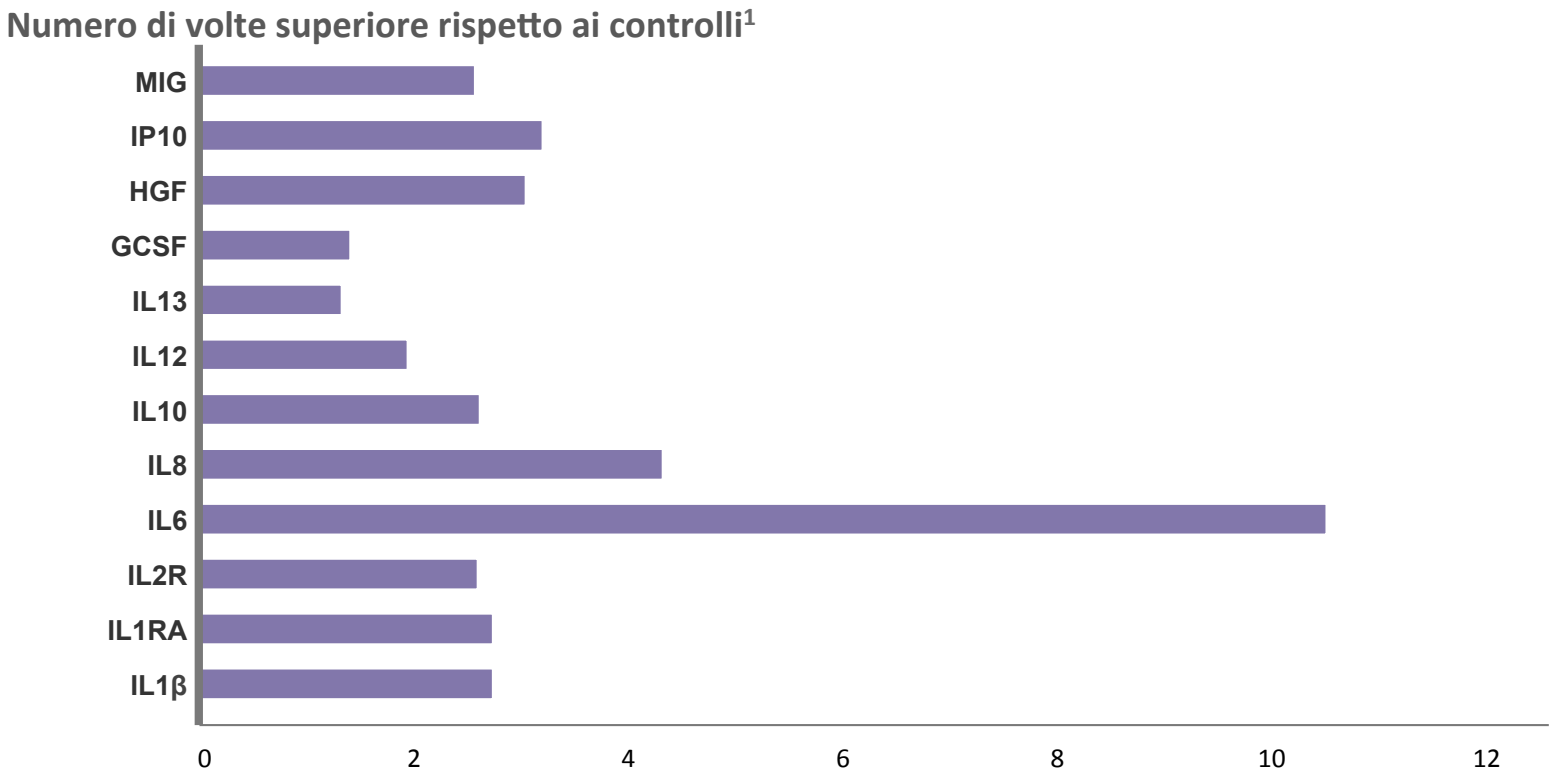
Mutazioni di CALR inducono analoga alterazione del signaling di JAK-STAT, che è presente anche nei pazienti triplo negativi

Sonbol et al. Ther Adv Hematol. 2013 Feb

Inflammation in MPNs: a target for therapy?



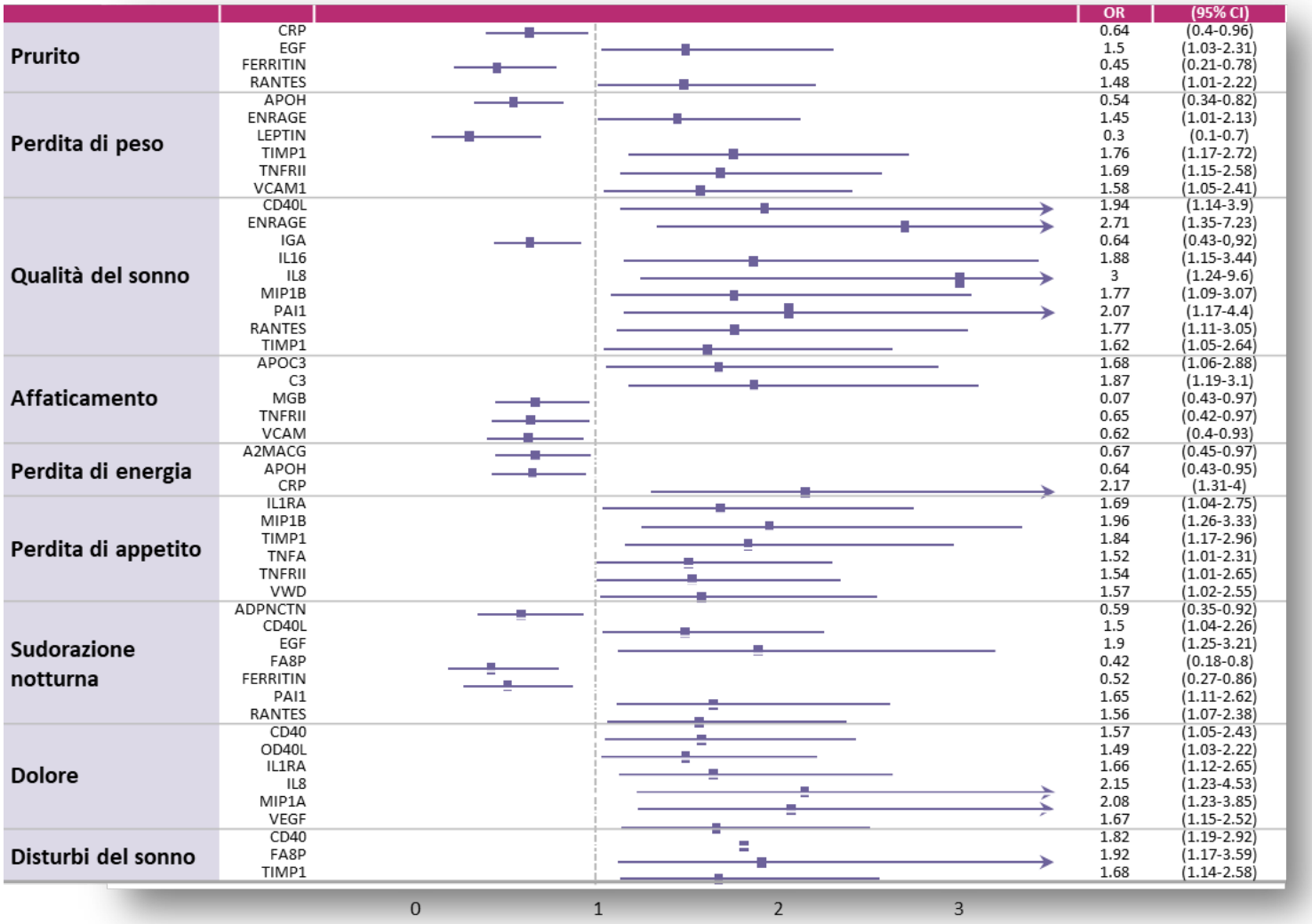
Cytokines levels are increased in MF patients compared to controls



- I livelli di INF gamma sono bassi

1.Tefferi A et al, JCO 2011;29:1356-1363; 2. Hsu HC, Journal of Laboratory and Clinical Medicine 1999;134:392–7; 3. Panteli KE, et al. British Journal of Haematology 2005;130:709–15; 4. Ho CL, et al. Leukemia Research 2007;31:1389–92; 5. Boissinot M, et al. Oncogene 2011;30: 990–1001; 6. Pardanani A, et al. American Journal of Hematology 2011;86:343–5.

Citokines levels correlate with the burden of symptoms in MF



1.Squires M, et al. Blood 2013; 122(21): Abs 4070

Proinflammatory cytokines affect prognosis in MF

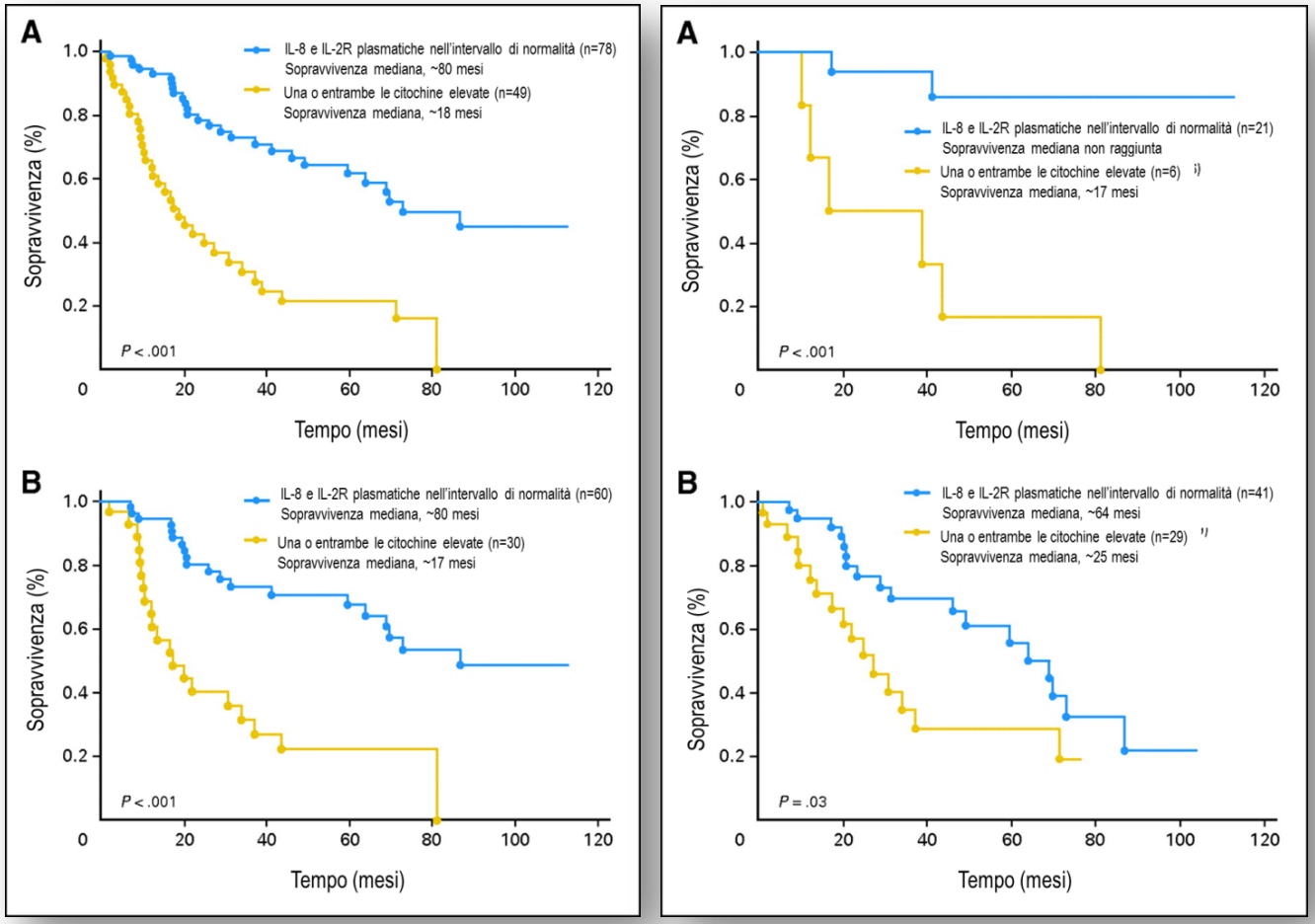
Livelli plasmatici aumentati di IL-8 e IL-2R sono correlati a una ridotta sopravvivenza libera da leucemia[1]

Tutti (n=127)

Nessuna terapia (n=90)

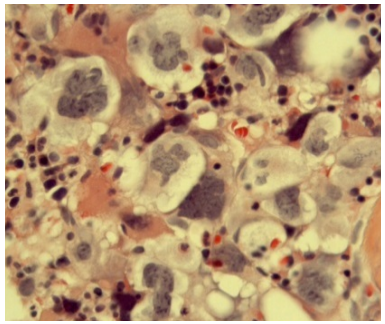
Int-1 (n=27)

Int-2 (n=70)



1. Tefferi A et al. JCO 2011;29:1356-1363.

JAK1 & *JAK2* signalling are responsible for the clinical phenotype of MF

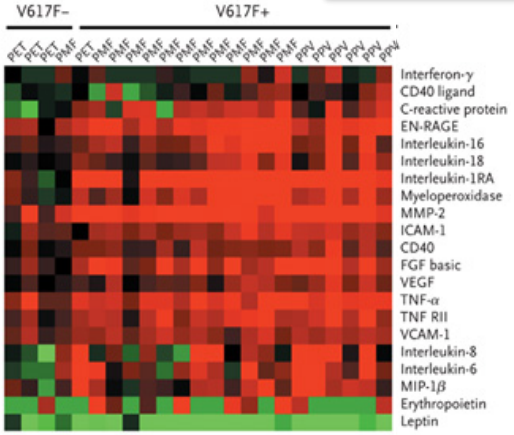


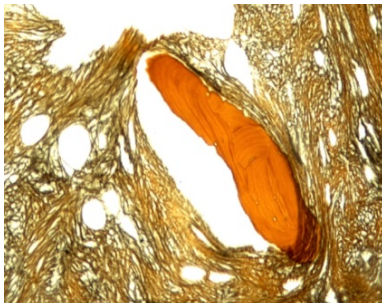
JAK2

JAK1

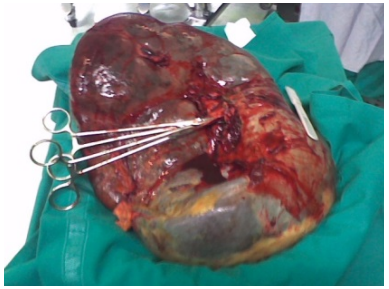
↑ Citochine infiammatorie

Mieloproliferazione





Fibrosi



Emopoiesi extramidollare (splenomegalia)

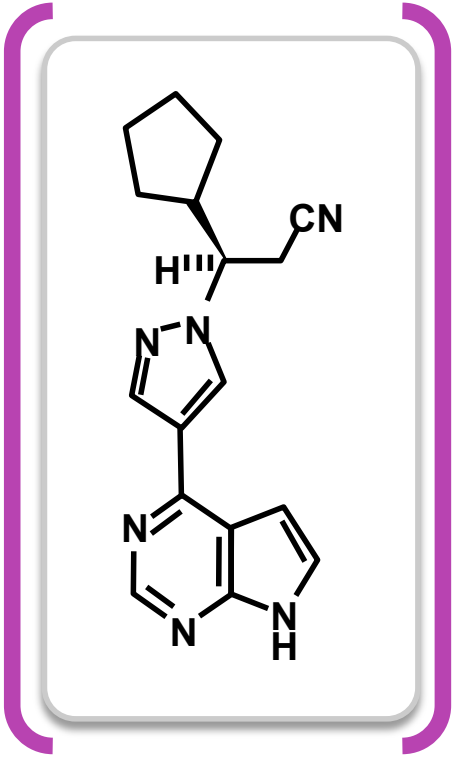
Eritropoiesi inefficace

Sintomi costituzionali

Verstovsek S, et al. N Engl J Med. 2010; 363:1117-27

Ruxolitinib is a *JAK1/JAK2* inhibitor

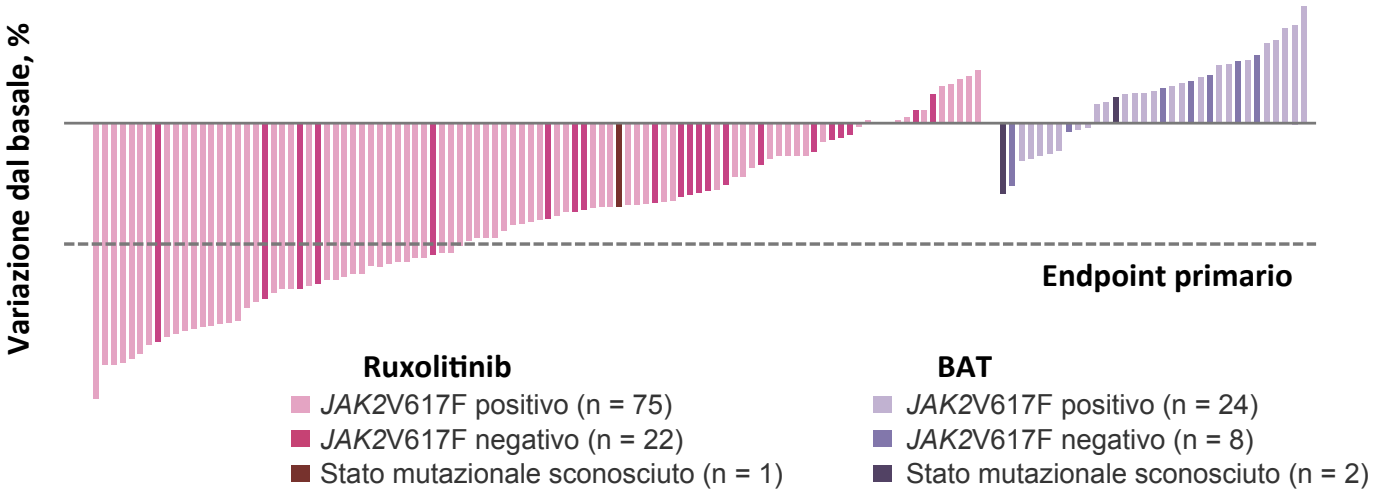
- Approvazione FDA per i pazienti con MF a rischio intermedio-alto
- Approvazione EMA per la terapia dei sintomi e/o della splenomegalia correlata alla MF e per i pazienti con PV intolleranti/resistenti a idrossiurea
- Italia: rimborsabile in pazienti con MF a rischio intermedio-1, intermedio-2 e alto con splenomegalia palpabile ad almeno 5 cm dall'arcata costale e nei pazienti con PV

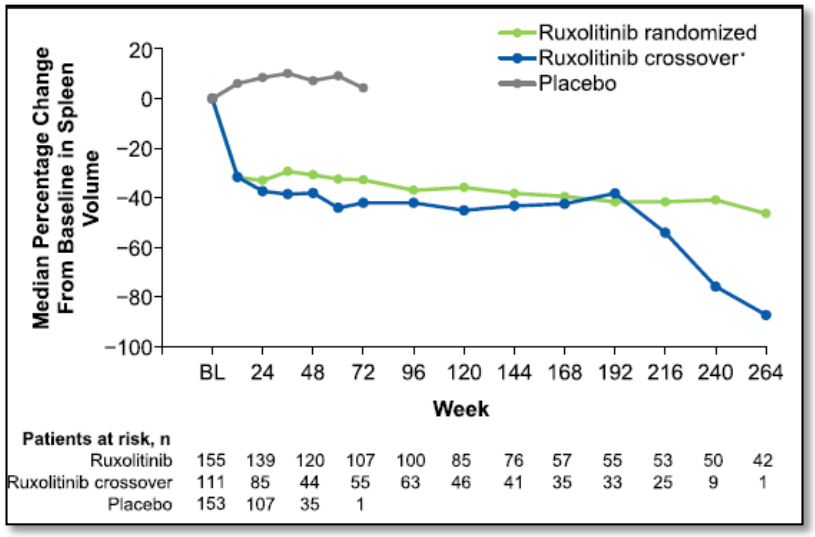


Chinasi	IC_{50} nM (media ± SD)
JAK1	**3,3 ± 1,2**
JAK2	**2,8 ± 1,2**
JAK3	428 ± 243
TYK2	19 ± 3,2
CHK2	>1000*
cMET	>10.000*
Attivazione nel sangue periferico	**IC_{50} nM (media ± SD)**
+IL-6	282 ± 54
+TPO	281 ± 62

Hasselbalch HC, et al. Cytokine Growth Factor Rev 2013; 133-145; Harrison C, et al. Expert Rev Hematol 2013; 6(5): 511-23; Quintás-Cardama A, et al. Blood 2010; 115(15): 3109-17;

Ruxolitinib is effective in reducing myeloproliferation in vivo in MF

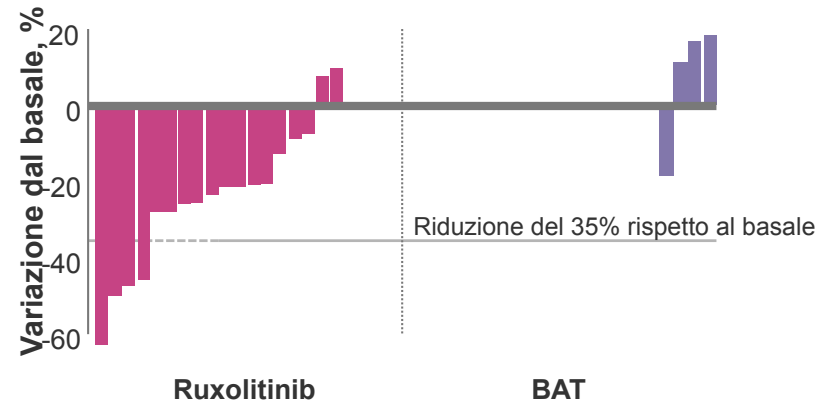


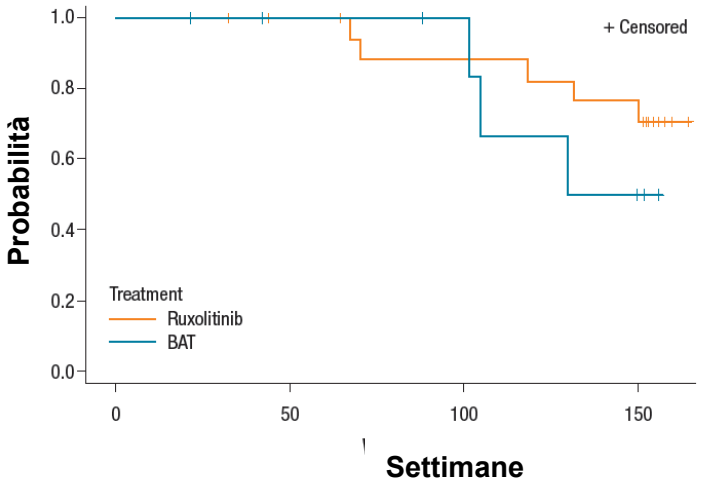


Tra i pazienti originariamente randomizzati a RUX, il 59.4% Ha ottenuto una riduzione ≥ 35% del volume della milza durante lo studio.
Il 50% dei pazienti responsivi ha mantenuto la risposta a 5 anni

Ruxolitinib is effective in reducing myeloproliferation in CALR+ MF

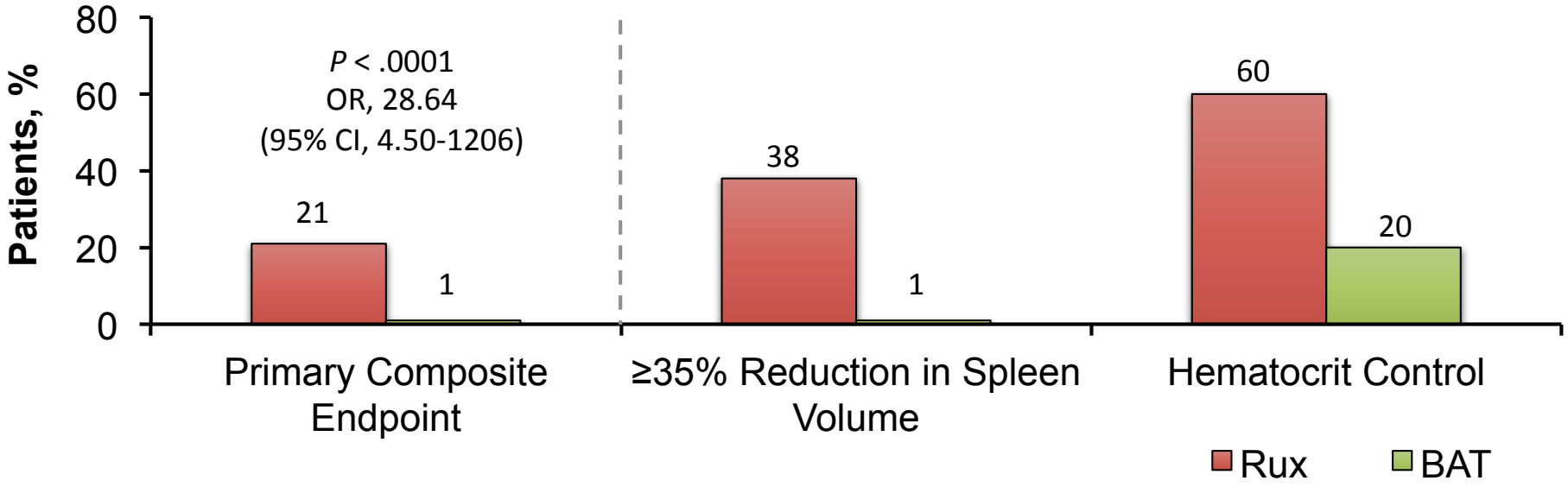
- 29/166 (17.5%) pazienti, con valutazione dello stato mutazionale al basale, era CALR+ (ruxolitinib, n=20 [Tipo 1 =15; Tipo 2 =3; del atipica=2]; BAT, n=9 [Tipo 1=5; Tipo 2=5])
- Tra i pazienti CALR+ è stata ottenuta riduzione del volume splenico ≥35% dal basale alla settimana 48 (endpoint primario) nel 20% dei pazienti del gruppo ruxolitinib (vs 0% nel braccio BAT)
- Il *burden* allelico di CALR è rimasto invariato nel corso dello studio in entrambi i gruppi; tuttavia 3 pazienti hanno ottenuto una significativa riduzione del *burden* allelico di CALR con ruxolitinib (>10% dal basale)
- La probabilità stimata dalla Kaplan-Meier della sopravvivenza a 144 settimane era di 0,76 nel braccio ruxoltinib (range, 0.49-0.90) vs 0,50 nel braccio BAT, (range, 0.11-0.80) con una riduzione relativa del rischio di morte sovrapponibile a quello dei pazienti del COMFORT-II (24% vs 19%).





Guglielmelli P et al. ASH 2014. Abs 1853

Ruxolitinib is effective in reducing myeloproliferation in vivo in PV

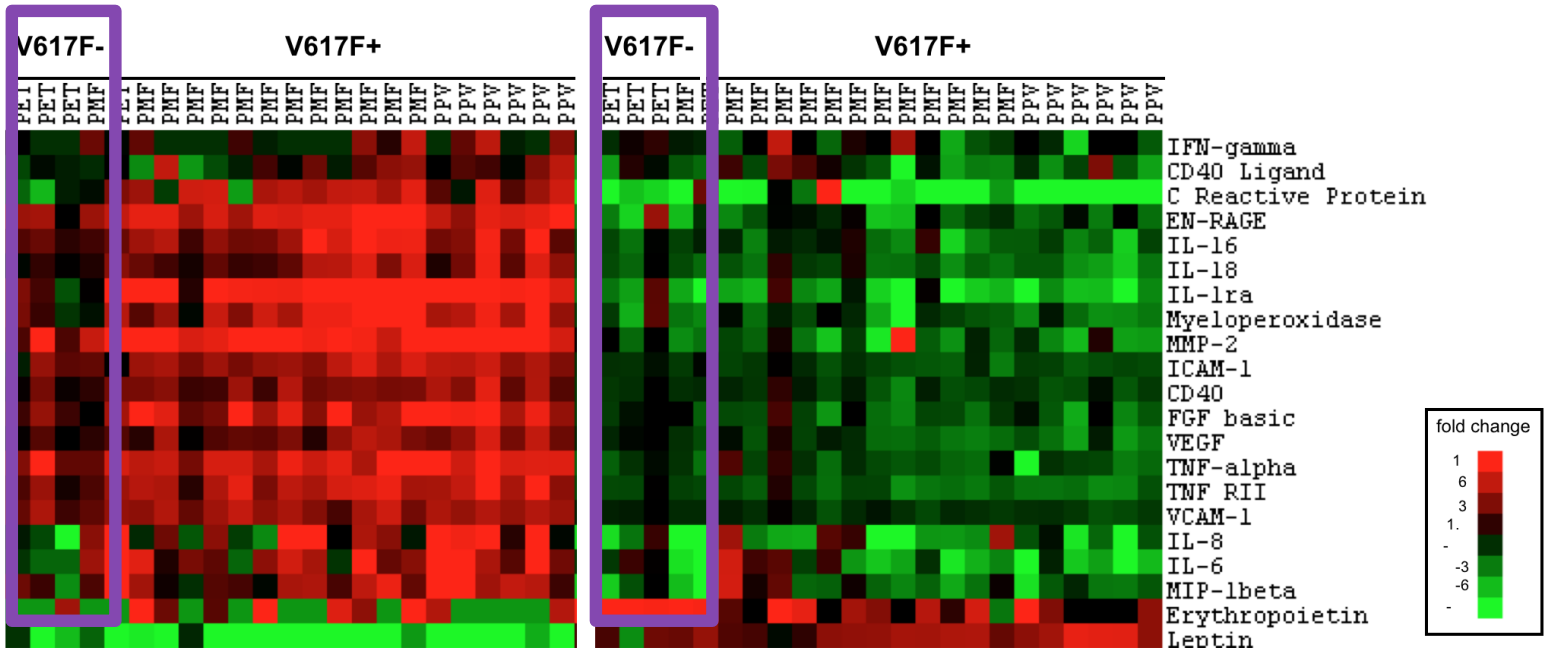


RESPONSE study: Primary Analysis at Wk 32

- 222 phlebotomy-dependent PV patients with splenomegaly, were randomized in a 1:1 ratio, to receive ruxolitinib (110 pts) or standard therapy (112 pts).
- Patients randomized to RUX achieved higher rates of Hct control and spleen reductions
- 73% of patients maintains Hct control at 4 years
- 86% of patients maintains at least a 35% reduction in the spleen volume at 4 years

Ruxolitinib riduces pro-inflammatory cytokines

Effetto di ruxolitinib sui livelli di citochine[1]

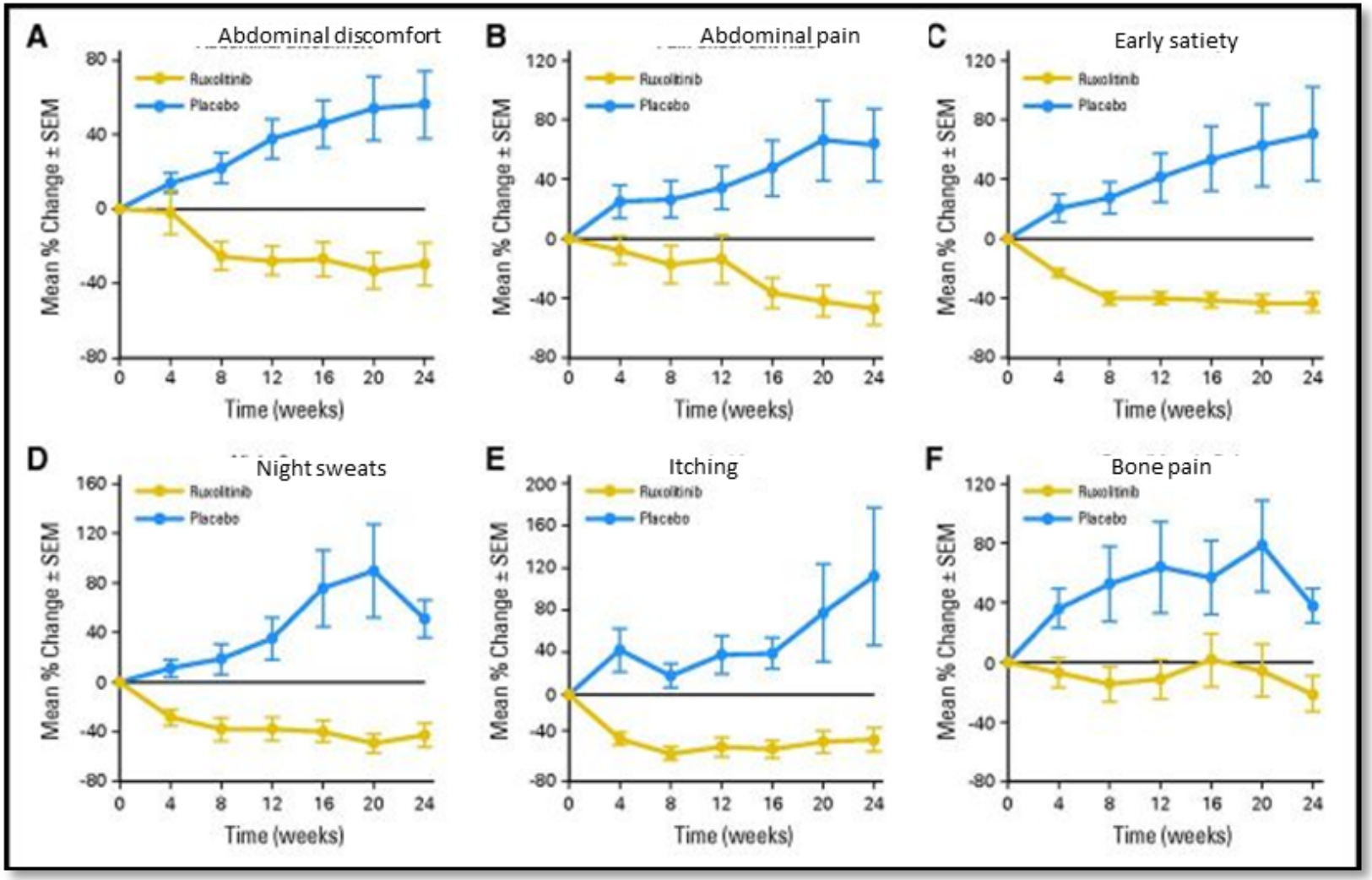


Pazienti con MF al basale *vs* controlli sani

Pazienti con MF, giorno 28 giorni *vs* basale

1.Verstovsek S, et al. N Engl J Med. 2010;363(12):1117-1127.

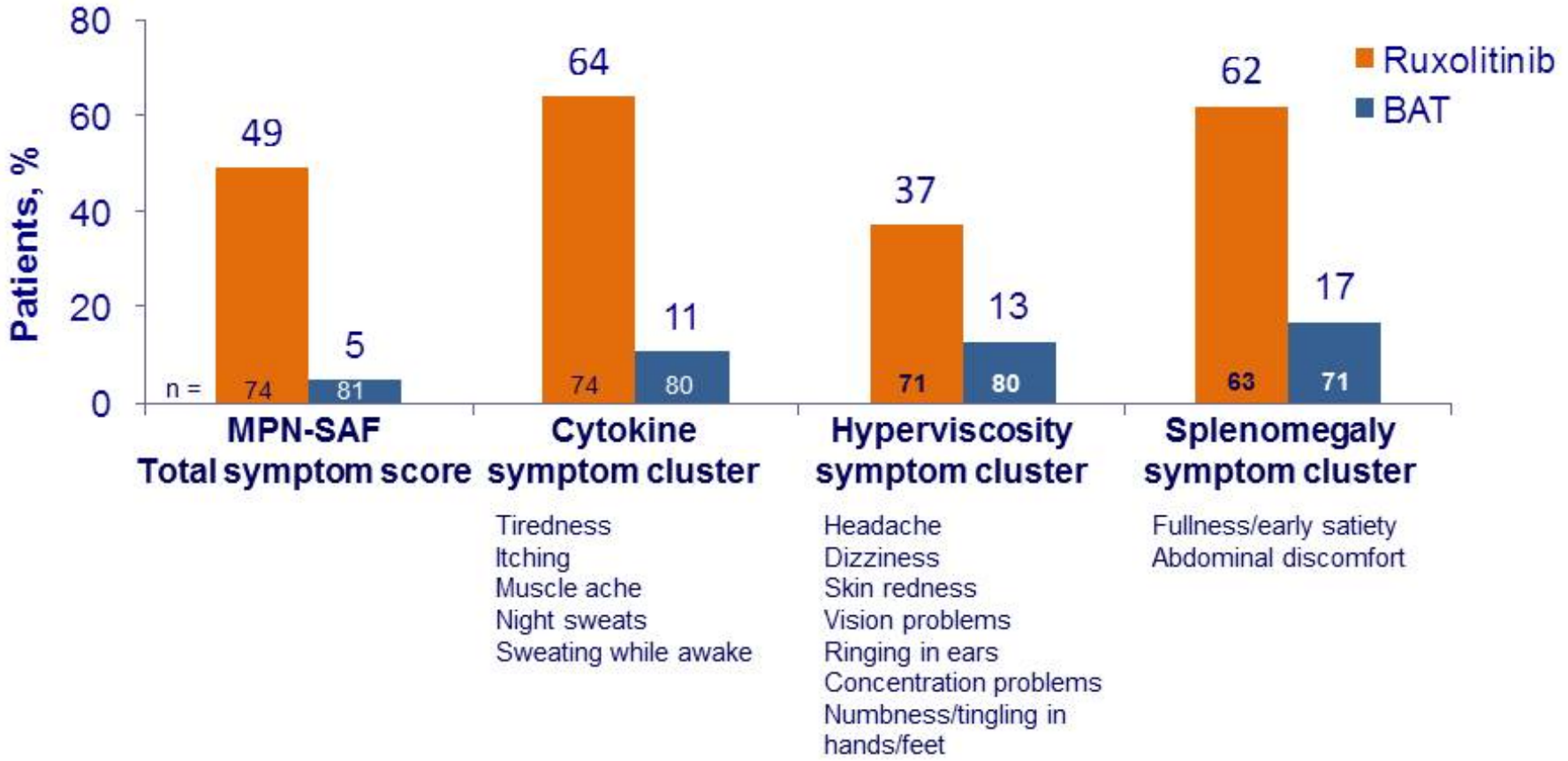
Ruxolitinib riduces the burden of symptoms in MF



1.Verstovsek S, et al. N Engl J Med. 2010;363(12):1117-1127.

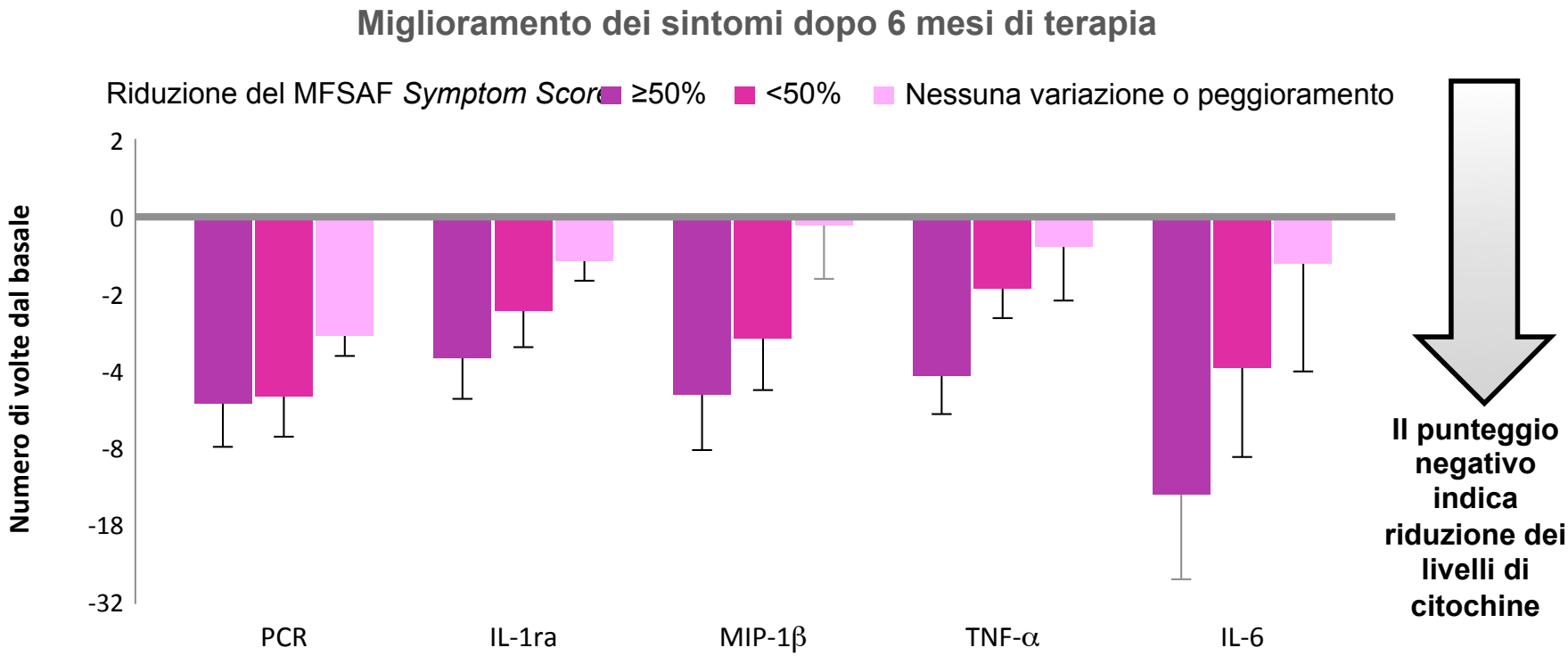
Ruxolitinib riduces the burden of symptoms in PV

- **Percentage of patients with a ≥50% improvement in MPN-SAF symptom score at week 32[a]**



Vannucchi et al, N Engl J Med. 2015 Jan 29;372(5):426-35.

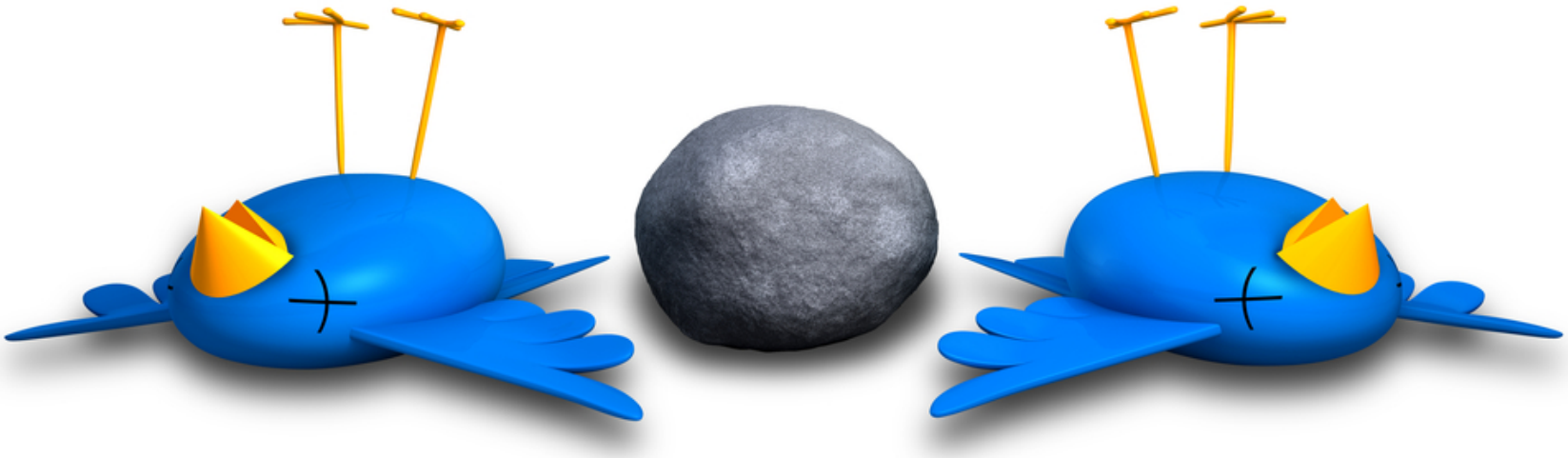
Improvement in symptoms correlates with the decrease of cytokines



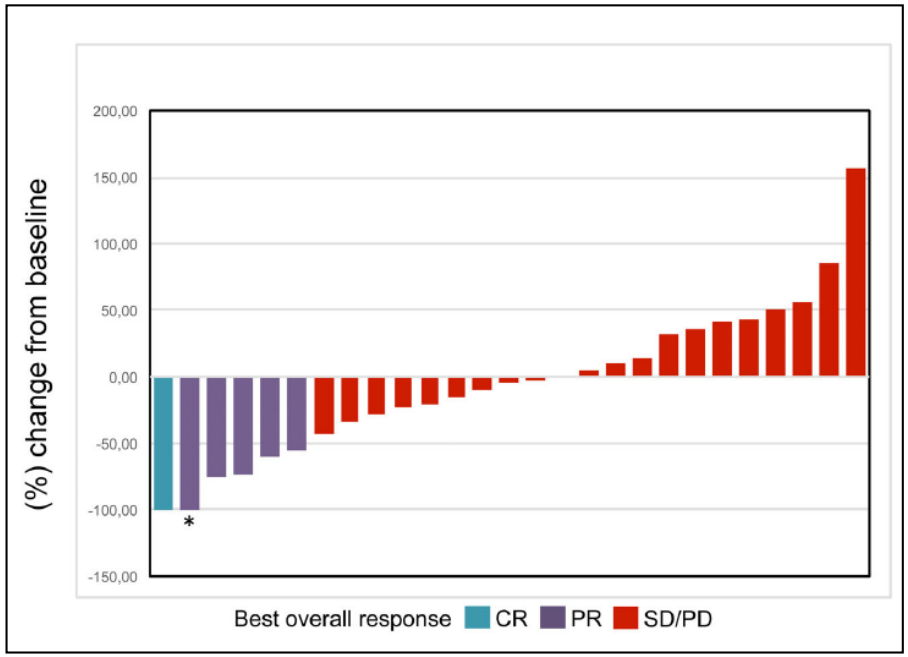
Il miglioramento dei sintomi è correlato alle variazioni dei livelli di citochine per prurito (ferritina), perdita di peso (leptina), qualità del sonno (CD40L), appetito (IL1RA) e sudorazioni notturne (ferritina)

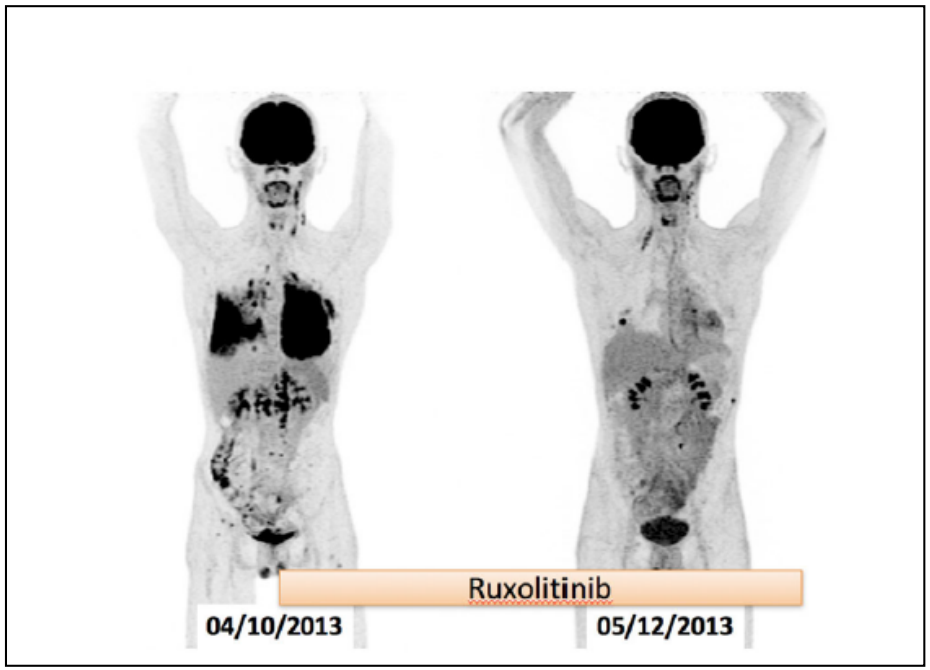
1.Verstovsek S, et al. N Engl J Med. 2010;363(12):1117-1127.

Ruxolitinib: the way to kill two birds with one stone



Ruxolitinib in Hodgkin Lymphoma

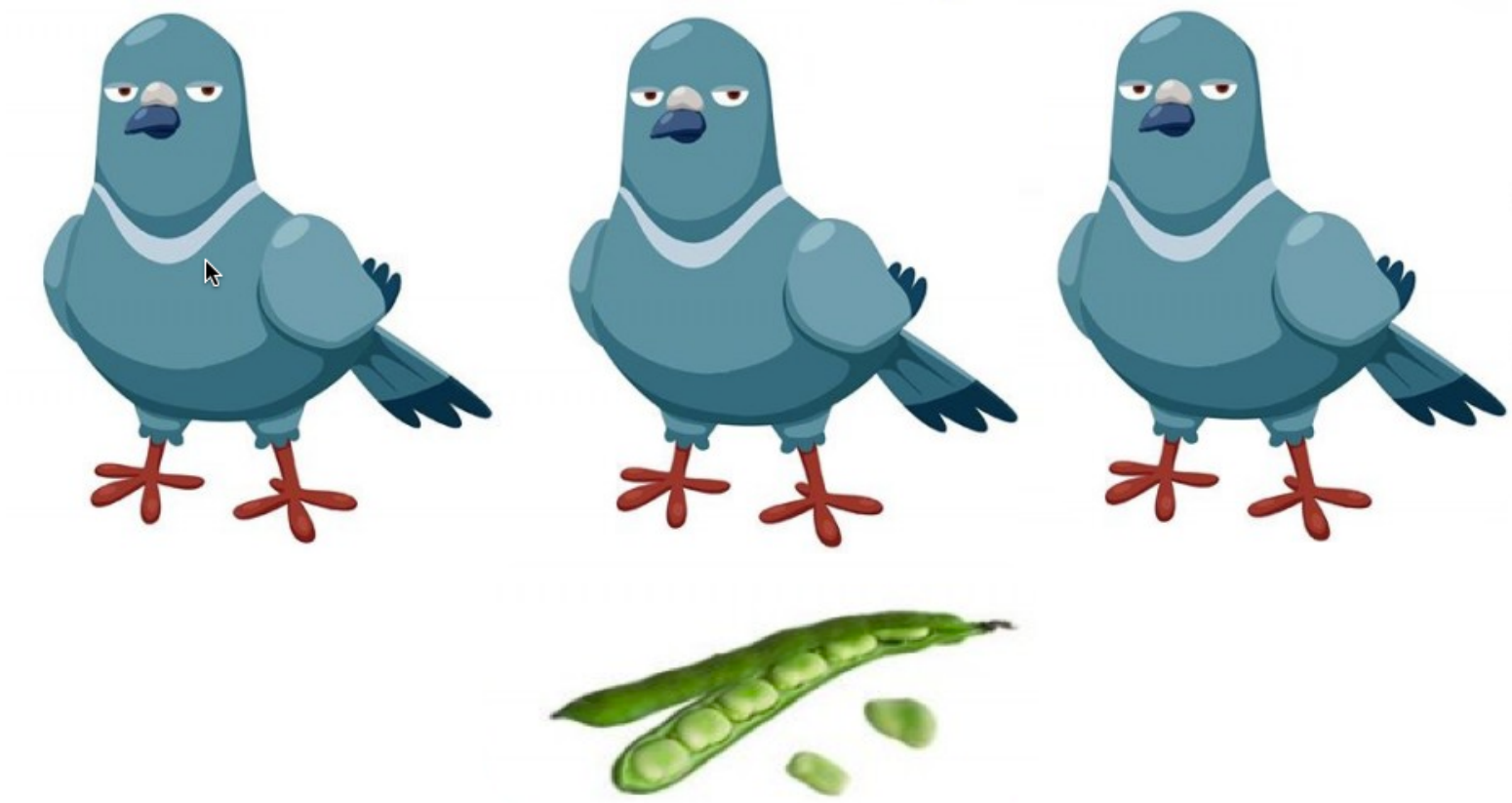




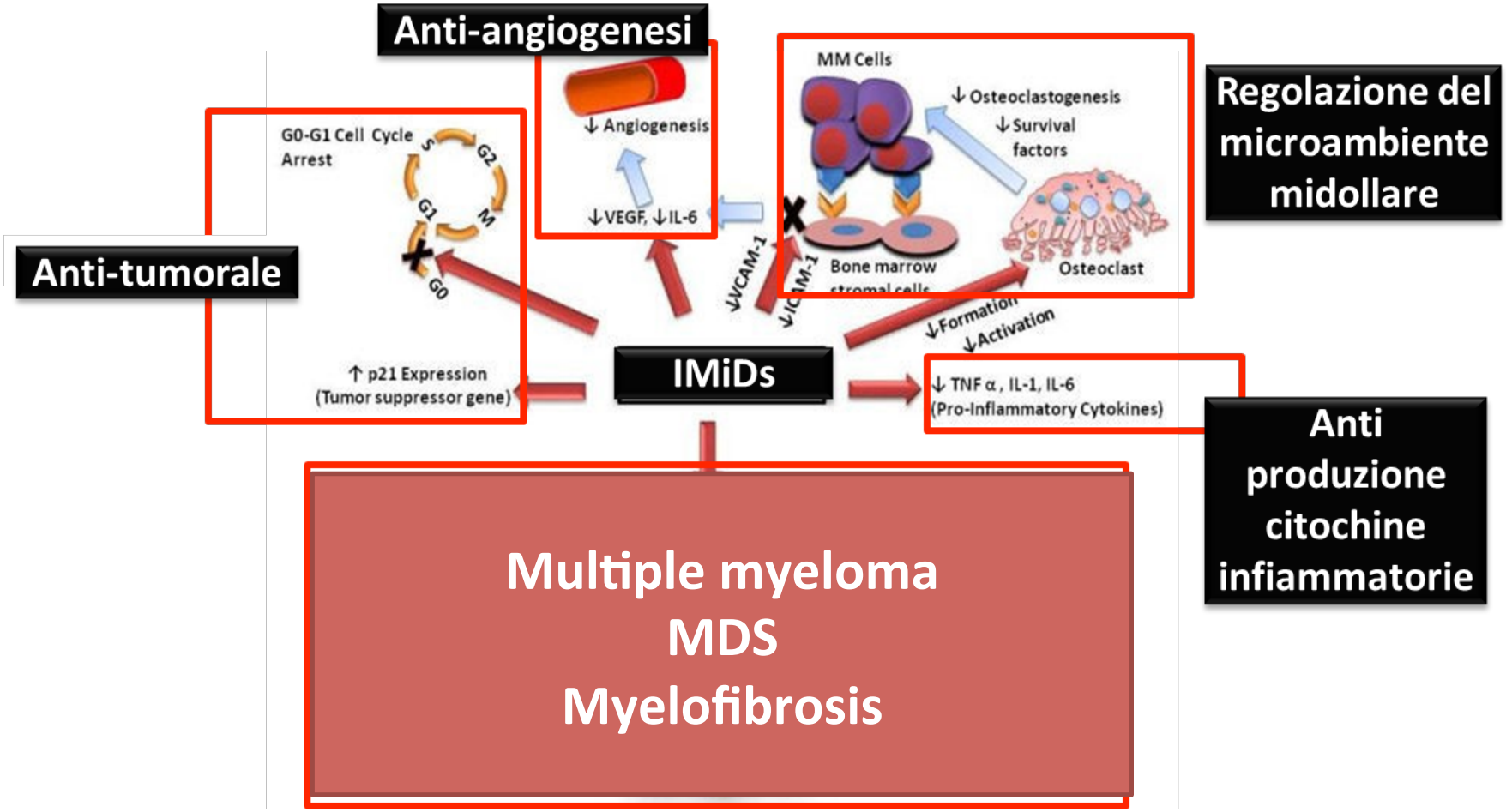
- JAK/STAT activation, driven by an aberrant network of cytokines and chemokines in the HL microenvironment, is critical for the proliferation and survival of neoplastic HRS cells.
- The JAK/STAT pathway also plays a role in immune evasion by HL cells via the secretion of chemokines
- Ruxolitinib significantly decreased the levels of PDGF-beta, IL-10, IL-12, IL-13, IL-17, FGF-b and VEGF, significantly reducing pruritus

Van Den Neste E et al, Haematologica 2018; Volume 103(5):840-848

Anti-inflammatory drugs: more than 2 birds with a stone?

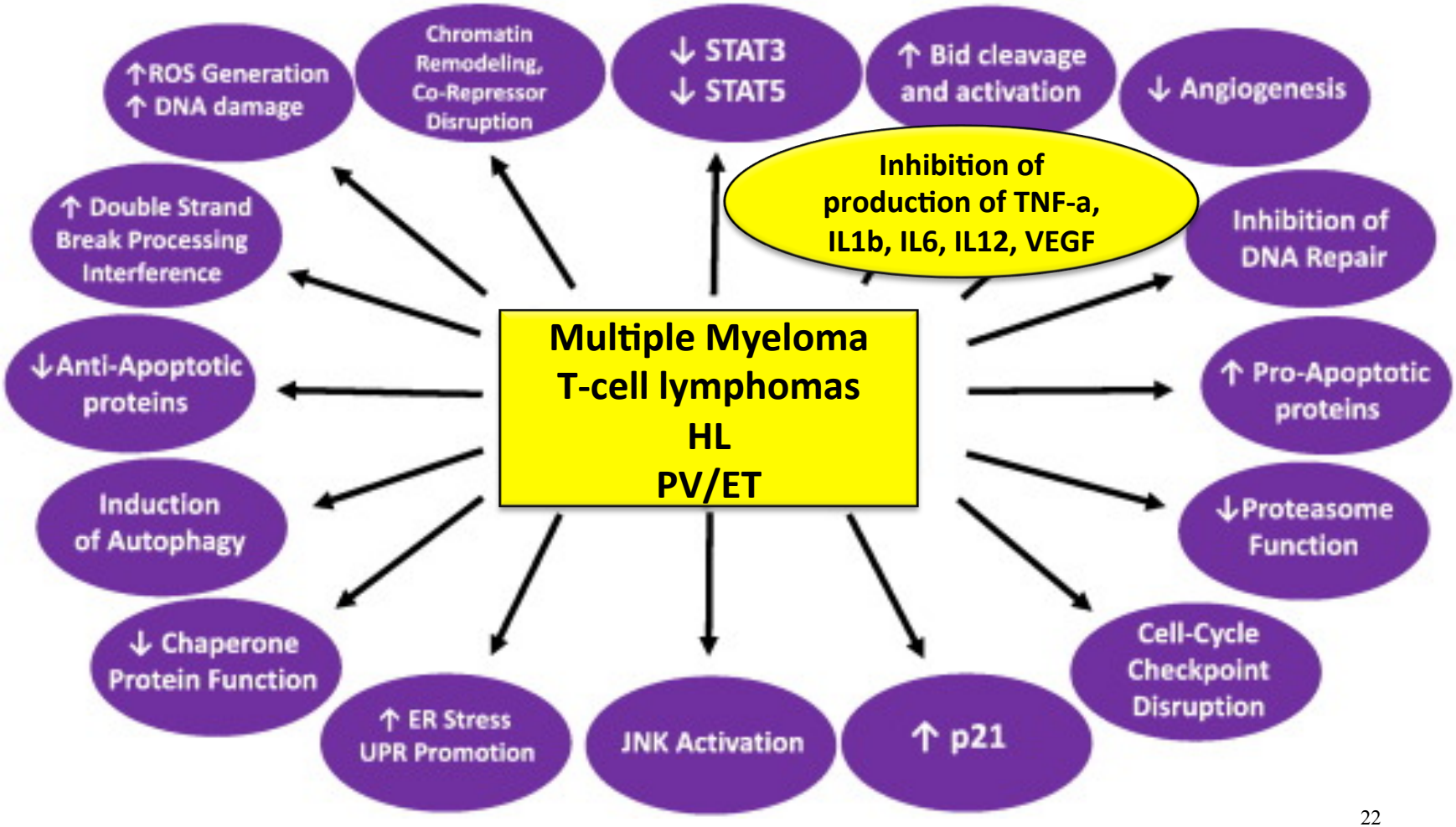


Immunomodulating agents (IMiDs) have anti-inflammatory activity

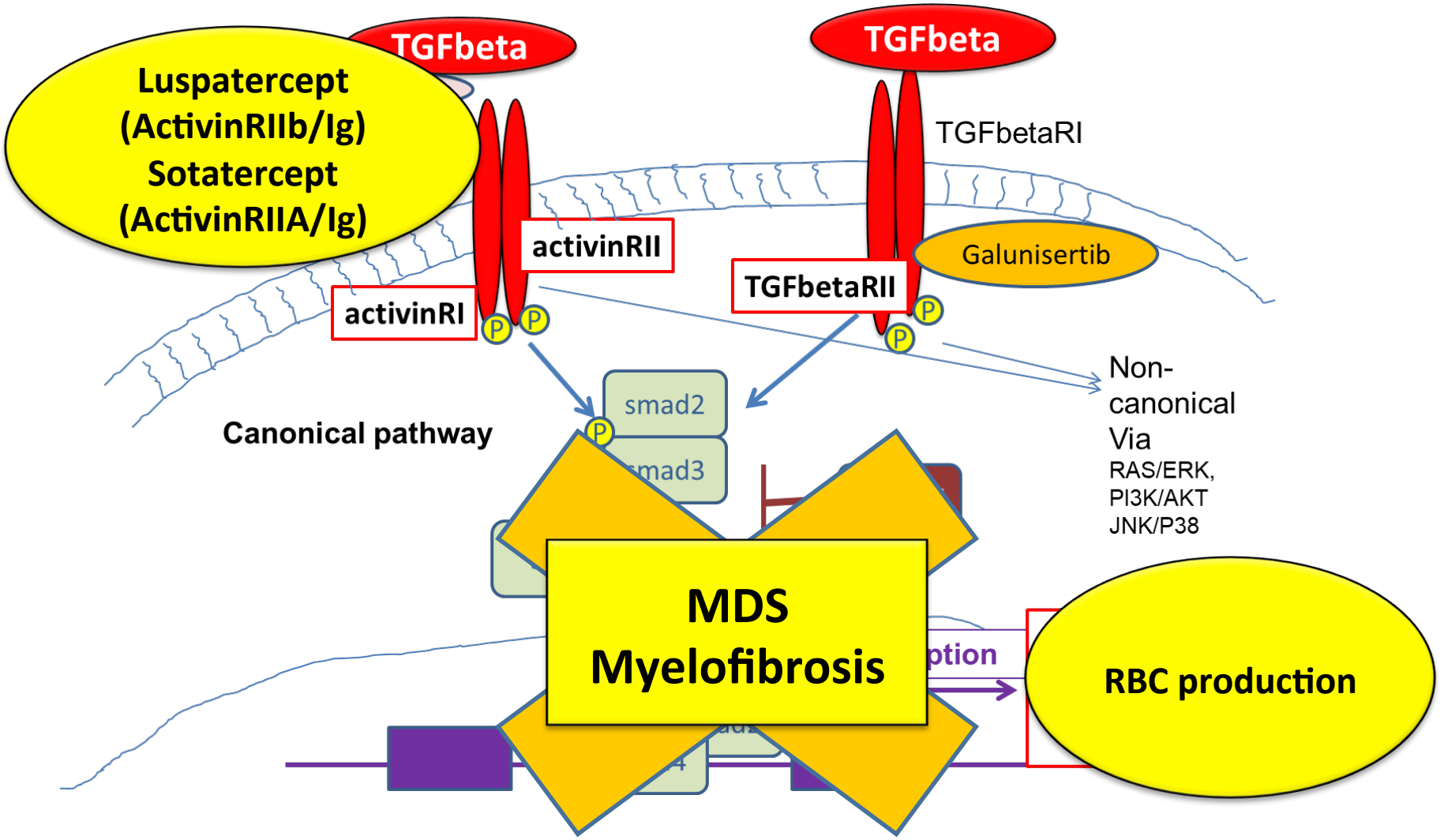


Kotla et al, J Hematol Oncol 2009

HDAC inhibitors have anti-inflammatory activity



TGF-beta inhibitors have anti-inflammatory activity



Conclusions

- Chronic inflammation is a powerful driver of the initiation/progression of hematological neoplasia
  - *Especially in MPNs, but also in other neoplasms*
- The efficacy of some drugs is directly (though never uniquely) related to their ability to control the chronic inflammation associated with the neoplasm
  - *This aspect is all the more important the more relevant the chronic inflammation in the pathogenesis of the disease*
- In particular, Ruxolitinib associates the anti-myeloproliferative effect (mediated by inhibition of *JAK2*) to the anti-inflammatory effect (mediated by inhibition of *JAK1*)
  - *Its therapeutic effect arises from the synergy between these two aspects*
- Other drugs, used in different hematological neoplasms, share the ability to limit the production of pro-inflammatory cytokines
  - *IMiDs decrease the production of pro-inflammatory cytokines*
  - *HDAC inhibitors inhibit STAT3 and pro-inflammatory cytokines release*
  - *TGF-beta inhibitors can facilitate the recovery of an effective erythropoiesis*

2018

Grazie!

Progetto Ematologia Romagna

AIL
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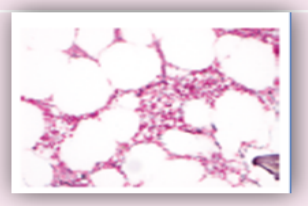
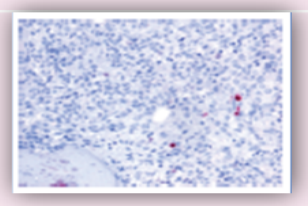
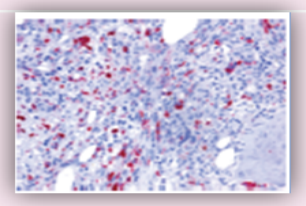
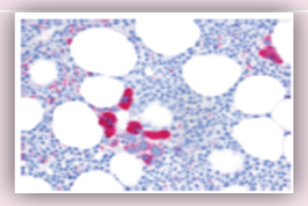
Marco Romano

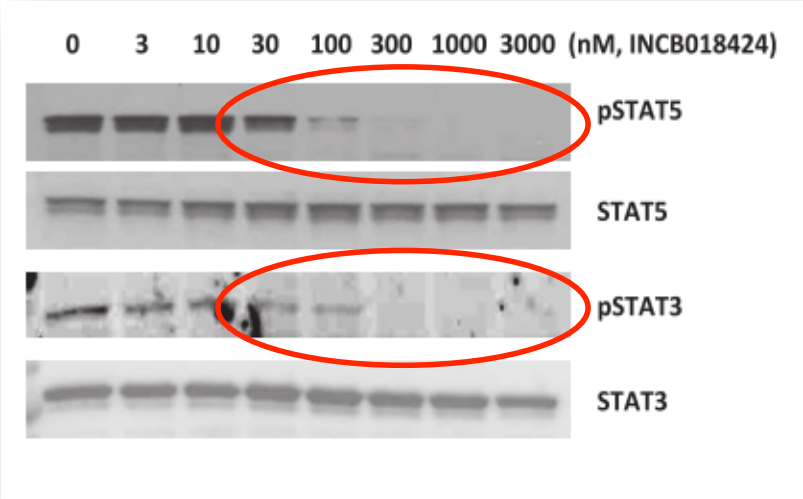
Cytokines and marrow fibrosis

Caratteristiche midollari	Grado di fibrosi	Frequenza di Plasmacellule	Frequenza di Macrofagi	Frequenza di MKC
Riduzione indotta dalla terapia (%)		70%	48%	52%
Citochine				
CRP	0,38	-0,77	0,15	0,78
IL-10	0,14	8,46	6,88	5,55
MDC	2,49	-3,20	3,78	-17,93
SCF	1,16	0,83	-0,92	6,23
TNF-alfa	-0,28	-1,84	-8,92	2,83
ApoA1	2,55	-1,23	-8,22	-0,26
Eotaxin	0,10	-0,13	-0,83	0,09
Aptoglobin	-1,35	5,01	-0,25	-3,64
IgE	1,91	0,66	-2,36	18,64
TIMP-1	-0,53	-2,44	-1,27	3,95

- Ruxolitinib treatment versus BAT was associated with greater odds of BM fibrosis improvement or stabilization and decreased odds of BM fibrosis worsening
- These changes were accompanied by a sustained decrease of inflammatory cytokines and higher level of individual spleen size reduction

Kvasnicka HK, et al. Blood 2014; 124: Abs 3182; Kvasnicka et al. Journal of Hematology & Oncology (2018) 11:42

Ruxolitinib inhibits myeloid proliferation & cytokines release



STAT5: Increased myeloproliferation

STAT3: Increased cytokines production

Effetti simili sulla fosforilazine di STAT3 e STAT5 sono stati ottenuti nelle linee cellulari umane HEL che esprimono in maniera endogena JAK2V617F

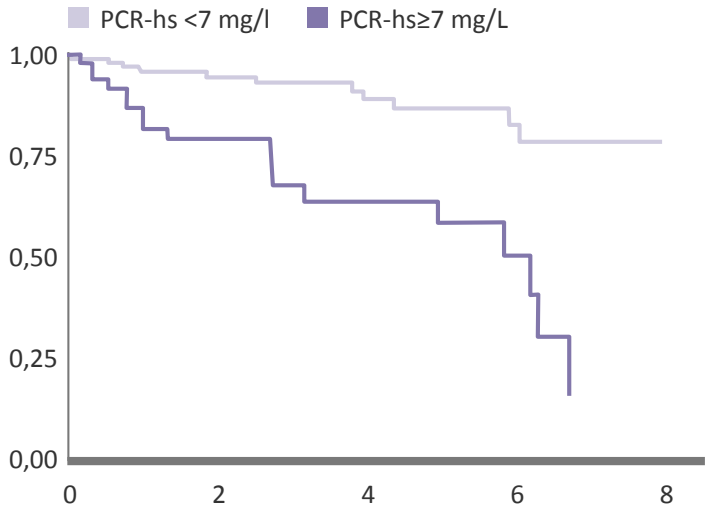
Quintas Cardama A, et al. Blood. 2010; 115(15): 3109-17; Spoerl S, et al. Blood. 2014; 123(24): 3832-42.

Levels of hs-PCR affect prognosis in MF

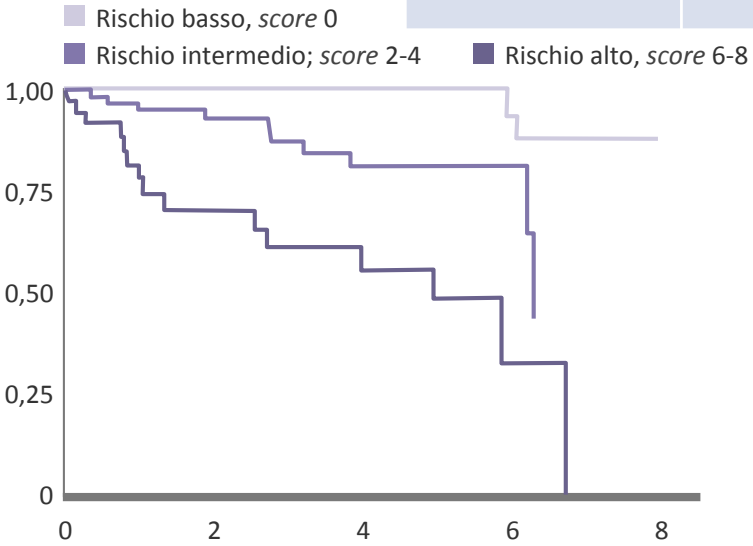
Livelli plasmatici aumentati di PCR nei pazienti con MF si associano a: [1,2]

- ridotta sopravvivenza libera da leucemia
- maggiore incidenza di trasformazione blastica
- rischio di morte più elevato

Eta > 65 aa	**2 punti**
Blasti > 1%	**4 punti**
PCR-hs > 7 mg/l	2 punti



PCR-hs									
<7 mg/l	99	(5)	72	(2)	45	(3)	20	(1)	6
≥7 mg/L	56	(9)	25	(4)	16	(2)	5	(3)	1



N. a rischio									
Rischio basso	37	(0)	30	(0)	26	(1)	16	(1)	5
Rischio intermedio	71	(4)	45	(4)	22	(0)	6	(2)	2
Rischio alto	37	(9)	15	(2)	11	(3)	2	(1)	0

1.Barbui T, et al. Leukemia 2013; 27(10): 2084-6; 2. Barosi G. Curr Hematol Malig Rep 2014;9 (4): 331-9