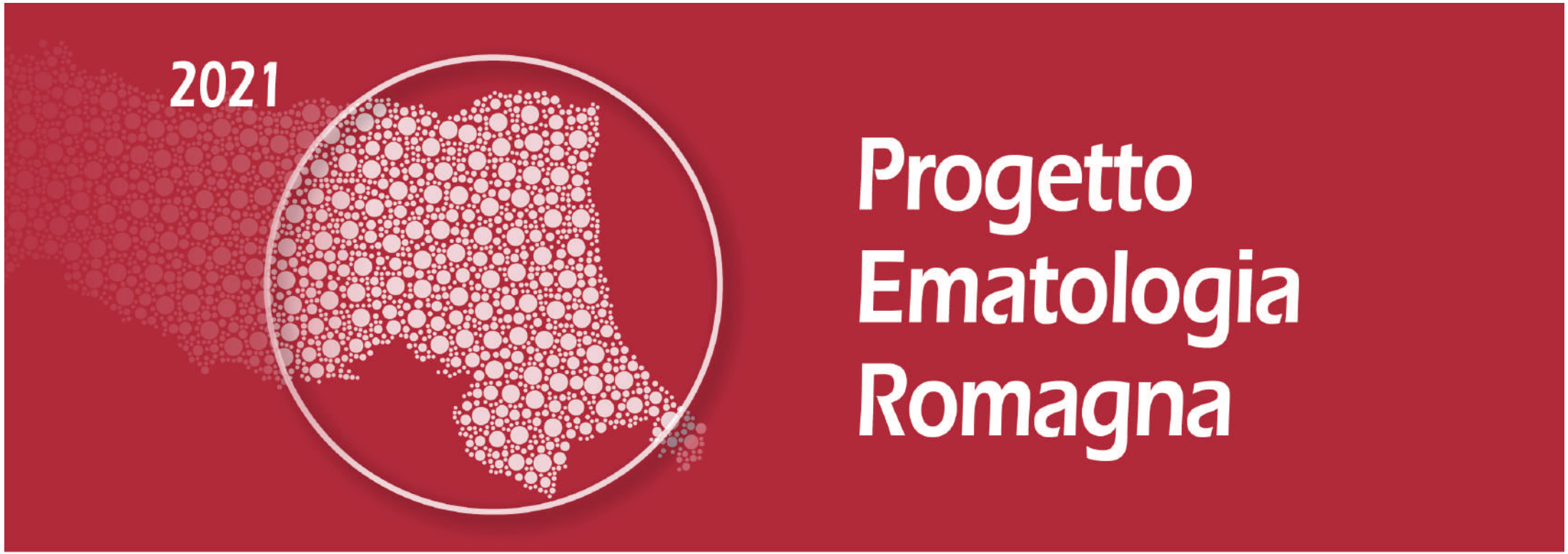
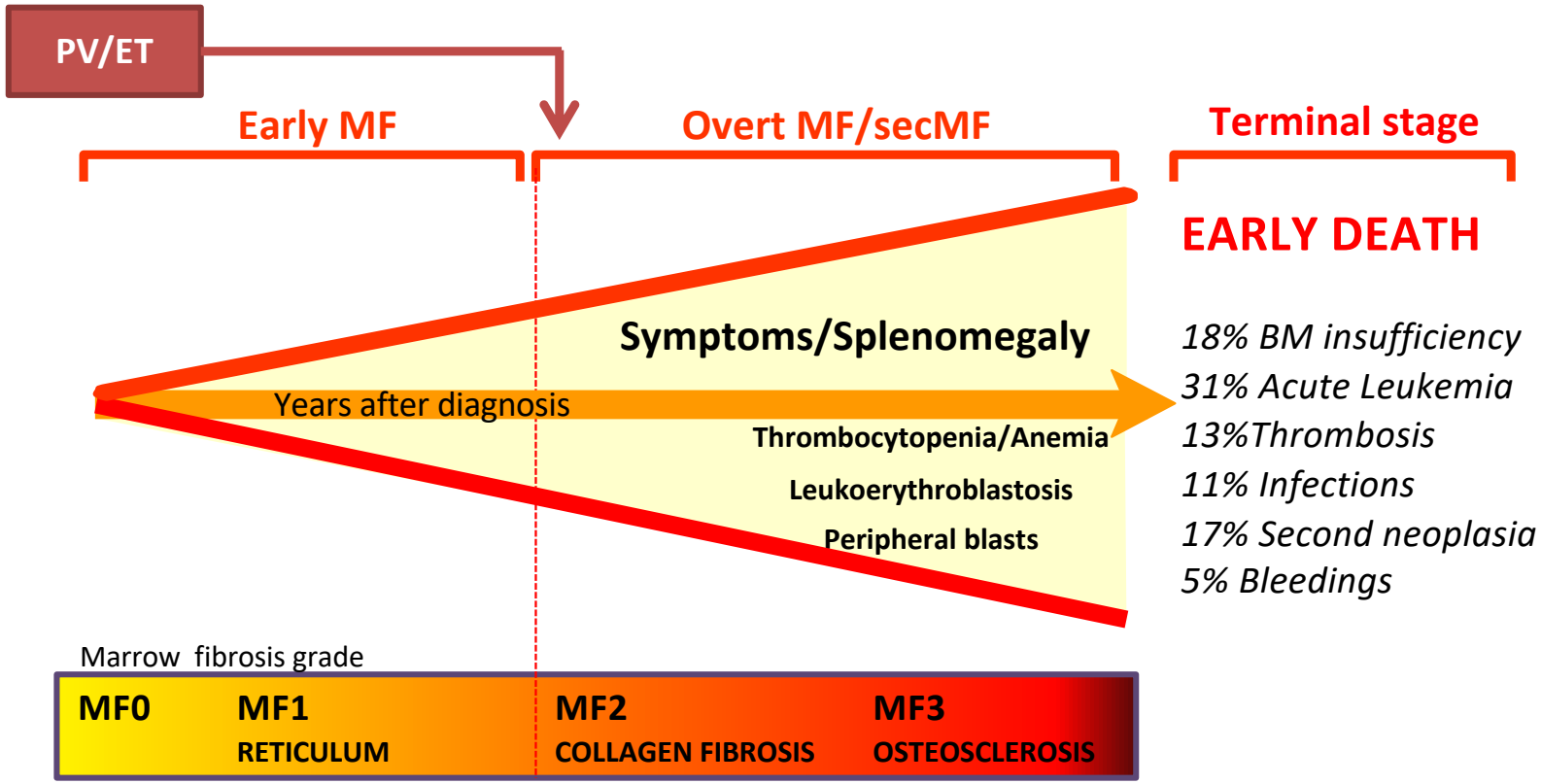


Mielofibrosi Primaria e Secondaria

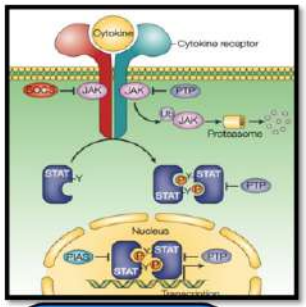
Francesca Palandri

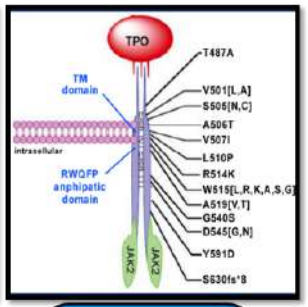
Myelofibrosis

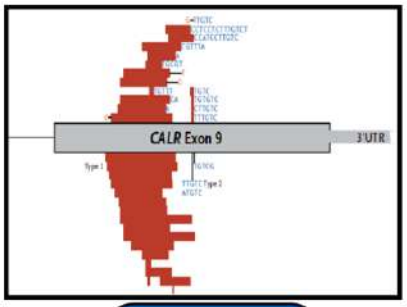


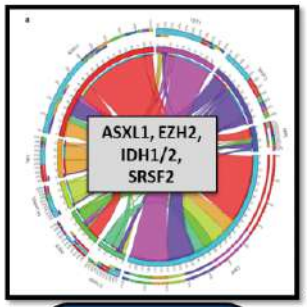
Barbui T, et al. J Clin Oncol. 2011 Feb 20;29(6):761-70. Caramazza D, et al. Leukemia. 2011 Jan;25(1):82-8.Tefferi A, et al. Leukemia. 2012 Jun;26(6):1439-41. Passamonti F, et al. Blood. 2010 Oct 14;116(15):2857-8. Cervantes F. Blood. 2009 Mar 26;113(13):2895-901. Arber et al. Blood. 2016; 127(20):2391-405. Thiele J, et al. Haematologica. 2005;90:1128-1132; Thiele J, Kvasnicka HM, et al. Ann Hematol. 2006;85(4):226-232, Vener C, et al. Blood. 2008, Palandri F et al. Leukemia 2015

MF pathogenesis









2005 *JAK2* 60%

2006 *MPL* 10%

Triple-negative 10%

2013 *CALR* 20%

2013 *HMR*

Hyperactivation of the JAK-STAT pathway

Chronic inflammation

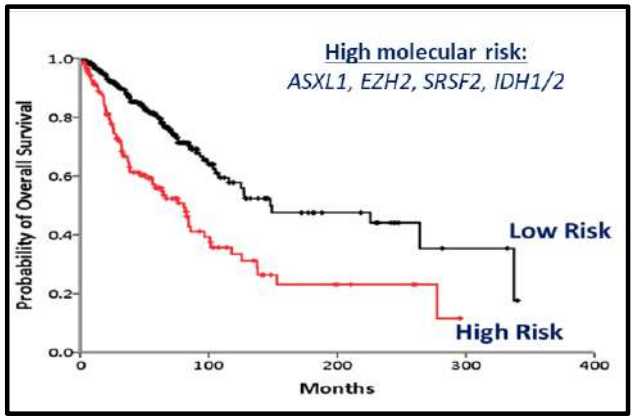
Uncontrolled myeloproliferation

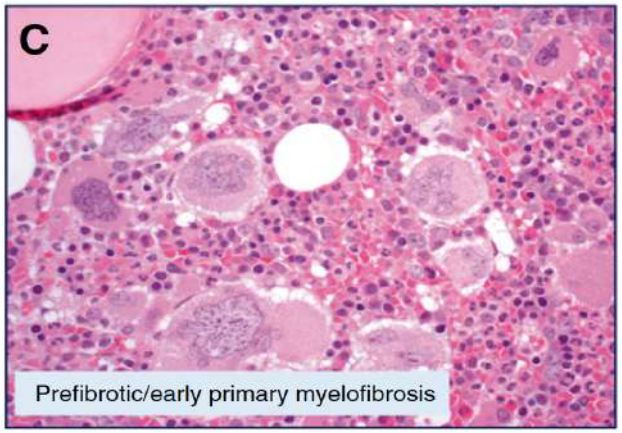
Uncontrolled release of pro-inflammatory cytokines

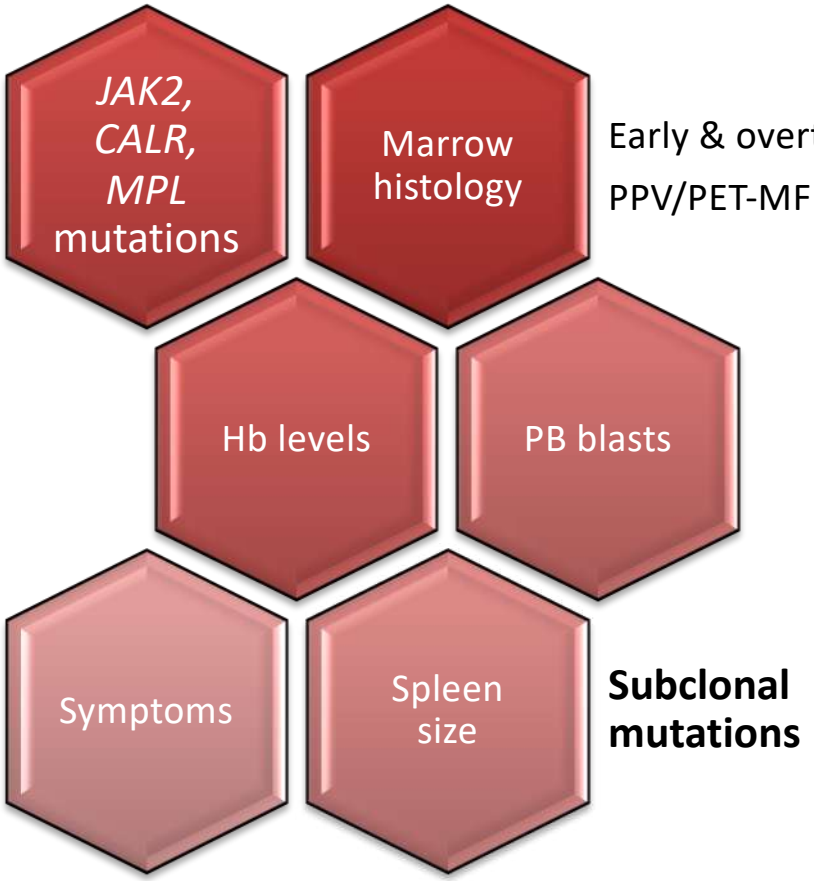
- Higher risk of AML
- Reduced OS

Levine A, Cancer Cell, 2005; Baxter EJ, Lancet 2005; Kralovics R, N Engl J Med 2005; James C, Nature 2005; Pikman Y, PLoS Med. 2006; Nangalia J. N Engl J Med 2013. Klampfl T. N Engl J 2013; Vannucchi A, Leukemia 2013

MF: Diagnostic Criteria







Early & overt MF

PPV/PET-MF

Subclonal mutations

WHO 2016: Early and Overt PMF

EARLY-MF diagnosis if: 1-3 plus one among 4-7	OVERT MF diagnosis if: 1-3 plus one among 4-8
1. Megakaryocytic proliferation and atypia, without reticulin **fibrosis ≤ grade 1**, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation and often decreased erythropoiesis	1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen **fibrosis grades 2 or 3**
2. Not meeting WHO criteria for ET, PV, BCR-ABL1-positive CML, AML, MDS or other myeloid neoplasms	2. Not meeting WHO criteria for ET, PV, BCR-ABL1-positive CML, MDS, or other myeloid neoplasms
3. Presence of *JAK2, CALR, MPL* mutations or in the absence, presence of **another clonal marker*** or absence of reactive BM reticulin fibrosis	3. Presence of *JAK2, CALR, MPL* mutations or in the absence, presence of **another clonal marker*** or absence of reactive BM reticulin fibrosis
4. Anemia not attributed to a comorbid condition	*4. Anemia not attributed to a comorbid condition*
5. ***Leukocytosis ≥ 11 x 10^9/L¶***	*5.* ***Leukocytosis ≥ 11 x 10^9/L***
6. Palpable splenomegaly	*6. Palpable splenomegaly*
7. Serum LDH increased to above ULN¶	*7. Serum LDH increased to above ULN*
	8. Leukoerythroblastosis

* in the absence of all 3 major clonal mutations, the search for the most frequent accompanying mutations (e.g. ***ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1***) is of help in determining the clonal nature of the disease

Arber et al. Blood. 2016; 127(20):2391-405.

Clinical presentation of pre-PMF

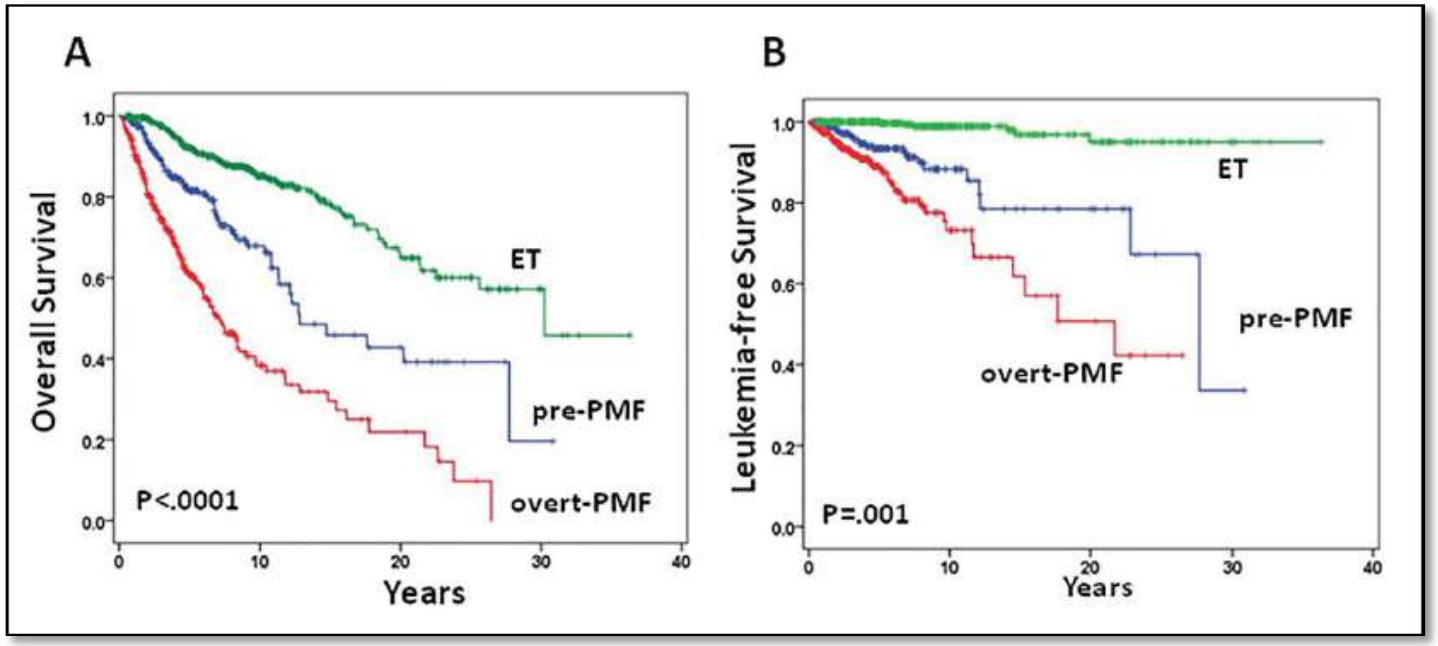
Variables	Pre-fibrotic PMF (n = 278)	Overt-PMF (n = 383)	P
Males, n (%)	156 (56.1)	249 (65.0)	.013
Age, y; median (range)	56.6 (18.0-90.3)	63.6 (14.0-89.8)	< .0001
Hemoglobin, g/L; median (range)	129 (107-175)	108 (47-150)	< .0001
Leucocytes, × 10^9/L; median (range)	9.1 (1.5-150)	8.2 (1.4-109.0)	.009
Leucocytes < 4.0 × 10^9/L; n (%)	10 (3.6)	57 (14.9)	< .0001
Platelets, × 10^9/L; median (range)	488 (310-1500)	249 (19-3279)	< .0001
Circulating blasts ≥ 1%; n (%)	33 (11.9)	99 (25.8)	< .0001
Constitutional symptoms; n (%)	57 (20.5)	129 (33.7)	< .0001
Splenomegaly; n (%) > 10 cm from LCM; n (%)	177 (63.7) 29 (10.4)	317 (82.8) 92 (24.0)	< .0001 < .0001
Patients with cytogenetics; n (%) Abnormal cytogenetics Unfavorable karyotype	150 (54.0) 27 (18.0) 6 (4.0)	182 (48.0) 69 (37.9) 22 (12.1)	< .0001 .006

Early-PMF includes patients with a less aggressive disease

Guglielmelli P, et al. Blood. 2017;129(24):3227-3236

Pre-PMF has a better outcome than Overt-PMF

- 661 PMF: 42% prePMF; 58% PMF
- Mortality: 23% (prePMF), 41% (PMF); Blast phase: 8% (prePMF), 13% (PMF)



Conventional scores (thrombosis & prognosis) may not be reliable in these patients!

Guglielmelli et al. Blood 2017; March(28)

Secondary MF

Required criteria (all required)
Documentation of a previous diagnosis of PV or ET by WHO criteria
Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)
Additional criteria (two are required)
Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy)
A leukoerythroblastic peripheral blood picture
Increasing splenomegaly*
Development of at least 1 of three constitutional symptoms**

*increase in palpable splenomegaly >5 cm or appearance of a newly palpable splenomegaly
**>10% weight loss in 6 months, night sweats, unexplained fever >37.5°C

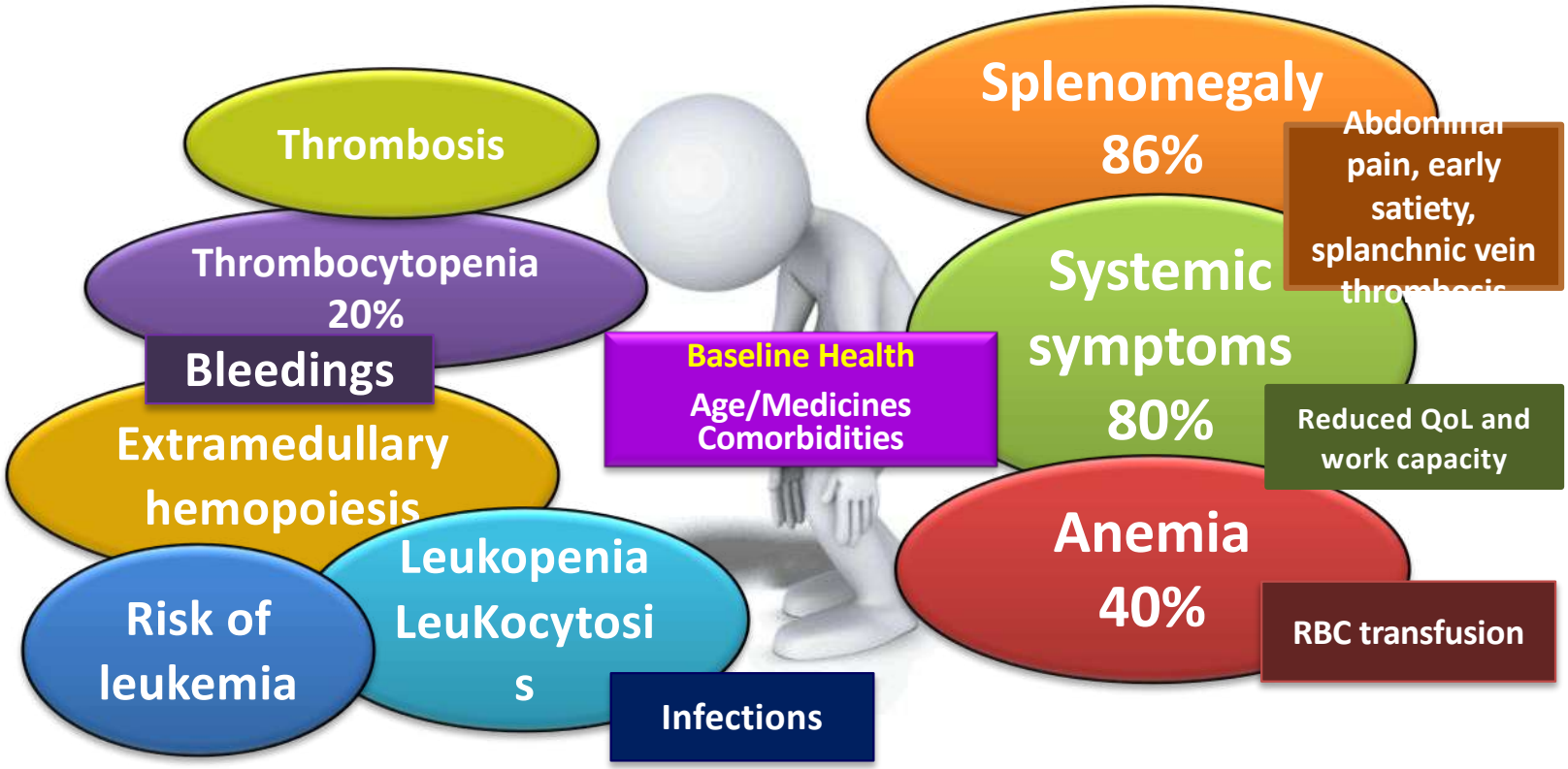
Barosi G et al, Leukemia 2008

PMF is distinct from SMF: the MDACC study

- 1099 patients: 755 PMF, 344 SMF (181 PPV MF, 163 PET MF)
- Diversity in clinical features
  - PMF: more RBC transfusion-dep, chr. 17 abnormalities
  - PPV MF: higher WBC count and symptomatology
  - PET MF: higher PLT count
- Survival was longer in PET MF than in PMF or PPV MF
- IPSS/DIPSS failed in predicting survival of SMF
  - PPV MF: int-2/high-risk undistinguishable survival
  - PET MF: low/int-1 risk as well as int-2/high risk undistinguishable survival

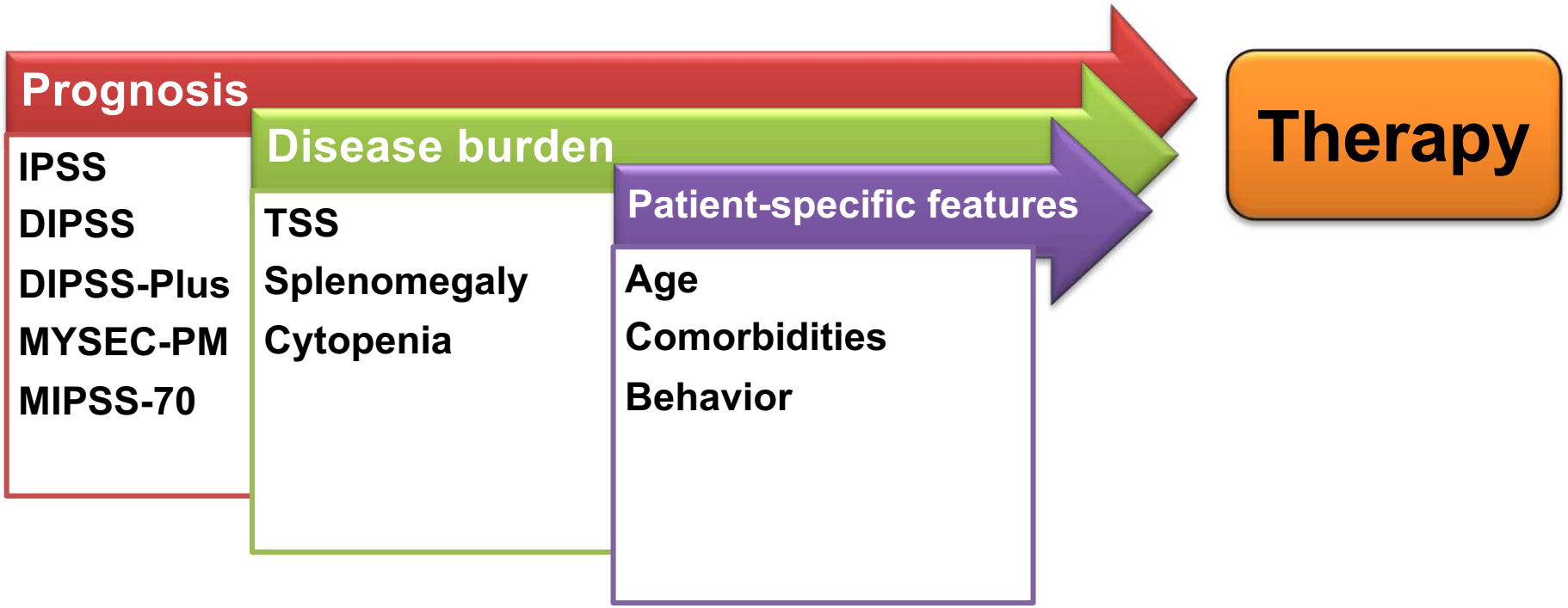
Masarova L et al, Leuk Res 2017

MF is a personalized disease



- A patient may present more than one clinical needs at the same time
- Prioritization of clinical needs may be necessary and may change over time
- Addressing one clinical need may worsen other clinical needs!

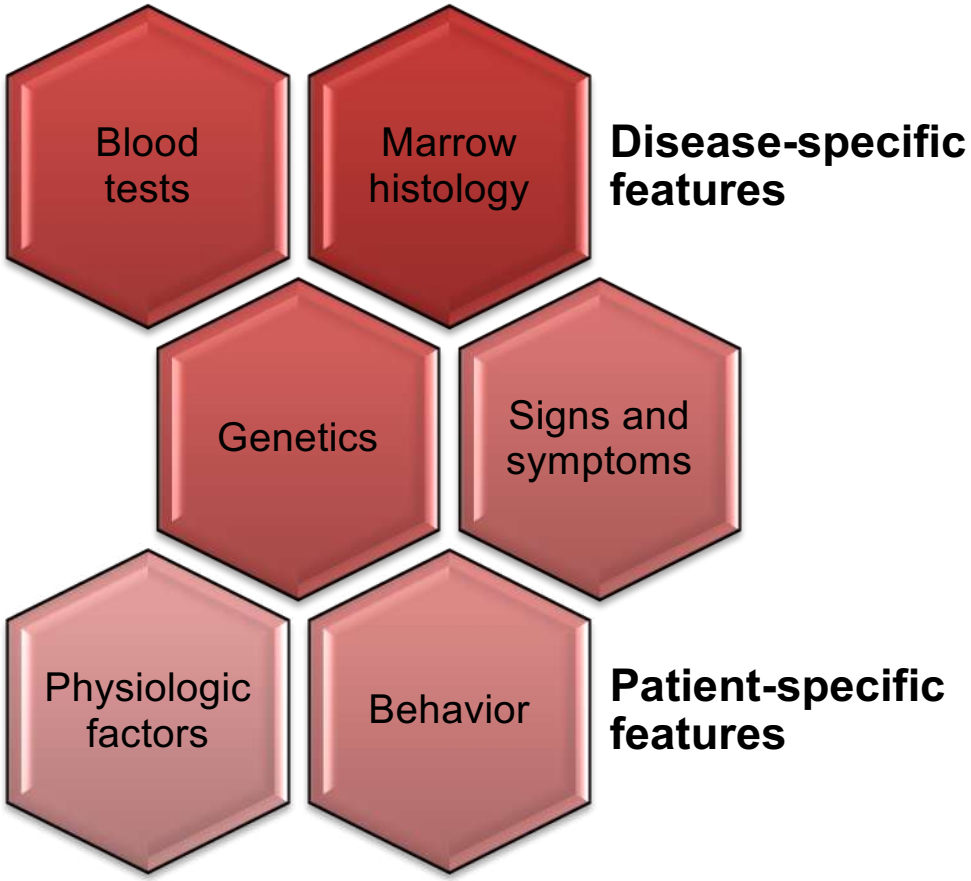
MF: Strategy Matters



DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System; MIPSS-70, Mutation-Enhanced International Prognostic Scoring System 70+; MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model; TSS, Total Symptom Score.

Tefferi A, et al. *Blood Cancer J.* 2018;8:72. Tefferi A, et al. *Am J Hematol.* 2021;96:145–62.

First: Assessing Prognosis

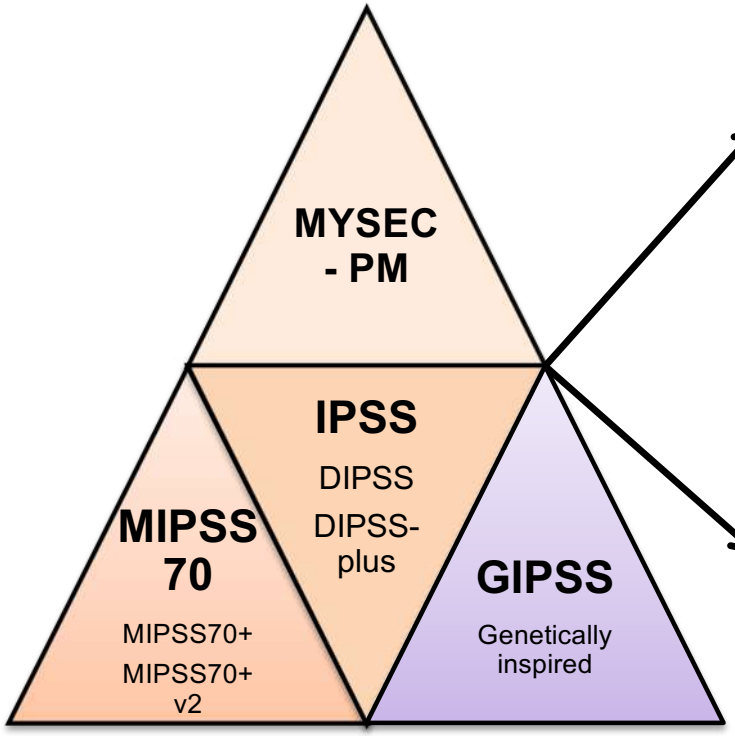


Tefferi A, et al. *Blood Cancer J.* 2018;8:72. Mesa et al. *BMC Cancer*. 2016:27;16:167.

First: Prognostic Scores

- Age
- Constitutional symptoms
- Hemoglobin
- Leukocyte count
- Circulating blasts
- Platelet count
- RBC transfusion need

- Unfavorable karyotype
- HMR mutations
- Marrow fibrosis grade



Lower risk
Survival > 5 years

Medical therapy

Higher risk
Survival < 5 years

AlloSCT indication

alloSCT, allogeneic stem cell transplantation; GIPSS, Genetically Inspired Prognostic Scoring System; HMR, high molecular risk.

Tefferi A, et al. *Blood Cancer J.* 2018;8:72. Cervantes F, et al. *Blood*. 2009;113:2895–901. Passamonti F, et al. *Blood*. 2010;115:1703–8. Gangat N, et al. *J Clin Oncol*. 2010;29:392–7. Passamonti F, et al. *Leukemia.* 2017;31:2726–31. Guglielmelli, *J Clin Oncol.* 2018;36:310–8. Tefferi A, et al. *J Clin Oncol.* 2018;36:1769–70. Tefferi A, et al. *Leukemia.* 2018;32:1189–99.

Real-World Risk Assessment of Patients With MF at Community Oncology Practices in the USA

- **1/3 of patients did not receive a risk categorization at diagnosis**
- In 50% of cases, risk categorization was based on clinical judgment without use of a formal risk stratification system
- In 30% of cases, risk categorization was based on DIPSS or DIPSS-Plus instead of IPSS
- **Risk categorizations were inaccurate in approximately 43% of patients, of which 85% were underestimated**

			Data-Derived Risk Categorizations (IPSS only)*		
		Total	Low	Intermediate	High
Risk categorization assigned by physicians	n (row %)	343	20 (5.8)	135 (39.3)	188 (54.8)
	Low	42	10 (23.8)	26 (61.9)	6 (14.3)
	Intermediate	200	10 (5.0)	97 (48.5)	93 (46.5)
	High	101	0	12 (11.9)	89 (88.1)
Incorrect risk categorization by physician, n (column %)		147 (42.9)	10 (50.0)	38 (28.1)	99 (52.7)
Underestimated, n (%)†		125 (85.0)	-	26 (68.4)	99 (100.0)
Overestimated, n (%)†		22 (15.0)	10 (100.0)	12 (31.6)	-
Risk not assigned by physician, n (row %)		148‡	12 (8.2)	72 (49.3)	62 (42.5)

CI, confidence interval; IPSS, International Prognostic Scoring System.
*Cohen's kappa (95% CI) = 0.2881 (0.2097–0.3664); $P < .001$. †Of incorrect total in each column. ‡In 2 patients, an IPSS risk categorization could not be determined because of missing data pertaining to peripheral blast percentage.

Failure to assess prognosis is common and has a very bad impact on treatment strategy and outcome

Verstovsek S, et al. *Ann Hematol*. 2020;99:2555–64.

Second: Assessing the Burden of MF

Progression to AML ? 2nd MDS

Vascular events

Cytopenias
Bleedings
Infections

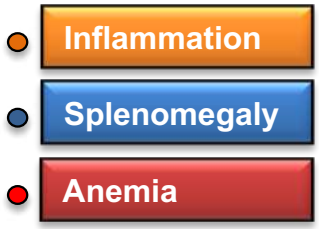
Splenomegaly
Pain not always a function of size

MPN symptoms
- **Fatigue**
- **Fever, weight loss, night sweats**
- **Bone pain**
- **Abdominal pain**

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.
Emanuel RM, et al. *Clin Oncol.* 2012;30:4098–103. Mesa R, et al. *Leuk Res.* 2013;8:911–6. Mesa R, et al. *BMC Cancer.* 2016;16:167.

MPN10-TSS

An Easy Tool to Assess Symptoms in MPNs



- In your practice, use the MPN10-TSS, a simple tool that in 10 quick questions describes symptoms related to inflammation, splenomegaly, and anemia

- MPN10 is important to evaluate:
  1. The burden of the disease at diagnosis
  2. The prognosis
  3. The response to therapies

	Value	Prognostic variable
Fatigue	0	1 to 10 ranking (0 if absent; 1 most favorable; 10 least favorable)
Early satiety	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Unintentional weight loss last 6 months	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
MPN10 score	0	

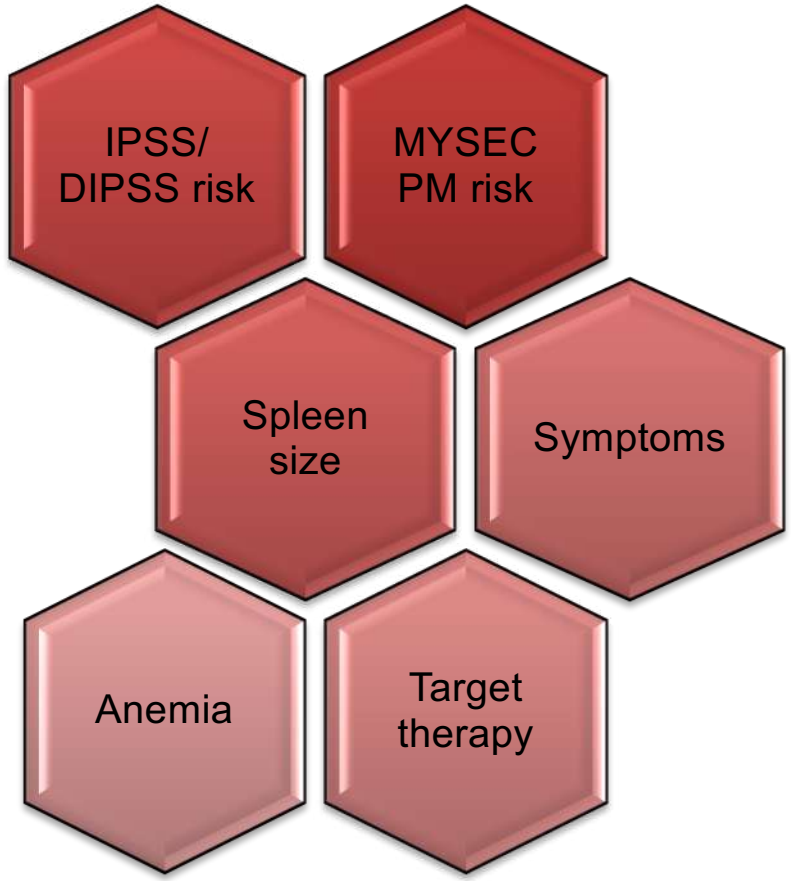
Scherber R, et al. *Blood.* 2011;118:401–8. Emanuel RM, et al. *J Clin Oncol.* 2012;30:4098–103.

Third: The Choice of Medical Therapy

SPLENOMEGALY

SYMPTOMS

ANEMIA



Tefferi A, et al. *Blood Cancer J.* 2018;8:72.

Splenomegaly

- Splenomegaly is one of the presenting features of PMF and PET/PPV-MF
  - It plays a causative role in abdominal pain, early satiety, splanchnic vein thrombosis, and cytopenias
- Splenomegaly is progressive during the course of the disease
  - It is larger and more frequently detected in overt MF compared to early MF
  - Around 20% of patients without baseline splenomegaly show spleen enlargement 1 year after diagnosis

Variables	prePMF (n = 278)	PMF (n = 383)	*P*
Hemoglobin, g/L; median (range)	129 (107–175)	108 (47–150)	**< .0001**
Platelets, × 10^9/L; median (range)	488 (310–1500)	249 (19–3279)	**< .0001**
Constitutional symptoms; n (%)	57 (20.5)	129 (33.7)	**< .0001**
Splenomegaly; n (%)	177 (63.7)	317 (82.8)	**< .0001**
>10 cm from LCM; n (%)	29 (10.4)	92 (24.0)	**< .0001**

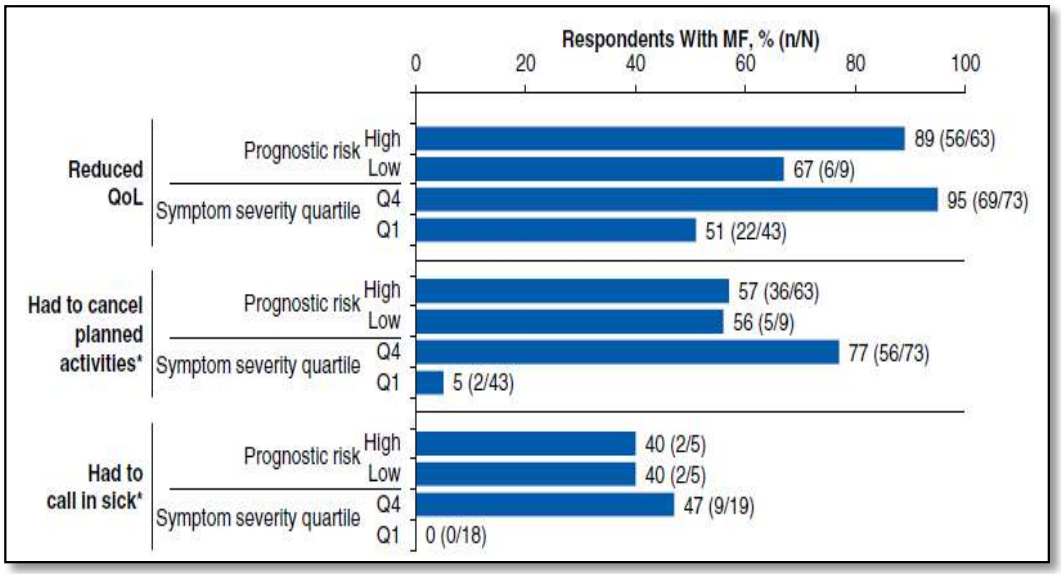
- **Hydroxyurea** was the most frequently used cytoreductive treatment in case of symptomatic splenomegaly, with dismal results
  - In a retrospective study of 40 patients, HU induced spleen response in 40% of cases; median response duration, 13.2 months (range, 3–126.2 months)

HU, hydroxyurea; LCM, left costal margin; MF, myelofibrosis; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post-polycythemia vera.

Passamonti F, et al. *Blood.* 2010;115:1703–8. Barbui T, et al. *Blood.* 2010;115:778–82. Guglielmelli P, et al. *Blood*. 2017;129:3227–36. Tefferi A, et al. *Mayo Clin Proc.* 2012;87:25–33. Martinez-Trillos A, et al. *Ann Hematol.* 2010;89:1233–7.

Symptoms

- Symptoms are frequently present in PMF and PET/PPV-MF, regardless of risk category
  - Constitutional symptoms are prognostic factors for survival
- Low response to corticosteroids



- DIPSS low-risk MF patients are moderately to highly symptomatic in 44% of the cases
- The reduction of QoL and social/working activity is similar in low and high-risk categories
- A cutoff criteria of the worst single symptom being > 5/10 using the MPN10 has been suggested for identifying patients who will most benefit from symptom-based treatment

Harrison C, et al. *Ann Hematol.* 2017;96:1653–65. Mesa R, et al. *BMC Cancer.* 2016;16:167. Scherber R, et al. *Blood.* 2011;118:401–8. Scherber, et. al. *EHA.* 2016;a2250. Marchetti M, et al. *Leukemia.* 2016;1–7.

2010: THE ADVENT OF RUXOLITINIB

First JAK1/2 inhibitor approved for treatment of splenomegaly and symptoms related to MF

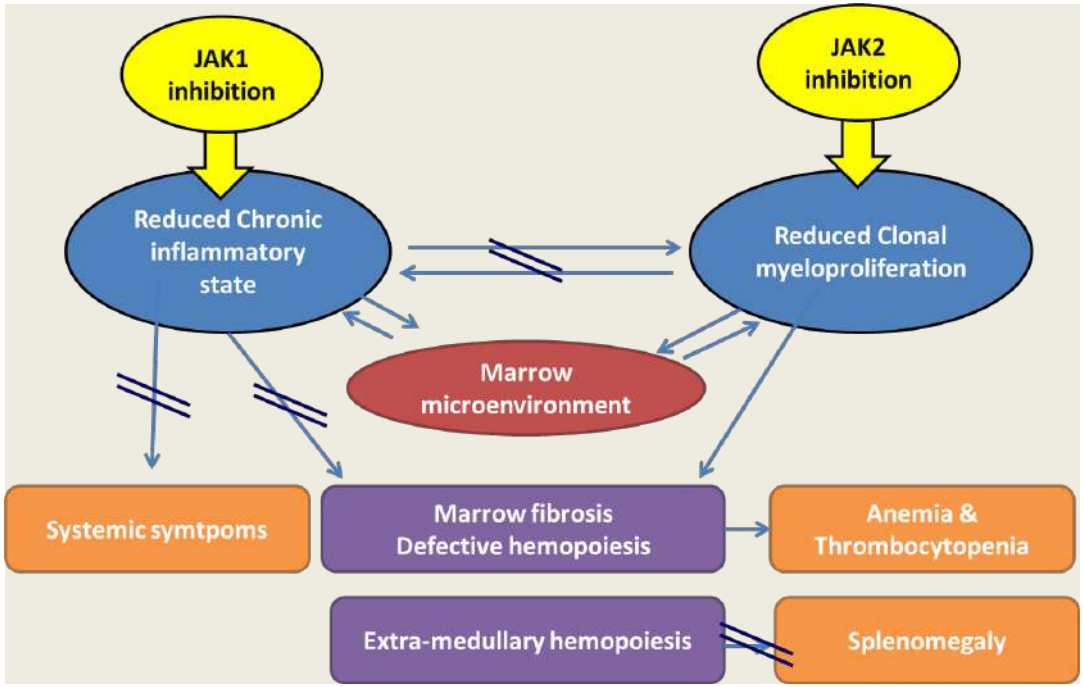
Orally available, twice-daily, no food requirements

Potential mechanism of action:

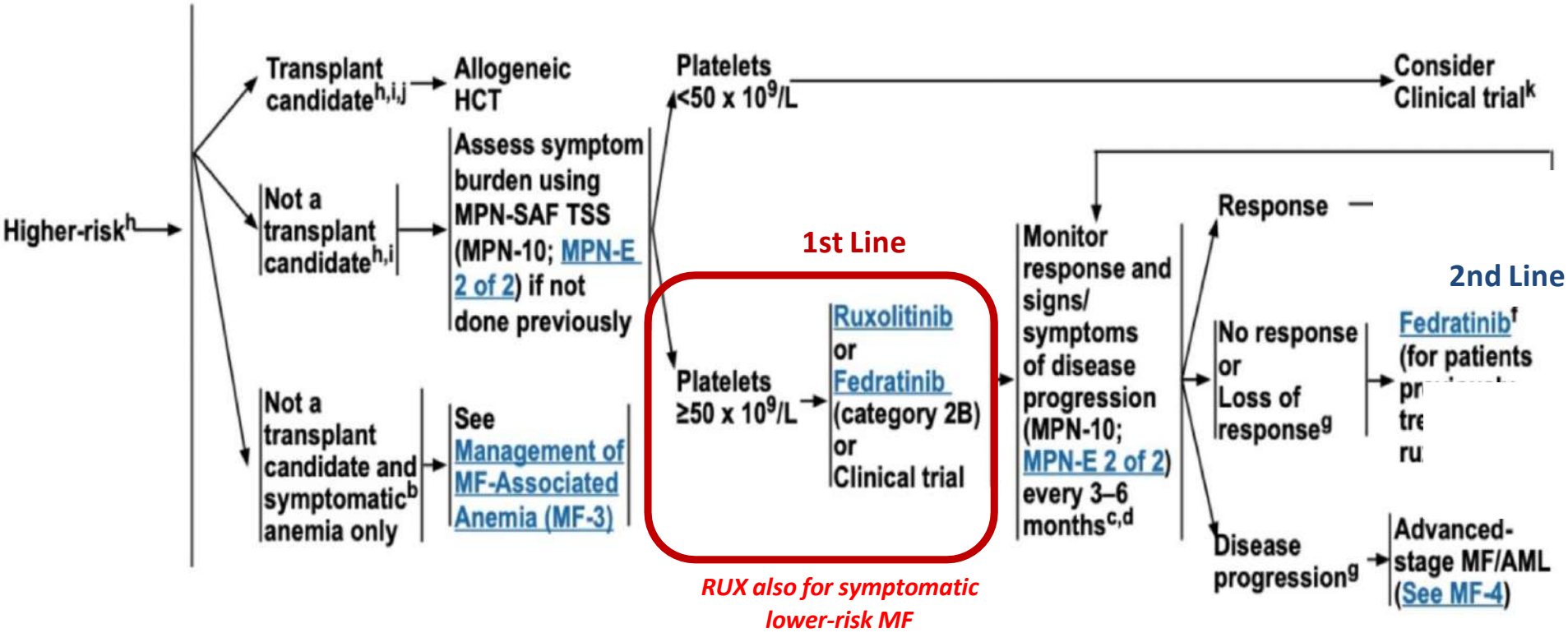
1. Suppresses the growth of malignant cells (*JAK2* inhibition)
2. Down-regulate the cytokines (*JAK1* inhibition) that contribute to hyperinflammation and hypermetabolic state

Not selective for *JAK2V617F* mutation

1. Benefit for patients with and without mutation
2. On-target side effects related to
   - *JAK2* inhibition (decreased erythropoiesis and thrombocytopoiesis)
   - *JAK1* inhibition (decreased immune surveillance)



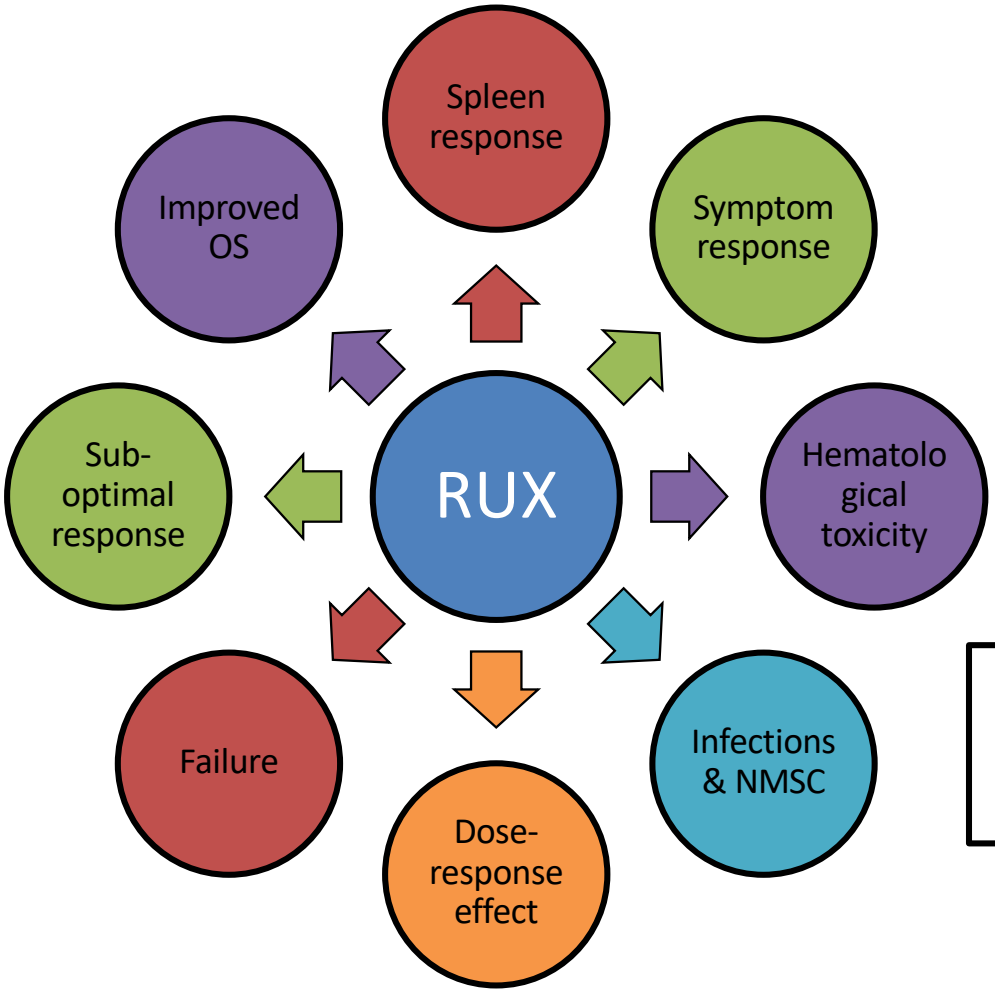
RUX is the 1st-line agent for MF with splenomegaly & symptoms



Higher risk MF: int-2 and high risk DIPSS/MYSEC-PM/DIPSS plus high risk MIPSS70

NCCN guidelines 2021

Cosa abbiamo imparato da ruxolitinib?



Prof. Giuseppe A. Palumbo
Università degli Studi di Catania

Status of Clinical Trials in MF

Piazza Maggiore, Bologna, Italy, 1950

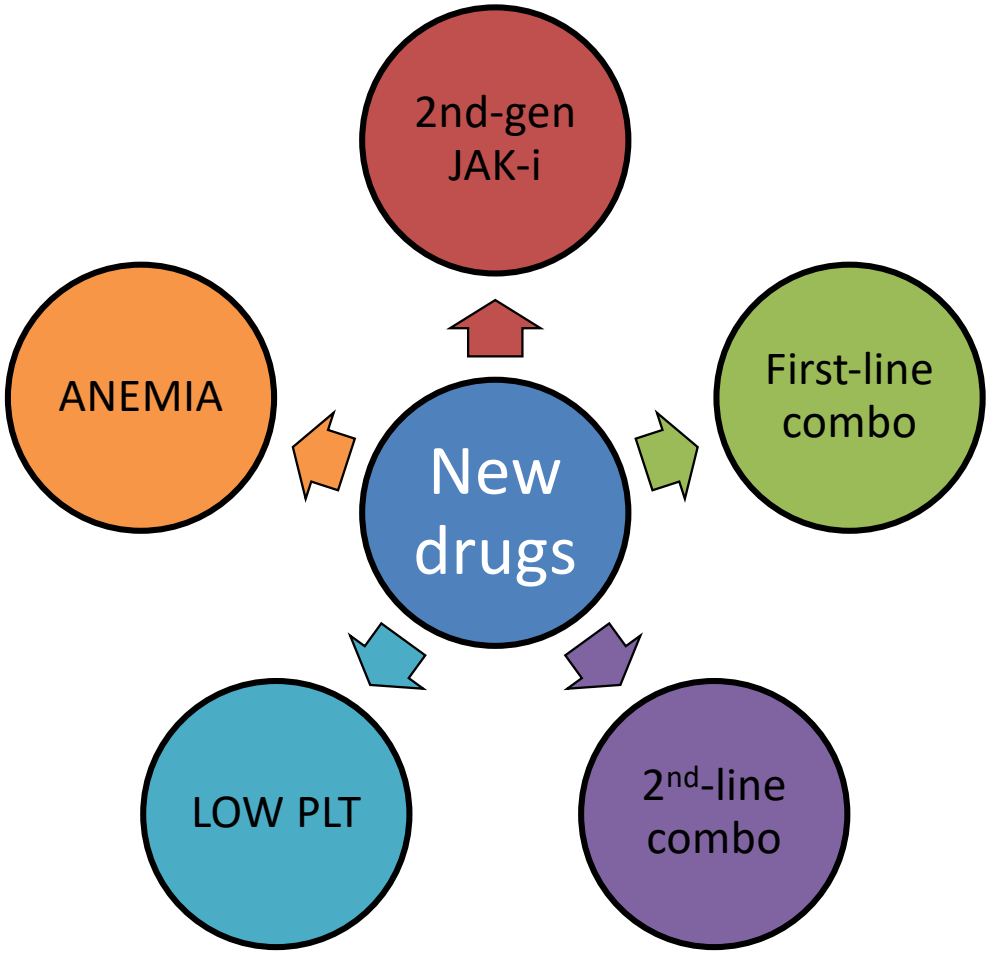
Status of Clinical Trials in MF

Piazza Maggiore, Bologna, Italy, 1950

Piazza Maggiore, Bologna, Italy, 2020

MF patients should be encouraged to participate in clinical trials

Quali sono i nuovi farmaci?



Prof. Massimo Breccia
Università degli Studi "La Sapienza", Roma

Grazie!

francesca.palandri@unibo.it