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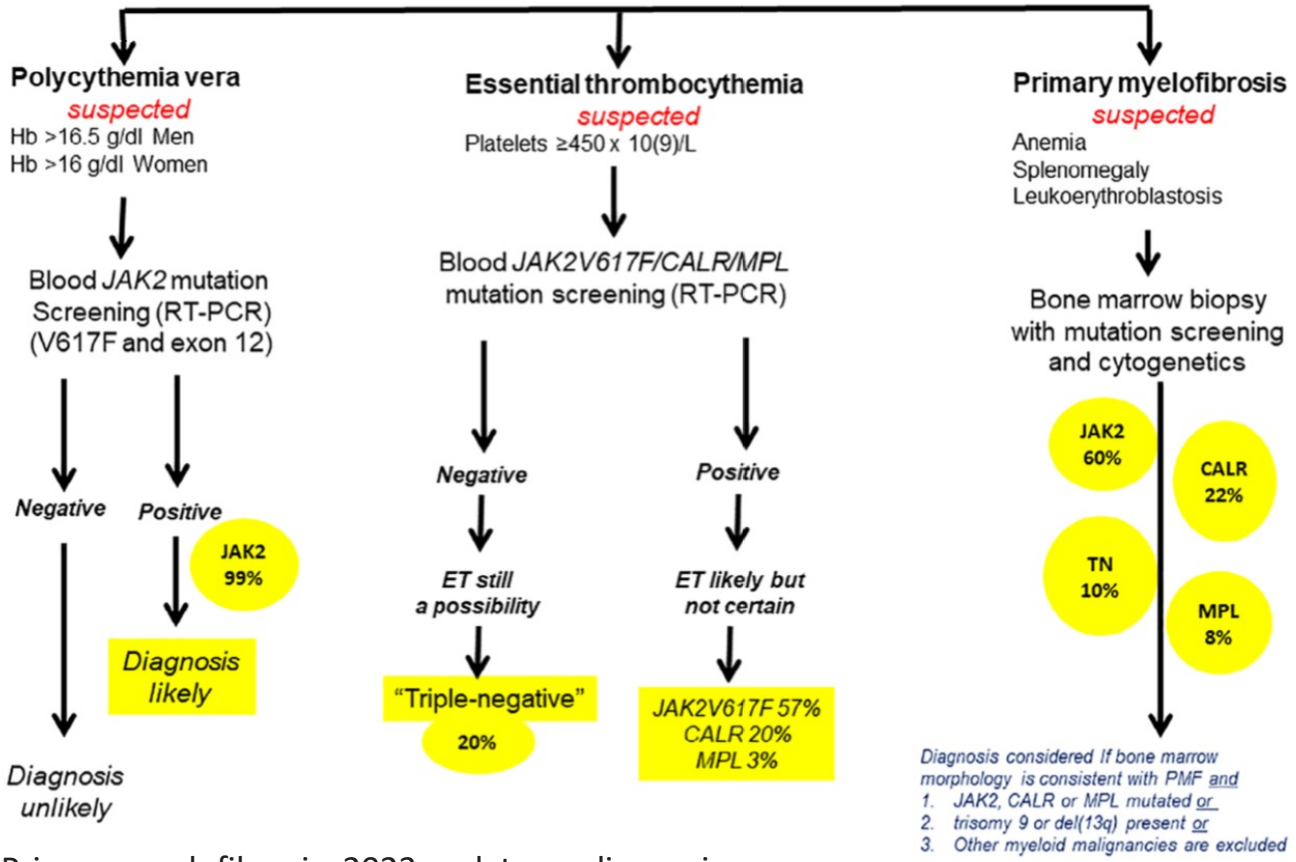
Mielofibrosi idiopatica: l'importanza della stratificazione del rischio nel paziente giovane per ottimizzare il programma terapeutico

Nessun conflitto d’interessi da dichiarare

CASO CLINICO

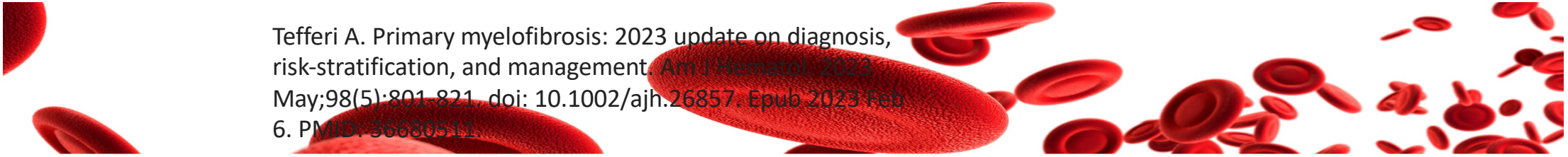
01/2022: Paziente di 46 anni
Giunge in ambulatorio per riscontro di splenomegalia (23cm)
eseguita ETG addome per senso di ingombro,
all'emocromo: hb12.4g/dl, plt162000/mmc, GB 7070mmc
Alla visita: milza palpabile a 12cm dall'arcata costale
Eseguito prelievo per infezioni virali: negativi CMV e EBV
ricerca Mutazione JAK2, riscontro di mutazione V617F



Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 May;98(5):801-821. doi: 10.1002/ajh.26857. Epub 2023 Feb 6. PMID: 36680511.

Primary myelofibrosis (Overtly fibrotic stage) (*Diagnosis requires meeting all 3 major criteria and one minor criterion*)	Primary myelofibrosis (Pre-fibrotic/early stage) (*Diagnosis requires meeting all 3 major criteria and one minor criterion*)
Major criteria: 1. Megakaryocyte proliferation and atypia,[a] accompanied by ≥grade 2 reticulin/collagen fibrosis[b] 2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis 3. Not meeting ICC criteria for other myeloid neoplasms	***Major criteria***: 1. Megakaryocyte proliferation and atypia,[a] accompanied by ≤grade 1 reticulin/collagen fibrosis, granulocyte proliferation/ decreased erythropoiesis 2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis 3. Not meeting ICC criteria for other myeloid neoplasms
Minor criteria: *Anemia not otherwise explained* *Leukocytosis* $\geq 11 \times 10^9$*/L* *Palpable splenomegaly* *Increased serum lactate dehydrogenase* *A leukoerythroblastic blood smear*	***Minor criteria***: *Anemia not otherwise explained* *Leukocytosis* $\geq 11 \times 10^9$*/L* *Palpable splenomegaly* *Increased serum lactate dehydrogenase*

[b]Diffuse often coarse fiber network with or without evidence of collagenization (trichrome stain).
[a]Aberrant nuclear/cytoplasmic ratio; hyperchromatic and irregularly folded nuclei; dense megakaryocyte clustering; these changes are often accompanied by increased cellularity, granulocytic proliferation and decreased erythropoiesis.



Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 May;98(5):801-821. doi: 10.1002/ajh.26857. Epub 2023 Feb 6. PMID: 36680511.

CASO CLINICO

Eseguita BOM: cellularita pari al 60%, incremento delle tre linee, megacariociti ipercromici e ipolobulati in cluster, cd34:4%, FIBROSI grado3. Quadro riconducibile a neoplasia mieloproliferativa cronica, tipo mielofibrosi.

Conta CD34: 0,5%
Cariotipo 46XY
paziente giovane, candidabile a HSCT,
CALCOLO RISCHIO:
IPSS : low
MIPSS70:?
Possibili donatori: padre con pregresso k colon, 2 fratelli, 4 figli (il più grande 14anni)
06/2022: inizia ruxolitinib dosaggio 15 bid

IPSS (*International Prognostic Scoring System*): classificazione prognostica alla diagnosi di MF[1]

Fattori che influenzano la sopravvivenza dei pazienti con MF – Scala IPSS[1]

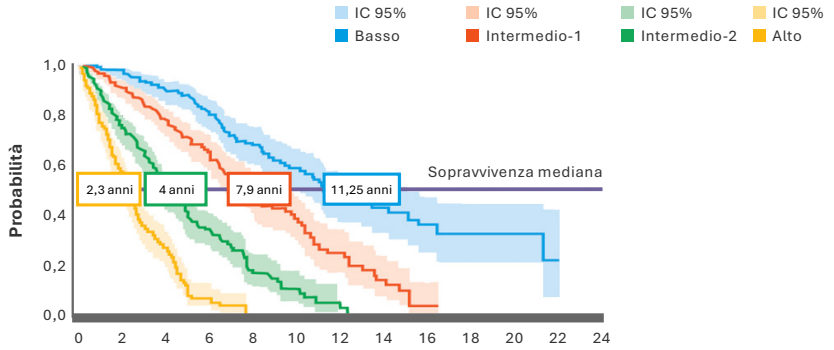
Fattori di rischio
(Ogni fattore di rischio vale 1 punto)

1. Età >65 anni
2. Sintomi costituzionali*
3. Livelli di emoglobina <10 g/dL
4. Conta leucocitaria >25X10^9/L
5. Blasti periferici circolanti >1%

Categorie di rischio	Punteggio
Rischio basso	0
Rischio intermedio-1	1
Rischio intermedio-2	2
Rischio alto	≥3

* Febbre, perdita di peso e sudorazioni notturne

Curve di sopravvivenza di pazienti con MF in base al gruppo di rischio[1]



DIPSS (*Dynamic International Prognostic Scoring System*): classificazione prognostica durante il *follow-up*[1]

Fattori che influenzano la sopravvivenza dei pazienti con MF – Scala DIPSS[1]

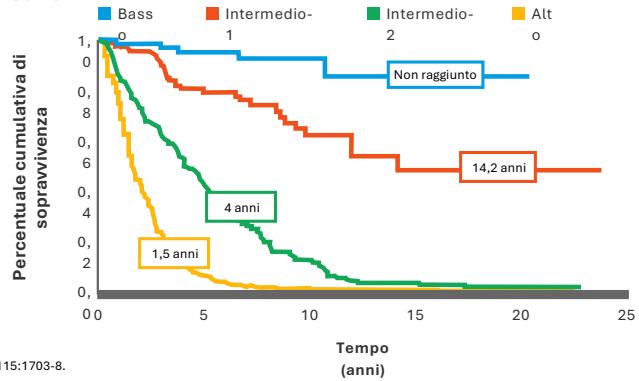
Fattori di rischio

1. Età >65 anni (1 punto)
2. Livelli di emoglobina <10 g/dL (2 punti)
3. Conta leucocitaria >25X10^9/L (1 punto)
4. Blasti periferici circolanti >1% (1 punto)
5. Sintomi costituzionali* (1 punto)

Categorie di rischio	Punteggio
Rischio basso	0
Rischio intermedio-1	1-2
Rischio intermedio-2	3-4
Rischio alto	5-6

* Febbre, perdita di peso e sudorazioni notturne

Curve di sopravvivenza di pazienti con MF in base al gruppo di rischio[1]



1.Passamonti F et al, Blood 2010;115:1703-8.

CASO CLINICO

10/2022: comparsa di piastrinopenia (pls 65000/mmc)
si deve ridurre ruxolitinib a 10bid, milza 10cm dall'arcata
12/2022: splenomegalia E pltpenia (80.000/mmc)
stazionarie aumenta a 15bid

REGULAR ARTICLE

blood advances

A prognostic model to predict survival after 6 months of ruxolitinib in patients with myelofibrosis

Margherita Maffioli,[1] Barbara Mora,[1,2] Somedeb Ball,[3] Alessandra Iurlo,[4] Elena Maria Elli,[5] Maria Chiara Finazzi,[6] Nicola Polverelli,[7] Elisa Rumi,[8,9] Marianna Caramella,[10] Maria Cristina Carraro,[11] Mariella D'Adda,[12] Alfredo Molteni,[13] Cinzia Sissa,[14] Francesca Lunghi,[15] Alessandro Vismara,[16] Marta Ubezio,[17] Anna Guidetti,[18] Sabrina Caberlon,[19] Michela Anghilieri,[20] Rami Komrokji,[3] Daniele Cattaneo,[4,6] Matteo Giovanni Della Porta,[17,21] Toni Giorgino,[22] Lorenza Bertù,[23] Marco Brociner,[1] Andrew Kuykendall,[3] and Francesco Passamonti[1,2]

RR6 MODEL

Ruxolitinib dose <20 mg bid	1 point
RBC transfusion at 3 and/or 6 months	1 point
Spleen reduction lenght <30% at 3 and 6 months	1.5 point
Need RBC transfusion at all timepoints	1.5 point

Low risk	0 points
Intermediate risk	1,1.5,2 points
High risk	2,5-4 points

N.B. Mutazione RAS/CBL predittiva per resistenza a ruxolitinib

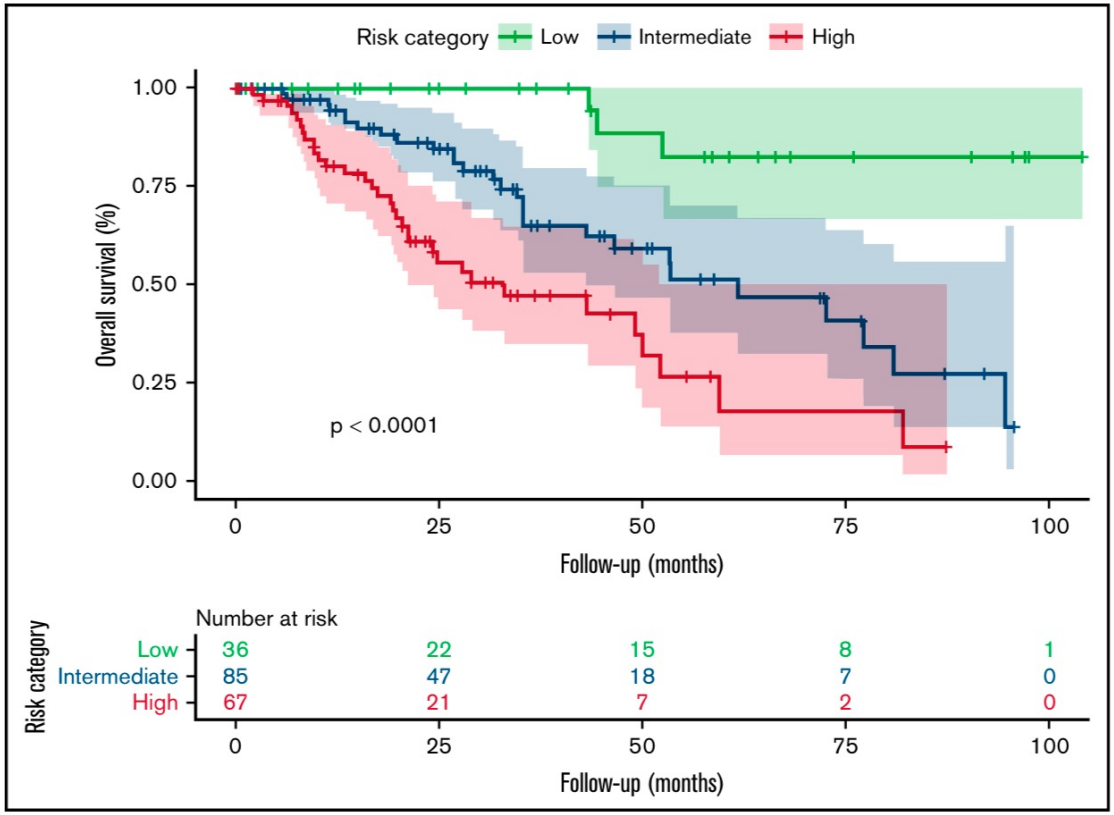


Figure 2. Actuarial survival curves of the 3 risk groups of patients according to the Response to Ruxolitinib After 6 Months (RR6) model developed in RUX-treated MF patients (training cohort).

TABLE 5 Efficacy and toxicity details for ruxolitinib, fedratinib, pacritinib, and momelotinib, in JAK inhibitor-naïve patients with myelofibrosis (*see text for references*).

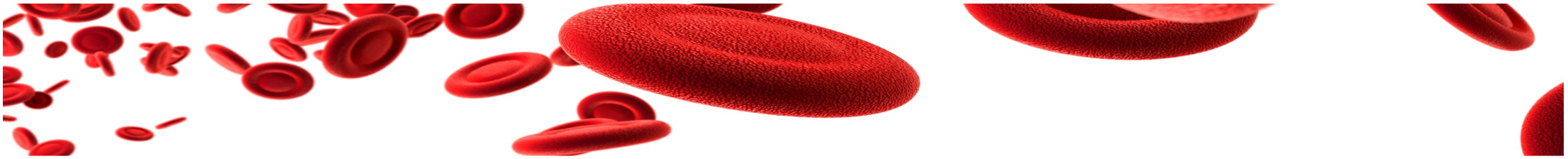
	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Myelofibrosis symptom-relevant targets	JAK1/2	JAK2	JAK2 ACRV1	JAK1/2 ACRV1
FDA-approved indication	IPSS* High/intermediate risk	IPSS* High/Intermediate-2 risk First-line and Second-line	DIPSS** High/Intermediate risk First-line and Second-line for platelet count $<50 \times 10^9$/L	Approval pending
FDA-approved dose and schedule	20 mg twice-daily (Platelet count $>200 \times 10^9$/L) 15 mg twice-daily (Platelet count $150–200 \times 10^9$/L)	400 mg twice-daily (Platelet count $\geq 50 \times 10^9$/L)	200 mg twice-daily (Platelet count $<50 \times 10^9$/L)	Approval pending (Expected 200 mg once-daily)
Spleen volume reduction ≥35% (radiographic)	42%% (COMFORT-1) 29% (COMFORT-2) 29% (SIMPLIFY-1)	36% (JAKARTA-1)	19% (PERSIST-1)	27% (SIMPLIFY-1)
Spleen response by palpation	32% (Mayo study)	83% (Mayo study)	Not reported	47% (Mayo study)
Anemia response in transfusion-dependent patients	30% (Mayo study)	10% (Mayo study)	25% (PERSIST-1)	51% (Mayo study)
Symptom response	57% (Mayo study) 46% (COMFORT-1) 42% (SIMPLIFY-1)	65% (Mayo study) 36% (JAKARTA-1)	19% (PERSIST-1)	48% (Mayo study) 28% (SIMPLIFY-1)
Adverse effects	Anemia Thrombocytopenia Withdrawal syndrome Opportunistic infections Poor response to COVID vaccines	Anemia Thrombocytopenia GI symptoms ↑Liver function tests ↑Amylase/lipase Wernicke's encephalopathy (Rare event)	GI symptoms (substantial) Peripheral edema Pneumonia Cardiac failure	Thrombocytopenia ↑Liver function tests ↑Amylase/lipase Peripheral neuropathy First-dose effect (Dizziness, Hypotension, Flushing, Nausea)

Abbreviations: **DIPSS, dynamic international prognostic scoring system; *IPSS, international prognostic scoring system; SVR, spleen volume reduction.

Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 May;98(5):801-821. doi: 10.1002/ajh.26857. Epub 2023 Feb 6. PMID: 36680511.

CASO CLINICO

- 06/2023 start Fedratinib, iniziale diarrea grado1, plt lentamente risalite fino a valori normali dopo circa 3mesi
- Milza 20cm



CASO CLINICO

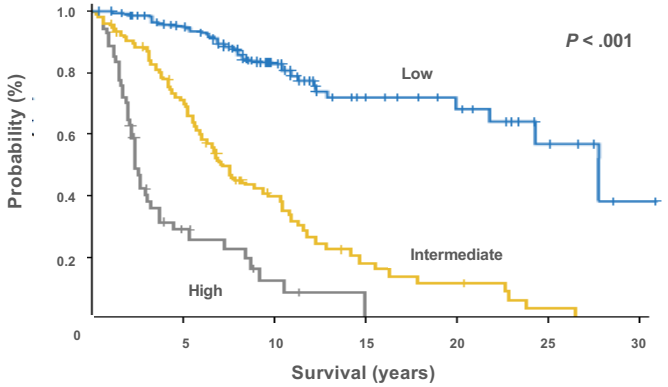
07/2023: Tipizzati i fratelli: non compatibili
Figlio valutato all'età di 15anni: HLA APLO, donatore non ideale perché cellule periferiche
Avviata ricerca MUD: non trovati donatori per HLA particolare

CD34:0,5%
Ricalcolo DIPSS :LOW
MIPSS70?

MIPSS70: Mutation Enhanced Prognostic Score System for Transplant-Age Patients With MF

Variables	Weighted value
Hb < 100 g/L	1
WBC > 25 × 10^9/L	2
PLT < 100 × 10^9/L	2
PB blasts ≥ 2%	1
Constitutional symptoms	1
Grade ≥ 2 BM fibrosis	1
Absence CALR Type 1	1
HMR category[a]	1
≥ 2 HMR mutations	2

Risk category	Score	OS (y)	HR
Low	0-1	27.7	1
Intermediate	2-4	7.1	5.5 (3.8-8.0)
High	≥ 5	2.3	16.0 (10.2-25.1)



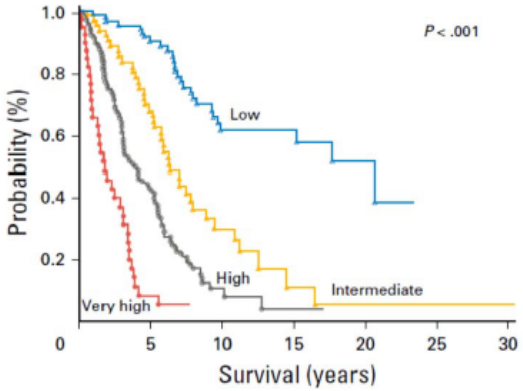
[a] HMR category was defined as having any mutation in *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*.

http://www.mipss70score.it/

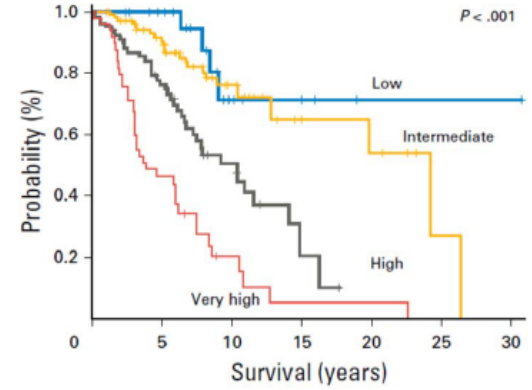
MIPSS70Plus:

- Punteggio di 1
  - Hb < 10
  - blasti circolanti ≥ 2
  - Sintomi costituzionali
  - 1 HMR
- Punteggio di 2
  - Assenza di mutazione di CARLty1
  - 2 o più HMR
- Punteggio di 3
  - Cariotipo sfavorevole**
- 4 categorie di rischio
  - Low (punteggio 0-2)
  - Intermediate(punteggio 3)
  - High(punteggio 4-6)
  - Very high (punteggio ≥7)

Guglielmelli et al, JCO 9 Dec 2017
**Tefferi et al, submitted

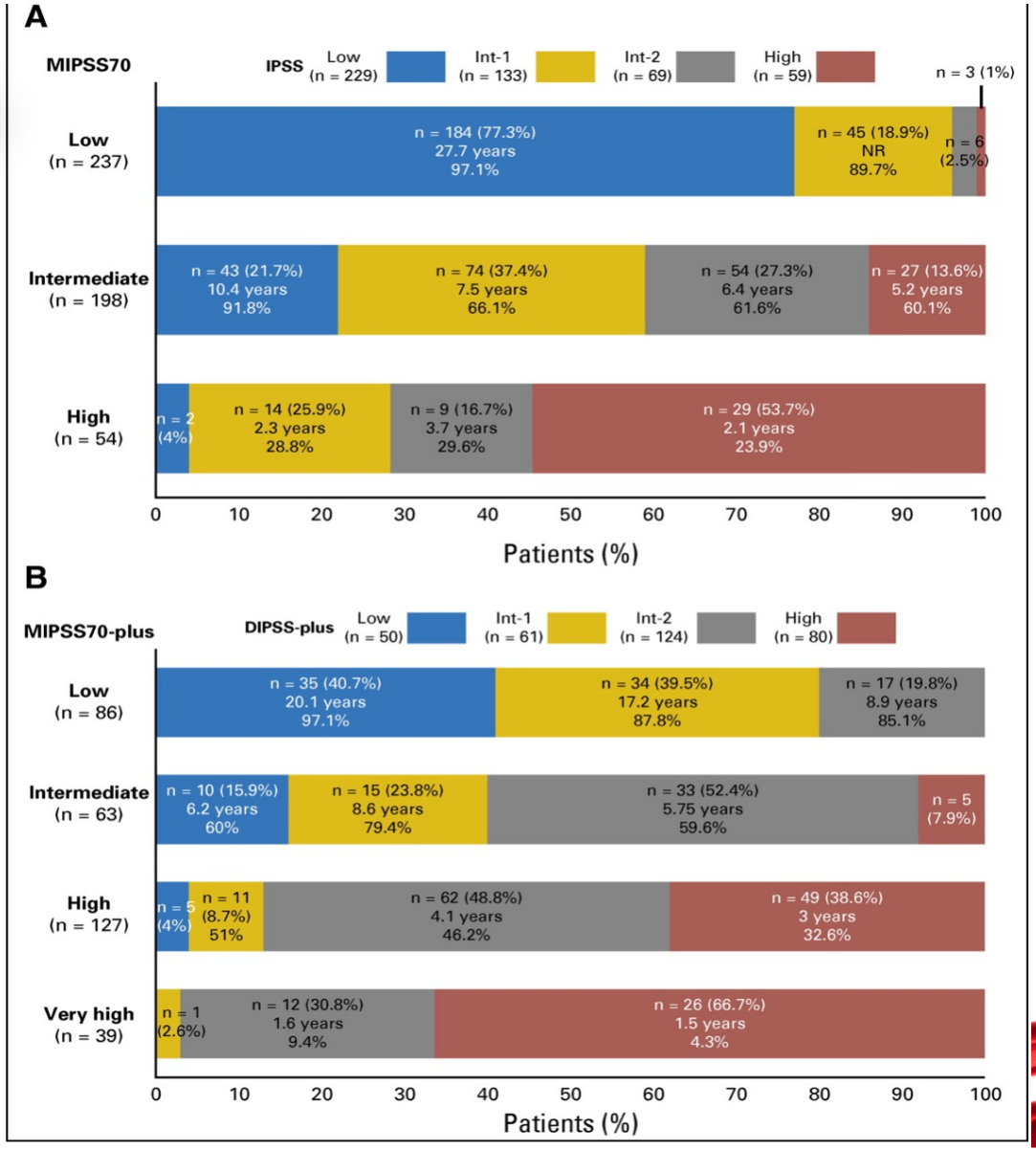


At risk time					
Low	86	67	28	17	4
Intermediate	63	38	10	12	1
High	127	43	4	1	0
Very high	39	3	0	0	0



At risk time					
Low	25	20	6	3	1
Intermediate	108	74	24	7	0
High	79	50	18	2	0
Very high	49	18	4	1	0

- * HMR + U2AF1Q157
- **VHR: -7, inv(3),i(17q),12p-,11q-, trisomies other than +8,+9
- unfavorable karyotype, defined as any abnormal karyotype other than normal karyotype or sole abnormalities of 20q-, 13q-,+9, chromosome 1 translocation/duplication, -Y, or sex chromosome abnormality other than -Y



Guglielmelli P, te al MIPSS70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis. J Clin Oncol. 2018 Feb 1;36(4):310-318. doi: 10.1200/JCO.2017.76.4886. Epub 2017 Dec 9. PMID: 29226763.

Leukemia (2017) **31,** 2726–2731

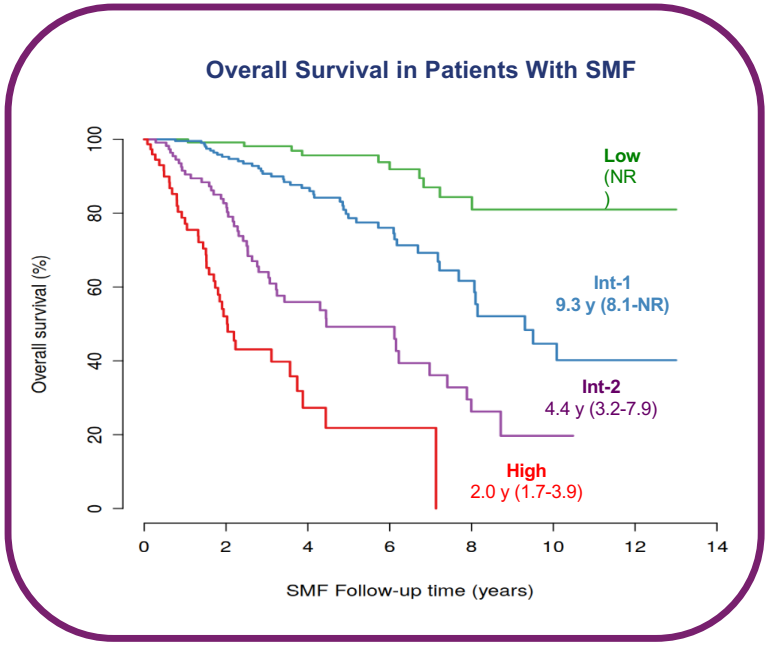
www.nature.com/leu

ORIGINAL ARTICLE

A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis

Covariate	HR (95% CI)	*P* value	Points
Age at MF diagnosis[a]	1.07 (1.05-1.09)	< .0001	0.15
Hb < 11 g/dL	2.3 (1.6-3.3	< .0001	2
PLT < 150 × 10⁹/L	1.7 (1.2-2.5)	.006	1
PB blasts ≥ 3%	2.9 (1.8-4.8	< .0001	2
CALR wild-type	2.6 (1.2-5.3)	.001	2
Constitutional symptoms	1.5 (1.0-2.0)	.03	1

[a] Continuous, 0.15 point/year.



Hb, hemoglobin; MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model; NR, not reached; PLT, platelet count; PB, peripheral blood; SMF, secondary MF.

MYSEC-PM Calculator:
http://www.mysec-pm.eu

Passamonti F, et al. *Leukemia*. 2017;31(12):2726-2731.

CASO CLINICO

07/2024: emocromo nella norma, milza 18cm all'ETG
Inviati campioni NGS
Per valutare candidabilita' trapiantologica e se proseguire nella ricercaMUD
10/2024: buone condizioni, saltuario prurito, emocromo nella norma (plt tra 130-150.000), milza9cm dall'arcata laterale
NGS: JAK2V617F
MIPSS70: intermedio
MIPSS70 PLUS: intermedio

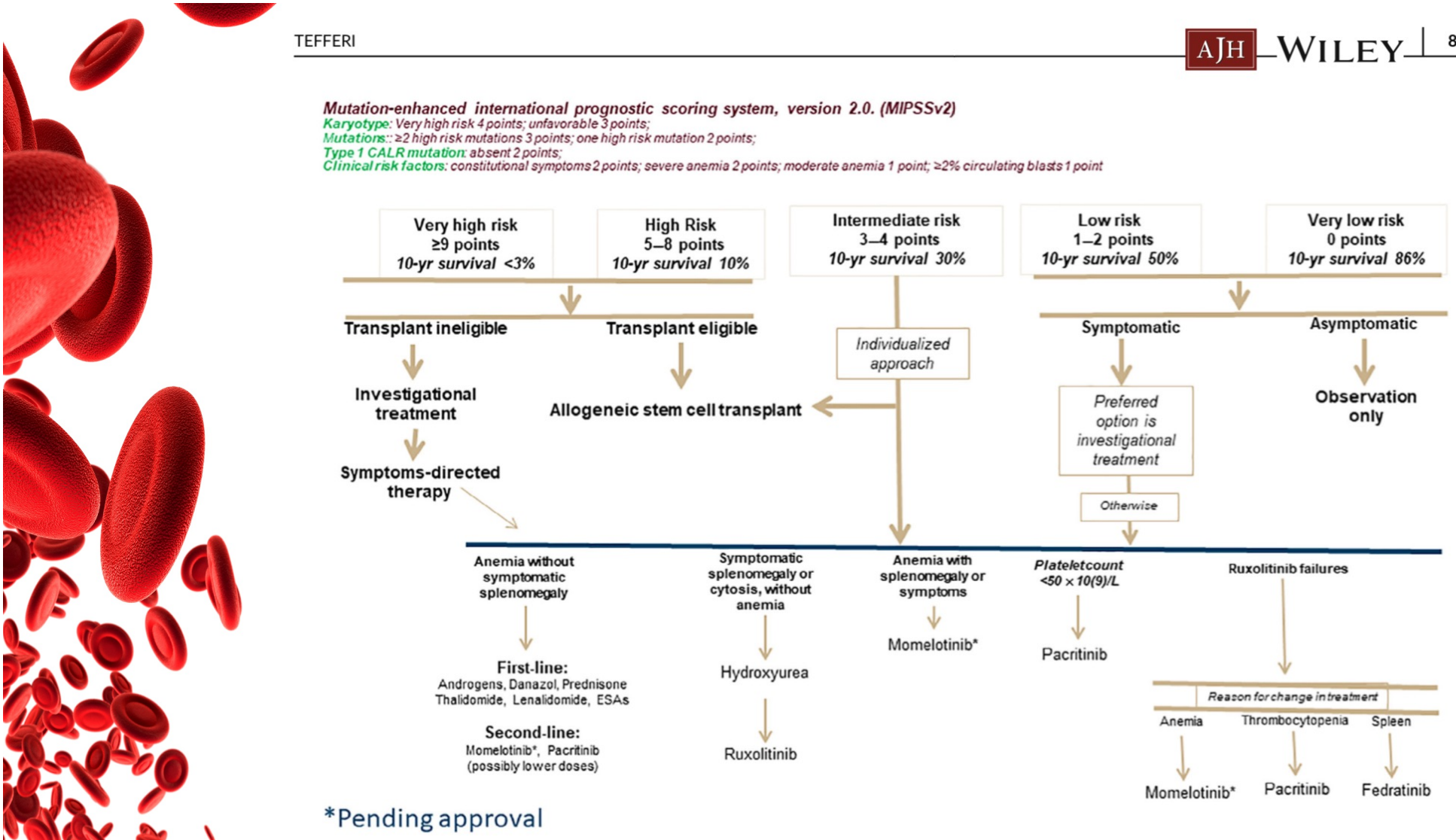


FIGURE 3 Risk-adapted treatment approach in primary myelofibrosis using the mutation-and karyotype-enhanced international prognostic system, version 2.0. (MIPSS v2; *see text for references*).

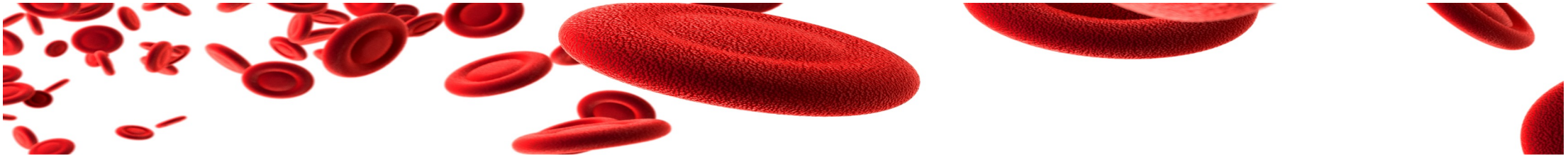
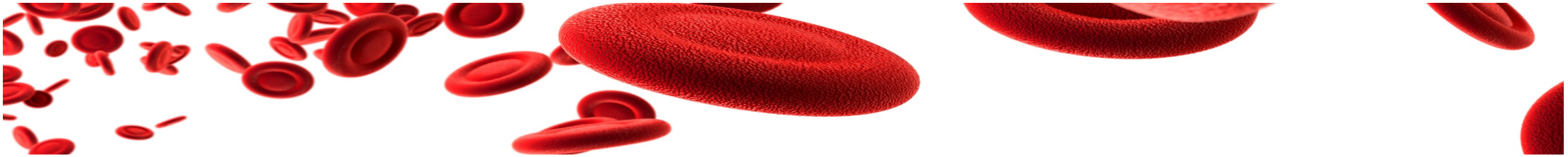


Figure 1. Myelofibrosis transplant scoring system (MTSS) to predict outcome after allogeneic transplantation[2]

Characteristics before transplantation	Score
Age ≥ 57 years	1
Leukocytes > 25 × 10^9/L	1
Platelets < 150 × 10^9/L	1
ASXL1 mutated	1
Non-CALR/MPL driver mutation	2
Karnofsky performance status < 90%	1
HLA-mismatch unrelated donor	2

Risk group (score)	5-year OS rates, %	5-year non-relapse mortality rates, %
Low (0–2)	90	10
Intermediate (3–4)	77	22
High (5)	50	36
Very high risk (6–9)	34	57

CALR, calreticulin; HLA, human leukocyte antigen; MPL, myeloproliferative leukemia virus; OS, overall survival



CASO CLINICO CONCLUSIONI

Calcolo MTSS: intermedio/alto (a seconda della conta piastrinica)
Al momento non indicazione a trapianto visto il rischio malattia di base, ma stretto monitoraggio splenomegalia e conta cd34

GRAZIE
DELL'ATTENZIONE