

La terapia nella Mielofibrosi

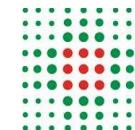
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**UNIVERSITÀ
DI PARMA**

DIPARTIMENTO DI MEDICINA E CHIRURGIA



**SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA**
Azienda Ospedaliero - Universitaria di Parma

Clinical spectrum of the disease

Gustav Heuck- 1879

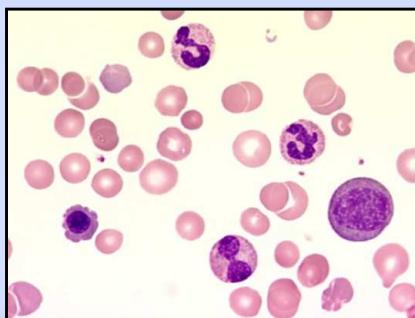
two pts with massive splenomegaly, circulating RBCs, increased WBCs and marrow fibrosis



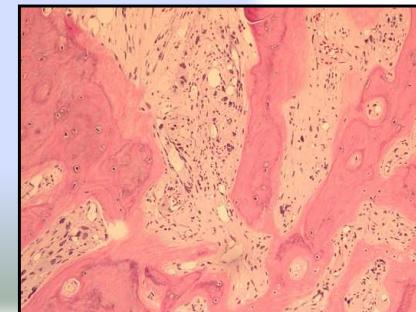
Anemia



Massive splenomegaly
cachexia



Leukoerythroblastic blood film



BM fibrosis

Median age at diagnosis:
66 years

61%
≥60 years of age

Annual incidence:
**0.1–1 per
100,000 people**

~6 years
median survival

Terapia

- ✓ Highly heterogeneous disease phenotype
- ✓ **Allogeneic stem cell transplant is the only curative option**
- ✓ Problem oriented approach
- ✓ Conventional treatments are largely unsatisfactory

MF patients have largely unmet clinical needs

“... The main goals of therapy in primary myelofibrosis are **prolongation of survival** and, if possible, also **cure**, which is currently only achieved by allogeneic stem-cell transplantation. If prolongation of survival or cure is not possible, **symptom-orientated palliation and quality of life** are the main goals”

Barbui T, et al. *J Clin Oncol.* 2011; 29:761-70

Common Symptoms of MF



Fatigue



Fever



Bone pain



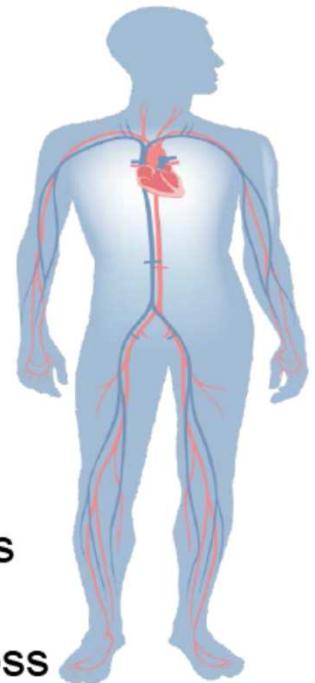
Pruritus
(itching)



Night sweats

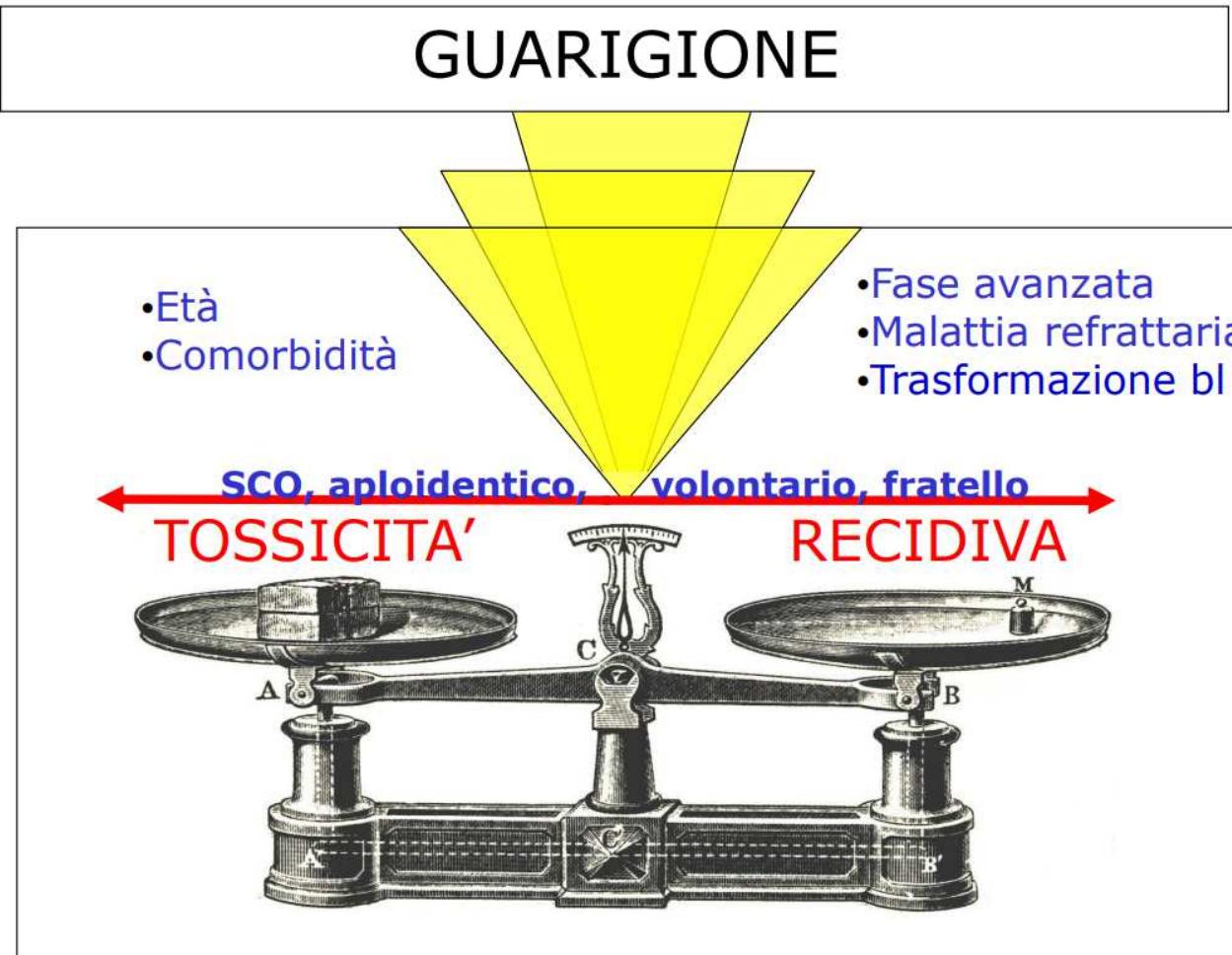


Weight loss
(cachexia)



Terapia

Only **CURATIVE** approach: ALLOGENIC BONE MARROW TRANSPLANT

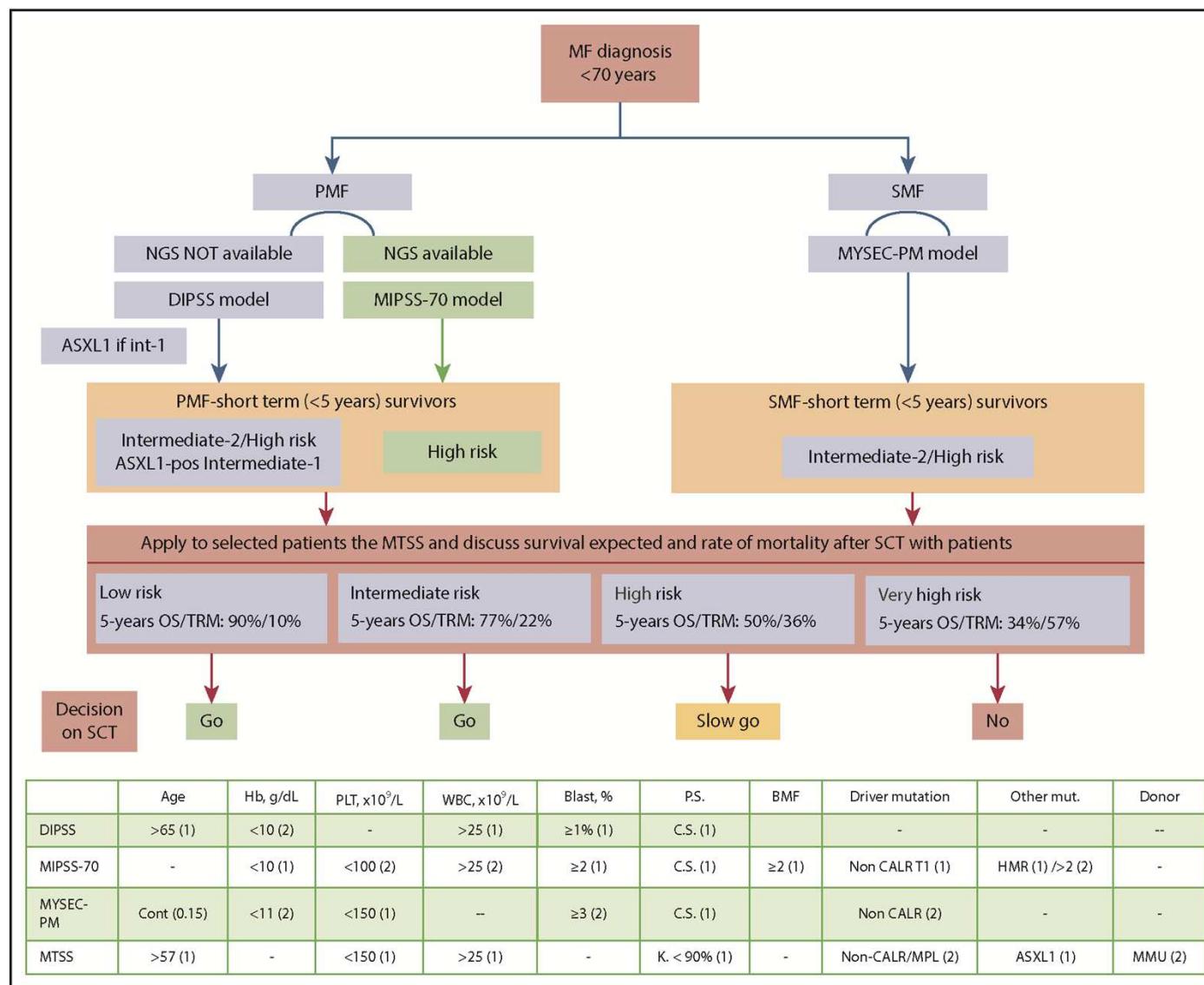


Passamonti F: “Stem cell transplant in MF: it’s time to personalize”

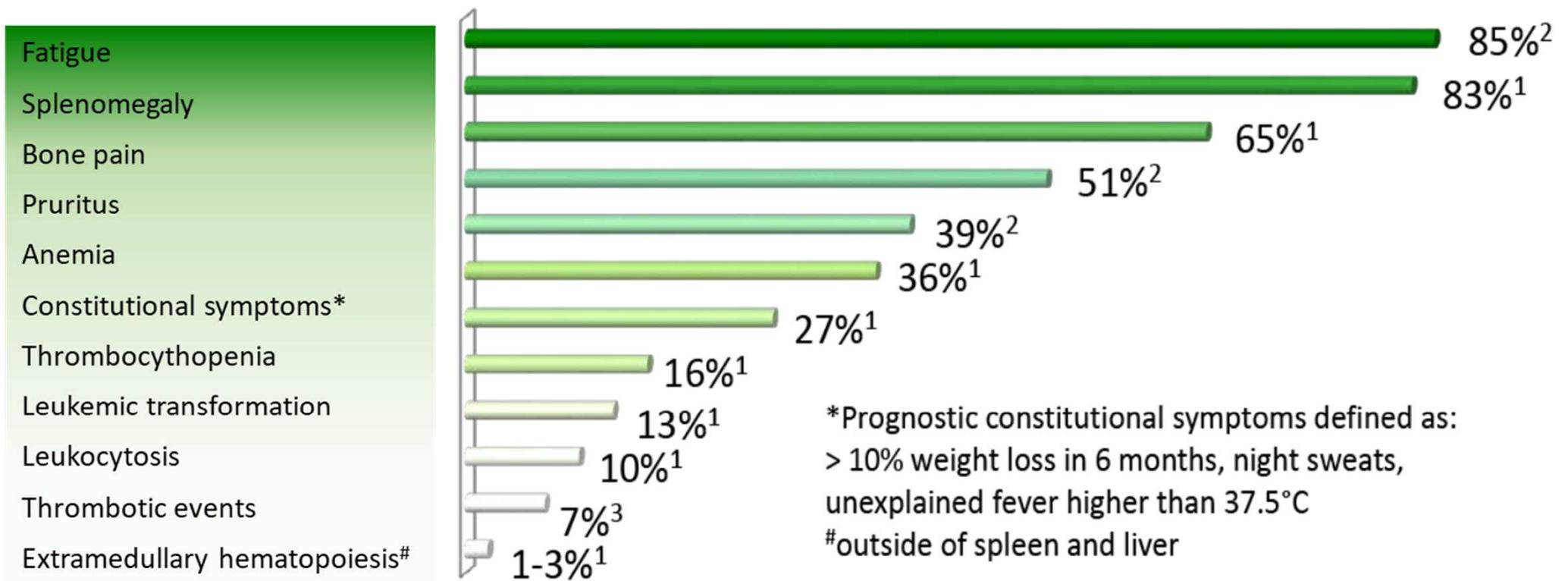
Blood, 2019



American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Problematiche cliniche che richiedono un intervento terapeutico



*Prognostic constitutional symptoms defined as:
> 10% weight loss in 6 months, night sweats,
unexplained fever higher than 37.5°C

#outside of spleen and liver

Passamonti F et al, Blood 2009

Mesa RA et al, Leuk Res 2009

Barbui T et al, Blood 2010

Approccio terapeutico «problem-oriented»

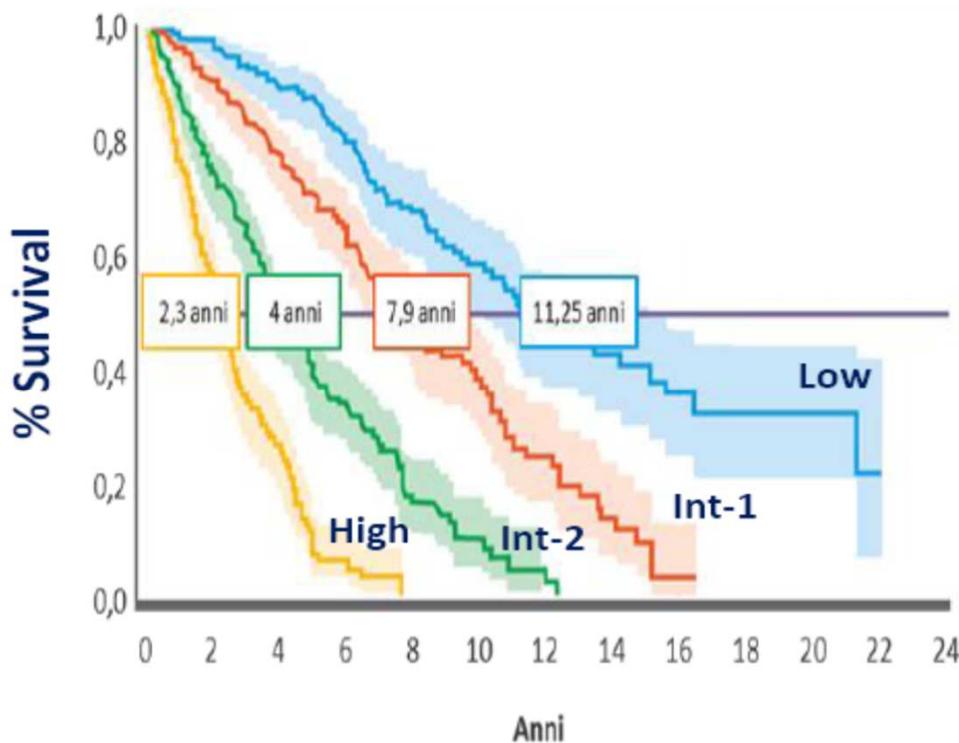
Clinical need	Intervention
Anemia	<ul style="list-style-type: none"> • Corticosteroids • <i>Danazol</i> • EPO (< 500 U/l) • IMIDs
Splenomegaly	<ul style="list-style-type: none"> • HU • Cladribine • JAKi <p><i>Splenectomy</i> <i>Splenic irradiation</i></p>
Extramedullary hematopoiesis	<ul style="list-style-type: none"> • JAKi <p>Radiation tp</p>
Thrombotic events	<ul style="list-style-type: none"> • ASA • HU • JAKi?
Constitutional symptoms	<ul style="list-style-type: none"> • Corticosteroids • JAKi
Risk of leukemic transformation	None (<i>HSCT</i>)
Survival improvement	<ul style="list-style-type: none"> • <i>HSCT</i> • <i>JAKi?</i>

Stratificazione rischio clinico: primo step per la decisione terapeutica

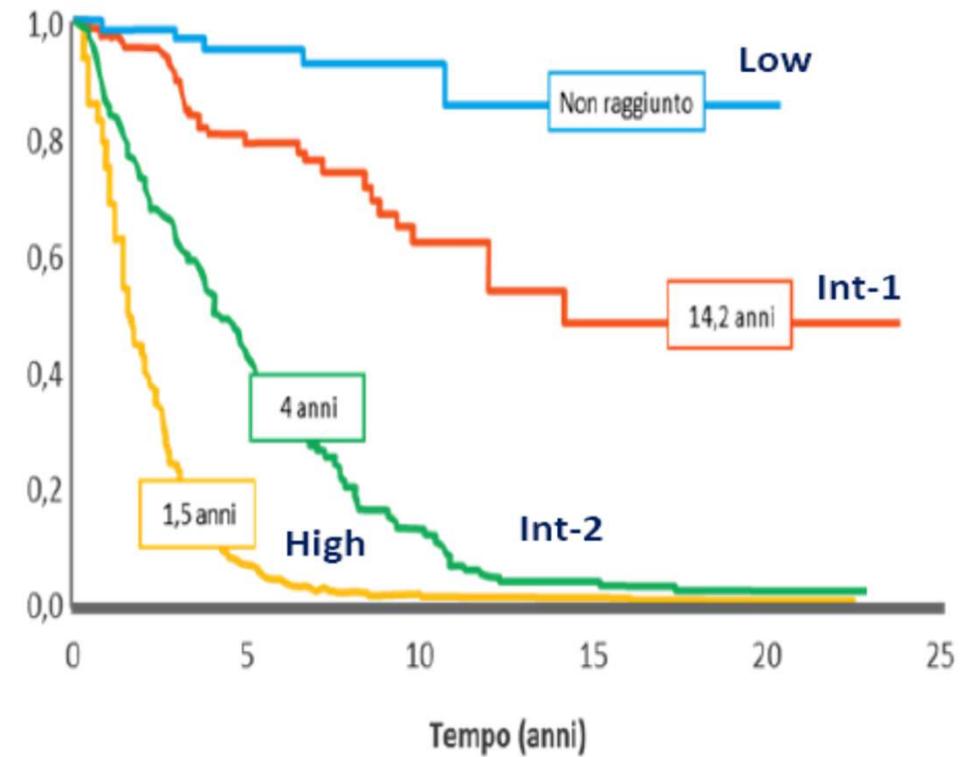
SCORE DI RISCHIO «CLINICI»: tutti i pz

Variable	IPSS	DIPSS	DIPSS-plus
Age >65 y	✓	✓	If DIPSS:
Constitutional symptoms	✓	✓	Low= 0
Hemoglobin <10 g/dL	✓	✓	Int-1= 1
Leukocyte count >25x10 ⁹ /L	✓	✓	Int-2=2
Circulating blasts <u>>1%</u>	✓	✓	High= 3
Platelet count <100x10 ⁹ /L			✓
RBC transfusion need			✓
Unfavorable karyotype +8,-7/7q-,i(17q),inv(3), -5/5q-,12p-, 11q23 rearr.			✓

International Prognostic scoring system (IPSS)

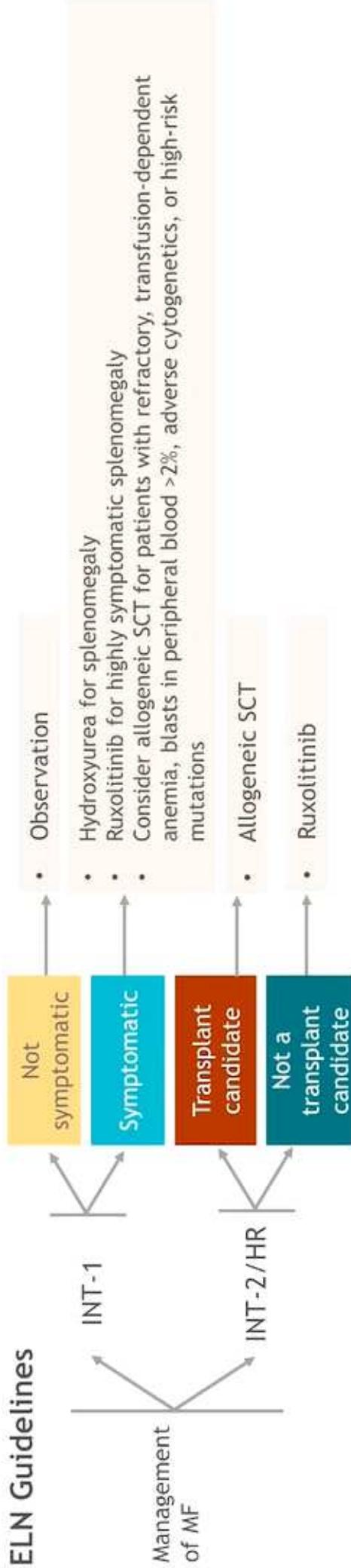


Dynamic IPSS (DIPSS)



ELN guidelines for the treatment of myelofibrosis

- For the initial treatment of MF, guidelines from the ELN recommend:
 - In patients with Int-1-risk disease, ruxolitinib is recommended for the treatment of highly symptomatic splenomegaly, whereas hydroxyurea is recommended for the treatment of splenomegaly in patients who are not symptomatic
 - Ruxolitinib for the treatment of MF-associated splenomegaly in untreated patients with Int-2-risk or high-risk disease
 - Allogeneic SCT for transplant-eligible patients with high-risk or Int-2-risk MF*

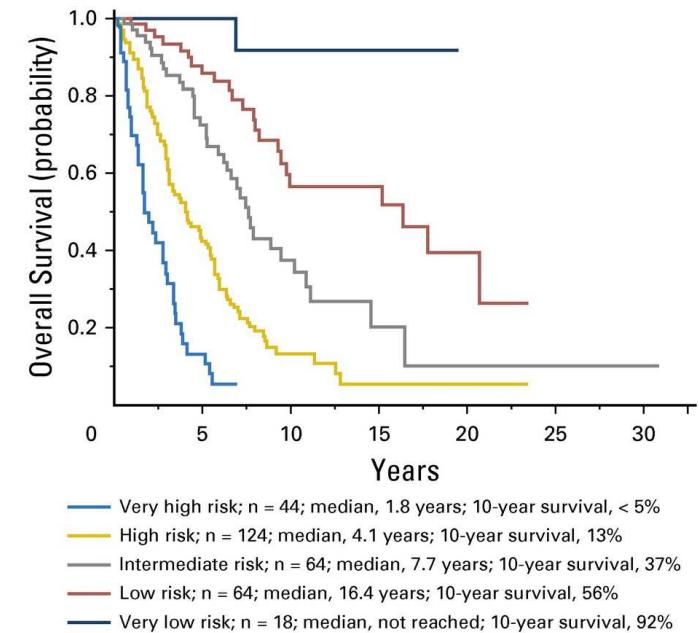


Stratificazione rischio clinico: primo step per la decisione terapeutica

SCORE DI RISCHIO «MOLECOLARI» → pz candidati a HSCT

#	Question	Answer
1	Severe Anemia (hemoglobin <80g/L)	<input type="radio"/> Yes <input type="radio"/> No
2	Moderate Anemia (hemoglobin 80-100g/L)	<input type="radio"/> Yes <input type="radio"/> No
3	Leucocytosis >25x10 ⁹ /L	<input type="radio"/> Yes <input type="radio"/> No
4	Thrombocytopenia (platelet count <100x10 ⁹ /L)	<input type="radio"/> Yes <input type="radio"/> No
5	Peripheral blood blast count ≥2%	<input type="radio"/> Yes <input type="radio"/> No
6	Bone marrow fibrosis grade ≥2	<input type="radio"/> Yes <input type="radio"/> No
7	Constitutional symptoms	<input type="radio"/> Yes <input type="radio"/> No
8	Absence of CALR type 1/like mutation	<input type="radio"/> Yes <input type="radio"/> No
9	HMR ¹ category	<input type="radio"/> Yes <input type="radio"/> No
10	≥2 HMR mutated genes	<input type="radio"/> Yes <input type="radio"/> No
11	Unfavorable karyotype ²	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not available
12	Very High Risk karyotype ³	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not available

Score	Result
MIPSS70	
MIPSS70-plus version 2.0	Karyotype-enhanced



Tefferi A et al, J Clin Oncol. 2018;36:1769-1770

Stratificazione rischio clinico: primo step per la decisione terapeutica

SCORE DI RISCHIO «MOLECOLARI» per la MF secondaria

Age at diagnosis:

40 64 90

40 45 50 55 60 65 70 75 80 85 90

Haemoglobin < 11 g/dL [+2 pt]

Platelets < 150 × 10⁹/L [+1 pt]

Blasts ≥ 3% [+2 pt]

CALR -unmutated genotype [+2 pt]

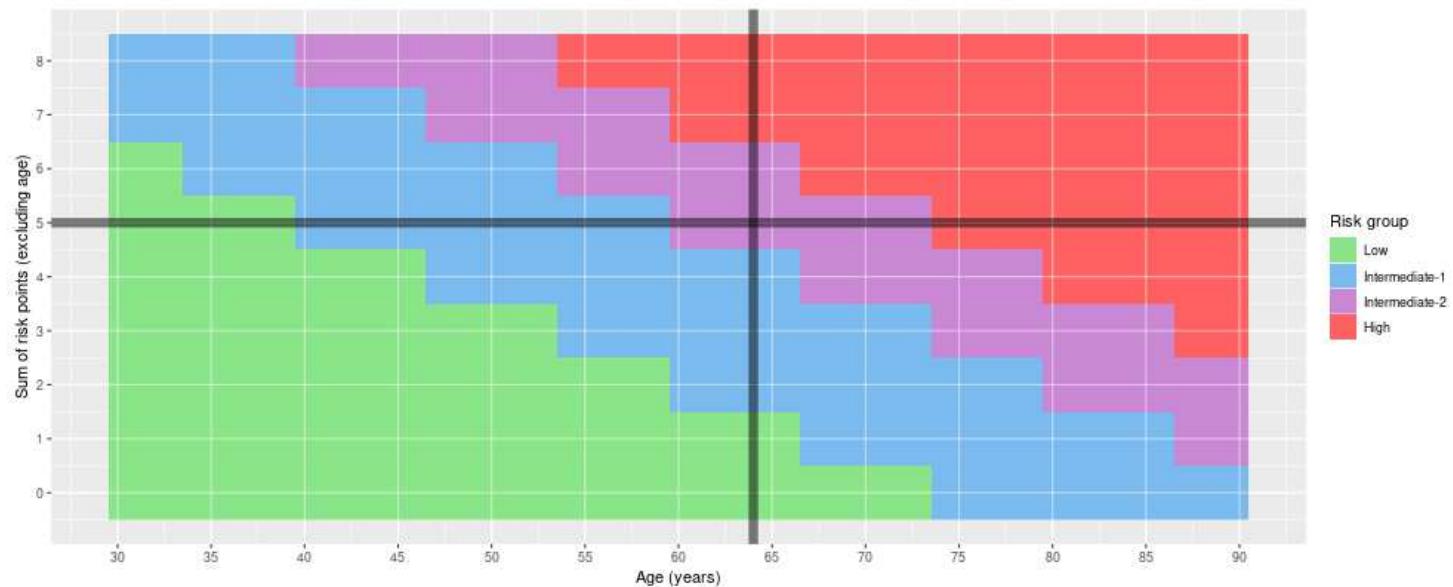
Constitutional symptoms [+1 pt]

Calculation

Risk points for age: **9.6**

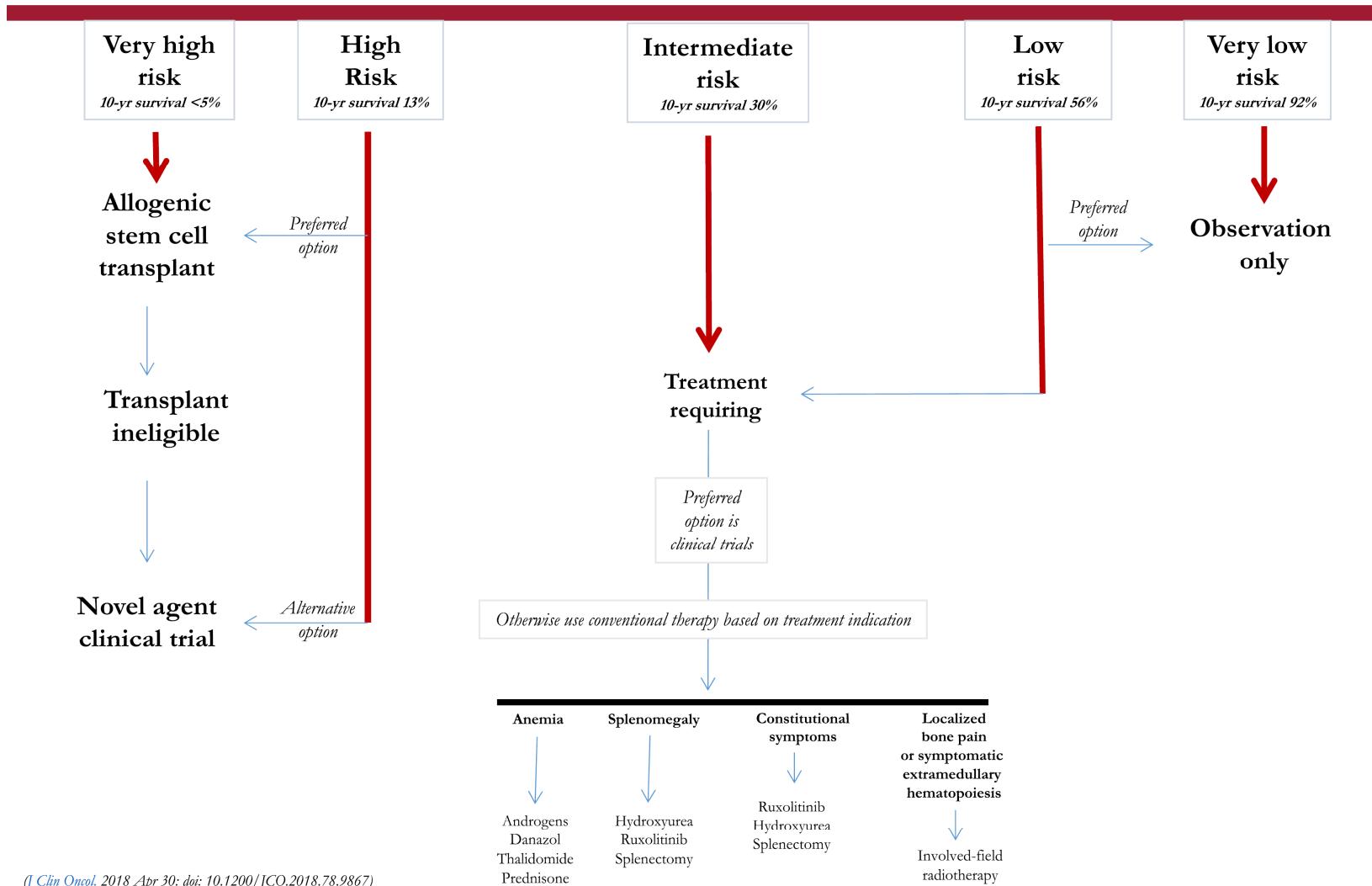
Risk points for non-age factors: **5**

Total risk: **14.6**



Treatment algorithm in myelofibrosis

based on risk stratification according to the mutation- and karyotype-enhanced international prognostic scoring system (MIPSS70+ version 2.0); see table 5 for risk variables and risk point allocations



JAK1/2 inhibitor Ruxolitinib

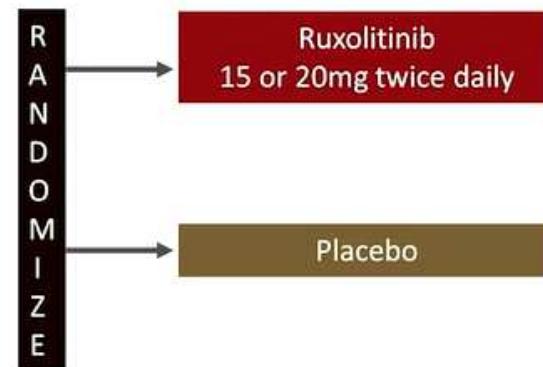
First JAKi approved for MF (2011 US, 2012 EU, 2013 Italia)

Phase III COMFORT-I and -II: Ruxolitinib in MF

COMFORT-I^{1,2}

PMF or PPV-MF, or PET-MF (N = 309)
Intermediate-2 or high risk by IWG-MRT
Palpable spleen ≥5cm below left costal margin
Platelet count ≥100 × 10⁹/L
JAK2-V617F positive or negative

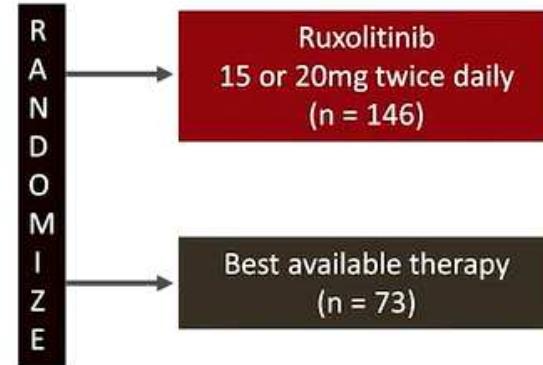
1:1



COMFORT-II³

Patients with PMF, PPV-MF, or PET MF with ≥2 IWG risk factors (N = 219)

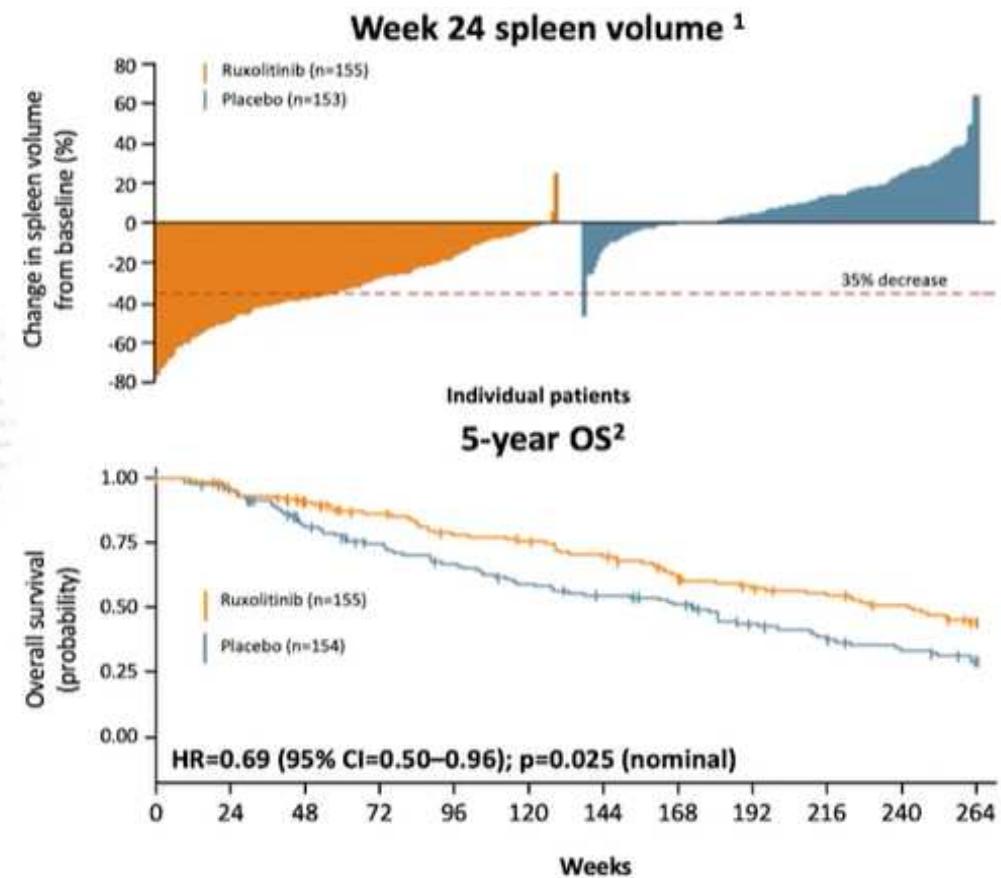
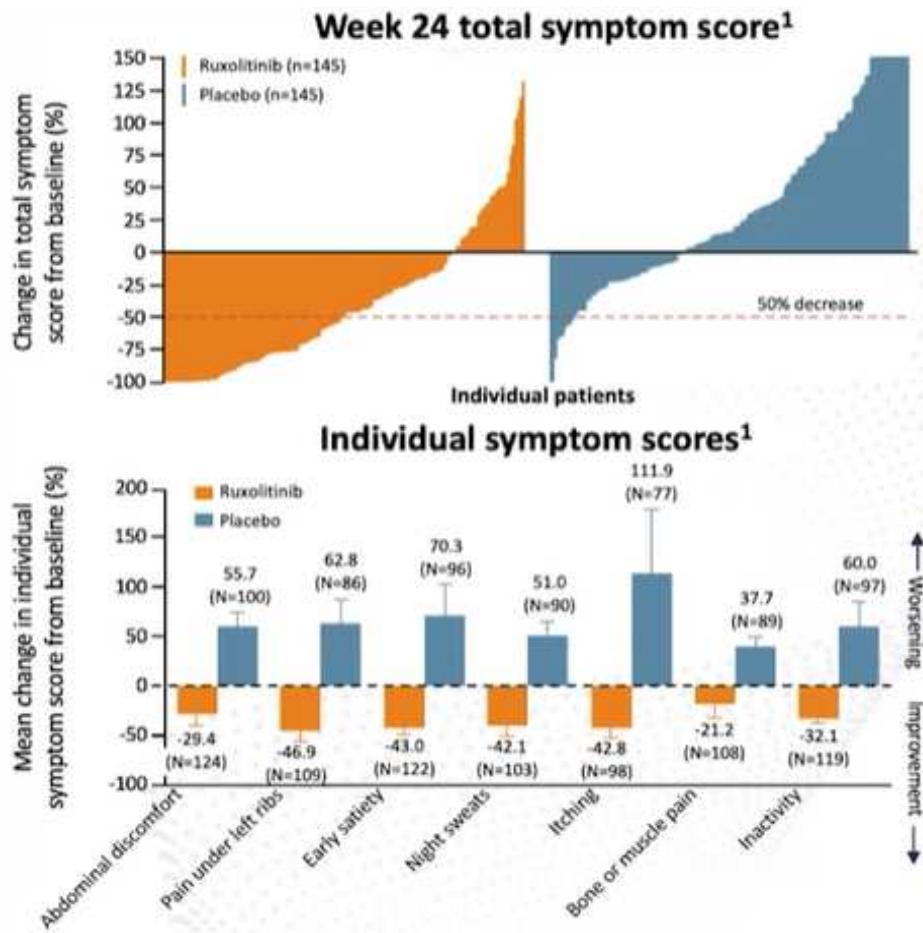
2:1



Best available therapy (BAT) arm: patients with PD eligible for crossover to ruxolitinib
Ruxolitinib arm: patients with PD eligible for extension phase

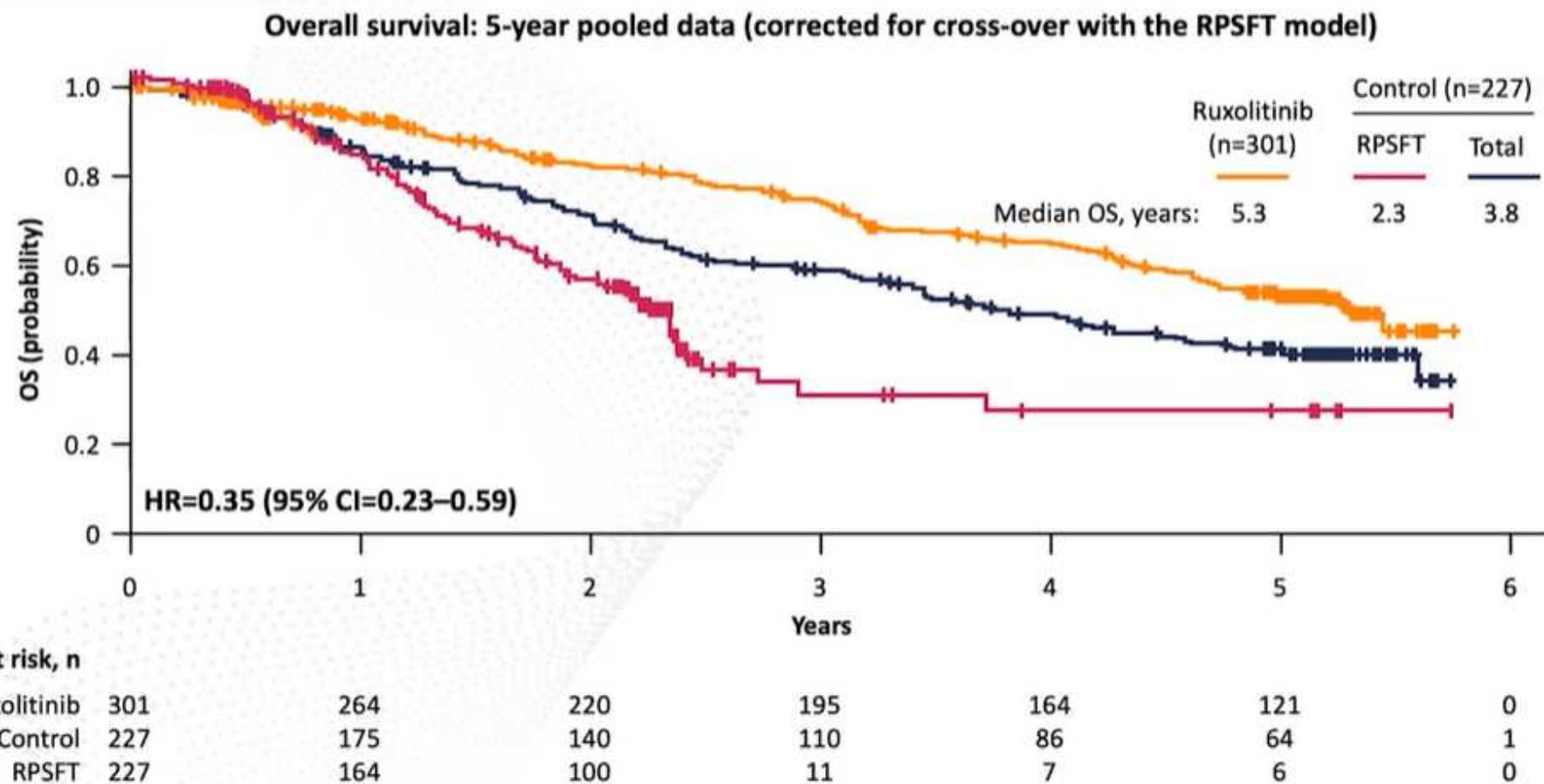
Verstovsek S, et al. *N. Engl. J. Med.* 2012;366(9):799–807
Harrison C, et al. *N. Engl. J. Med.* 2012; 366(9), 787–798

Ruxolitinib improves spleen size, symptoms and OS compared to placebo (COMFORT-1 & updates)



1. Verstovsek S, et al. N Engl J Med 2012; 366:799–807; 2. Verstovsek S, et al. J Hematol Oncol 2017; 10:55.

5-years survival benefit of Ruxolitinib vs. placebo/BAT (COMFORT-1 and COMFORT-2)



BAT, best available therapy; RPSFT, rank-preserving structural failure time.

Verstovsek S, et al. J Hematol Oncol 2017; 10:156.

Ruxolitinib treatment related toxicities

Table III. Treatment-emergent adverse drug reactions (safety set).

	Prevalent users				
	Long-term N = 180	Short-term N = 79	Total N = 259	New users N = 32	Ruxolitinib-switch N = 57†
Patient-years‡	463·6	172·9	636·5	67·4	92·7
Patients with ADRs§, n (%)	91 (50·6)	34 (43·0)	125 (48·3)	13 (40·6)	31 (54·4)
Incidence rate¶ (≥1·0 in any cohort; by preferred term) of ADRs (n/100 patient-years)					
Any ADR	19·6	19·7	19·6	19·3	33·4
Thrombocytopenia	5·4	5·2	5·3	5·9	10·8
Anaemia	4·1	2·9	3·8	8·9	10·8
Epistaxis	1·3	3·5	1·9	0	3·2
Urinary tract infection	1·3	1·7	1·4	0	2·2
Herpes zoster	1·3	1·2	1·3	1·5	3·2
Haematoma	1·3	1·2	1·3	0	2·2
Bronchitis	0·9	1·2	0·9	0	0
Platelet count decreased	1·1	0·6	0·9	1·5	1·1
Pneumonia	1·1	0·6	0·9	1·5	1·1
Sepsis	1·1	0	0·8	0	0
Diarrhoea	0·6	1·2	0·8	0	1·1
Contusion	0·6	1·2	0·8	0	0
Pyrexia	0·4	1·2	0·6	0	1·1
Lung infection	0·4	1·2	0·6	0	0
Upper respiratory tract infection	0·6	0	0·5	1·5	0
Weight increased	0·4	0·6	0·5	0	2·2

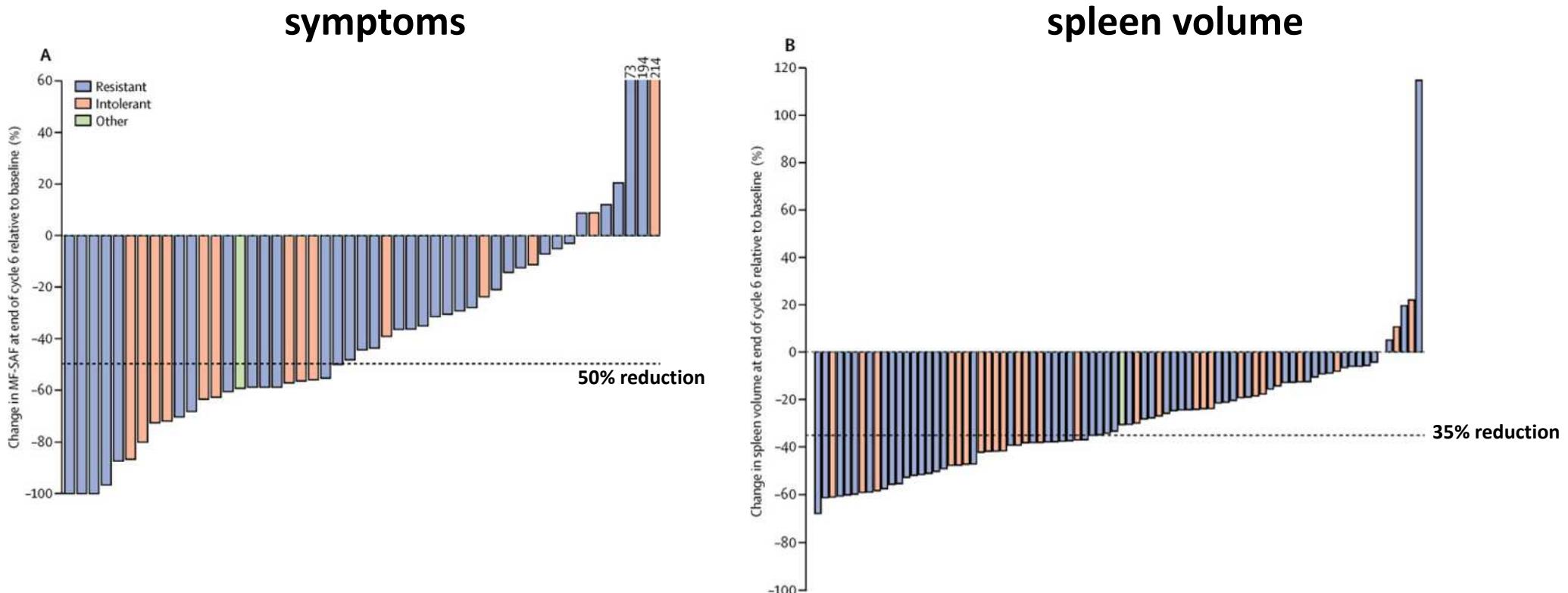
JAK2 & FLT3 inhibitor Fedratinib (US and EU approved)

Second JAKi approved for MF (2019 US, 2021 EU) as FIRST and SECOND line in MF
 Clinical hold (2013-2017) for suspected fatal encephalopathy, including Wernicke encephalopathy

Table 2. Comparison of JAKARTA (frontline) and JAKARTA-2 (second-line) trials

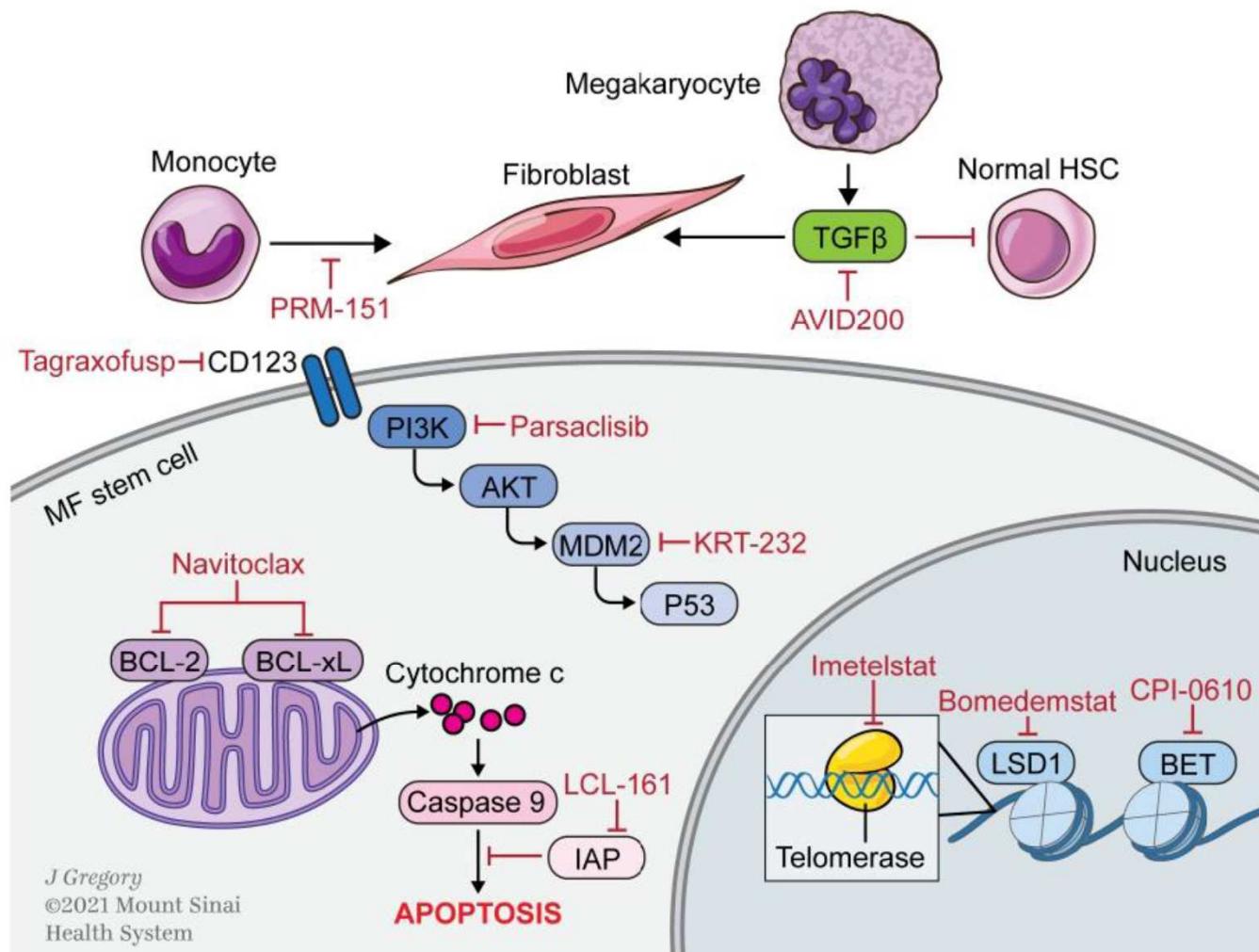
	JAKARTA1 (frontline) ²³	JAKARTA2 (second line) ²⁴
Design	Phase 3/randomized PB controlled	Single arm
Dosing/arms	Placebo FEDR 400 mg FEDR 500 mg	FEDR 400 mg
Inclusion	Disease: primary, post-ET/PV MF Risk: DIPSS INT-2, high risk Prior RX: JAK-inhibitor naive	Disease: primary, post-ET/PV MF Risk: DIPSS INT-1 (symptomatic), INT-2, high risk Prior RX: ruxolitinib intolerant/refractory
Primary end point	>35% SVR	>35% SVR
Key secondary end point	≥50% reduction in MFSAF-TSS	≥50% reduction in MFSAF-TSS
Enrollment	N = 289	N = 97
Initial published response rates		
Spleen volume response (>35% volume reduction)	FEDR 400 mg (36%) FEDR 500 mg (40%) Placebo (1%)	FEDR 400 mg (55% of 83 evaluable)
MFSAF-TSS (>50% reduction)	FEDR 400 mg (36%) FEDR 500 mg (34%) Placebo (7%)	FEDR 400 mg (26% of 90 evaluable)
Toxicity	Grade 1-2 GI toxicities Grade 3-4 cytopenias Suspected WE (more so in 500-mg arm) led to trial hold	Consistent with JAKARTA study toxicity <ul style="list-style-type: none"> • Low-grade GI TOX • Grade 3-4 anemia/thrombocytopenia

Fedratinib reduces splenomegaly and symptoms as 2 line therapy (JAKARTA-2)



Change in total symptom score (A) and spleen volume (B) from baseline to end of cycle 6, according to reason for ruxolitinib discontinuation

Novel agents



Myelofibrosis: conclusions

MF is heterogenous in presentation and course

Risk stratification requires molecular testing

Treatment is goal-oriented

JAKi therapy represented the first major advance in MF treatment

Patients have still largely unmet clinical needs

Complications: thrombosis, therapy-related toxicities, risk of AML evolution