Disclosures for Angela Fleischman

Principal investigator role	Sierra, Incyte
Employee	None
Consultant	None
Major Stockholder	None
Speakers' Bureau	Incyte
Scientific Advisory Board	None

Presentation includes discussion of the following off-label use of a drug or medical device: Hydroxyurea, Interferon-alpha, Busulfan, Thalidomide, Lenalidomide, Pomalidomide, Ruxolitinib, Androgen preparations, Erythropoiesis stimulating agents

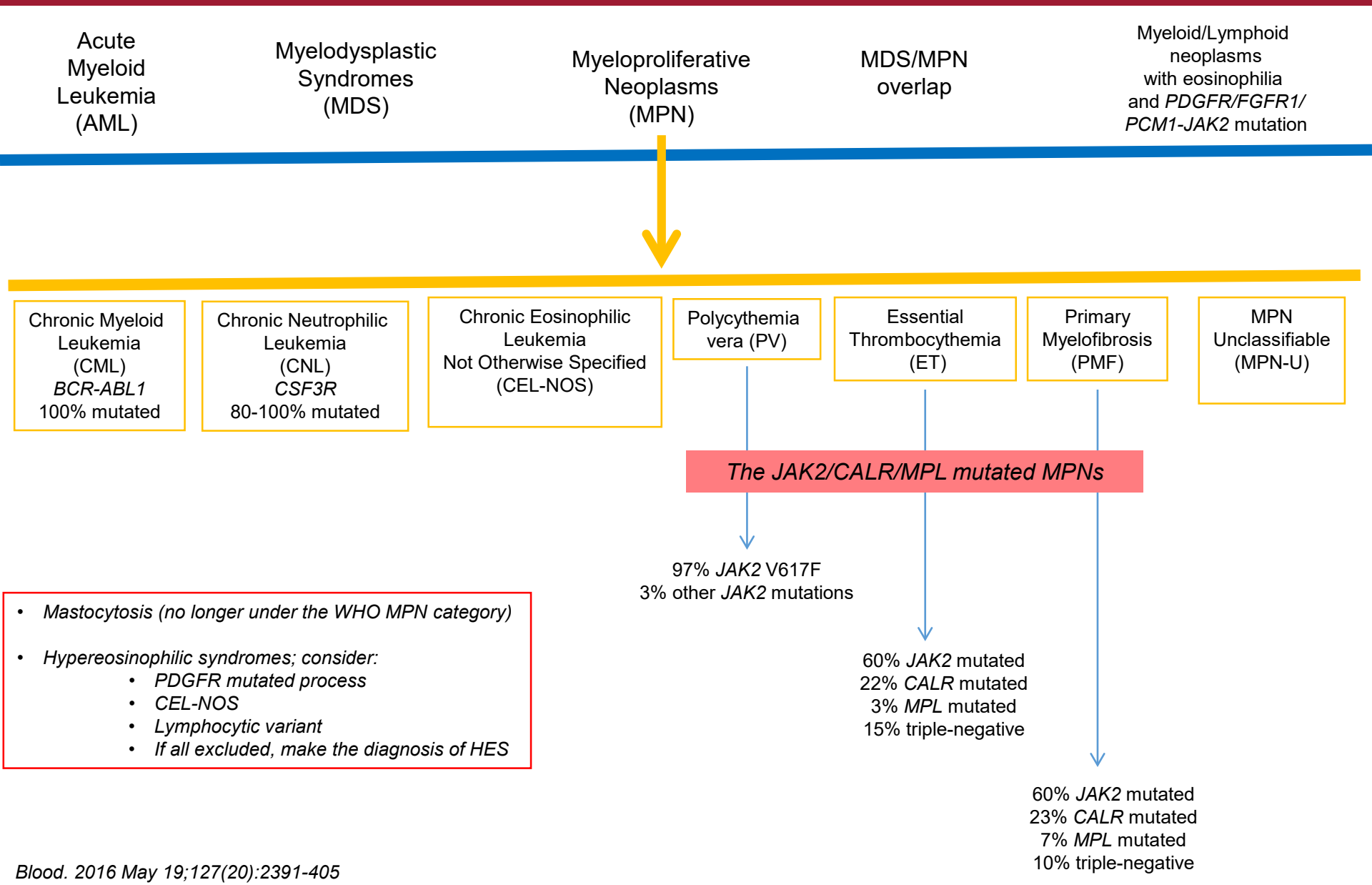
Myeloproliferative Neoplasms—*2019 Update*

Ayalew Tefferi, MD
Professor of Medicine and Hematology
Mayo Clinic College of Medicine

Topics

- WHO diagnostic criteria
- Practical diagnostic algorithms
- Genetic prognostication
- Contemporary treatment algorithms

2016 WHO Classification of Myeloid Malignancies



- *Mastocytosis (no longer under the WHO MPN category)*
- *Hypereosinophilic syndromes; consider:*
  - *PDGFR mutated process*
  - *CEL-NOS*
  - *Lymphocytic variant*
  - *If all excluded, make the diagnosis of HES*

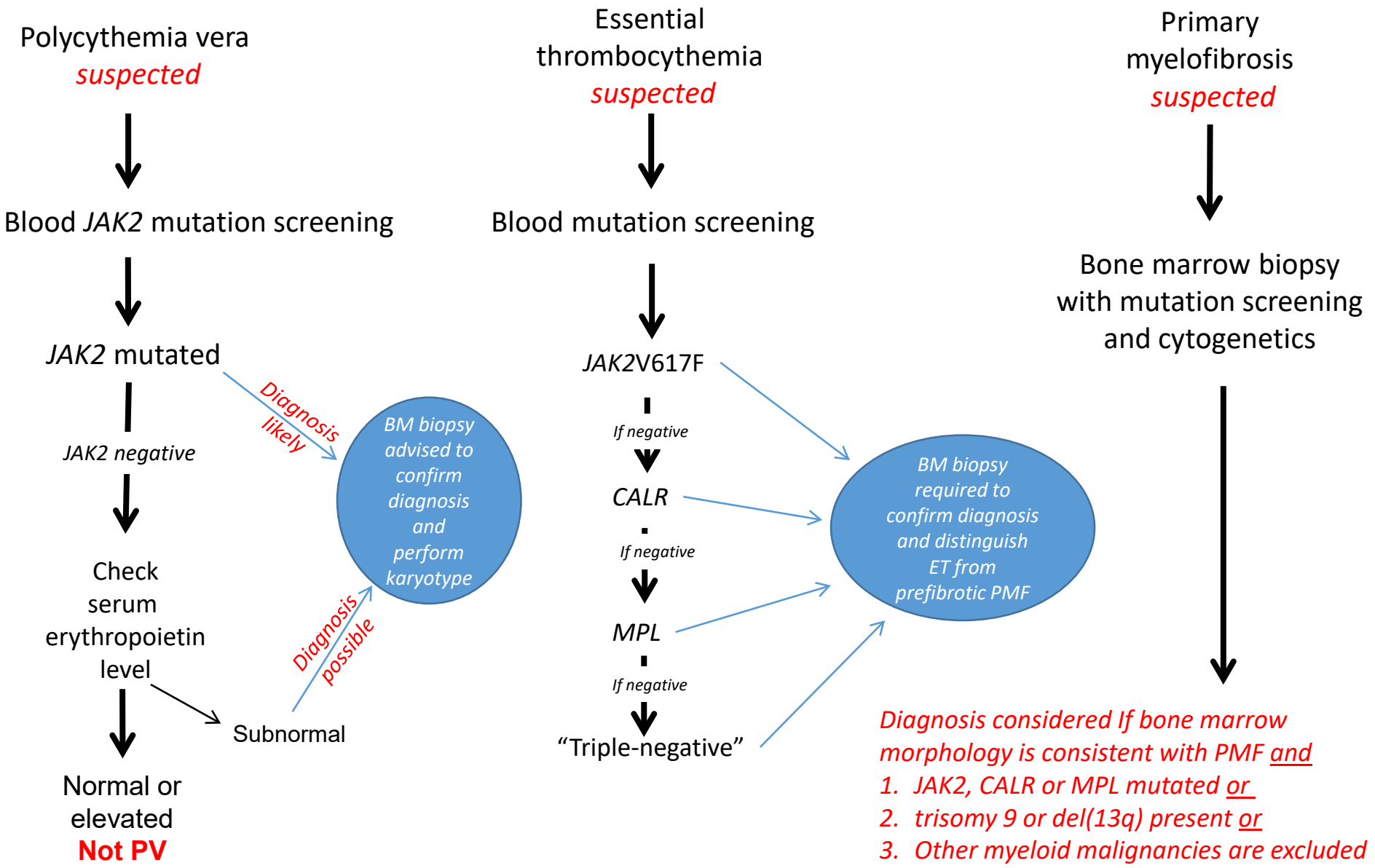
Blood. 2016 May 19;127(20):2391-405

2016 WHO Diagnostic Criteria for PV, ET and PMF

	Polycythemia vera (PV)	Essential thrombocythemia (ET)	Primary myelofibrosis (PMF)
	Diagnosis requires all major criteria or first 2 major plus minor	*Diagnosis requires all major criteria*	*Diagnosis requires all major criteria plus one minor*
Major criteria	**Hemoglobin** >16.5 g/dl in men >16 g/dl in women	**Platelets** ≥450 x 10^9/l	**Bone marrow** Megakaryocytes in tight clusters Hyperchromatic/irregularly folded nuclei <grade 2 fibrosis (prePMF) ≥grade 2 fibrosis (overt PMF)
	Bone marrow Tri-lineage myeloproliferation Pleomorphic megakaryocytes	**Bone marrow** Megakaryocyte proliferation large and mature forms loose clusters	
		Not meeting WHO criteria *for other myeloid neoplasms*	*Not meeting WHO criteria* *for other myeloid neoplasms*
	JAK2 mutated	*JAK2/CALR/MPL* mutated	*JAK2/CALR/MPL* mutated or other clonal marker present or no evidence for reactive marrow fibrosis
Minor criteria	• Subnormal serum erythropoietin	• Other clonal marker present or no evidence for reactive thrombocytosis	• Anemia • Leukocytosis • Palpable splenomegaly • Increased LDH • Leukoerythroblastosis (overt)

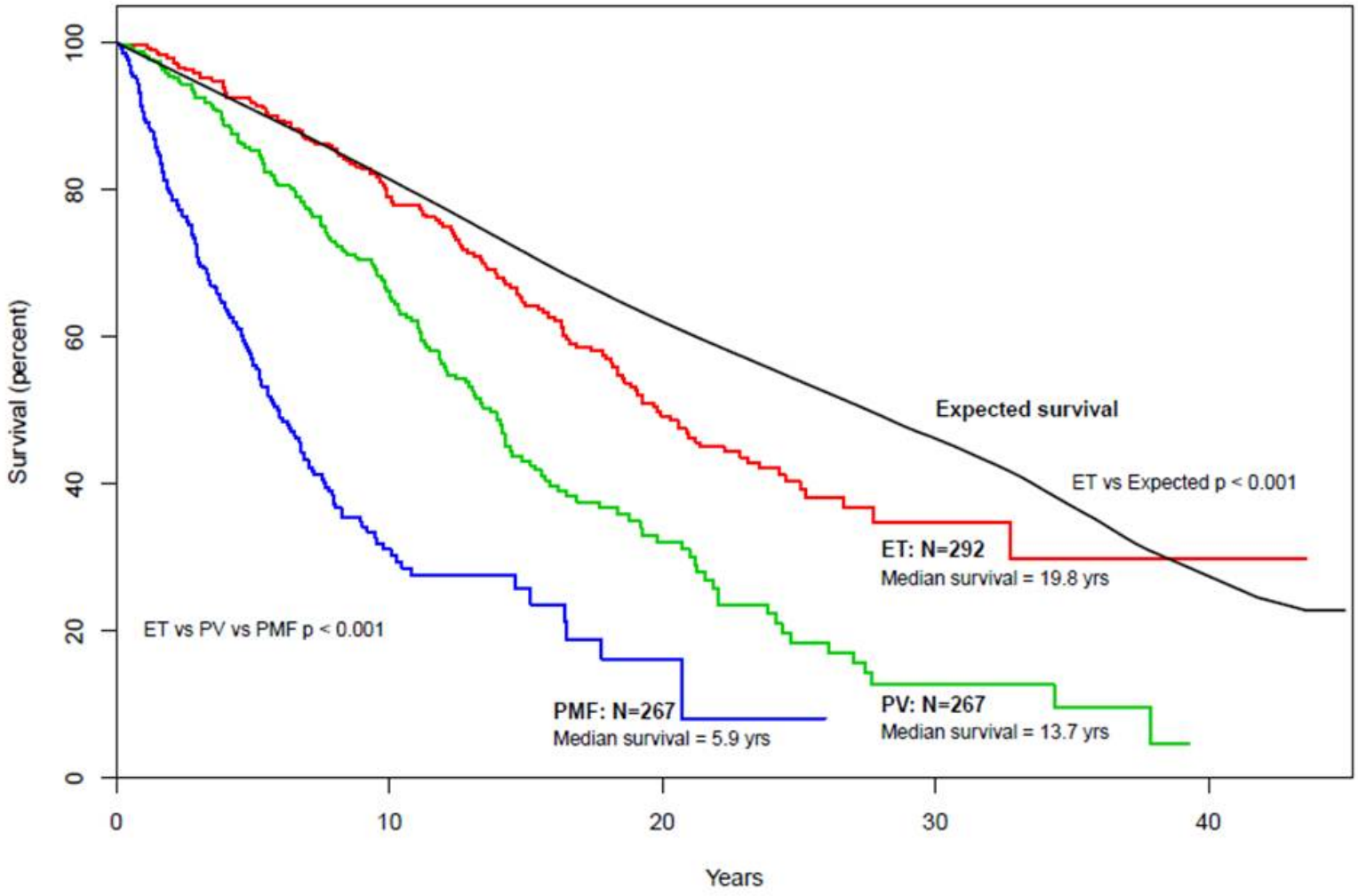
Blood. 2016 May 19;127(20):2391-405

Practical diagnostic algorithm



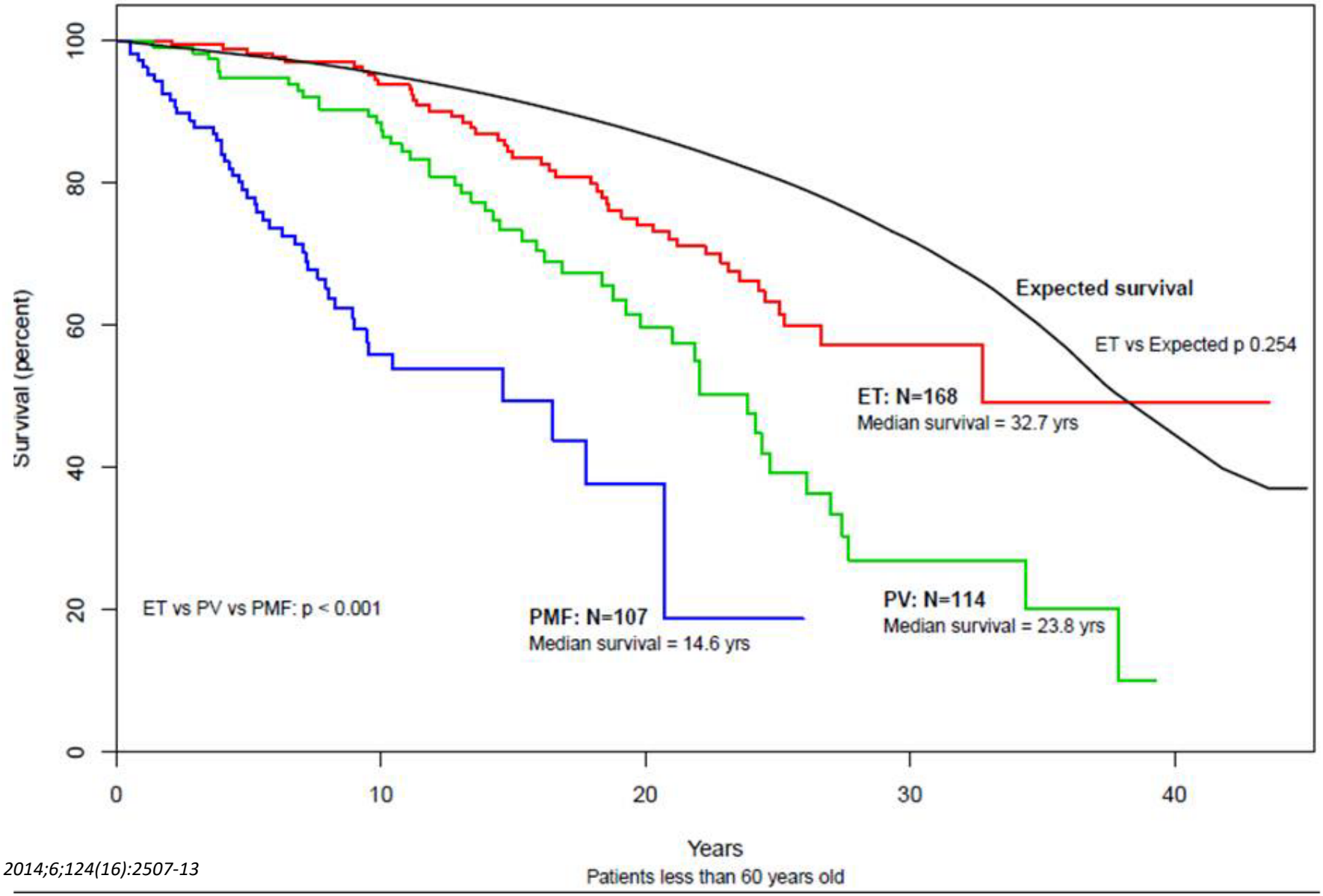
Survival in myeloproliferative neoplasms

Comparison of survival in 826 Mayo Clinic patients with essential thrombocythemia vs polycythemia vera vs primary myelofibrosis.



Blood. 2014;6;124(16):2507-13

Survival and prognosis in young patients with myeloproliferative neoplasms



Blood. 2014;6;124(16):2507-13

PROGNOSTIC SCORING SYSTEMS IN MPN

MIPSS70

(*mutation-enhanced international prognostic system for transplant-age patients*)

J Clin Oncol. 2018;36:310

MIPSS70+

(*karyotype-enhanced MIPSS70*)

J Clin Oncol. 2018;36:310

MIPSS70+ *version 2.0.*

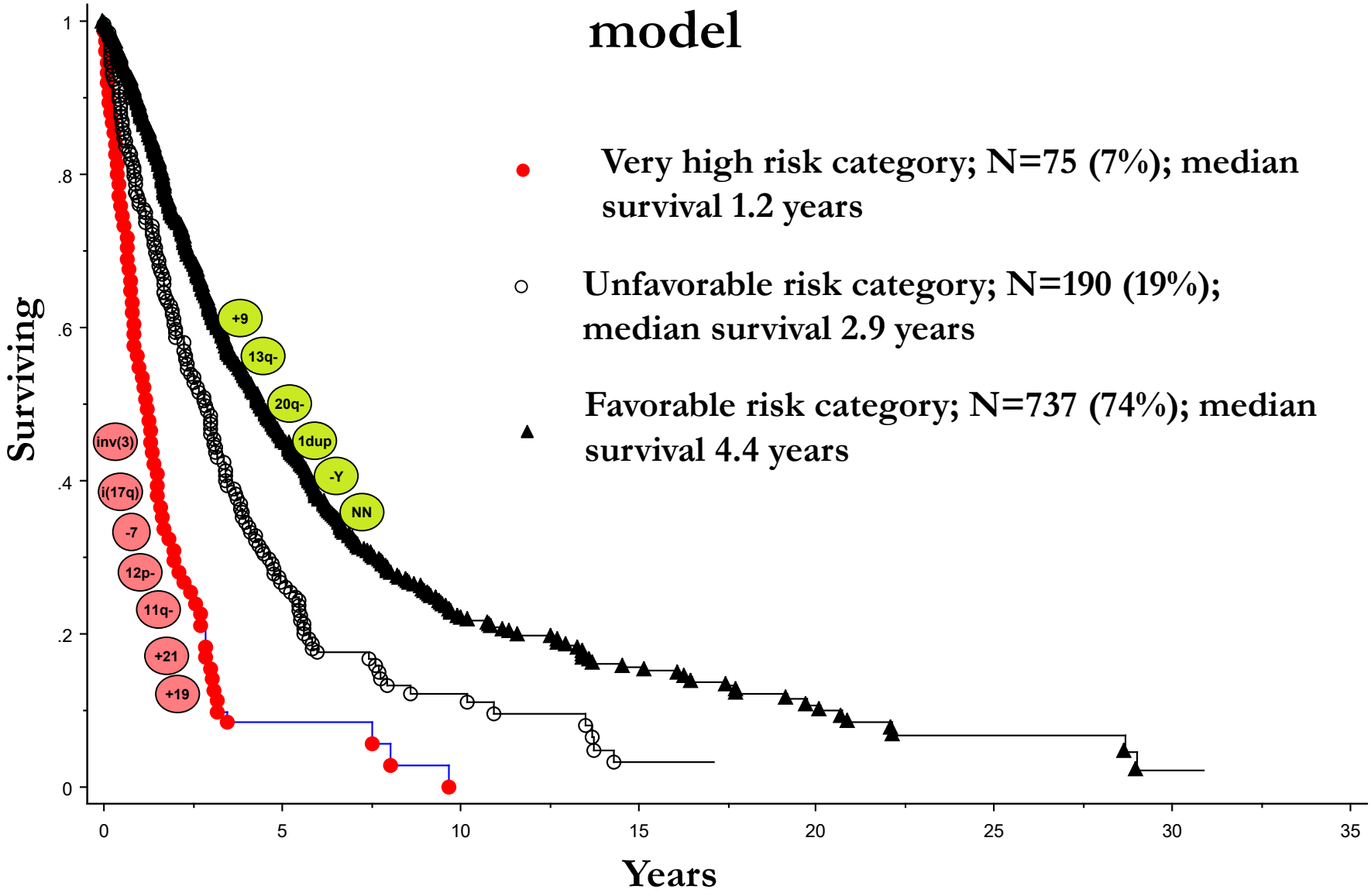
J Clin Oncol. 2018;36:1769

GIPSS

(*genetically-inspired prognostic scoring system*)

Leukemia. 2018;32:1631

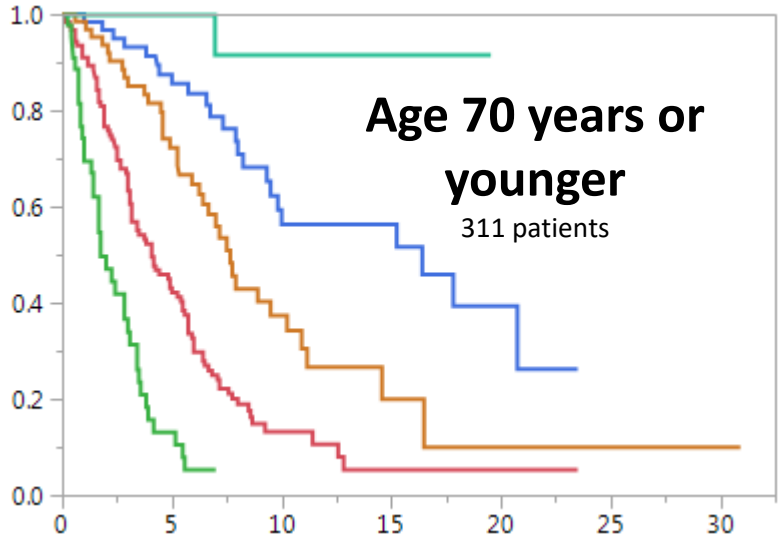
Survival of 1,002 patients with primary myelofibrosis stratified by the revised three-tiered cytogenetic risk model



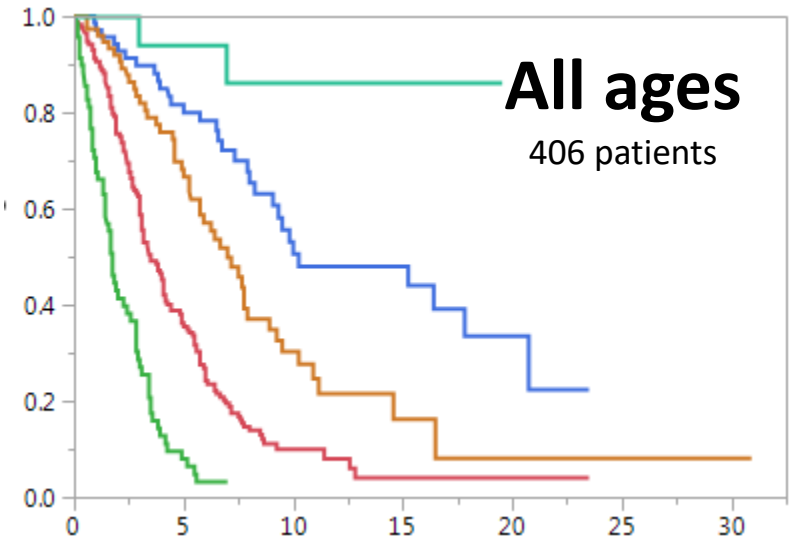
Leukemia. 2018;32:1189

Survival data on Mayo Clinic patients with primary myelofibrosis stratified by MIPSS70+ *version 2.0*

Risk categories: very high risk ≥9 points; high risk 5-8 points; **intermediate risk 3-4 points**; **low risk 1-2 points**; and **very low risk 0 points**



- Very high risk; *n*=44; median 1.8 years; 10-year survival <5%
- High risk; *n*=124; median 4.1 years; 10-year survival 13%
- Intermediate risk; *n*=64; median 7.7 years; 10-year survival 37%
- Low risk; *n*=61; median 16.4 years; 10-year survival 56%
- Very low risk; *n*=18; median not reached; 10-year survival 92%



- Very high risk; *n*=69; median 1.8 years; 10-year survival <3%
- High risk; *n*=172; median 3.5 years; 10-year survival 10%
- Intermediate risk; *n*=76; median 7 years; 10-year survival 30%
- Low risk; *n*=70; median 10.3 years; 10-year survival 50%
- Very low risk; *n*=19; median not reached; 10-year survival 86%

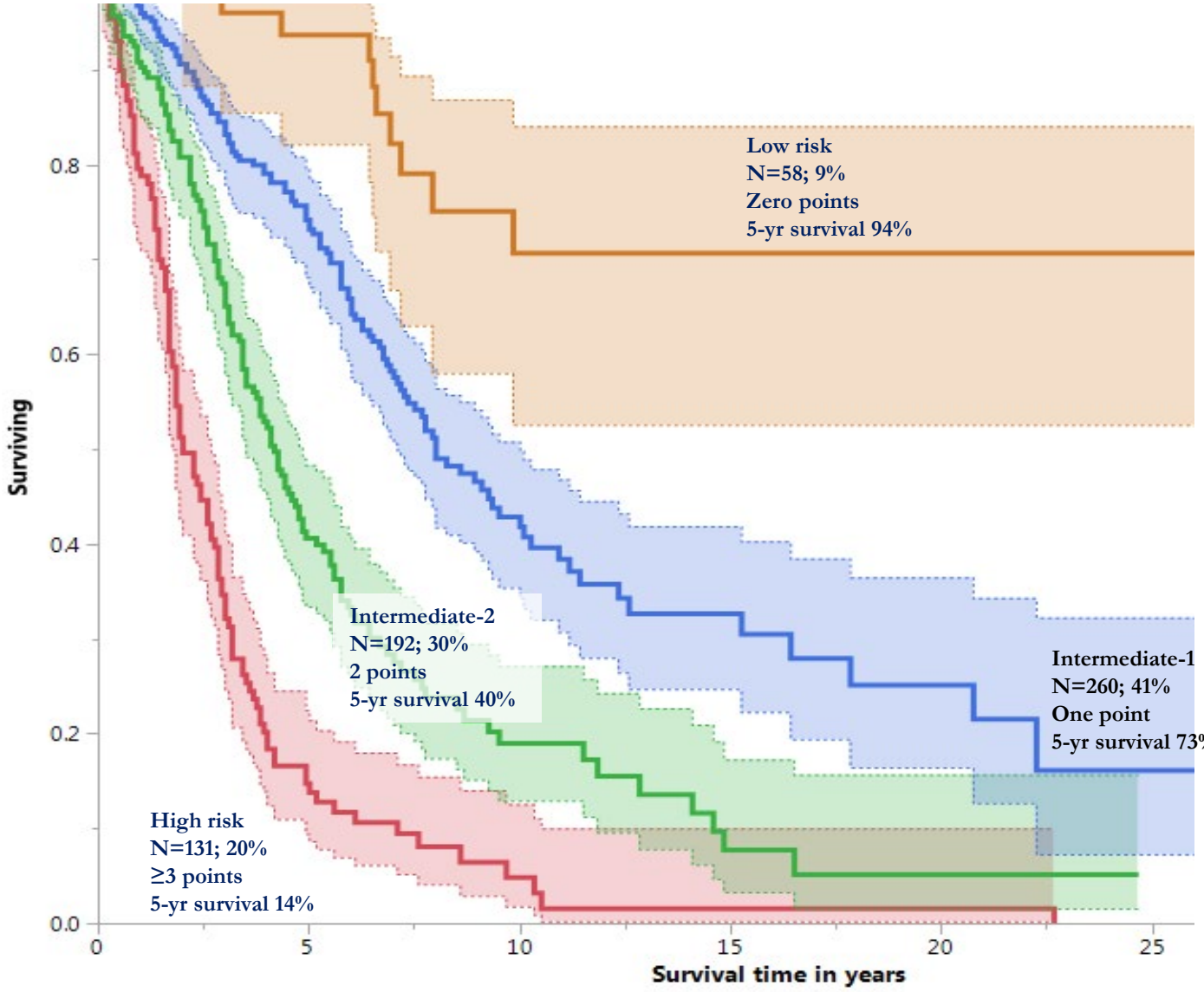
Very high risk karyotype	**4 points**
Unfavorable karyotype	**3 points**
≥2 HMR mutations	**3 points**
One HMR mutation	**2 points**
Type 1/like CALR mutation absent	**2 points**
Constitutional symptoms	**2 points**
Severe anemia	**2 points**
Moderate anemia	**1 point**
≥2% circulating blasts	**1 point**

J Clin Oncol. 2018;36:1769

http://www.mipss70score.it/

GIPSS

Genetically-Inspired Prognostic Scoring System-stratified survival data in 641 patients with primary myelofibrosis



Karyotype:
Very high risk = 2 points
Unfavorable = 1 point

Driver mutations:
Type 1/like *CALR* absent = 1 point

High risk mutations:
ASXL1 mutation = 1 point
SRSF2 mutation = 1 point
U2AF1 Q157 mutation = 1 point

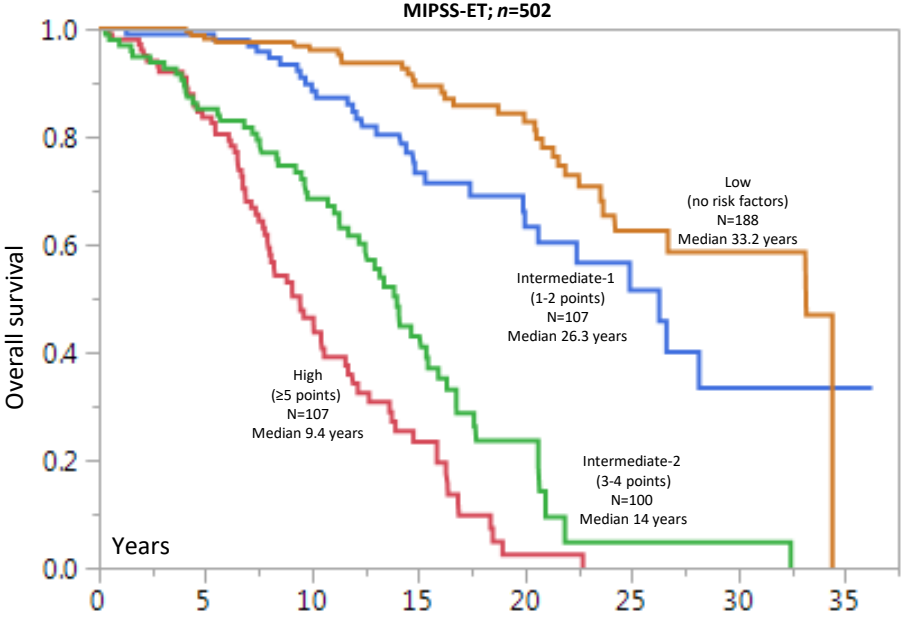
Leukemia. 2018;32:1631

Mutation-enhanced international prognostic scoring systems in essential thrombocythemia (MIPSS-ET) and polycythemia vera (MIPSS-PV)

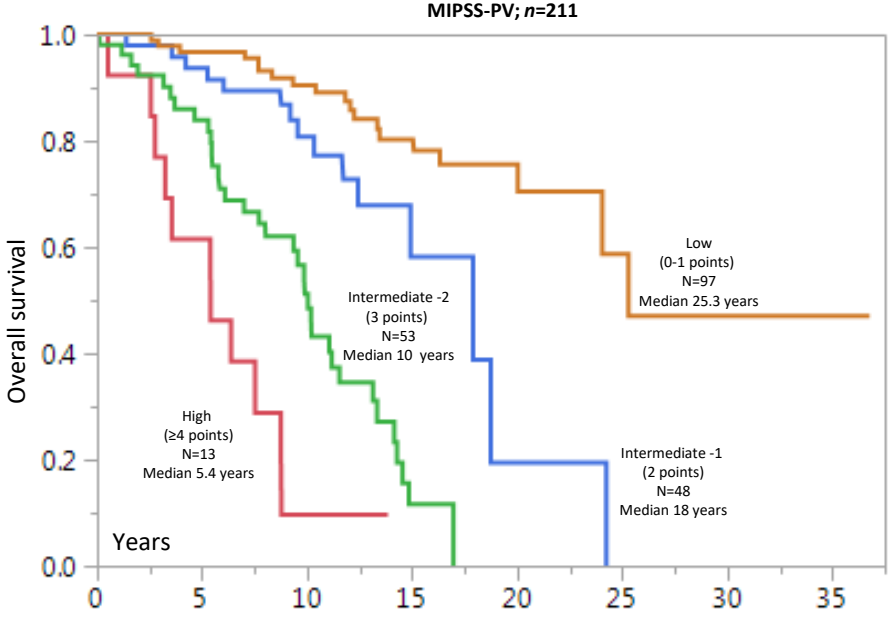
ET survival risk factors: *SRSF2/SF3B1 mutations (2 points), age >60 years (4 points) and male sex (1 point)*

PV survival risk factors: *SRSF2 mutations (2 points), age >60 years (2 points), leukocyte count ≥11 x 10^9/l (1 point) and abnormal karyotype (1 point)*

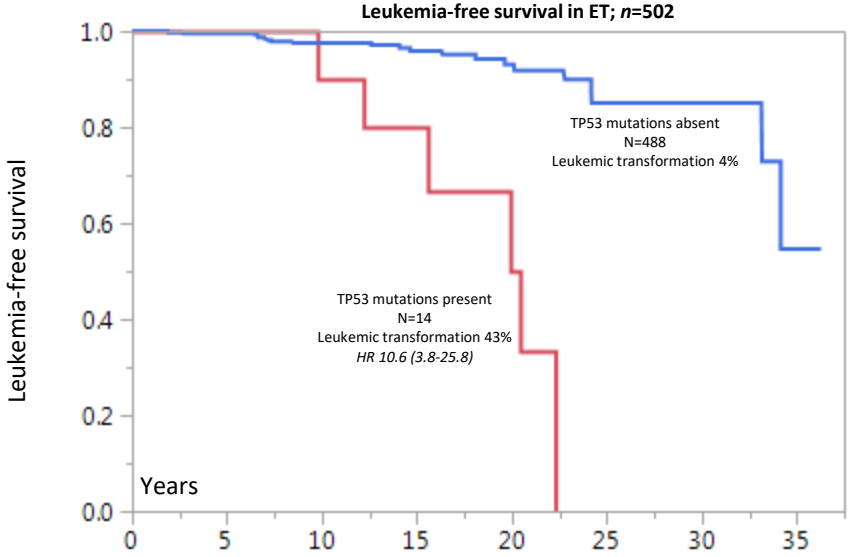
MIPSS-ET; *n*=502



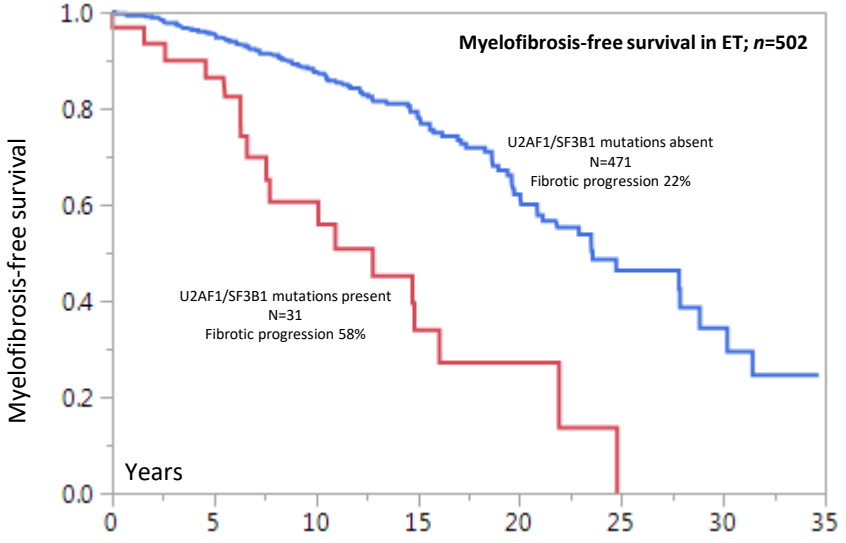
MIPSS-PV; *n*=211



Leukemia-free survival in ET; *n*=502

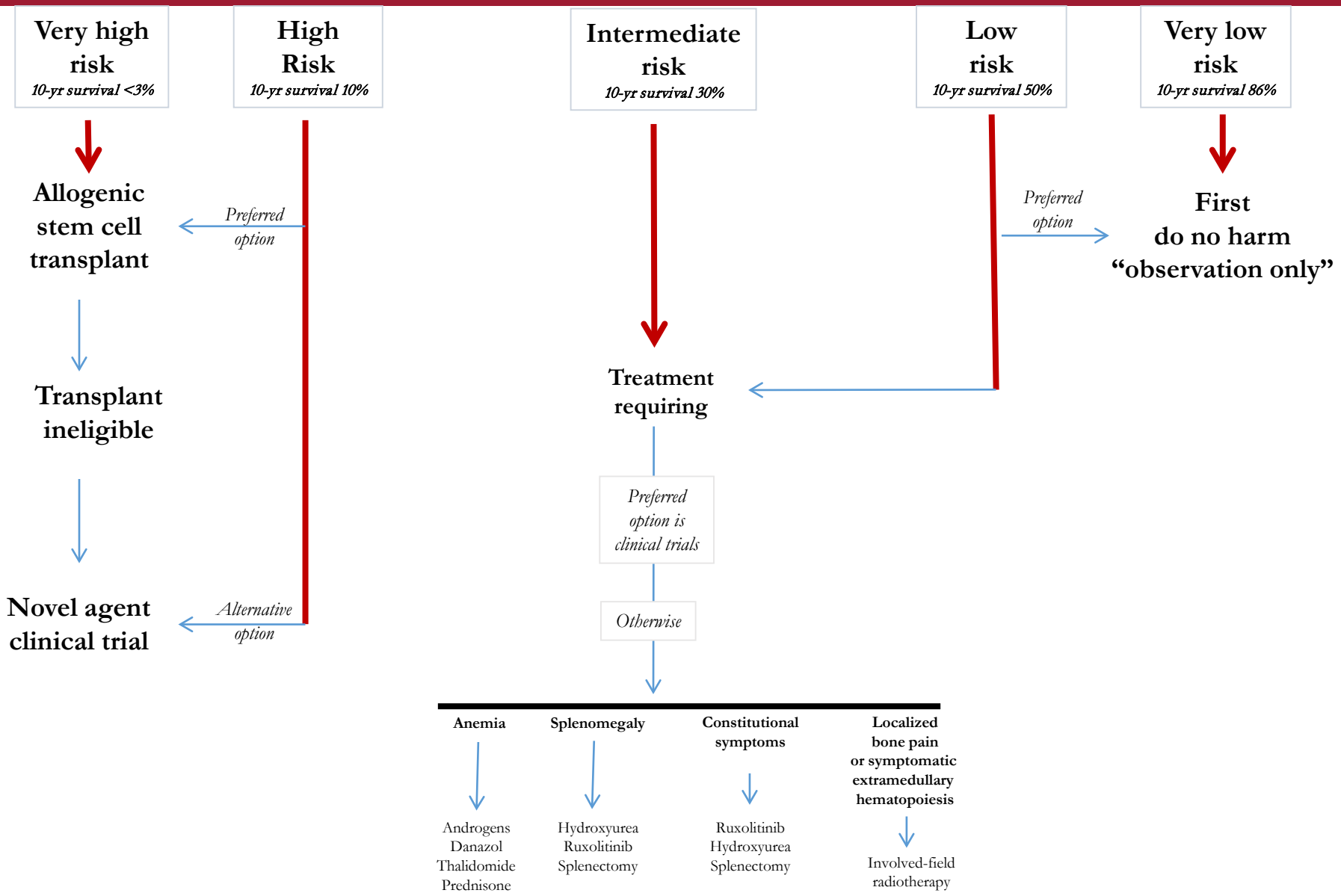


Myelofibrosis-free survival in ET; *n*=502



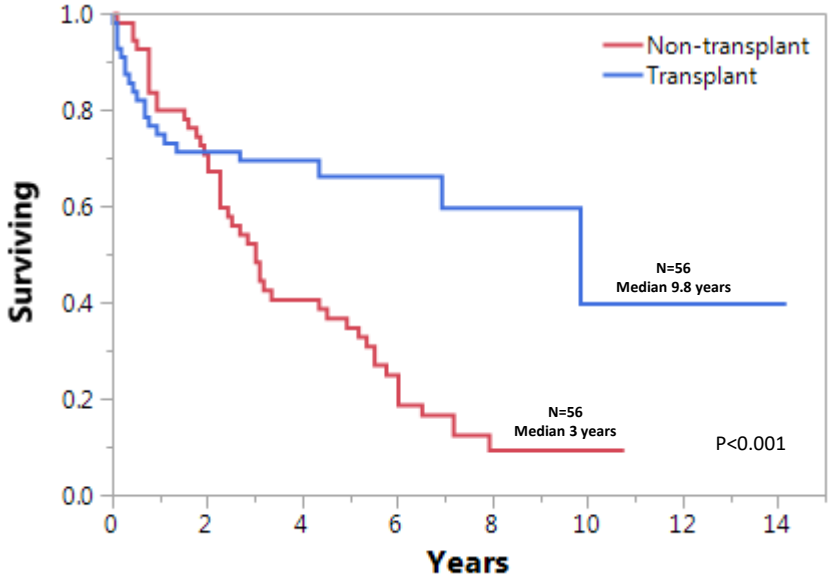
Treatment Algorithm in Myelofibrosis

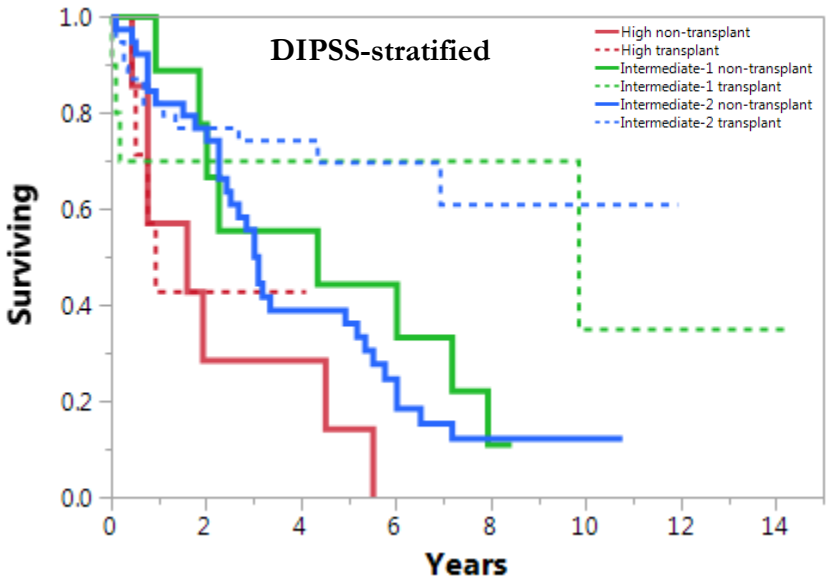
based on risk stratification according to MIPSS70+ version 2.0

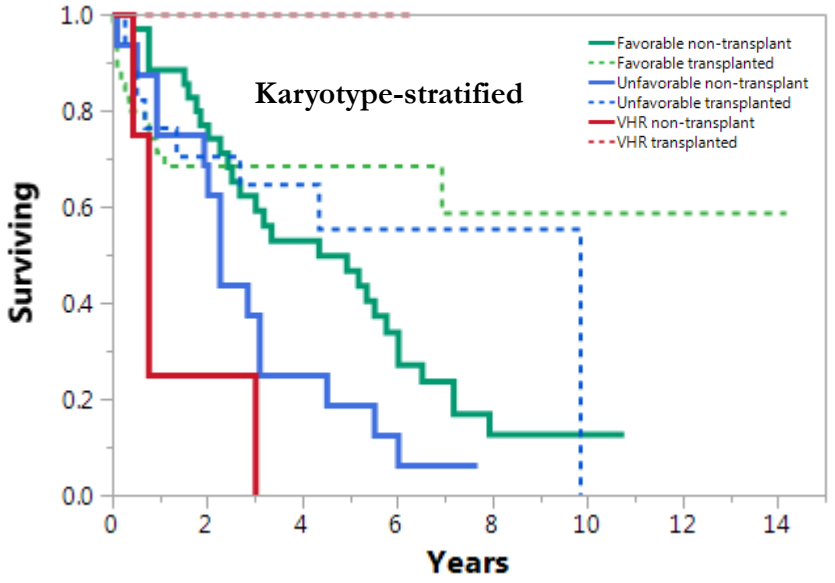


Blood Cancer J. 2018 Jul 31;8(8):72.

Transplant myelofibrosis (*n*=56) vs no transplant primary myelofibrosis (*n*=56), stringently matched for age, DIPSS and karyotype







Am J Hematol. 2018 Feb 1. doi: 10.1002/ajh.25053

Phase-3 tested JAK inhibitors in myelofibrosis

2013 revised IWG-MRT response rates for 166 JAKi treated Mayo Clinic patients

	CR	PR	1-2-3 years discontinuation rates
Momelotinib (*n*=100)	0%	1%	31%-52%-71%
Ruxolitinib (*n*=51)	0%	0%	49%-71%-86%
Fedratinib (*n*=15)	0%	0%	20%-67%-80%

	JAK targets	Other targets	Symp. resp.	Spleen resp.	Anemia resp.	Side effects
Ruxolitinib (FDA-approved)	JAK1 JAK2	TRK-B, ACK1 FAK, LCK RET	Yes	32-42% (MRI)	14%	↓Hgb/Plts Ruxolitinib withdrawal synd. Opportunistic infections
Fedratinib (SAR302501) Phase-3 completed FDA approval pending	JAK2	FLT3, RET, ACK1 JNK1	Yes	47% (MRI)	NR	↓Hgb/Plts Nausea/Diarrhea ↑LFTs/Lipase/amylase Encephalopathy
Pacritinib (SB1518) Phase-3 completed	JAK2	FLT3	Yes	37% (MRI)	NR	Diarrhea/Nausea
Momelotinib (CYT387) Phase-3 completed	JAK1 JAK2	PKD3, PKCμ CDK2, ROCK2 JNK1, TBK1 ALK-2	Yes	39% (PE)	53%	↓Plts 1st dose effect ↓BP/dizzy Neuropathy/Headache ↑LFTs/Lipase/Amylase

Leukemia 2014

Ruxolitinib practice points

Indications

1. Marked splenomegaly that is symptomatic and resistant to hydroxyurea
2. Severe constitutional symptoms including pruritus, night sweats, fatigue and cachexia
3. Sometimes there is no other option, even in the presence of severe cytopenias

Short-term side effects

1. Anemia, including becoming transfusion-dependent
2. Thrombocytopenia

Long-term side effects

1. Immunosuppression
2. Opportunistic infections
3. Protracted myelosuppression

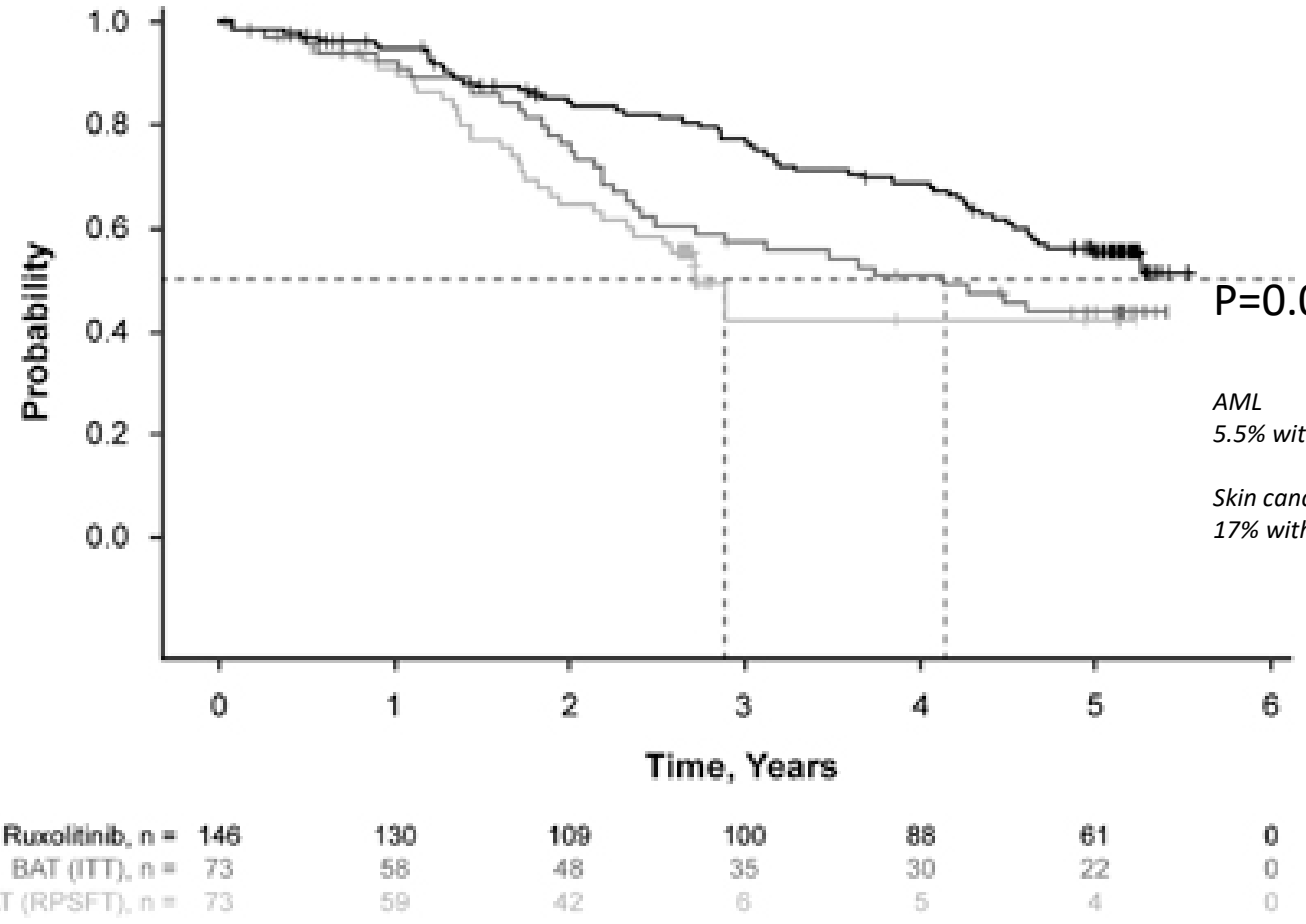
Special concerns

1. Might compromise future eligibility for clinical trials because of protracted myelosuppression
2. Effect lasts for an average of approximately one year; might be prudent to save it until HU fails
3. **BEWARE** of withdrawal symptoms that might include SIRS and overt and immediate relapse of splenomegaly/symptoms

COMFORT-2 Ruxolitinib vs best available therapy (BAT) long-term follow-up

Median f/u 4.3 years

27% ruxo-randomized patients completed 5-year treatment



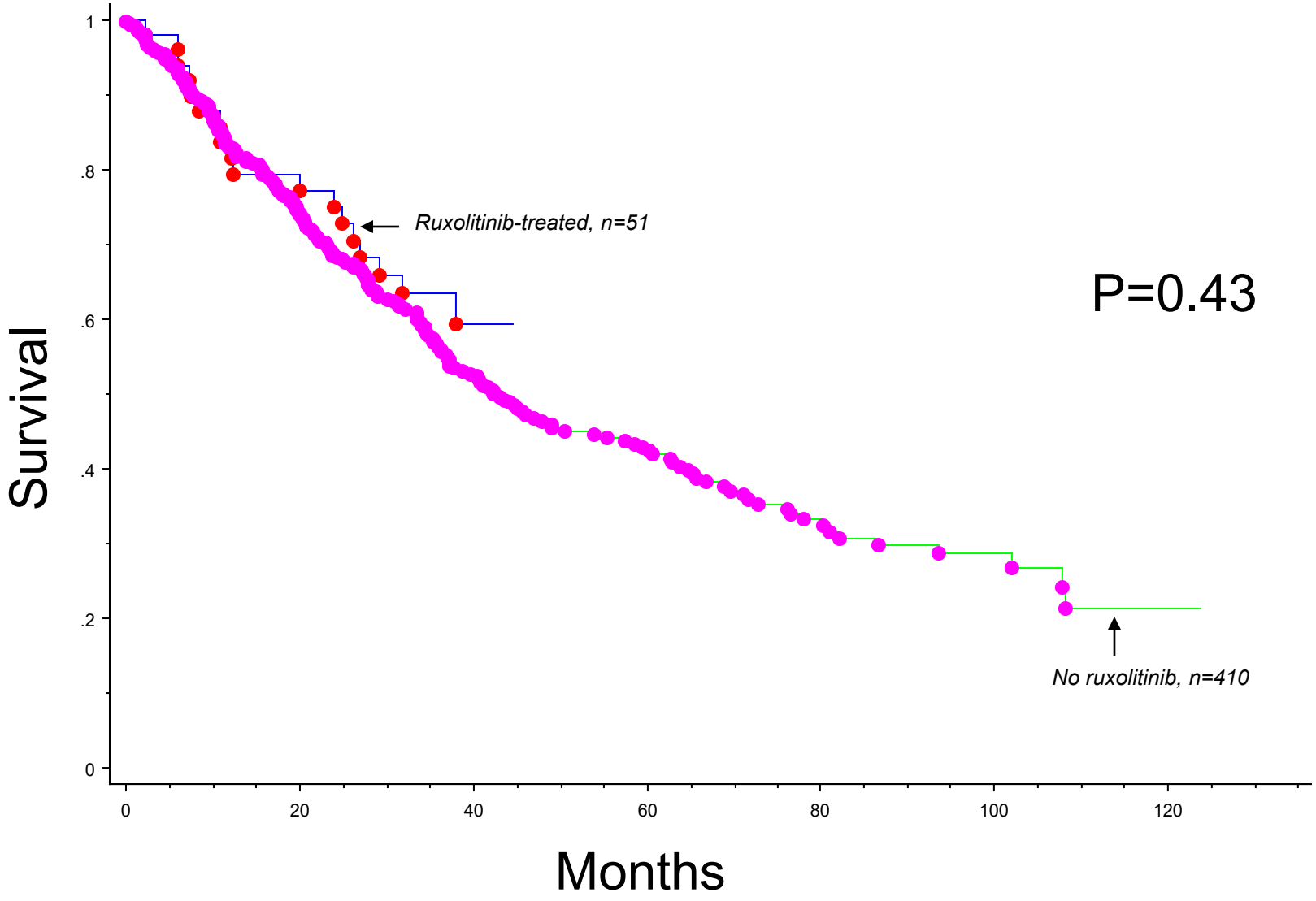
P=0.06

AML
5.5% with ruxo and 6.8% with BAT

Skin cancer
17% with ruxo and 3% with BAT

Leukemia (2016) 30, 1701

Survival impact of ruxolitinib in myelofibrosis: Mayo Clinic study

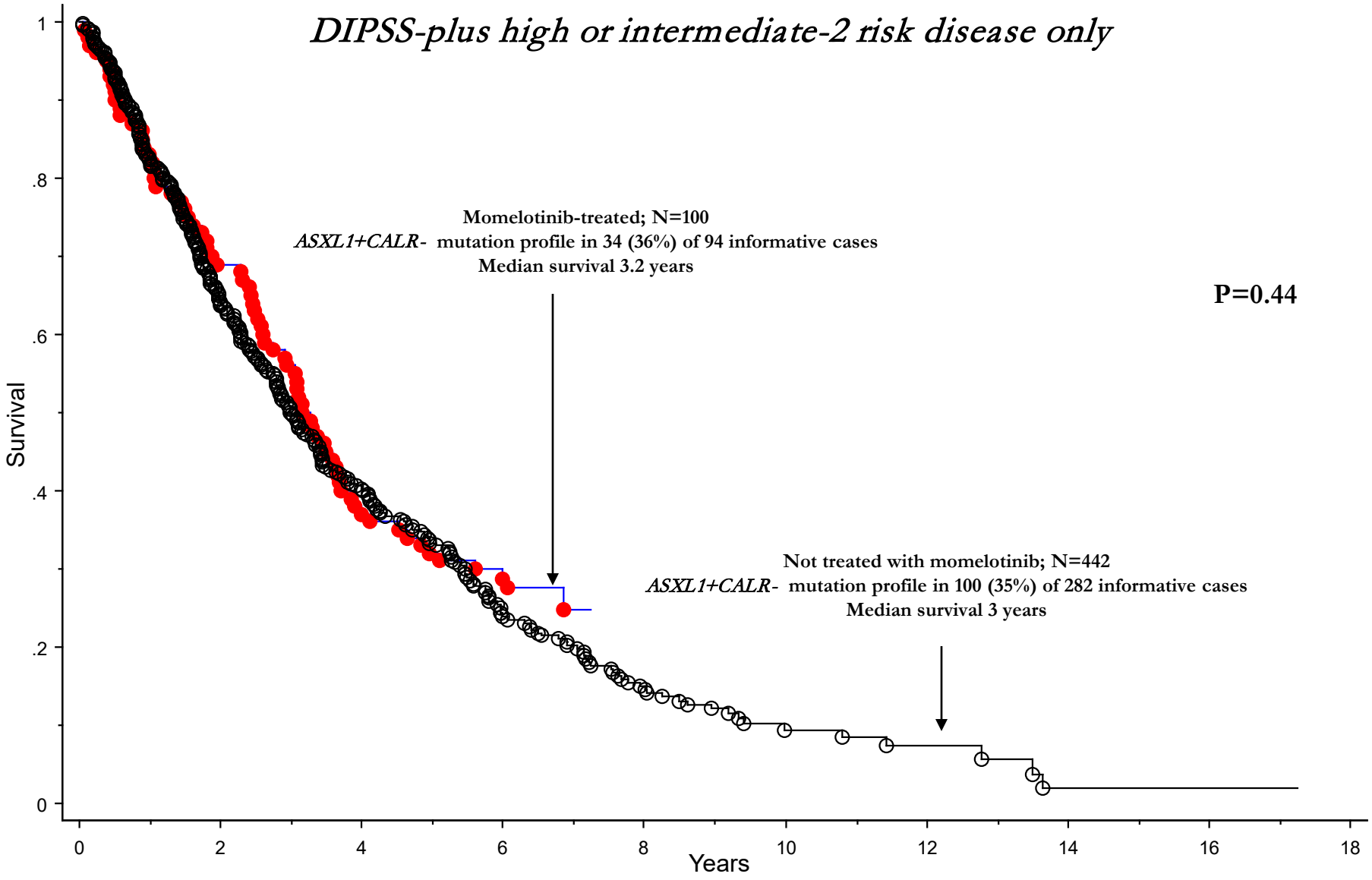


NEJM 2011:365;15

Momelotinib therapy in myelofibrosis 7-year follow-up

Comparison of survival between 100 momelotinib treated patients and 442 not receiving momelotinib

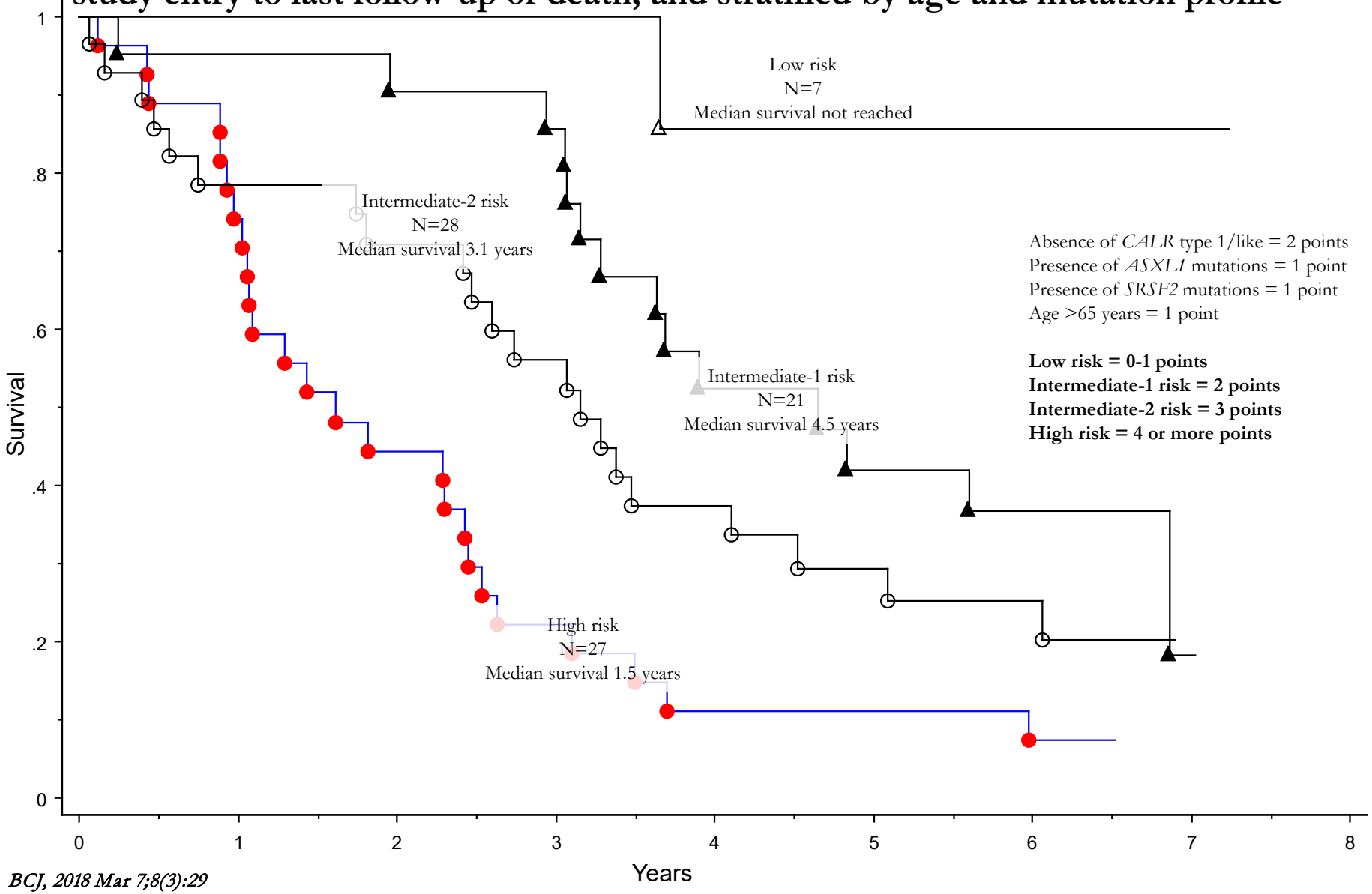
DIPSS-plus high or intermediate-2 risk disease only



BCJ 2018 in press

Momelotinib therapy in myelofibrosis 7-year follow-up

Survival of 83 molecularly-annotated patients from time of momelotinib study entry to last follow-up or death, and stratified by age and mutation profile



BCJ, 2018 Mar 7;8(3):29

Current Treatment Algorithm in Polycythemia Vera

Blood Cancer J. 2018 Jan 10;8(1):3

Current Treatment Algorithm Series

Phlebotomy to hematocrit <45% in both male and female patients

+

Once-daily baby aspirin (81 mg)

Low-risk Disease
- No history of thrombosis
- Age ≤60 years

Consider twice-daily aspirin in the presence of:

- *Cardiovascular risk factors*
- *Hypertension*
- *Leukocytosis*
- *Persistent microvascular symptoms*

High-risk disease
- History of thrombosis

or
- Age >60 years

Hydroxyurea (500 mg BID starting dose)

Arterial thrombosis history → Consider twice-daily aspirin

Venous thrombosis history → Add systemic anticoagulation

Hydroxyurea intolerant or resistant

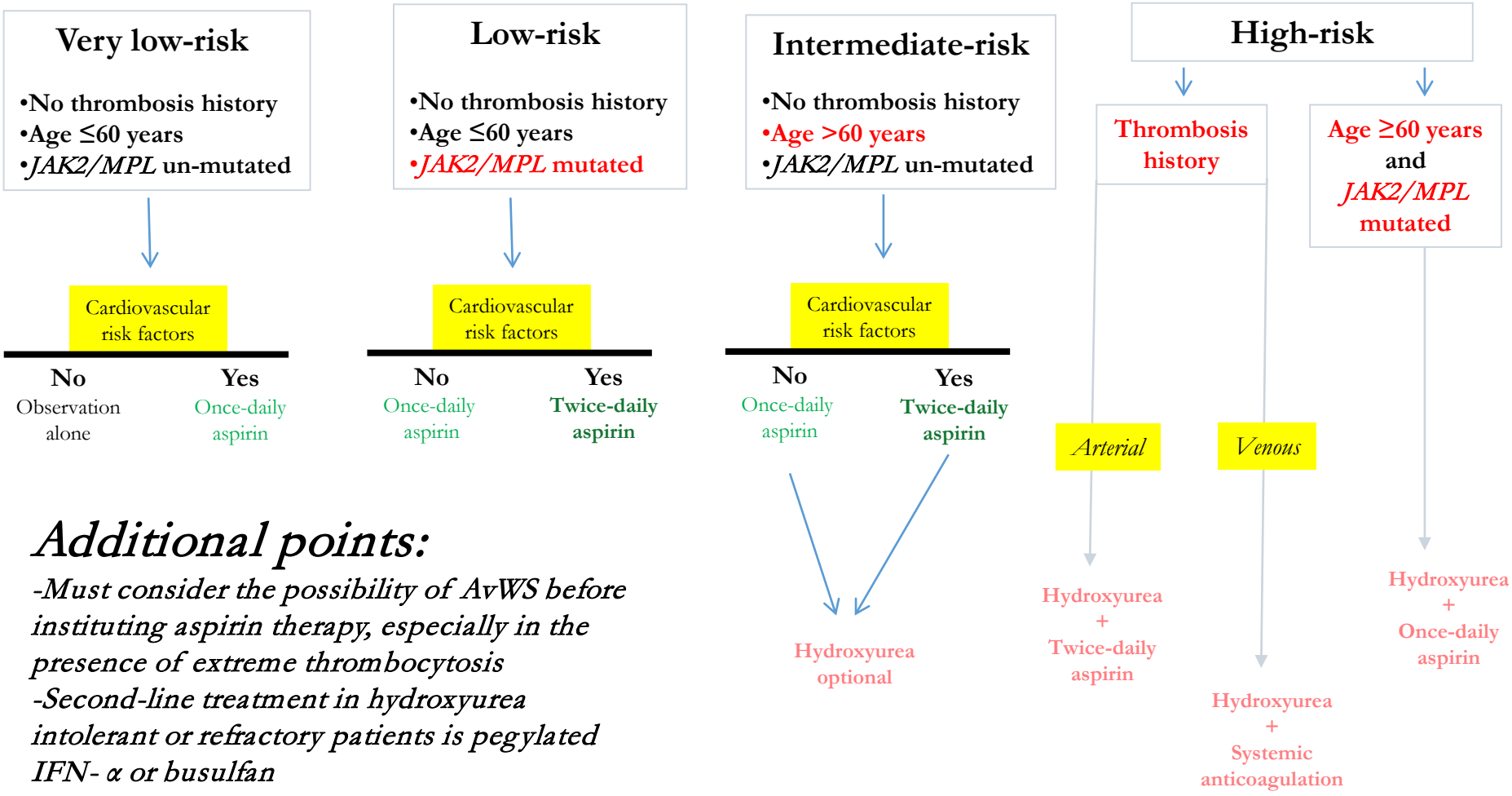
→ Pegylated IFN-α (Age <65 years)

→ Busulfan (Age ≥65 years)

→ Ruxolitinib (If all the above fails)

Current Treatment Algorithm in Essential Thrombocythemia

Blood Cancer J. 2018 Jan 10;8(1):2
Current Treatment Algorithm Series



Additional points:

-Must consider the possibility of AvWS before instituting aspirin therapy, especially in the presence of extreme thrombocytosis

-Second-line treatment in hydroxyurea intolerant or refractory patients is pegylated IFN- α or busulfan

Treatment in essential thrombocythemia and polycythemia vera

1. What if you can't use hydroxyurea
    i. Interferon alpha

    (*Qunitas-Cardama et al. Blood 2013; CHR **76%** in PV, **77%** in ET; CMR **18%** in PV and **17%** in ET)*

    i. Busulfan

    *(Alvarez-Larran et al. Ann Hematol 2014; CHR in HU-refractory PV or ET was **83%**; Kuriakose et al. Haematologica 2013; CMR in 2 (**33%**) of 6 PV patients)*

    i. Anagrelide

    (Not recommended because of its association with disease progression into myelofibrosis and increased thrombosis risk in ET phase-3 study; Harrison et al, NEJM 2005)

    i. Ruxolitinib

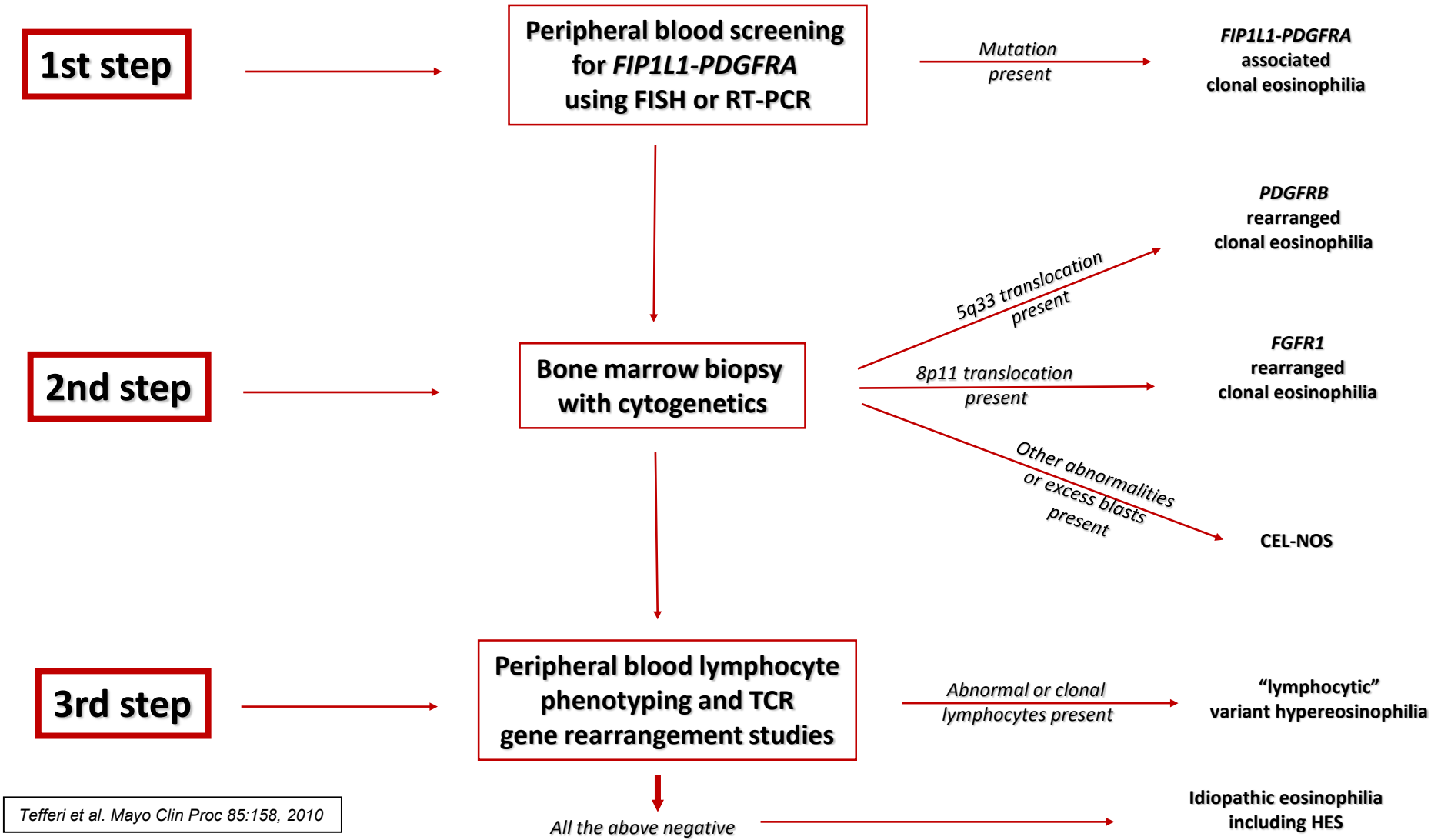
    *(Vannucchi et al. NEJM 2015; randomized study in HU-refractory PV with ruxo vs standard therapy; **59%** of patients on standard therapy received HU??? **21%** of ruxo treated patients achieved both hematocrit control and 35% reduction in spleen volume; 60% hematocrit control; 49% symptoms control; CHR **24%**; No CMR reported)*

2. What about treatment during pregnancy?
    i. Low-risk…ASA only
    ii. High-risk…IFN alpha

3. What about treatment of pruritus?....paroxetine, IFN-alpha, UVB, ruxolitinib

Primary eosinophilia

Diagnostic algorithm



Tefferi et al. Mayo Clin Proc 85:158, 2010

Hyper-eosinophilic syndrome/idiopathic eosinophilia

Prognostication

NGS revealed 11% harbored pathogenic mutation;
TET2=3, *ASXL1* =2, *KIT*=2, and *IDH2*, *JAK2*, *SF3B1 and TP53*=1 each.
15% harbored a variant of unknown significance;
TET2=8, *ASXL1*=2, *SETBP1*=2, and *CALR*, *CEBPA* and *CSF3R*=1 each.

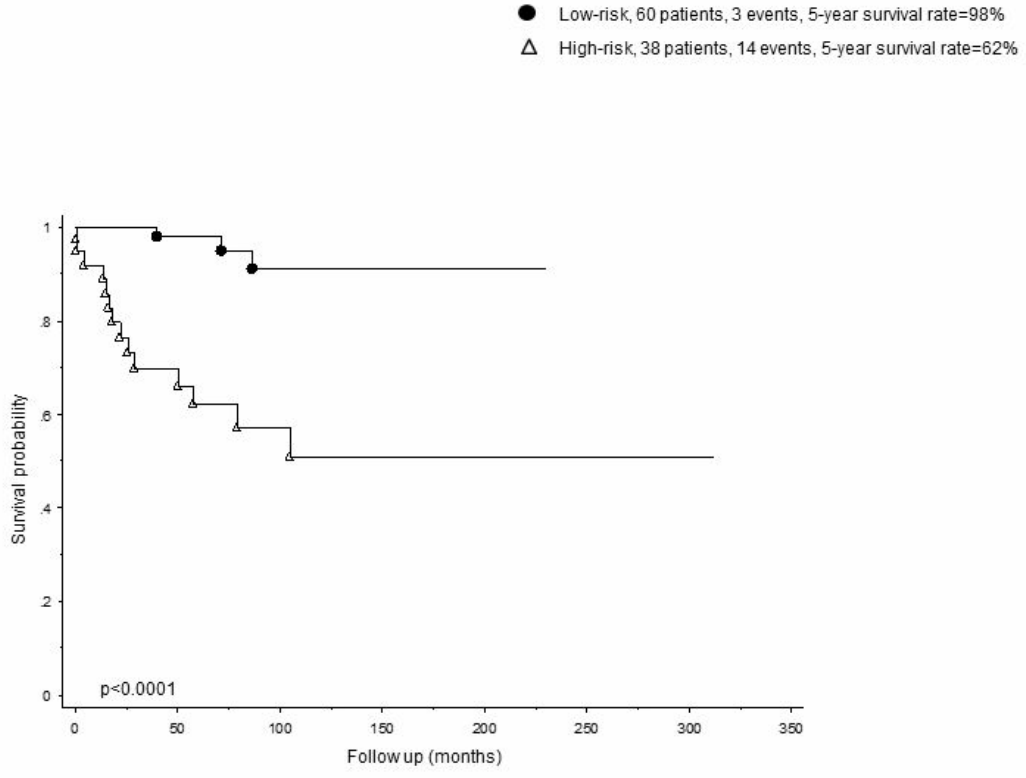
NO DIFFERENCE IN MUTATED VS NON-MUTATED IN PHENOTYPE
MUTATED PATIENTS HAD INFERIOR SURVIVAL IN UNIVARIATE ANALYSIS

98 Mayo Clinic patients with WHO-defined HES/IH (*Pardanani et al. Leukemia 2016;30:1924*)

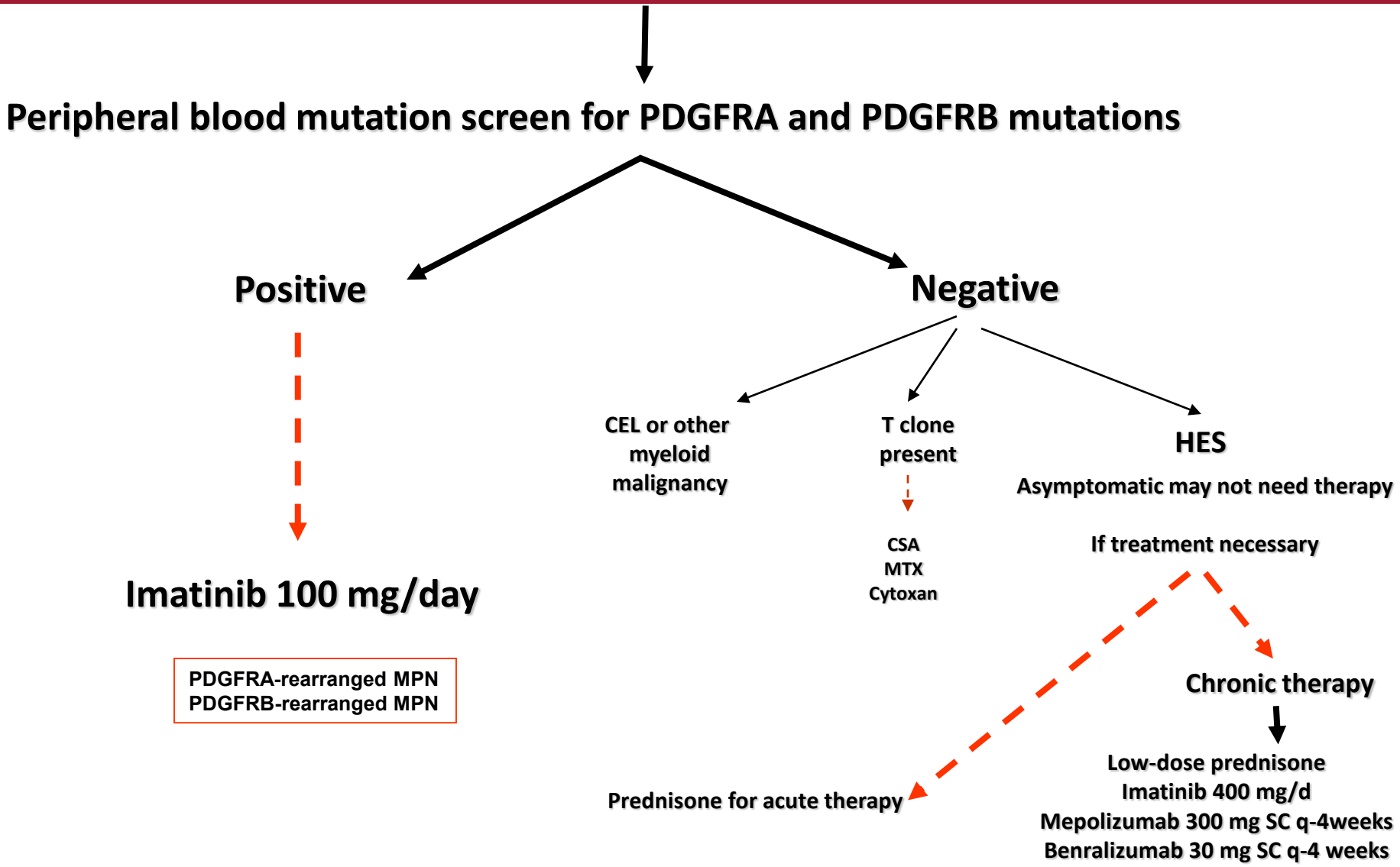
Risk factors for survival:

Advanced age (2 points)
Hgb <10 g/dl (one point)
Cardiac involvement (one point)
Hepatosplenomegaly (3 points)

Low risk 0-1 points
High risk 2 or more points



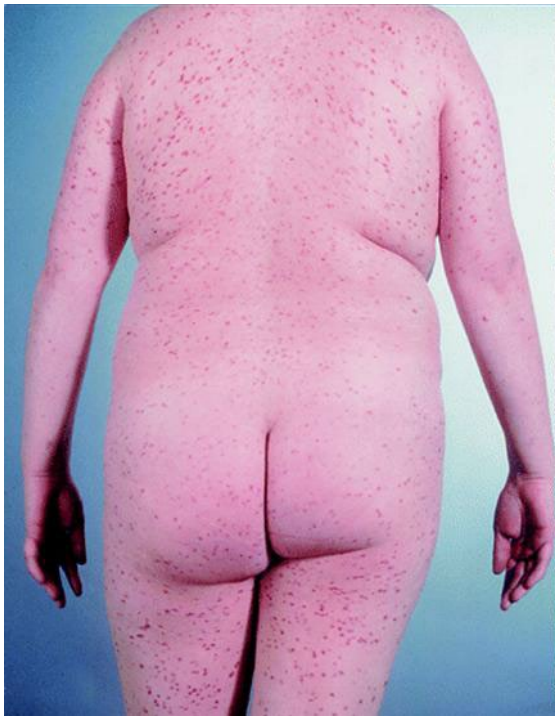
Management approach to HES or HES-like eosinophilic disorder



Mastocytosis

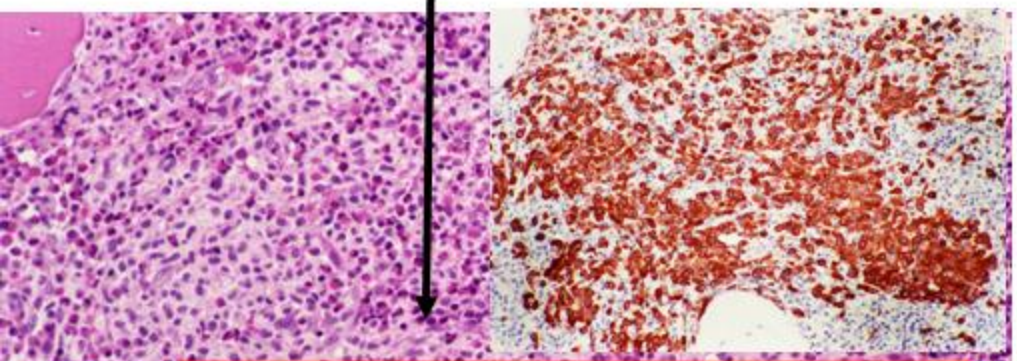
When should you suspect it?

- Urticaria pigmentosa-like lesions
- Mast cell mediator symptoms
  - Anaphylactoid symptoms/dizziness
  - Diarrhea
  - Flushing/urticaria
- Osteopenia/unexplained fractures

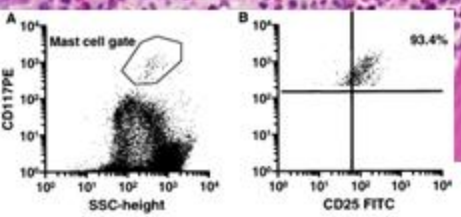


Diagnostic Evaluation in Systemic Mastocytosis

serum tryptase



Bone marrow biopsy with tryptase stains

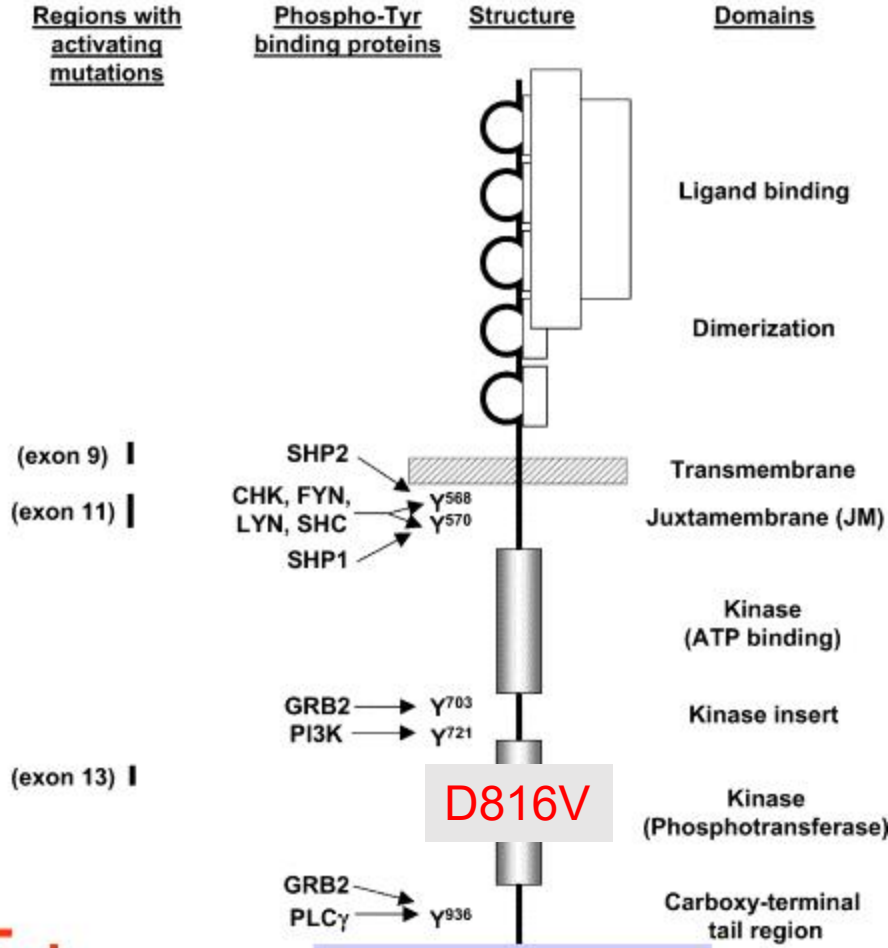


Bone marrow mast cell flow cytometry

Normal mast cells —
CD117+, CD25-, CD2-

Abnormal mast cells —
CD117+, CD25+, CD2 ±

Pardanani et al. BJH 2003;120:691



±C-kit mutations
Asp816Val (kinase domain)
Val560Gly (JM domain)

Sattler & Salgia, Leukemia Research, 2004

Practical classification of mast cell disease

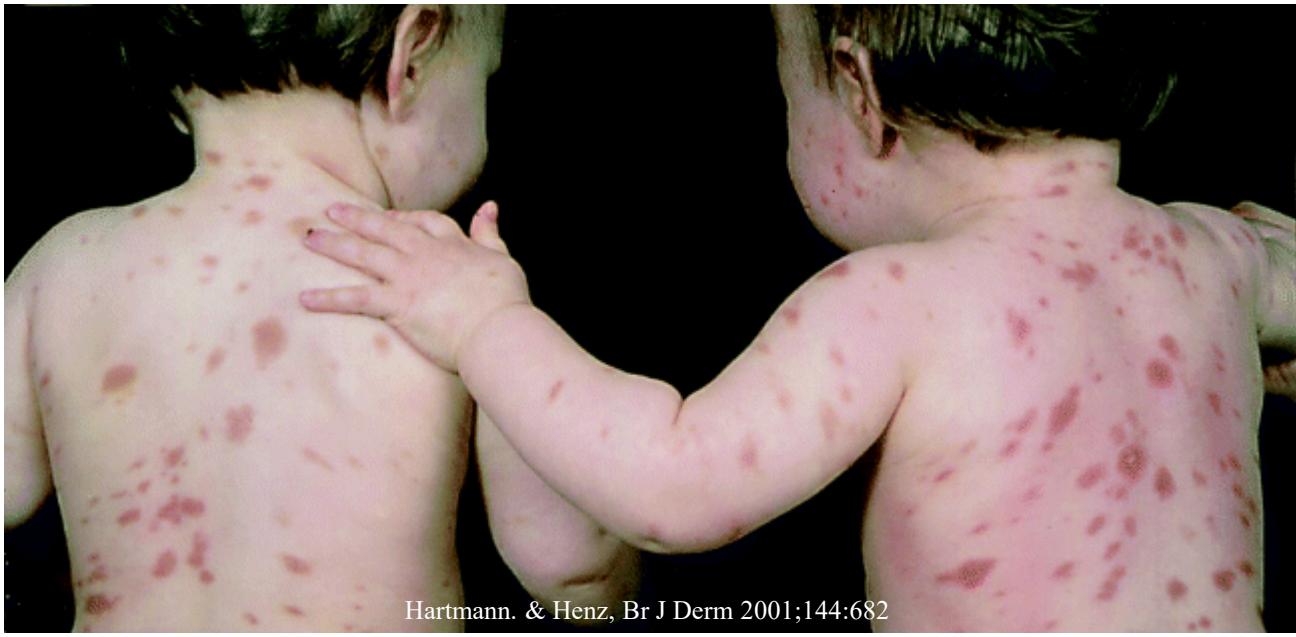
1

Cutaneous mastocytosis (skin-only disease)

Both can manifest mast cell mediator release symptoms

2

Systemic mastocytosis (SM)



i

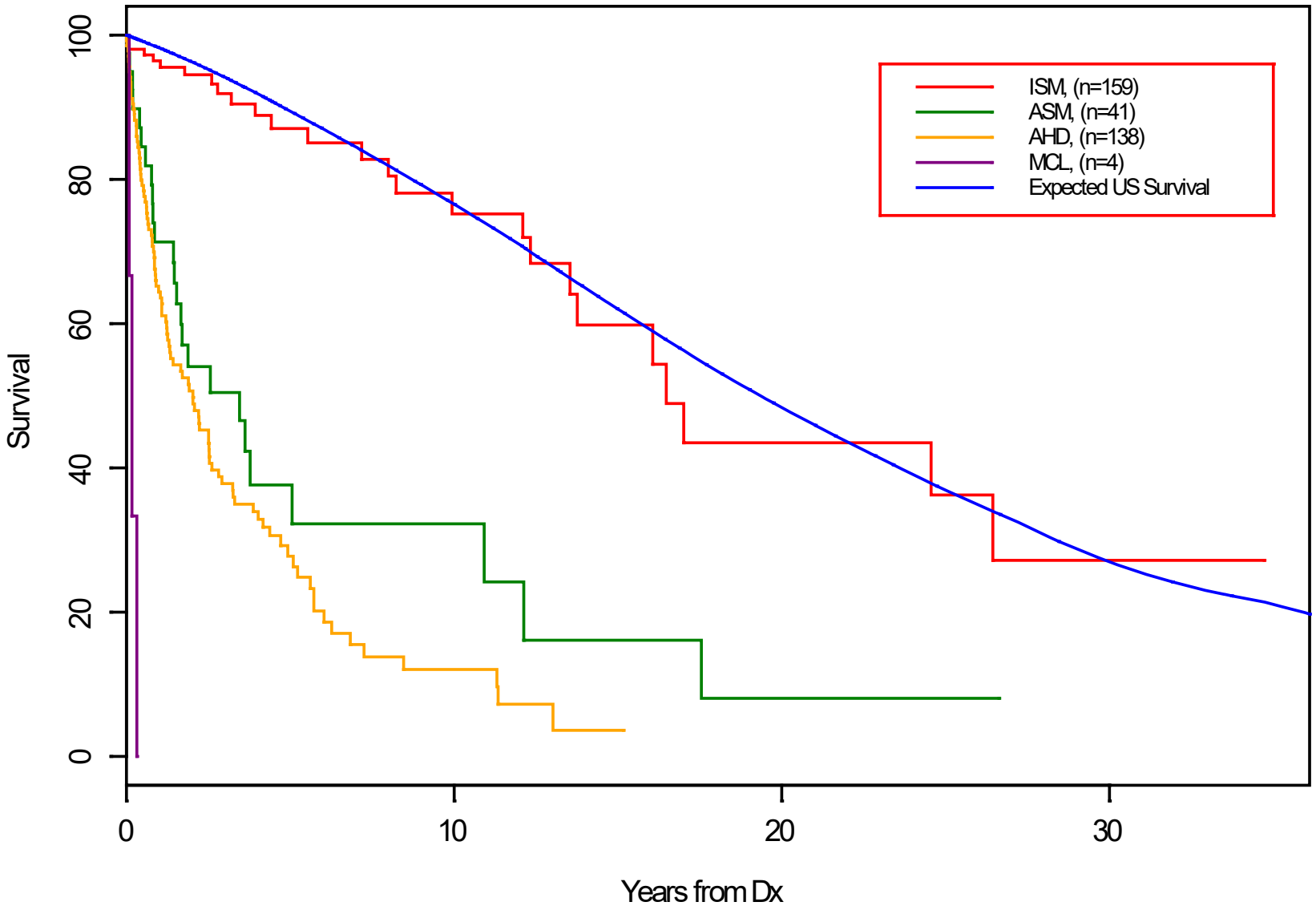
Indolent SM → *No organopathy*
(i.e. no cytopenia, bone disease or organomegaly)
±Uritcaria pigmentosa
±Mast cell mediator symptoms

ii

Advanced SM (cytopenia, bone disease, organomegaly, etc.)

1. Aggressive SM
2. SM associated 2nd myeloid neoplasm (SM-AHN)
3. Mast cell leukemia

Survival for 342 systemic mastocytosis patients classified by disease type compared with the expected age and gender matched US Population's survival

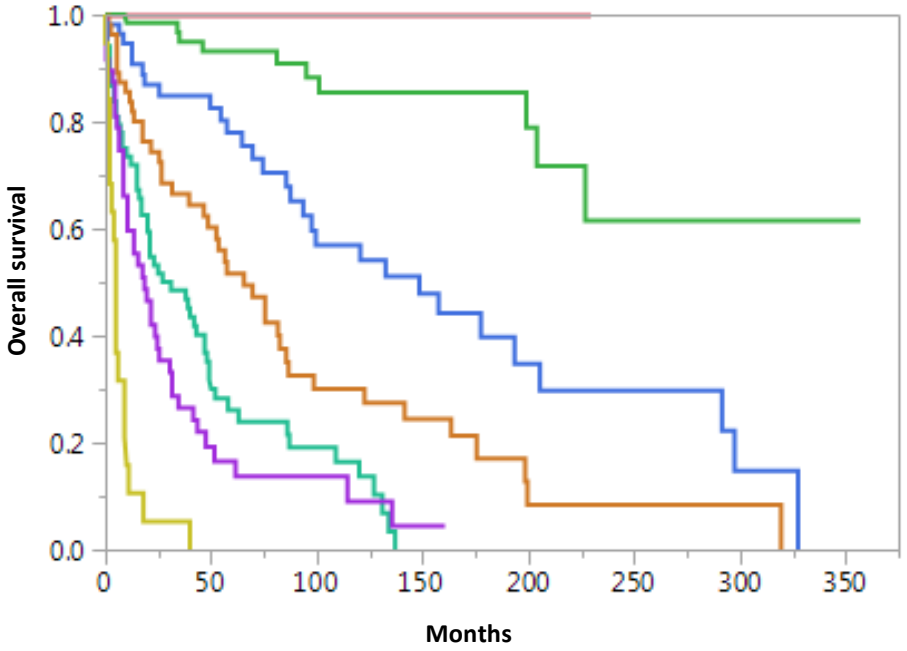


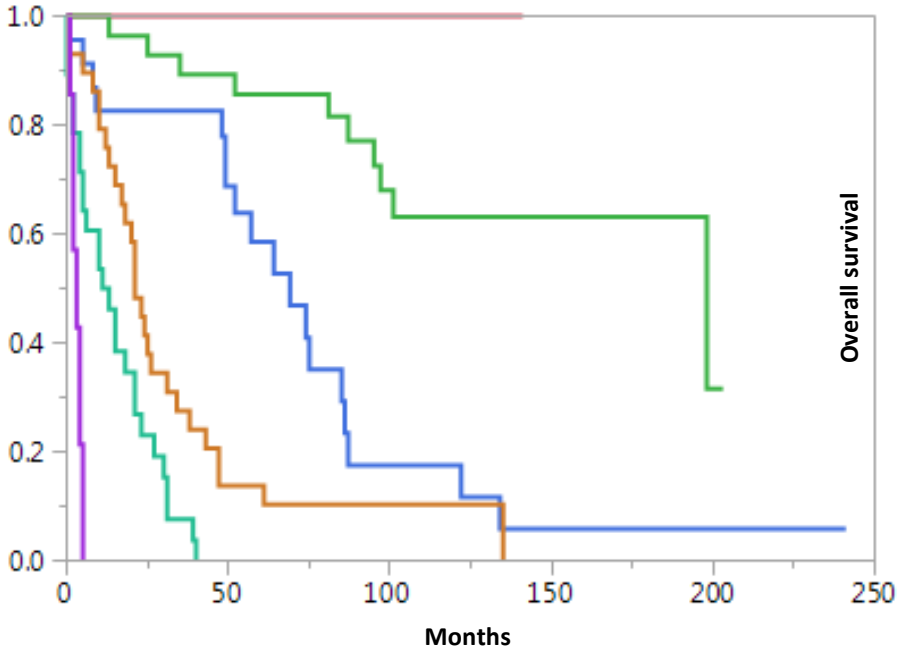
Lim et al. Blood 2009;113:5727.

Figure 1a: A “clinical” risk model for systemic mastocytosis (N=380)

ASH 2018

Figure 1b A “clinical-molecular” risk model for systemic mastocytosis (N=129)





No of Risk factors	No of Patients	Median survival
0	41	Not reached
1	81	Not reached
2	63	148 months
3	59	65 months
4	68	31 months
5	49	18 months
6	19	5 months

Risk factors

Clinical model

Advanced SM
Age >60 years
Platelet <150 x 10^9/l
Anemia
↑ALP
↓Albumin

No of Risk factors	No of Patients	Median survival
0	10	Not reached
1	32	198 months
2	23	69 months
3	29	21 months
4	28	12 months
5	7	3 months

Risk factors

Molecular model

Advanced SM
Age >60 years
Platelet <150 x 10^9/l
↑ALP
↓Albumin
Adverse mutations
ASXL1, RUNX1, NRAS

Systemic Mastocytosis Treatment

- Indolent
- Aggressive
- Mast cell leukemia
- Associated with another hematologic neoplasm (SM-AHN)

H1 and H2 blockers
Leukotriene antagonist
Cromolyn
Phototherapy
Topical steroids

If this fails, try cladribine
5 mg/m2
2-hour infusion x 1-5 days
every 4 to 12 weeks

Cetrizine 5-10 mg QD
Fexofenadine 60 mg BID
Hydroxyzine 25 mg q 6 hours

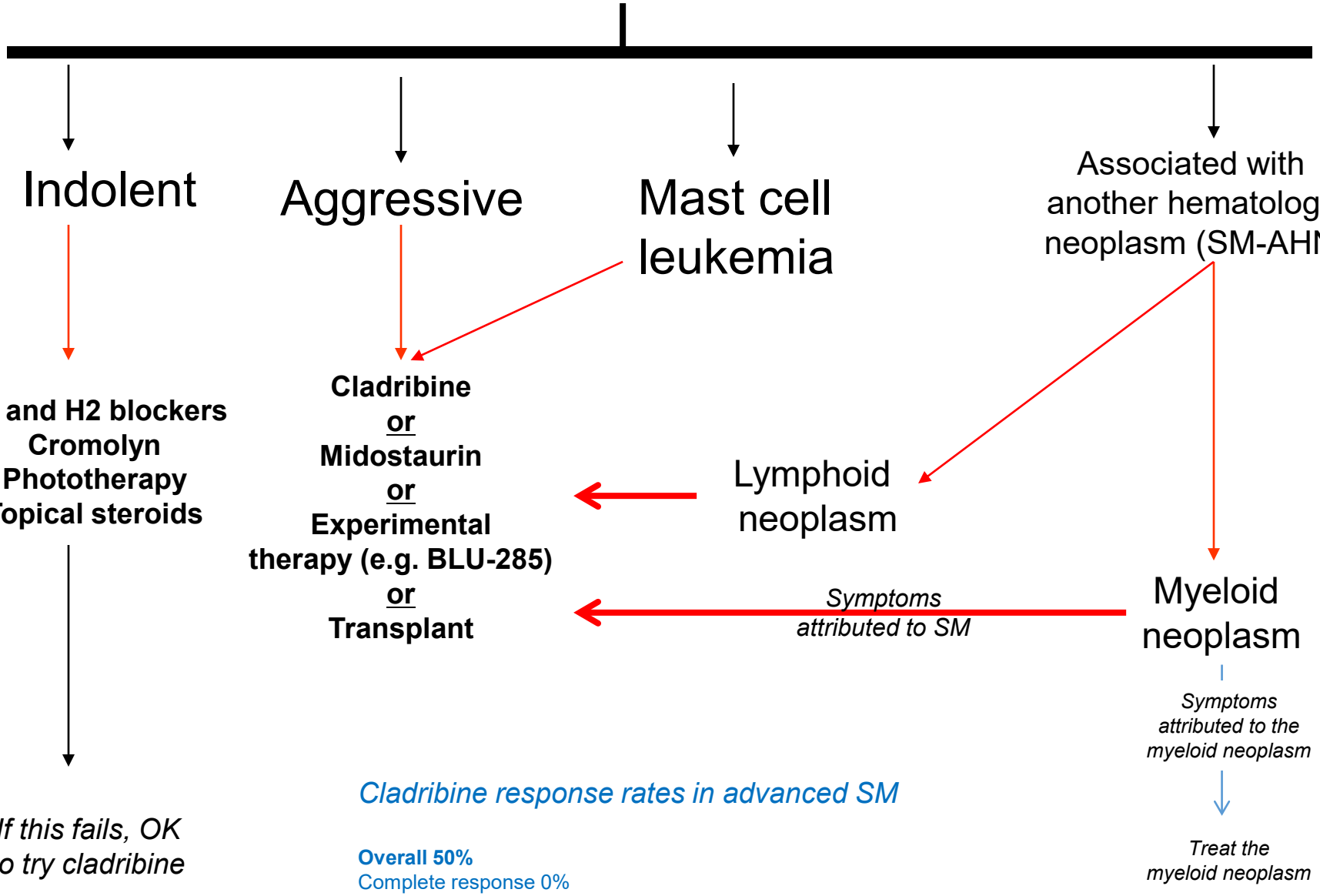
Ranitidine 150 mg BID
Famotidine 10 mg BID
Cimetidine 400 mg BID

Montelukast 10 mg QD
Zafirlucast 20 mg BID

Sodium cromolyn 100-200 mg QID

Osteoporosis prevention
Alendronate 70 mg weekly
Risedronate 35 mg weekly
Pamidronate IV 90 mg q-4 weeks
Zolendronic acid 4 mg IV q 4 weeks

Systemic Mastocytosis Treatment



Cladribine response rates in advanced SM

Overall 50%
Complete response 0%
Major response 38%
Partial response 13%

Blood 2015 126:1009