Disclosures for Ayalew Tefferi

Principal investigator role	Janssen, Geron, Celgene, Sanofi-Aventis, Gilead Sciences, Incyte
Employee	None
Consultant	None
Major Stockholder	None
Speakers' Bureau	None
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—*2018 Update*

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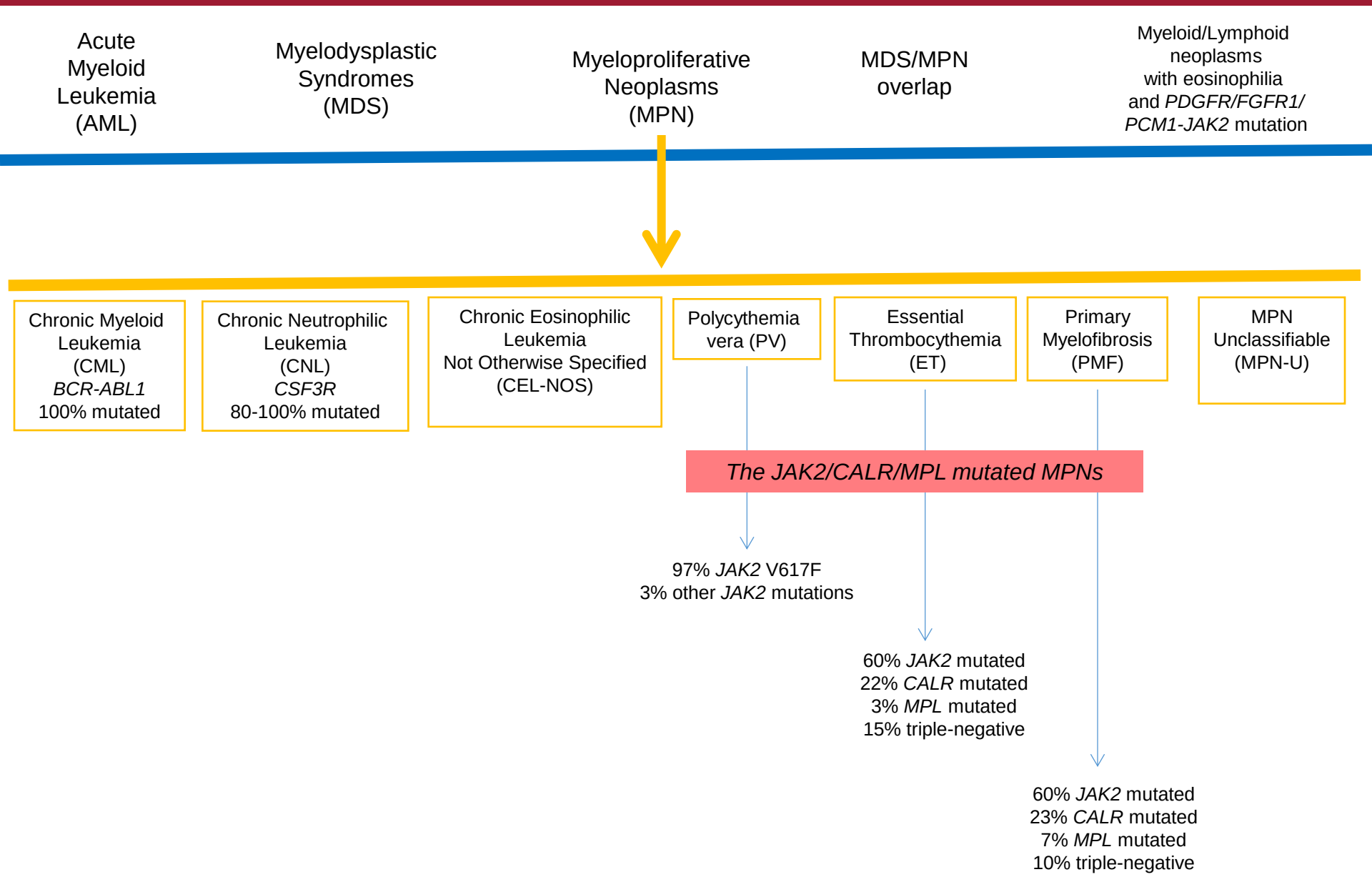
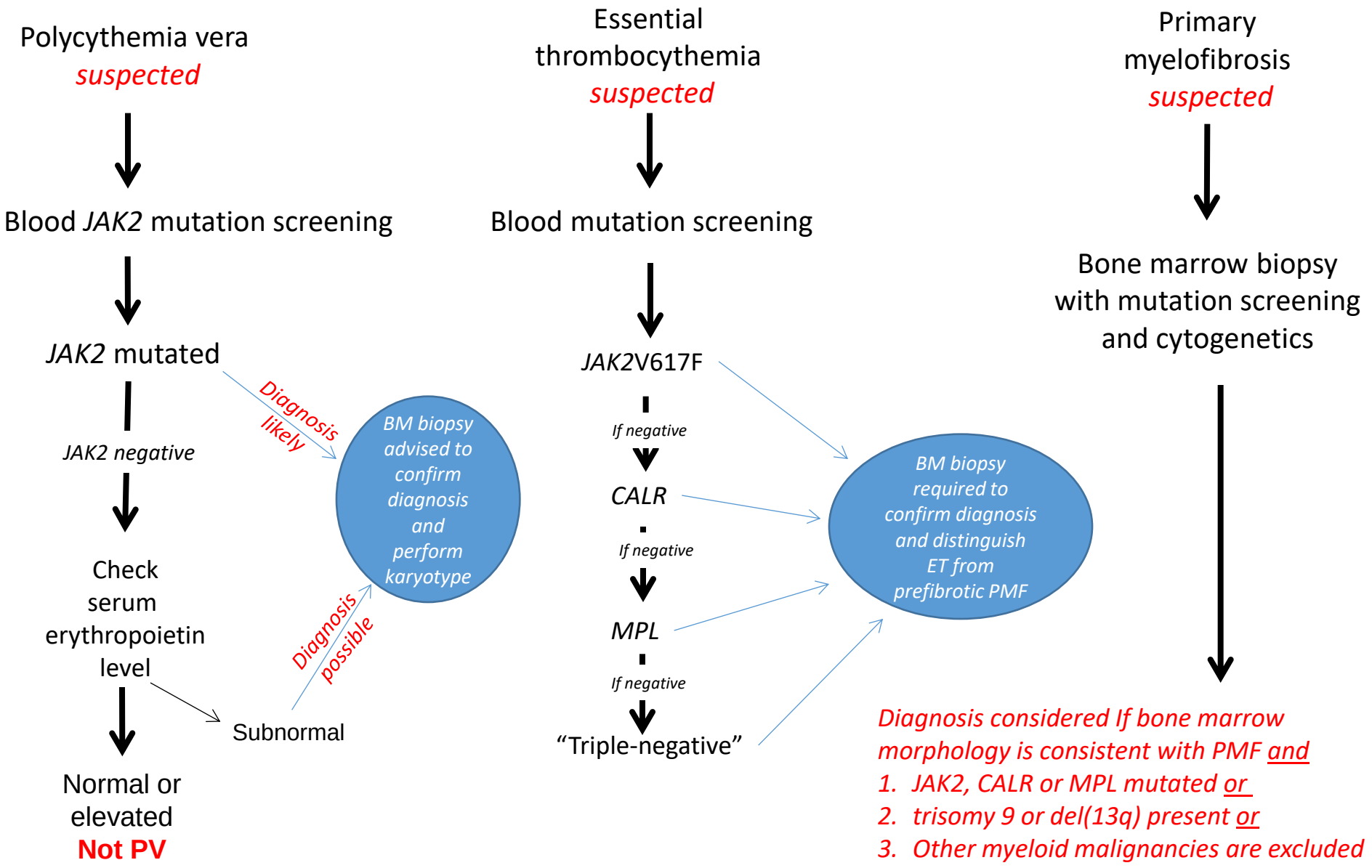
Objectives

- 2016 WHO highlights
- Practical diagnostic algorithms
- Genetic prognostication
- Treatment algorithms
- Noteworthy abstracts from ASH 2017

2016 WHO Classification of Myeloid Malignancies

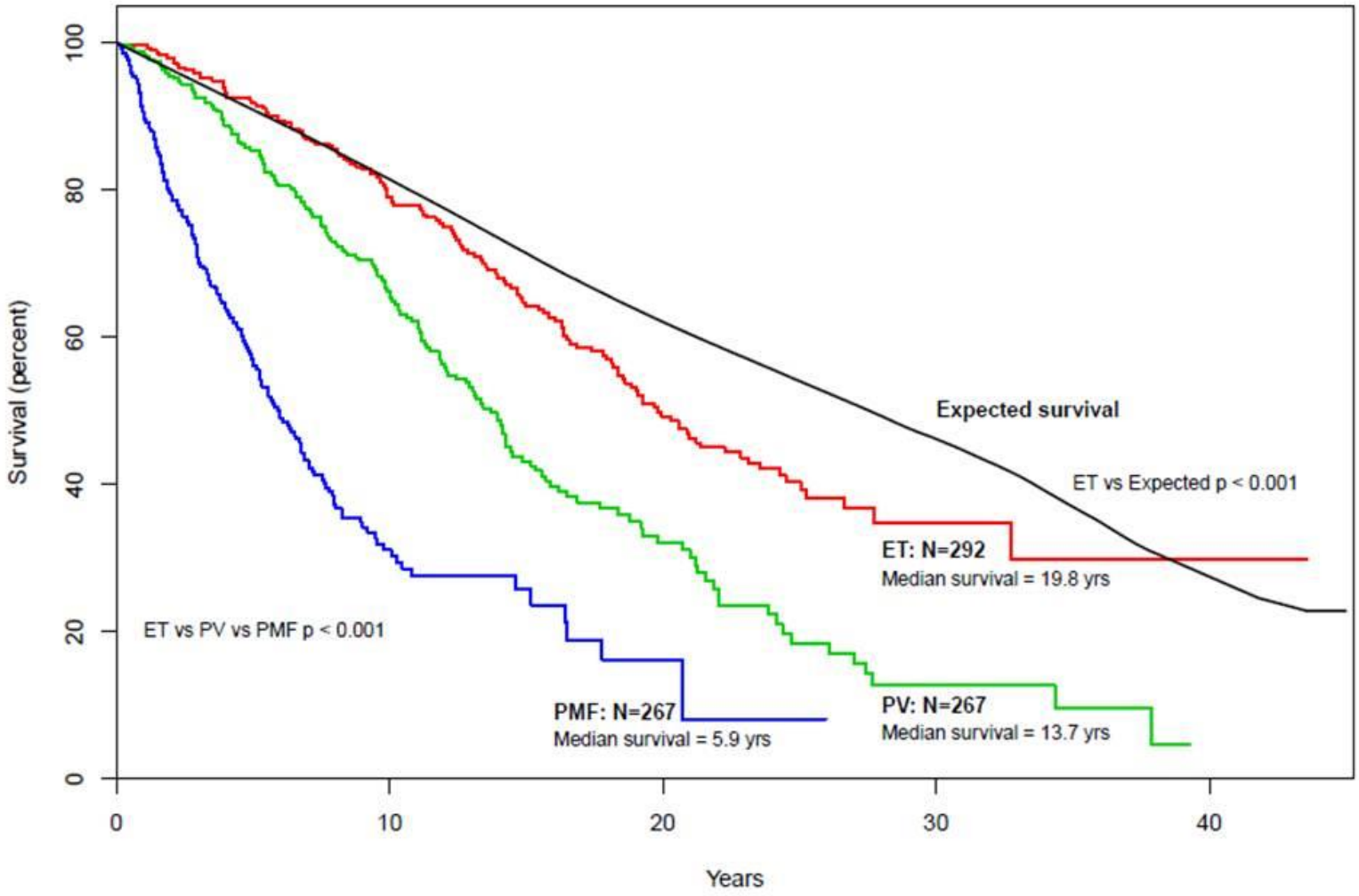


Practical diagnostic algorithm



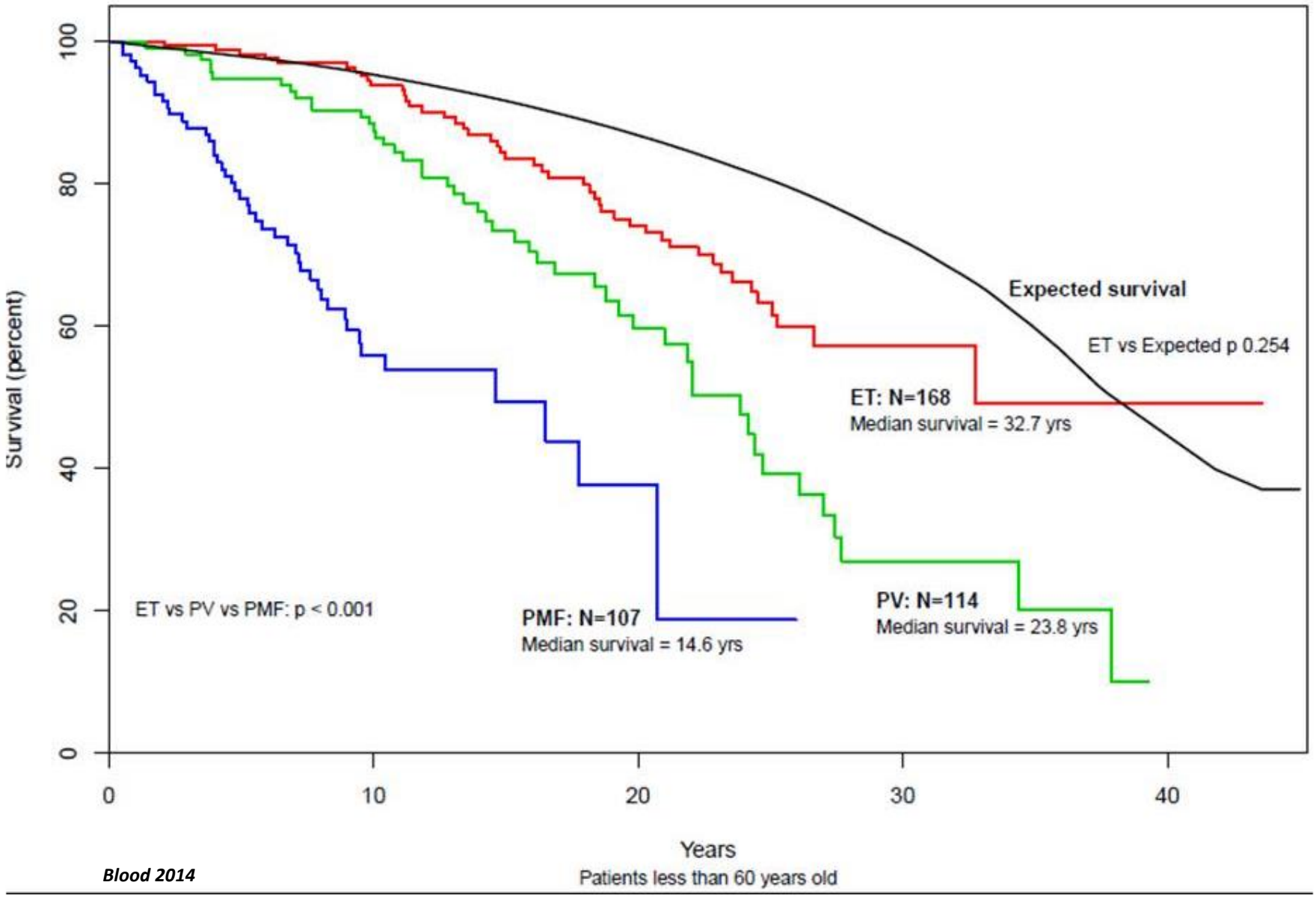
Survival in myeloproliferative neoplasms

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



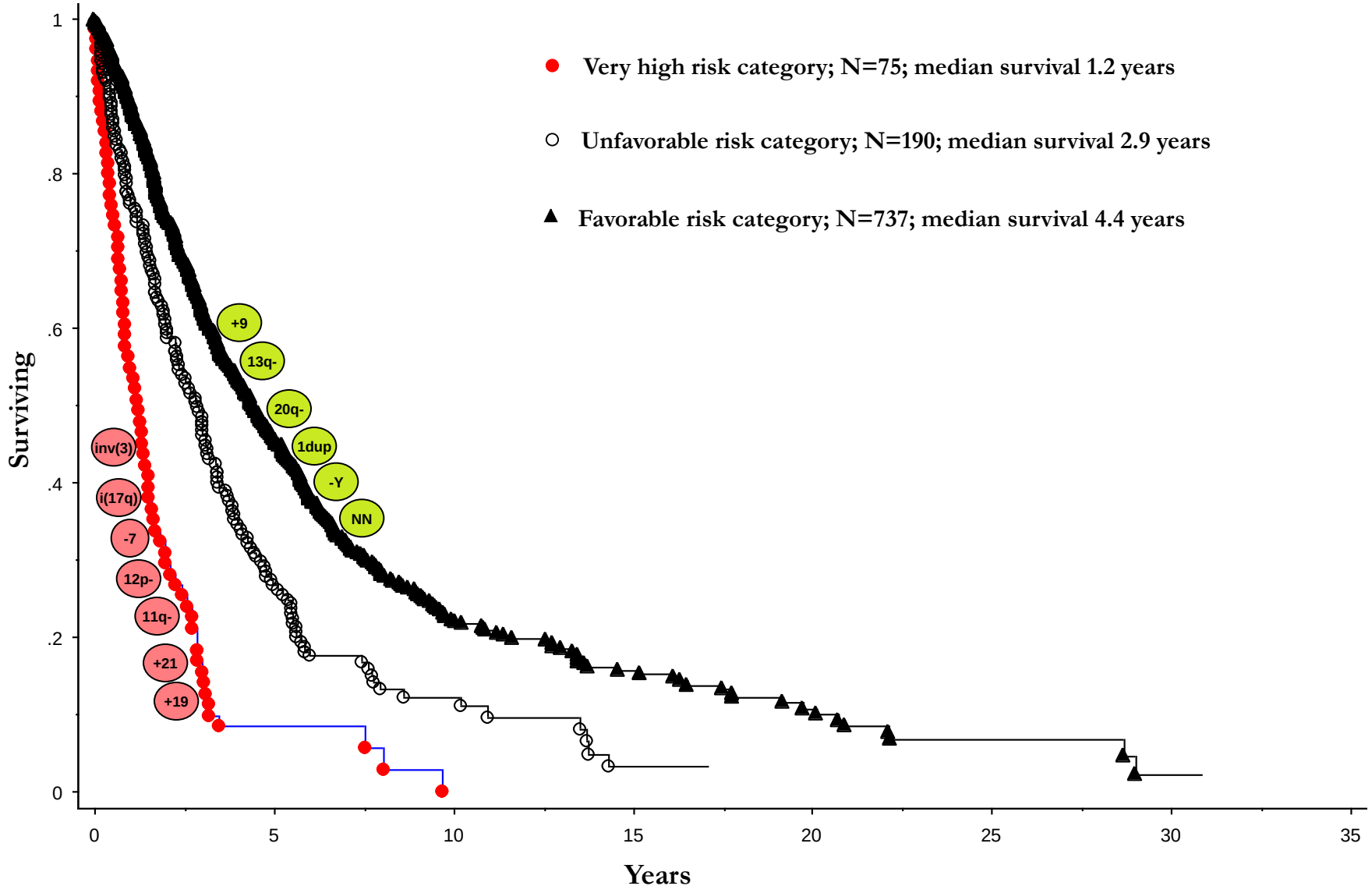
Blood 2014

Survival and prognosis in young patients with myeloproliferative neoplasms



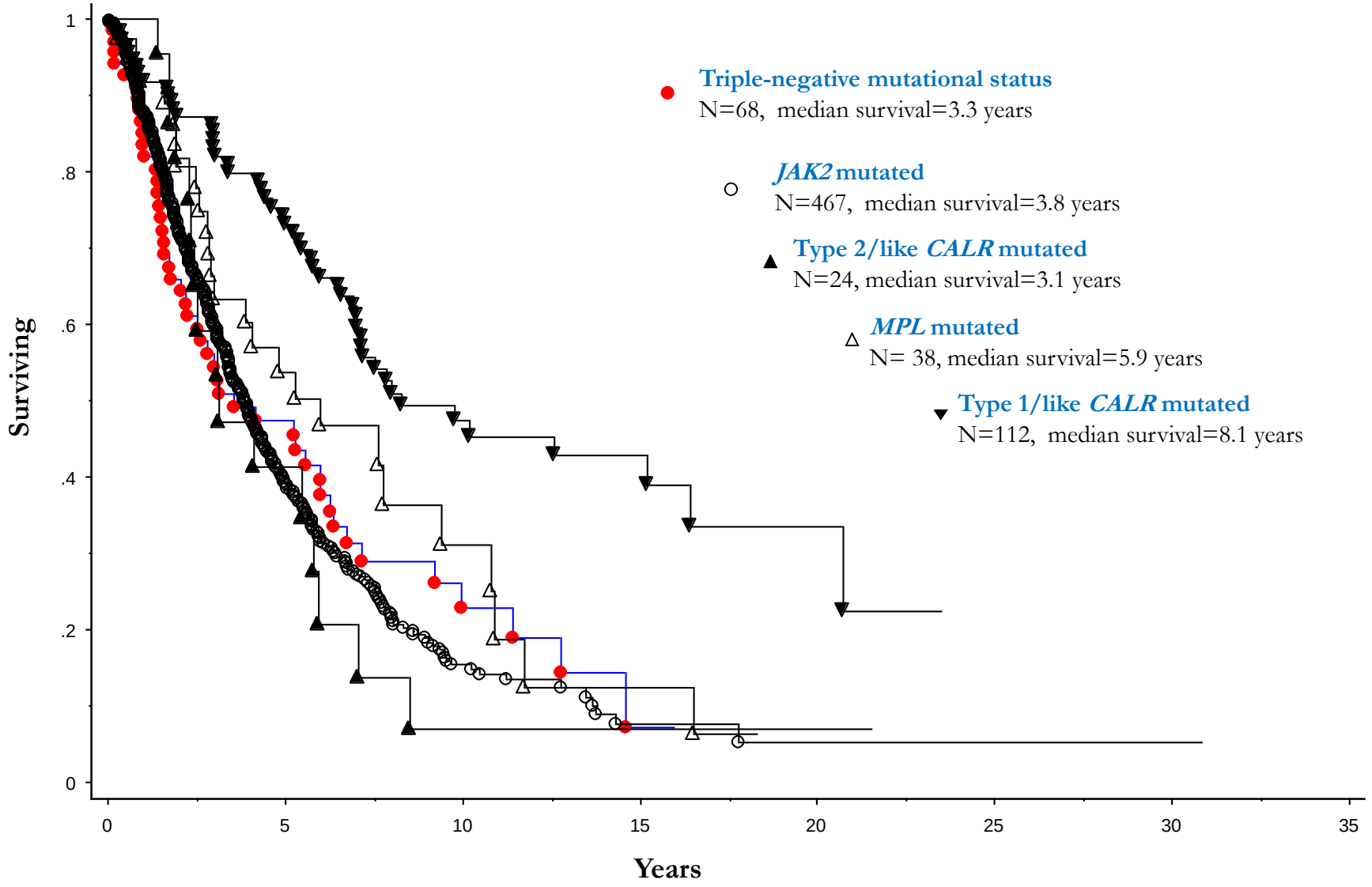
Blood 2014

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



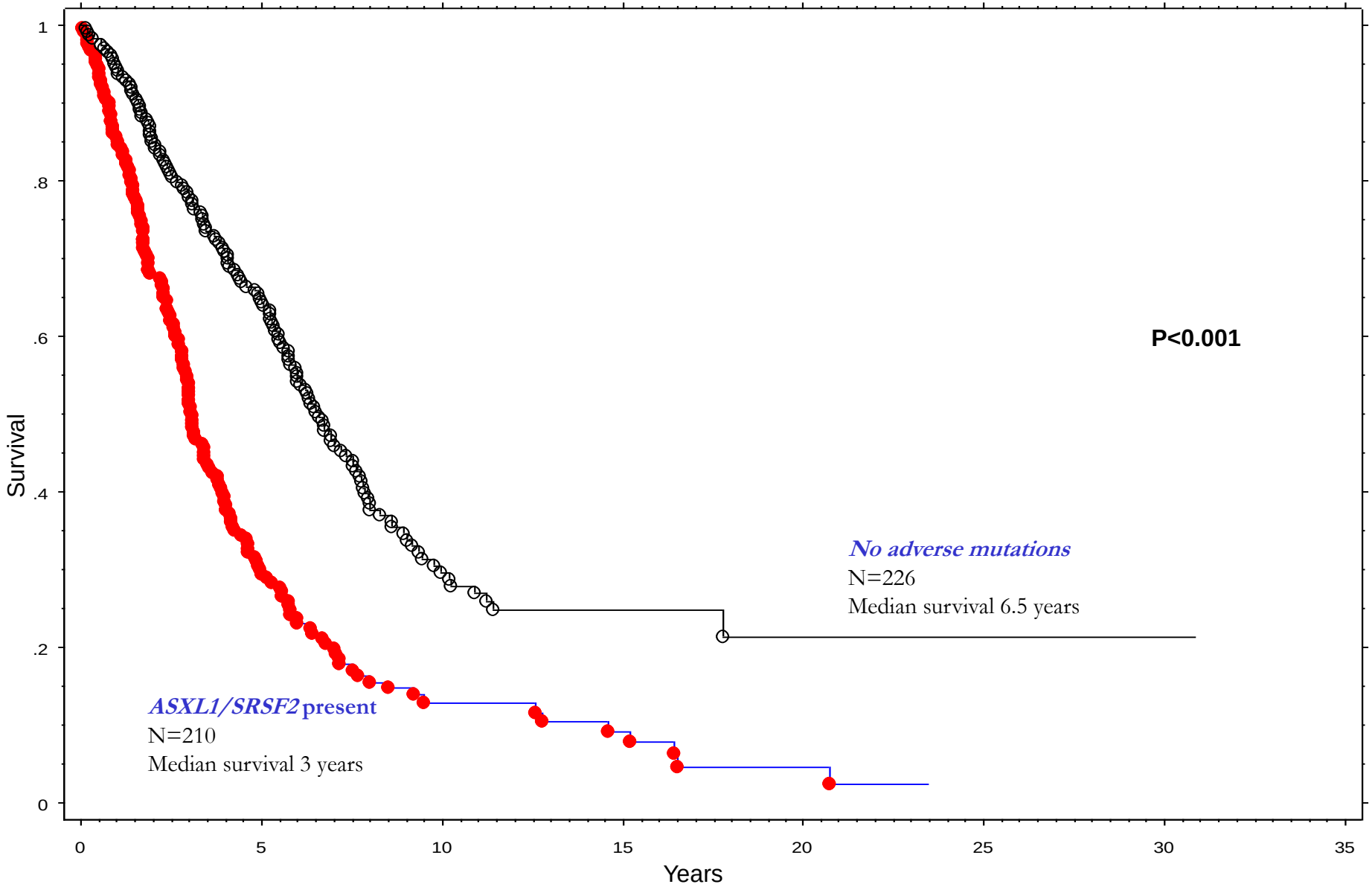
Leukemia 2018

Survival of 709 primary myelofibrosis patients from the Mayo Clinic, stratified by driver mutational status



AJH 2018

Survival in 436 patients with primary myelofibrosis stratified by presence or absence of *ASXL1* or *SRSF2* mutations

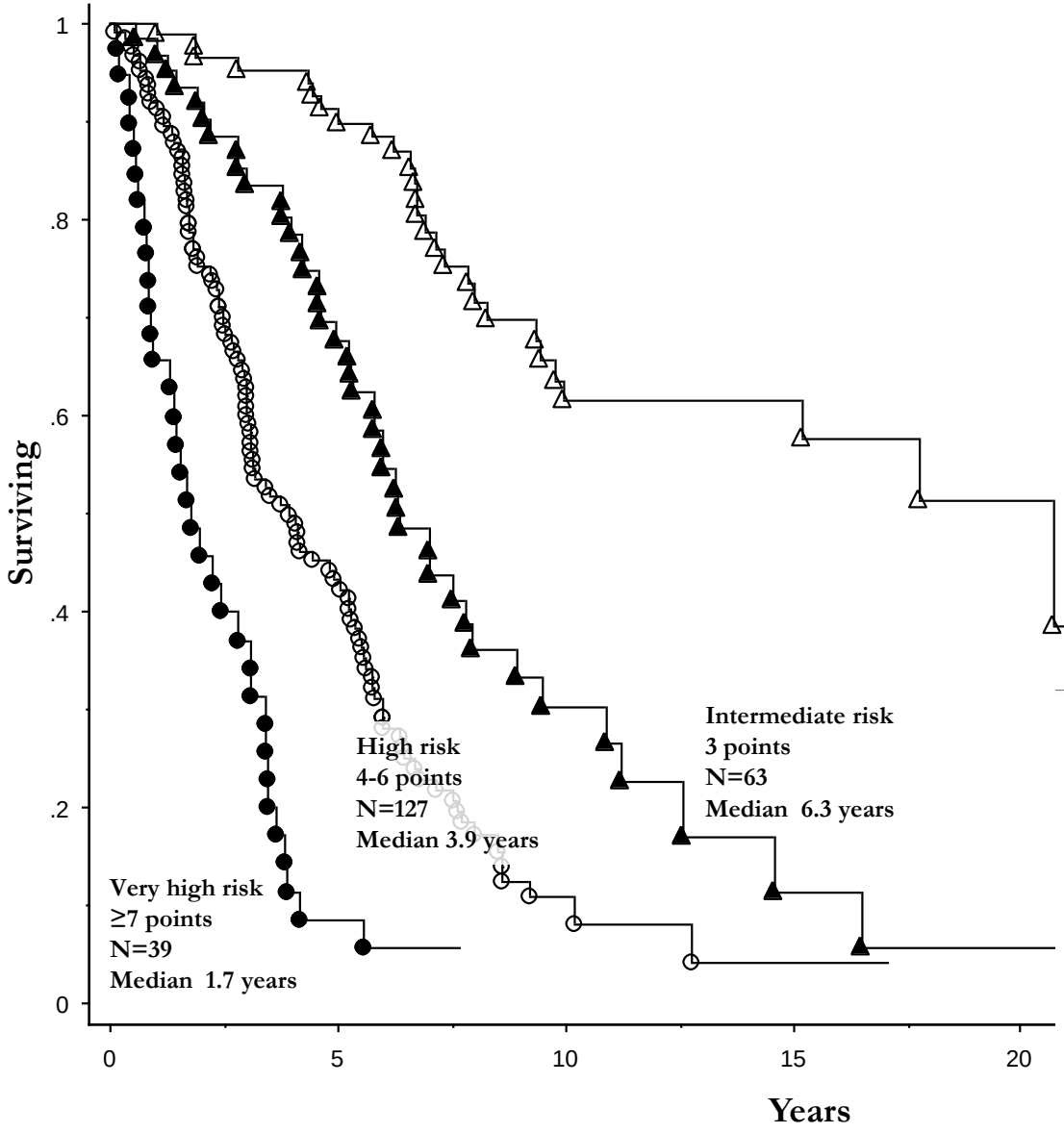


2018 Mayo Clinic updated data

JCO 2017

MIPSS70: mutation-enhanced international prognostic scoring system

Survival of 315 patients with primary myelofibrosis and age ≤70 years, stratified according to MIPSS70-plus



Adverse points

Genetic risk factors:

Karyotype (unfavorable)	3
Driver mutation (type 1/like *CALR* absent)	2
Two or more high risk mutations	2
One high risk mutation	1

Clinical risk factors:

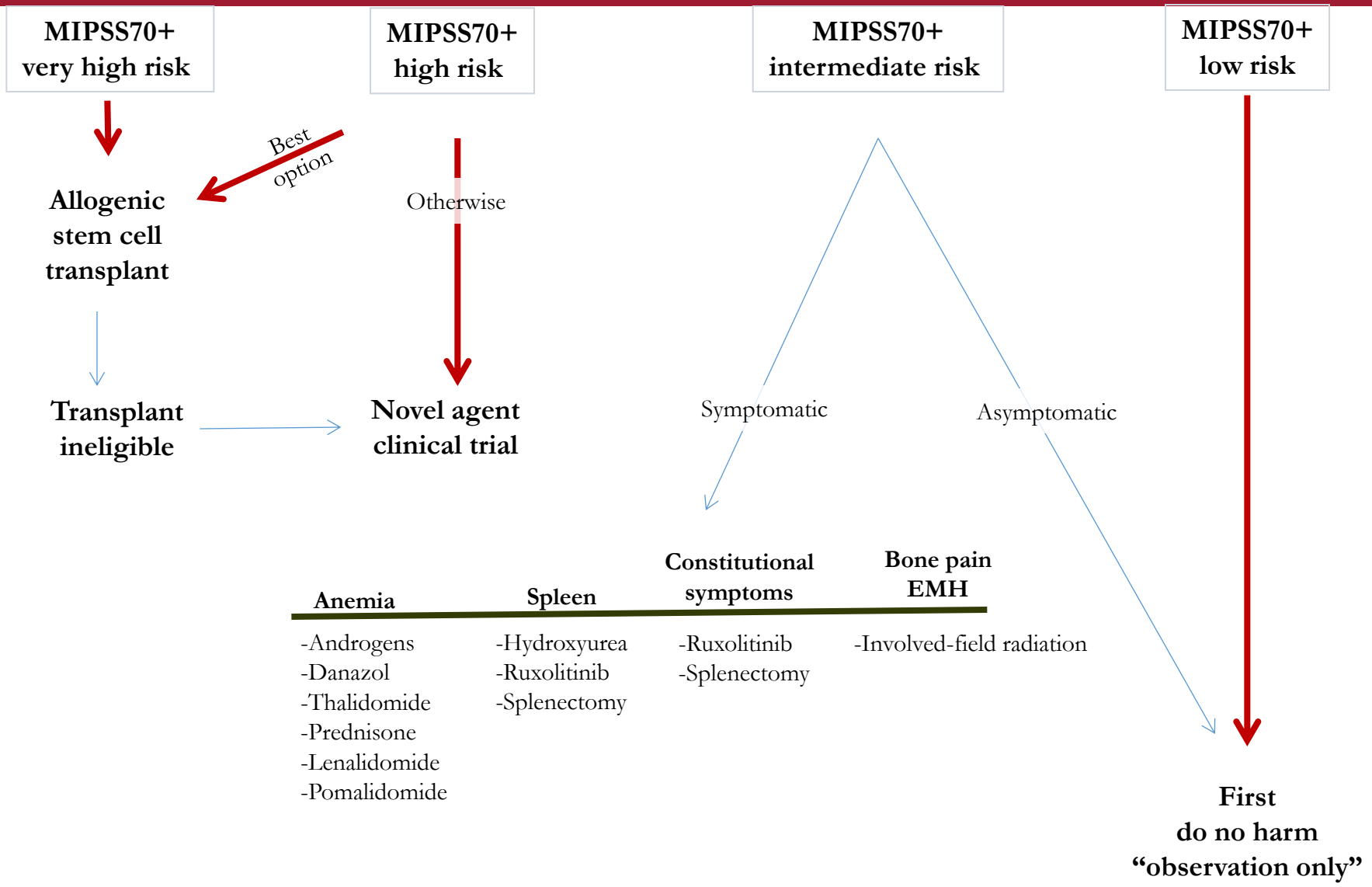
Hemoglobin <10 g/dl	1
Leukocyte count >25 x 10^9/l	1
PB blasts ≥2%	1
Constitutional symptoms	1

http://www.mipss70score.it/

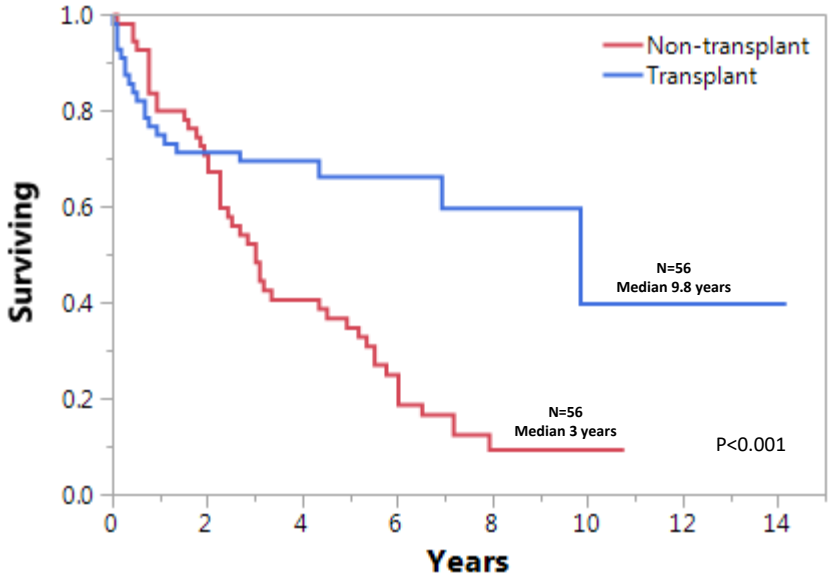
#	Question	Answer
1	Anemia (hemoglobin <100g/L)	Yes / No
2	Leucocytosis >25x10⁹/L	Yes / No
3	Thrombocytopenia (platelet count <100x10⁹/L)	Yes / No
4	Peripheral blood blast count ≥2%	Yes / No
5	Bone marrow fibrosis grade ≥2	Yes / No
6	Constitutional symptoms	Yes / No
7	Absence of CALR type 1/like mutation	Yes / No
8	HMR* category	Yes / No
9	≥2 HMR mutated genes	Yes / No
10	Unfavorable karyotype**	Yes / No / Not available

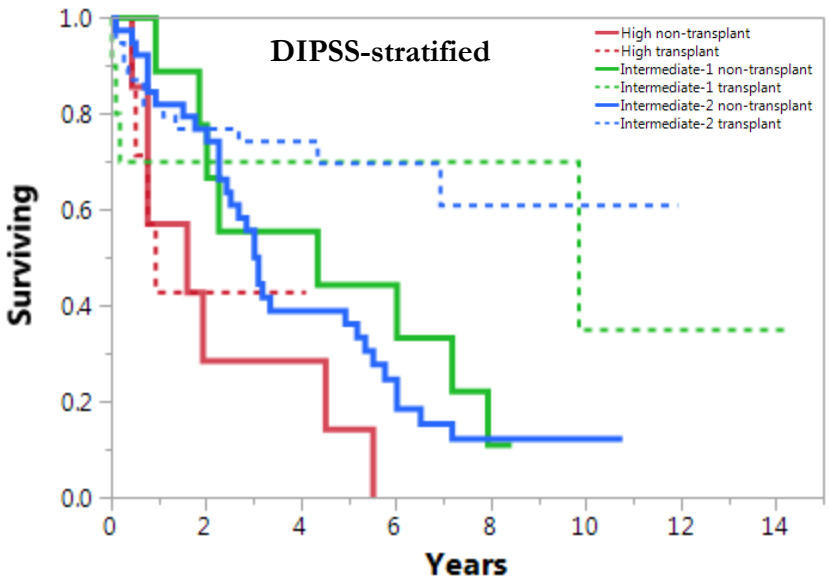
Score	Result
MIPSS70	HIGH RISK [5-year OS= 34%]
MIPSS70-plus	VERY HIGH RISK [5-year OS= 46%]

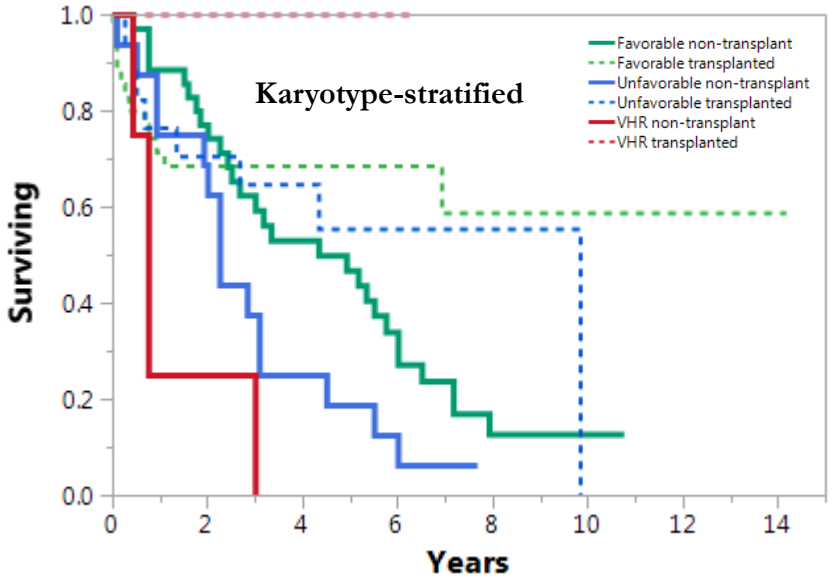
Treatment Algorithm in Myelofibrosis



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







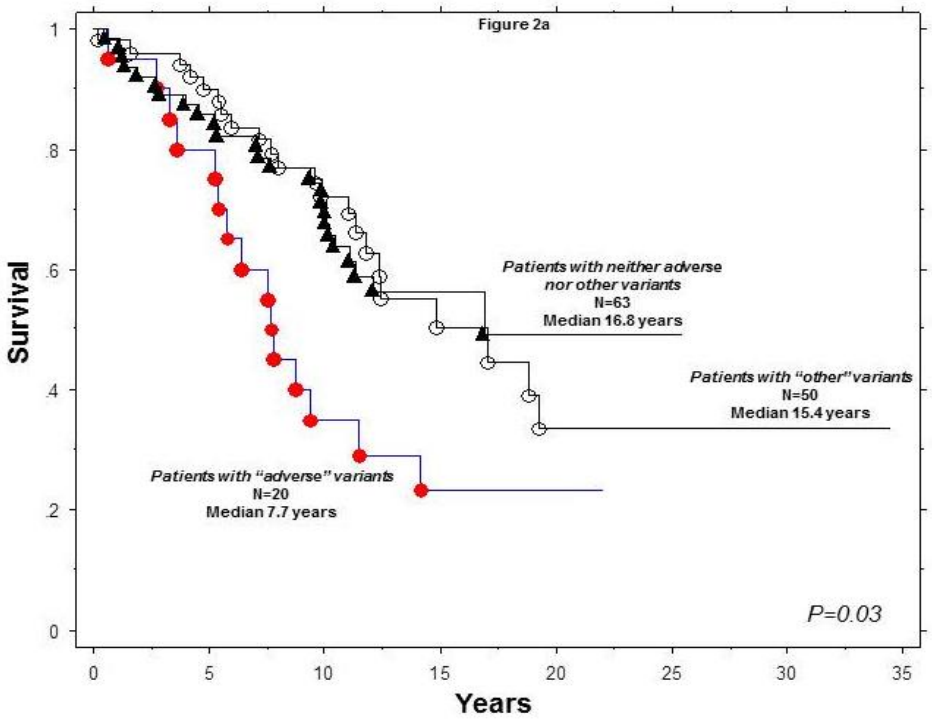
AJH 2018

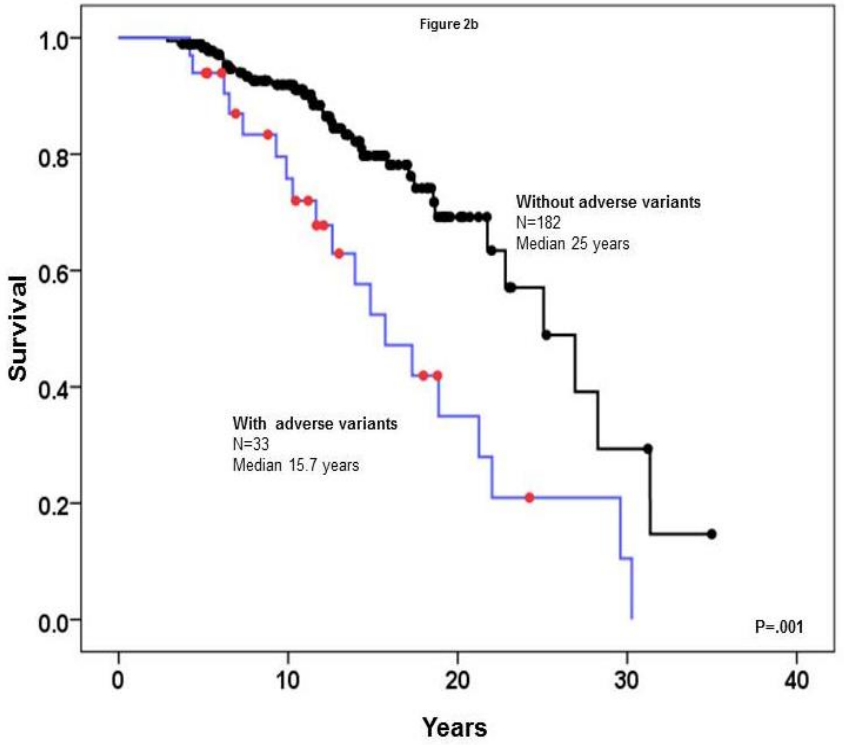
Genetic prognostication in polycythemia vera

- Prevalence of mutations other than JAK2/CALR/MPL = 53%
- Most frequent were *ASXL1* and *TET2*
- 30%, 20% and 3% harbored 1, 2 or ≥3 such mutations
- "3" genes were identified as being affected by adverse mutations/variants

ASXL1, SRSF2, IDH2

PV





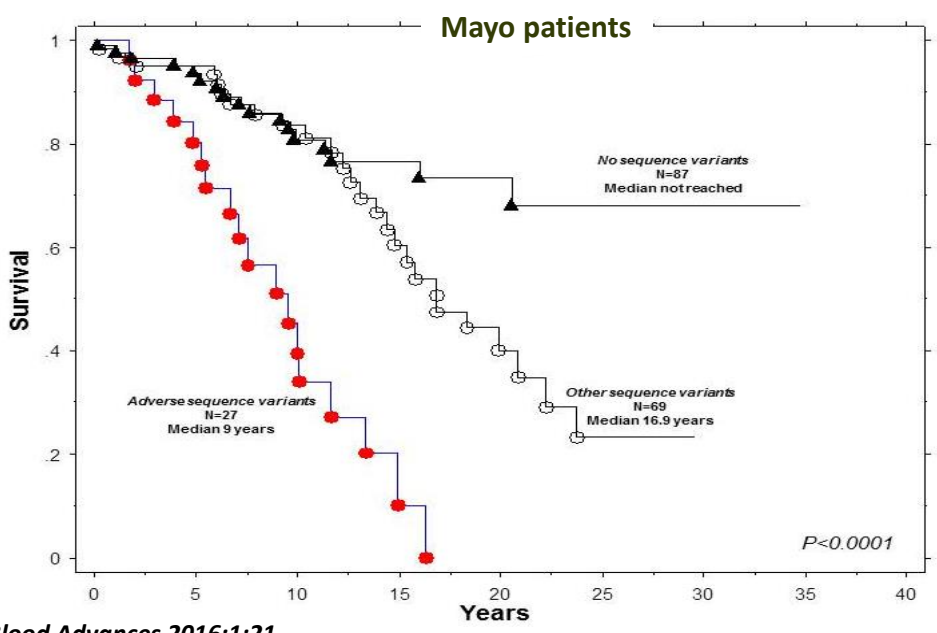
Blood Advances 2016;1:21

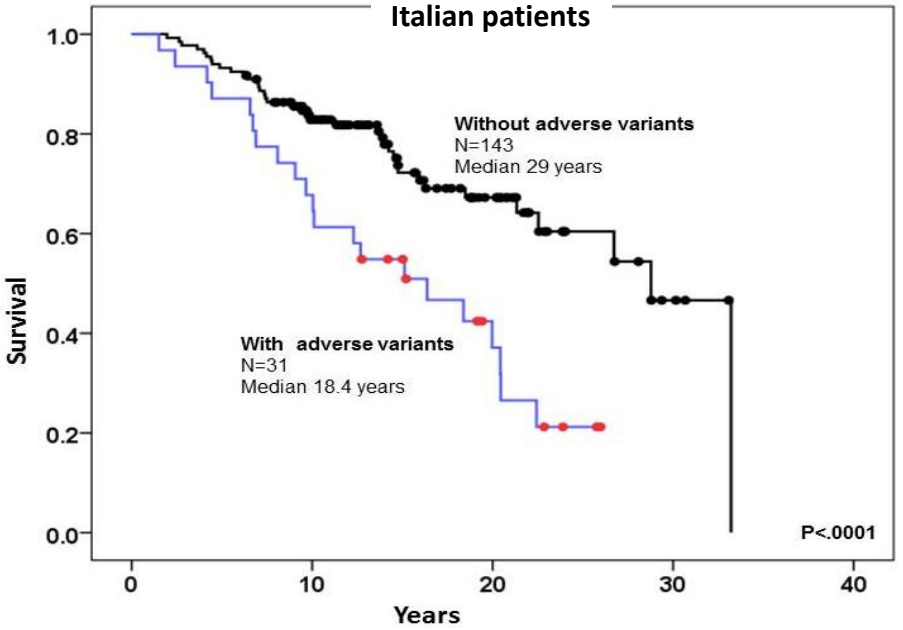
Genetic prognostication in essential thrombocythemia

- Prevalence of mutations other than JAK2/CALR/MPL = 53%
- Driver mutational status did not affect prevalence
- Most frequent were *ASXL1* and*TET2*
- 41%, 8% and 4% harbored 1, 2 or ≥3 mutations
- "6" genes were identified as being affected by adverse mutations/variants

  SF3B1, SH2B3, EZH2, TP53, U2AF1, IDH2 (15% affected)

ET





Blood Advances 2016;1:21

Current Treatment Algorithm in Polycythemia Vera

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

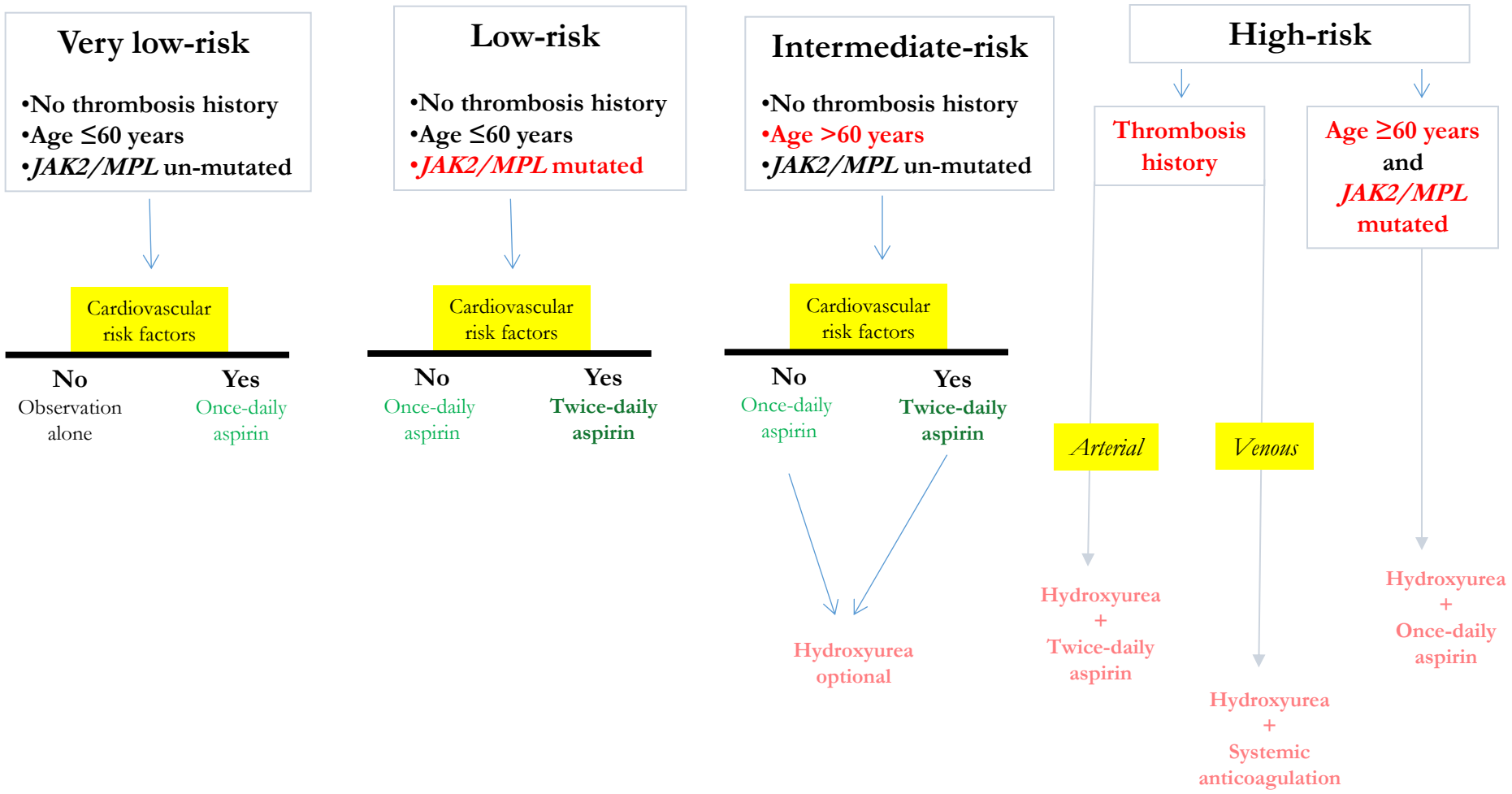
Hydroxyurea intolerant or resistant

→ Pegylated IFN-α (Age <65 years)

→ Busulfan (Age ≥65 years)

→ Ruxolitinib (If all the above fails)

Current Treatment Algorithm in Essential Thrombocythemia



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

Phase-3 tested JAK2 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%

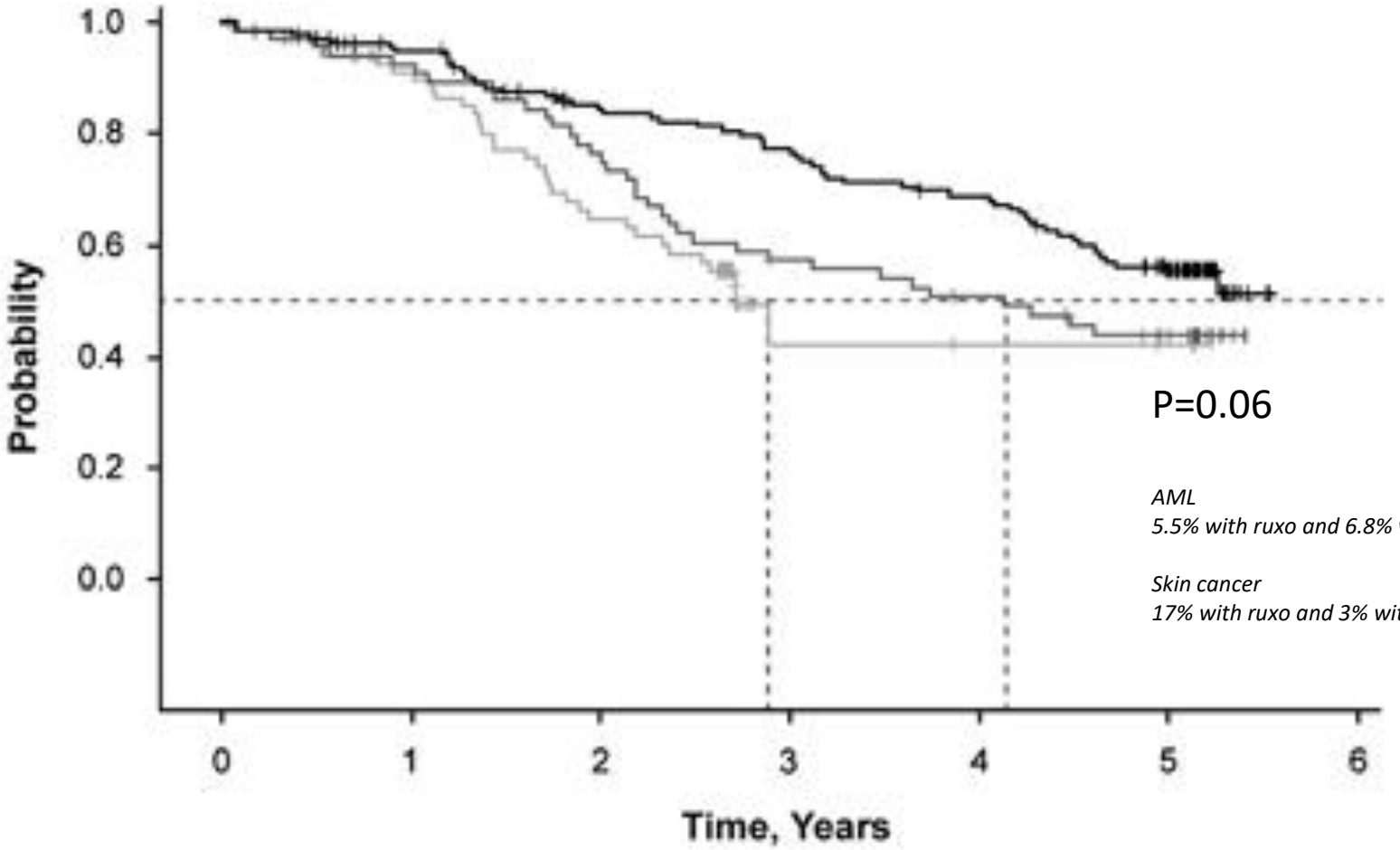
	JAK targets	Other targets	Symp. resp.	Spleen resp.	Anemia resp.	Side effects
Ruxolitinib (FDA-approved)	JAK1 JAK2	TRK-B, ACK1 FAK, LCK RET	Yes	32-42% (MRI)	14%	↓Hgb/Plts Ruxolitinib withdrawal synd. Opportunistic infections
Fedratinib (SAR302501) Phase-3 completed FDA approval pending	JAK2	FLT3, RET, 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

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



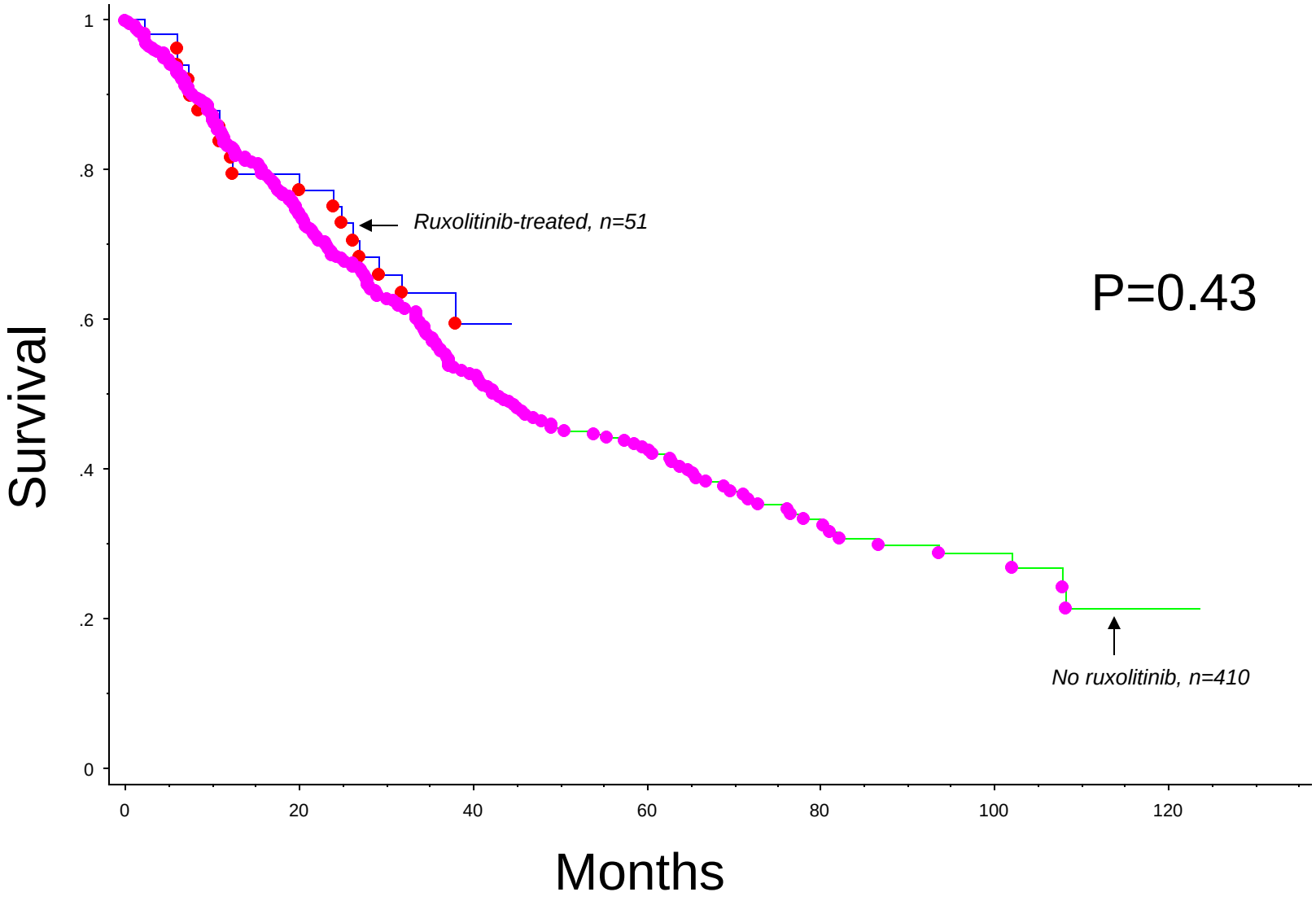
Ruxolitinib, n =	146	130	109	100	88	61	0
BAT (ITT), n =	73	58	48	35	30	22	0
BAT (RPSFT), n =	73	59	42	6	5	4	0

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: MC study



NEJM 2011:365;15

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