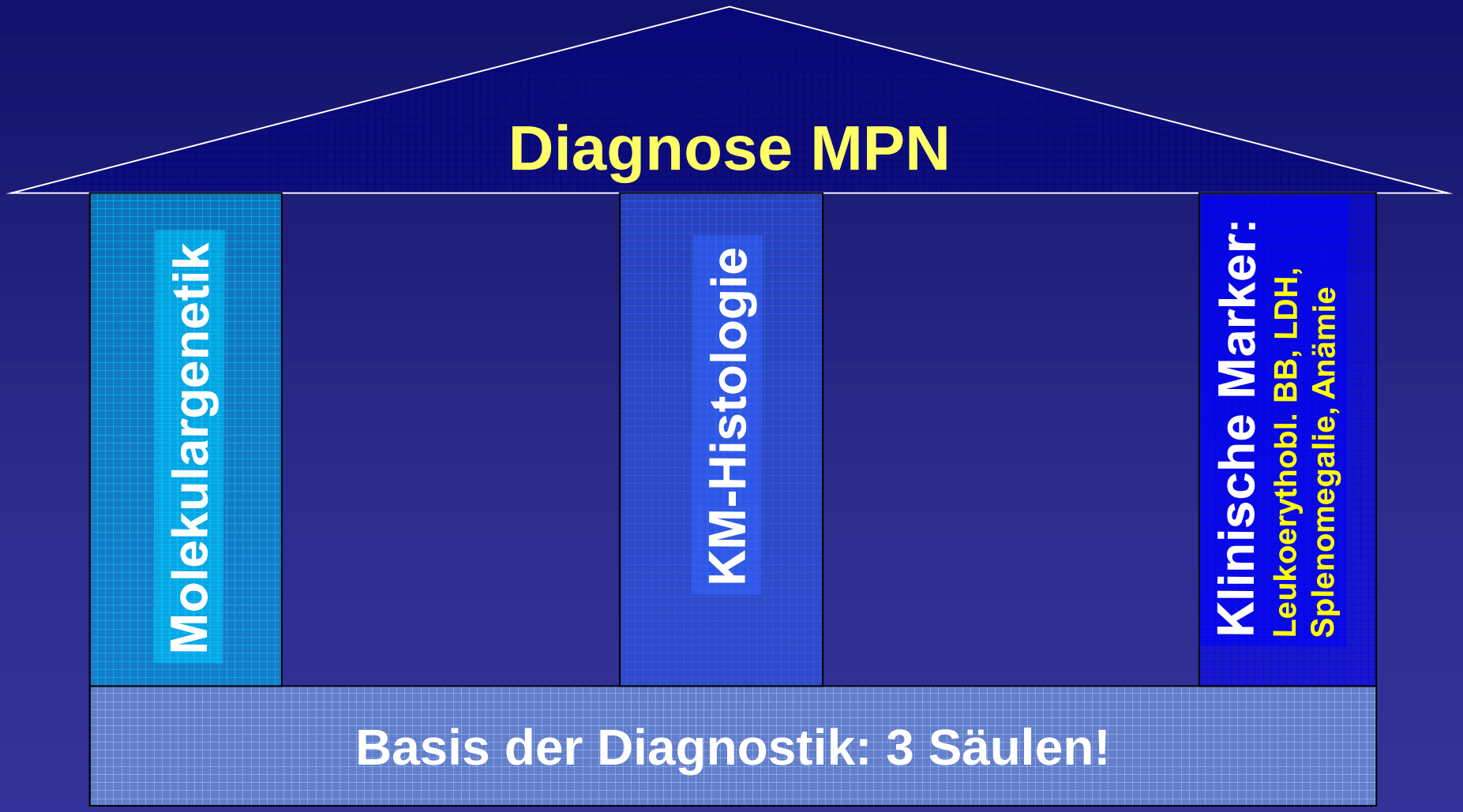
Update classic MPN

Johannes Wesling Klinikum
Minden

Martin Griesshammer
Klinik für Hämatolgie, Onkologie
Hämostaseologie und Palliativmedizin

Hannover, 22.01.2016

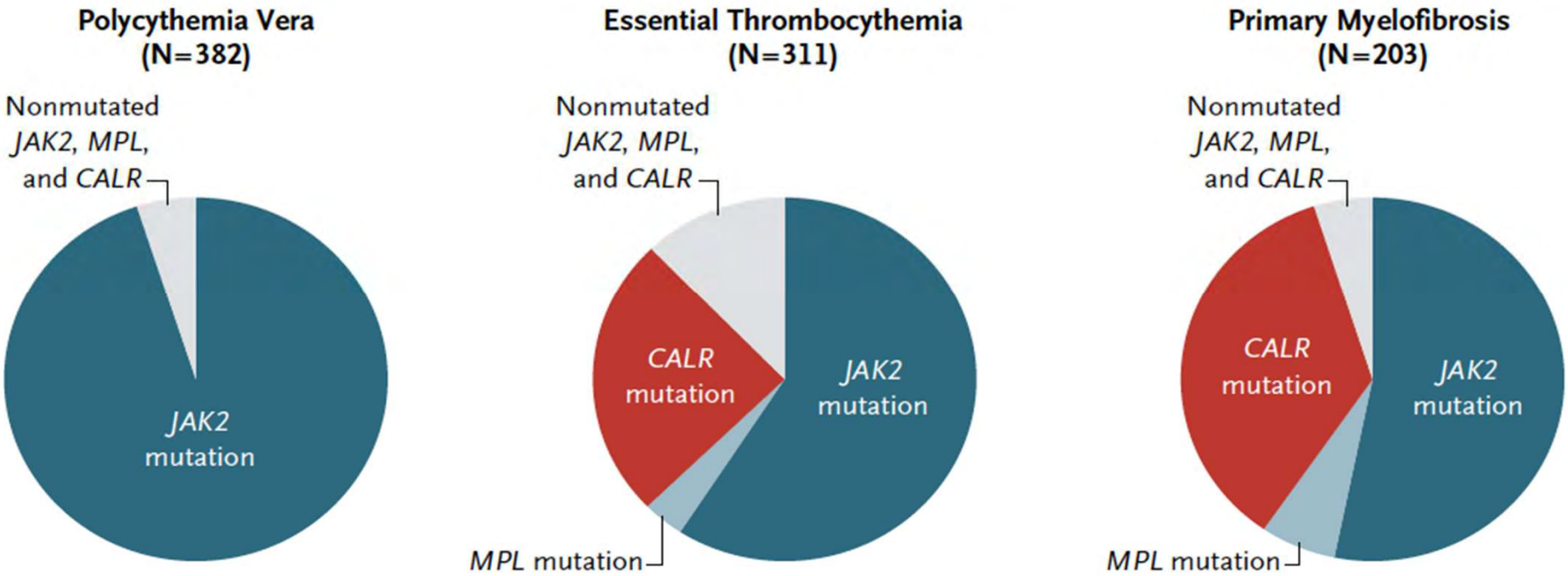
Diagnosestellung MPN nach WHO



DGHO, Onkopedia 2014

Myeloproliferative neoplasms (MPN)

3 Driver-Mutations JAK2, CALR und MPL

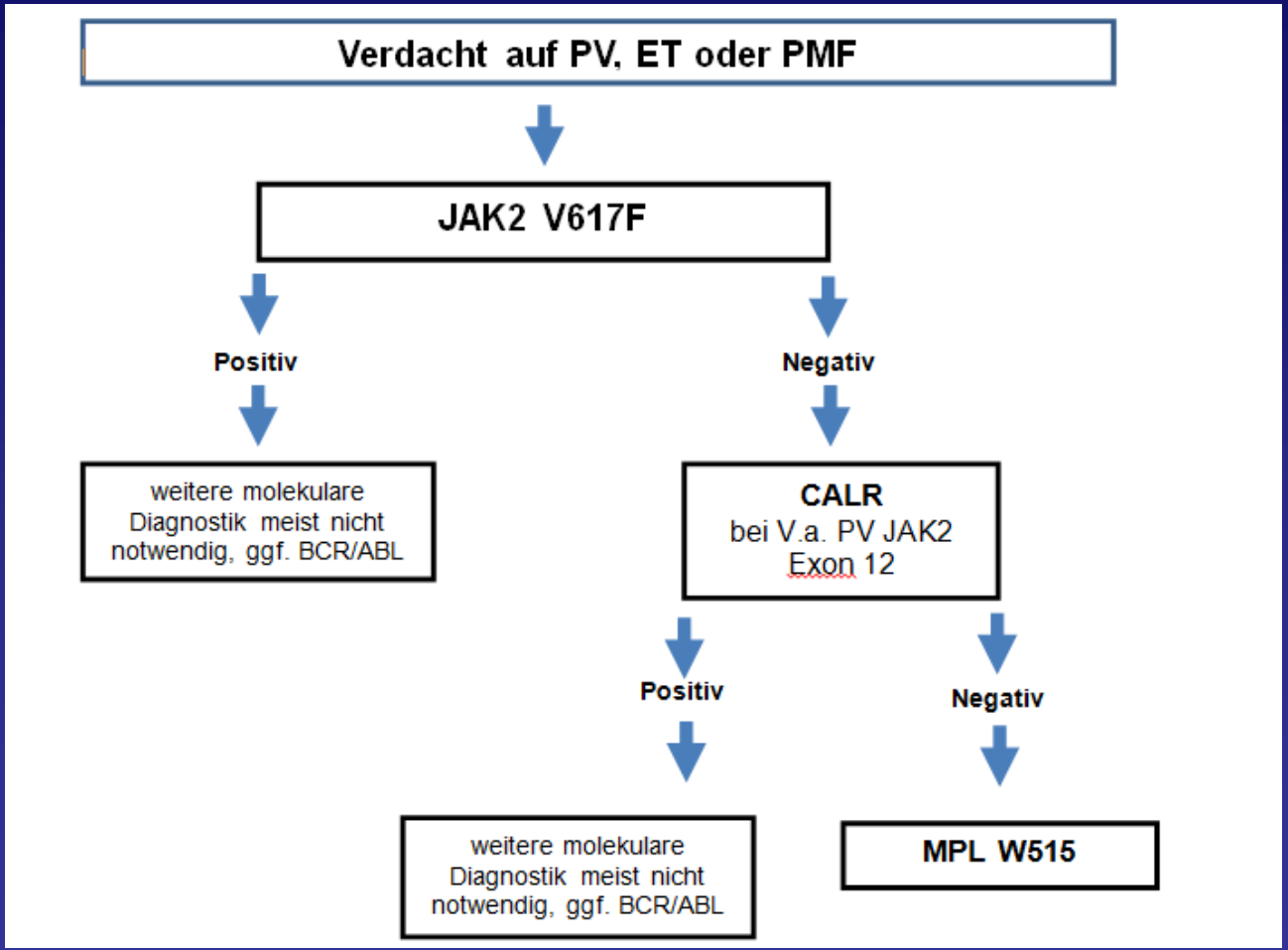


Other somatic mutations (*TET2*, *CBL*, *EZH2*, *DNMT3A, ASXL1*, etc.):

- are not mutually exclusive with *JAK2*, *MPL* and *CALR* mutations
- are not specific for MPN

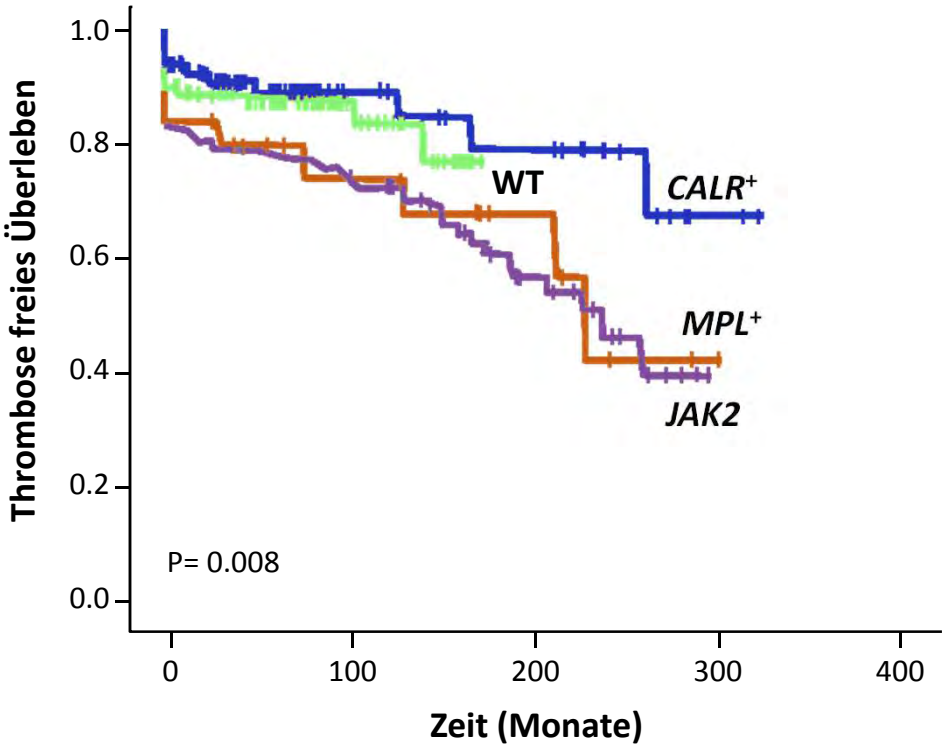
Klampfl, NEJM; 2013

Stufenweise molekulare Testung bei Verdacht auf eine MPN



H.M. Kvasnicka & M Griesshammer, J Lab Med 2015

CALR mutierte ET Patienten mit niedriger Thromboserate



aus Rotunno G, *et al. Blood.* 2014; 123:1552-5

	HR	95% CI
JAK2 mut	1.78	1.06-3.18
MPL mut	1.65	1.70-3.92
CALR mut	0.74	0.33-1.00

N.B. Wildtyp Patienten wurden als Referenz Population genommen

HR-Hazard ratio

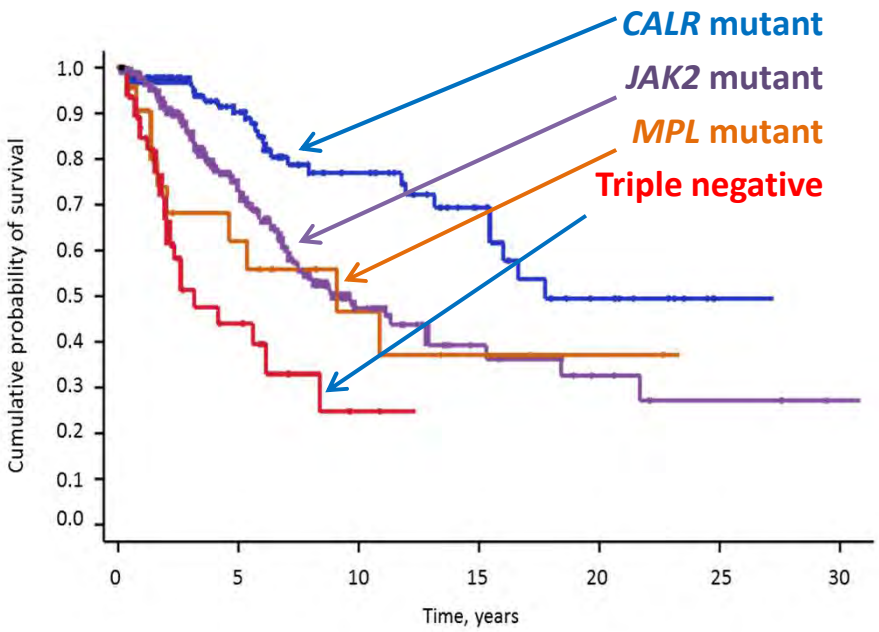
aus Rotunno G, *et al. Blood.* 2014; 123:1552-5

- **Triple-negative Patienten haben ein besonders niedriges Thromboserisiko und eine sehr gute Prognose – Effekt der *CALR* Mutation besonders evident bei jüngeren Patienten**

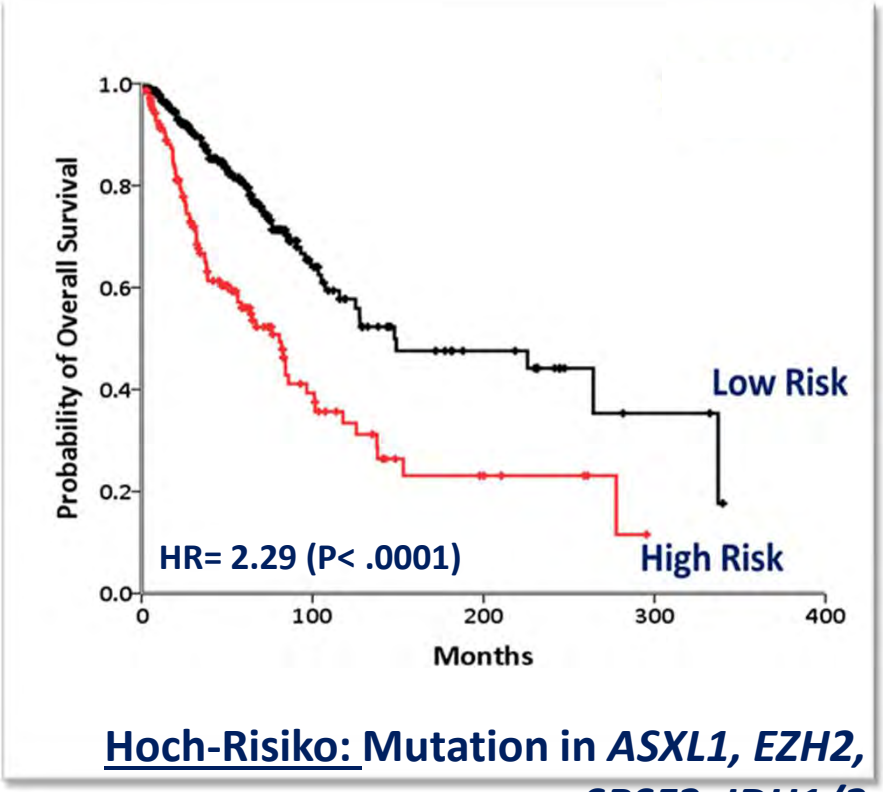
Gangat N, et al. Eur J Haemtol 2014

Prognostische Bedeutung molekularer Mutationen bei PMF

- **Der Mutationsstatus von *JAK2*, *MPL* und *CALR* und andere Mutationen sind prognostisch relevant!**

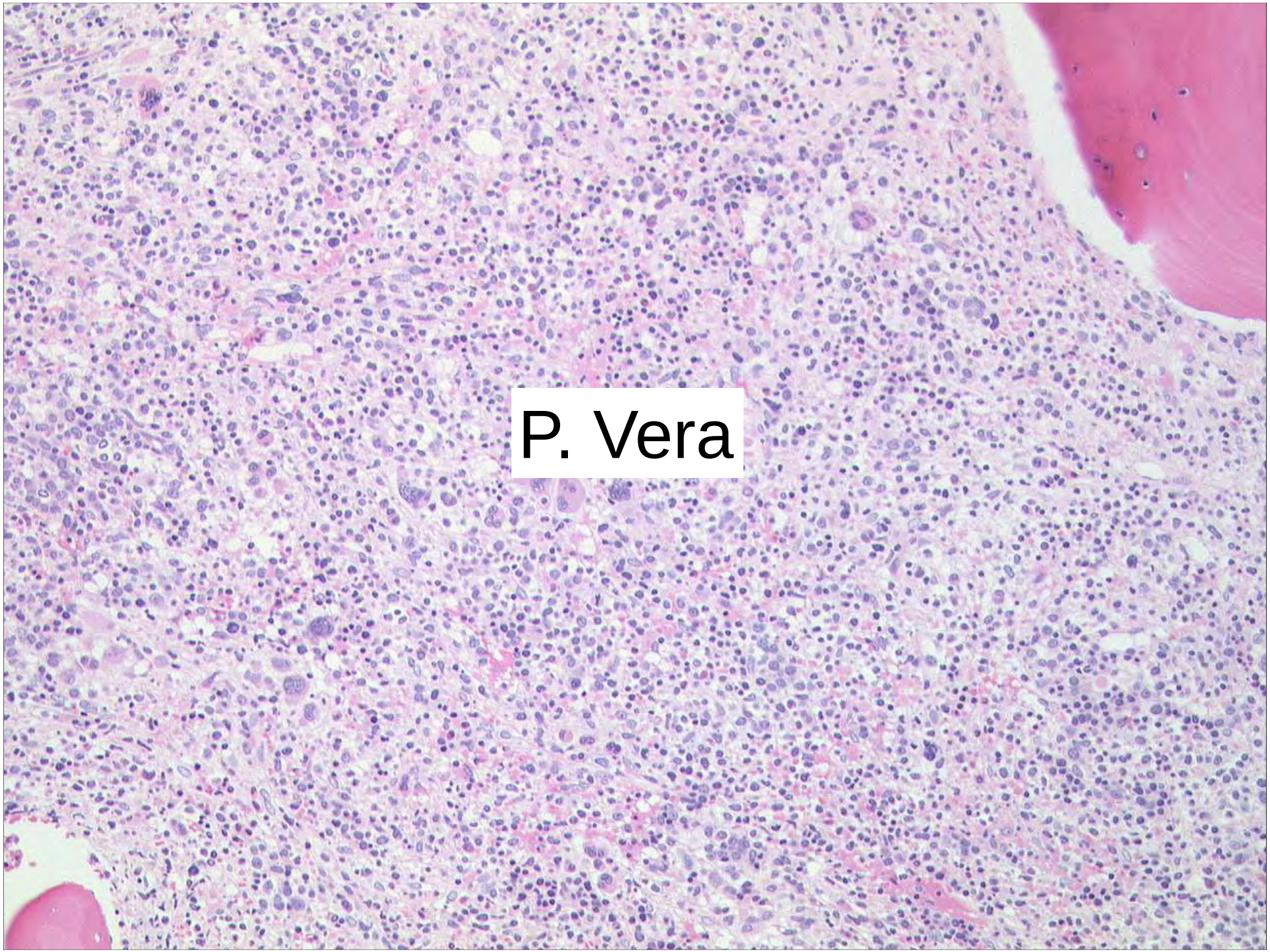


HR: 2.3 für *JAK2*V617F (P<.001)
2.6 für *MPL (P=.009)*
6.2 für TN *(P<.001)*

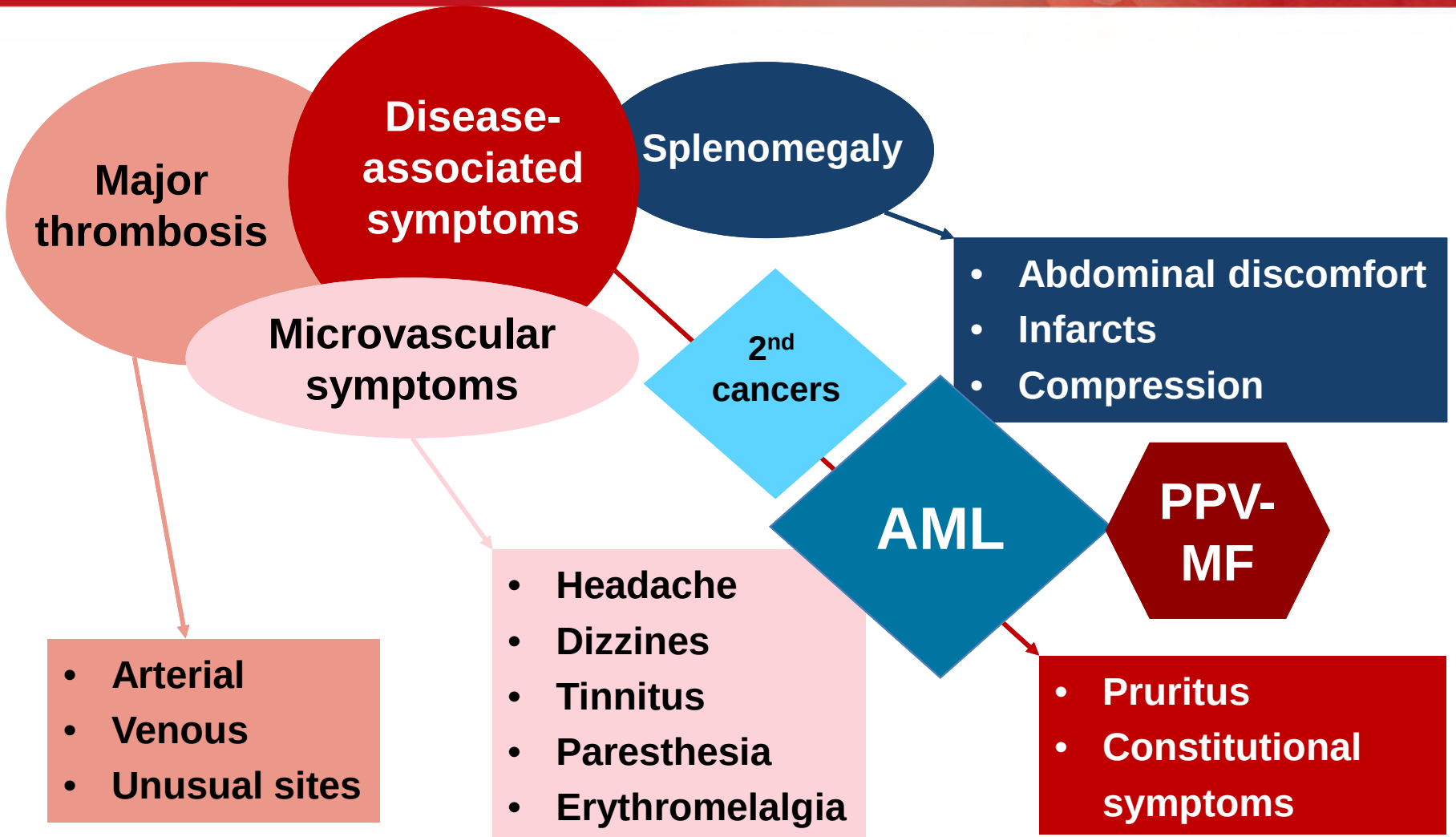


Hoch-Risiko: Mutation in ***ASXL1, EZH2, SRSF2, IDH1/2***

Rumi E et al, Blood 2014; 124:1062-9; Vannucchi AM et al, Leukemia 2013; 27:1861-9


P. Vera

PV is a multifaceted disease



Polyzythämia vera

- WHO Diagnose Kriterien 2008 -

I. **HAUPTKRITERIEN**

a) Hb > 18,5 g/dl ♂, > 16,5 g/dl ♀, bzw. andere Hinweise auf erhöhte Erythrozytenmasse

b) JAK2-Mutatation

II. NEBENKRITERIEN

a) Typische PV Knochenmarkhistologie

b) Serum EPO ↓

c) EEC Bildung in vitro

Diagnose PV falls I.a)+b) und 1 x II. <u>oder</u> I a) und 2 x II.

Tefferi et al., Blood 2007

Polyzythämia vera
Was ändert sich gem. WHO Kriterien 2016

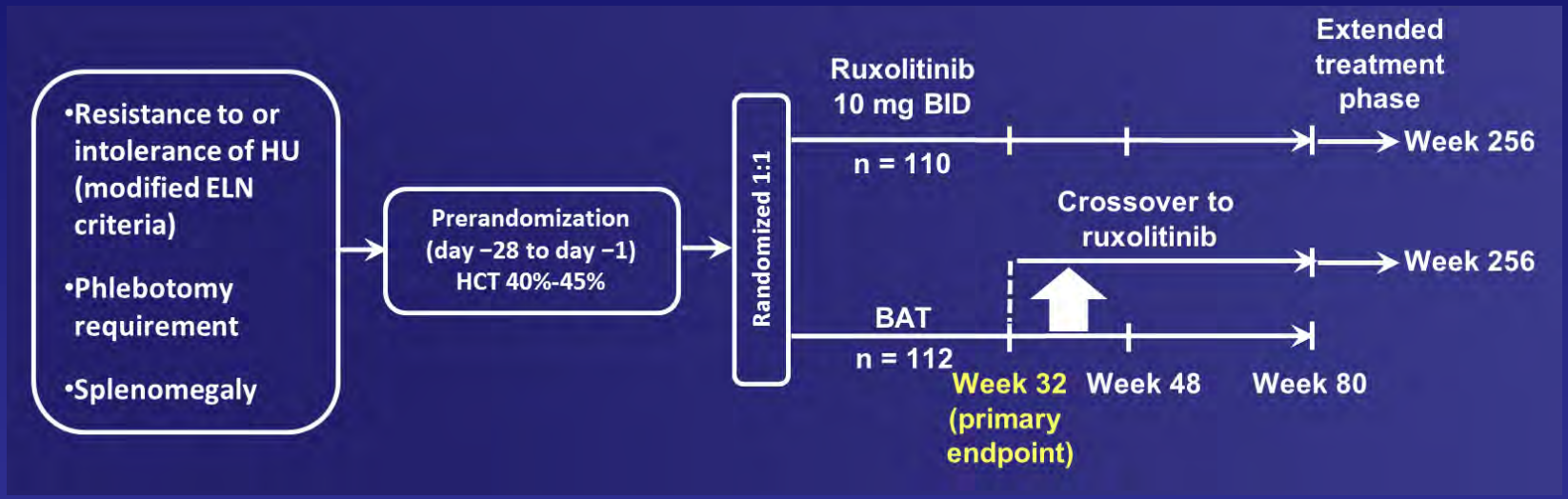
- Hämatokrit (Hkt) Hämoglobin (Hb) Schwellenwerte signifikant erniedrigt **(Männer: Hb > 16.5 g/dL oder Hkt > 49%; Frauen: Hb > 16.0 g/dL oder Hkt >48%**), um insbesondere auch frühe Formen der Erkrankung diagnostisch zu erfassen

- In Analogie zur ET und PMF Knochenmarksmorphologie als Hauptkriterium

- Bei klinisch eindeutiger Erythrozytose (Männer: Hb >18.5 g/dL, Hkt >55.5%; Frauen: Hb >16.5 g/dL, Hkt > 49.5%) und JAK2 Mutation kann auf eine Knochenmarksbiopsie verzichtet werden

RESPONSE Trial

Study Design



Primary endpoint (composite): % of patients who achieved both HCT control and spleen response at Week 32

1. HCT control

No phlebotomy from week 8 to 32, with up to 1 post-randomization phlebotomy up to week 8

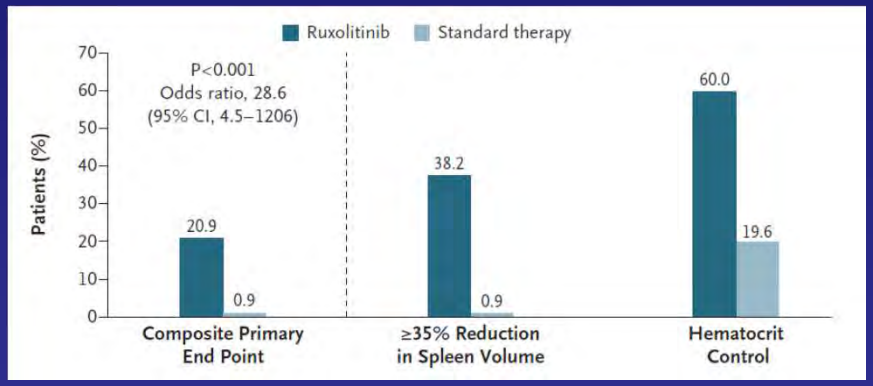
2. Spleen response

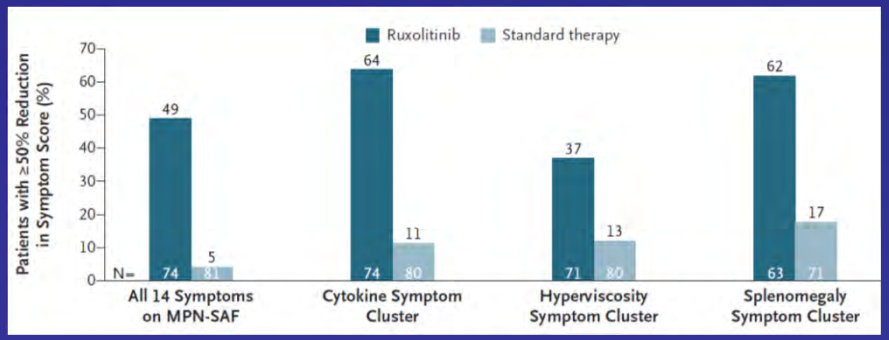
≥ 35% reduction from baseline in spleen volume by MRI

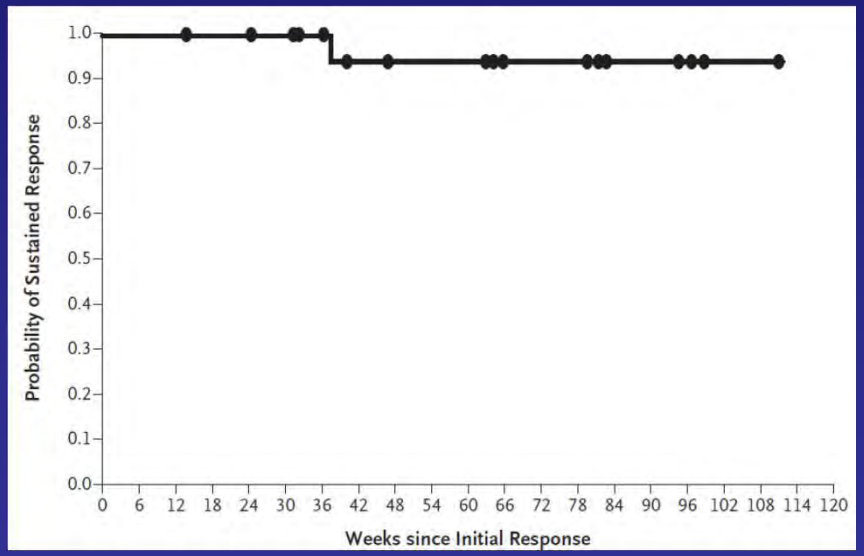
ORIGINAL ARTICLE

Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

Alessandro M. Vannucchi, M.D., Jean Jacques Kiladjian, M.D., Ph.D., Martin Griesshammer, M.D., Tamas Masszi, M.D., Ph.D., Simon Durrant, M.D., Francesco Passamonti, M.D., Claire N. Harrison, D.M., Fabrizio Pane, M.D., Pierre Zachee, M.D., Ph.D., Ruben Mesa, M.D., Shui He, Ph.D., Mark M. Jones, M.D., William Garrett, M.B.A., Jingjin Li, Ph.D., Ulrich Pirron, Ph.D., Dany Habr, M.D., and Srdan Verstovsek, M.D., Ph.D.







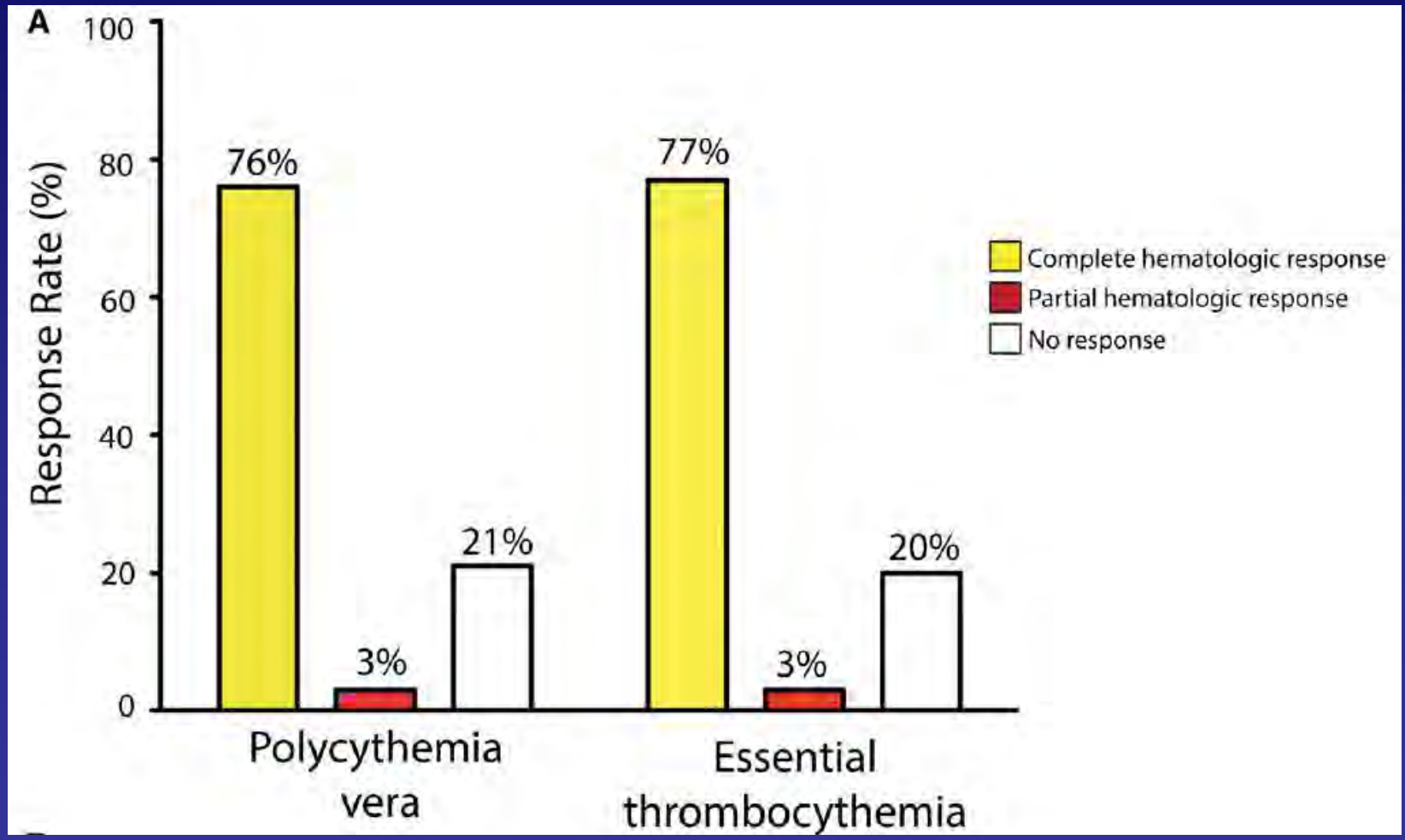
N ENGL J MED 372;5 NEJM.ORG JANUARY 29, 2015

Role for interferon alpha?

- **IFN-α has shown evidence of**
  - **Molecular responses** in patients with early stages of PV[1,3]
  - Relieving pruritus in some patients[2]
  - Inducing complete hematologic responses[1,2,3]
  - Based upon phase II studies in a limited number of patients IFN-α affects rates of thrombosis, the evolution to AML or secondary MF, and the development of bone marrow fibrosis[1]
  - Data from phase III trials are eagerly awaited[1]

1. Mascarenhas J, et al. *Haematologica*. 2014;99:945-949; 2. Barbui T, et al. *Blood Rev.* 2012;26:205-211; 3. Kiladjian JJ, et al. *Blood.* 2008;112;3065-3072.

Molecular analysis of patients with PV or ET receiving pegylated interferon α-2a



Quintas-Cardama A, et al. *Blood.* 2013;122(6):893-901.

Molecular analysis of patients with PV or ET receiving pegylated interferon α-2a

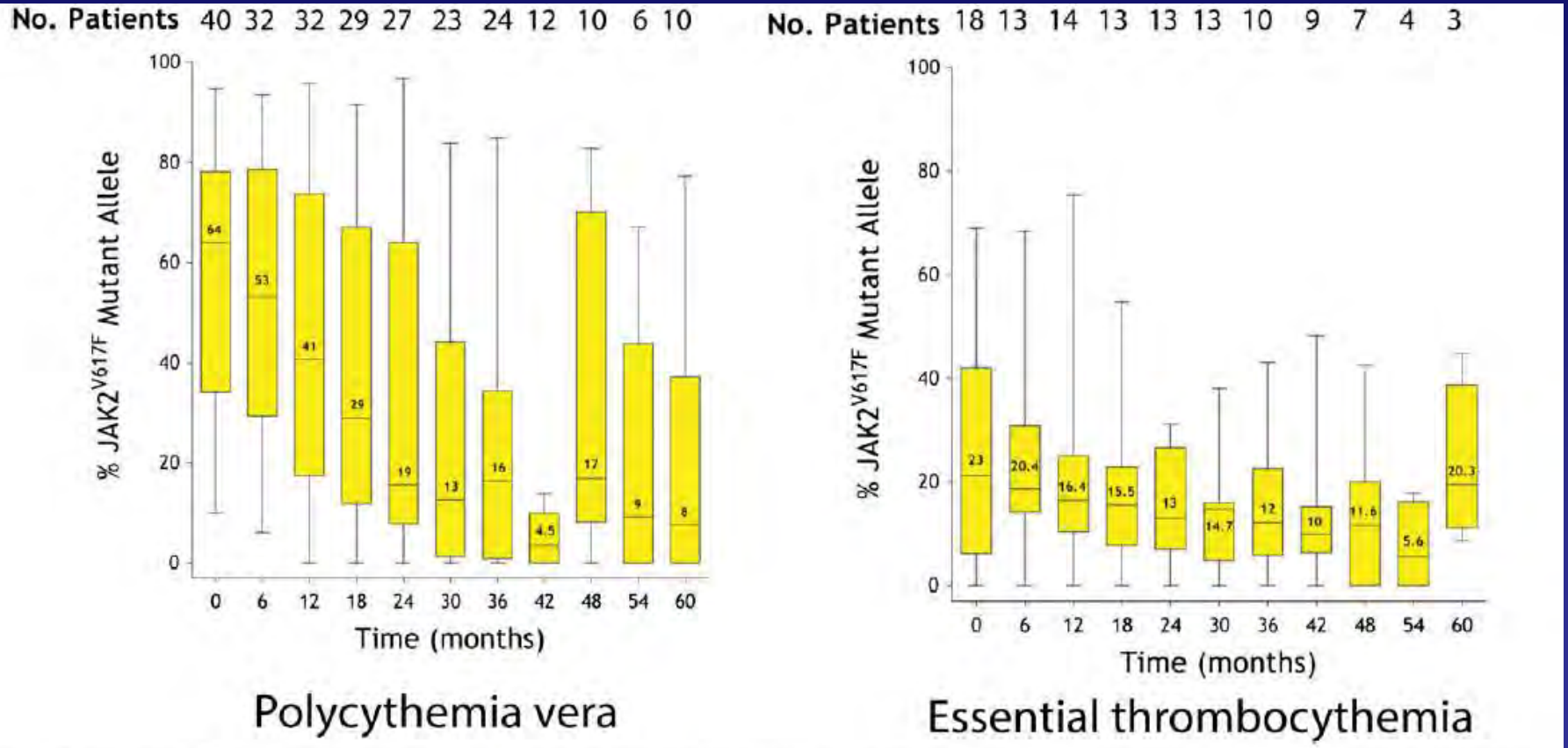
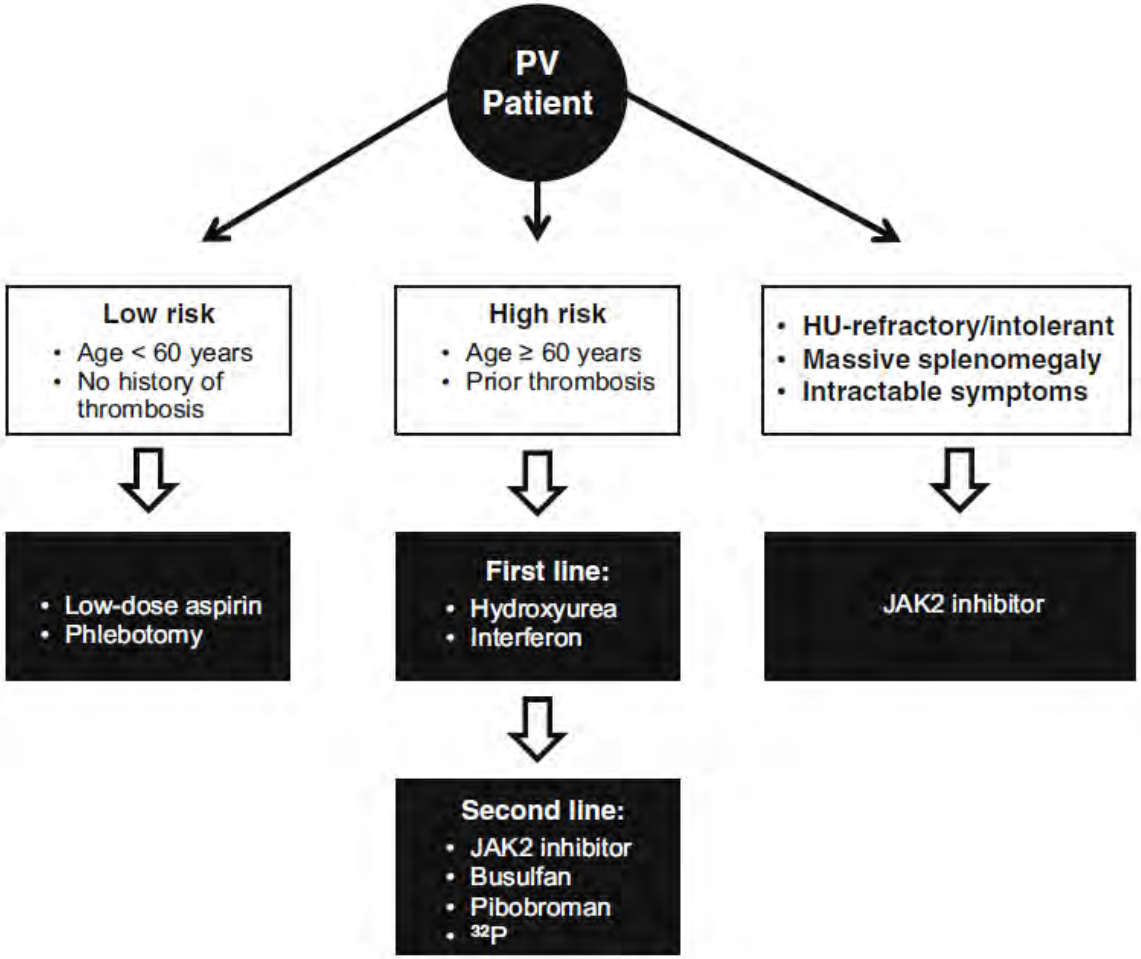


Figure 1. Long-term follow-up of response to PEG-IFN-α-2a. (A) Hematologic response in patients with PV or ET. (B) Dynamics of *JAK2*V617F mutant allele burden in patients with PV or ET over time. Black horizontal lines indicate median values; black bars represent minimum and maximum values; yellow rectangular boxes represent values included between the 25% and the 75% percentiles.

Quintas-Cardama A, et al. *Blood.* 2013;122(6):893-901.

Management outlook in the era of novel therapies

Suggested treatment algorithm in PV [1]



1. Griesshammer M, et al. *Ann Hematol*. 2015;94 (6): 901-10.

What about oral anticoagulation in PV and ET?

Outcomes of 150 patients with PV and ET treated with vitamin K antagonists (VKA) for arterial or venous thrombosis depending on the observation periods in which patients were receiving anticoagulationor not

	On-VKA 764 patients-years		Off-VKA 199 patients-years		
	No. of events	Incidence rate* (95% CI)	No. of events	Incidence rate* (95% CI)	*P*
Major thrombosis	34	4.5 (3.0-6.2)	24	12.0 (7.7-18)	<0.0005
Arterial thrombosis	13	1.7 (0.9-2.7)	9	4.5 (2.0-8.5)	0.03
Venous thrombosis	21	2.7 (1.7-4.2)	15	9.0 (4.2-12)	<0.0005
Major bleeding	14	1.8 (1.0-3.0)	3	1.5 (0.3-4.4)	0.8

* Events per 100 patient-years

Hernández-Boluda *et al.* Ann Hematol 2015 Feb 14

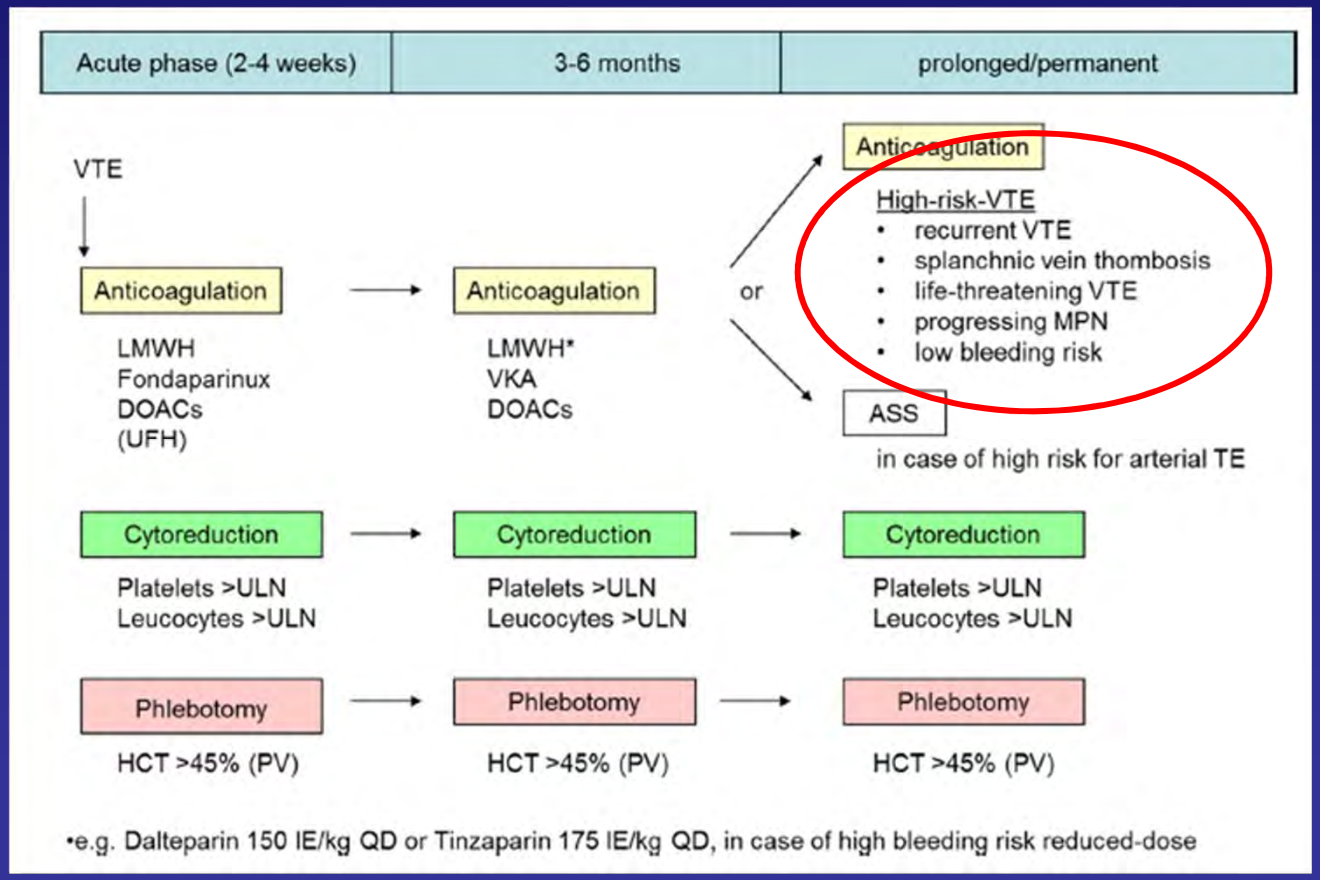
Hospital del Mar

Parc de Salut MAR Barcelona

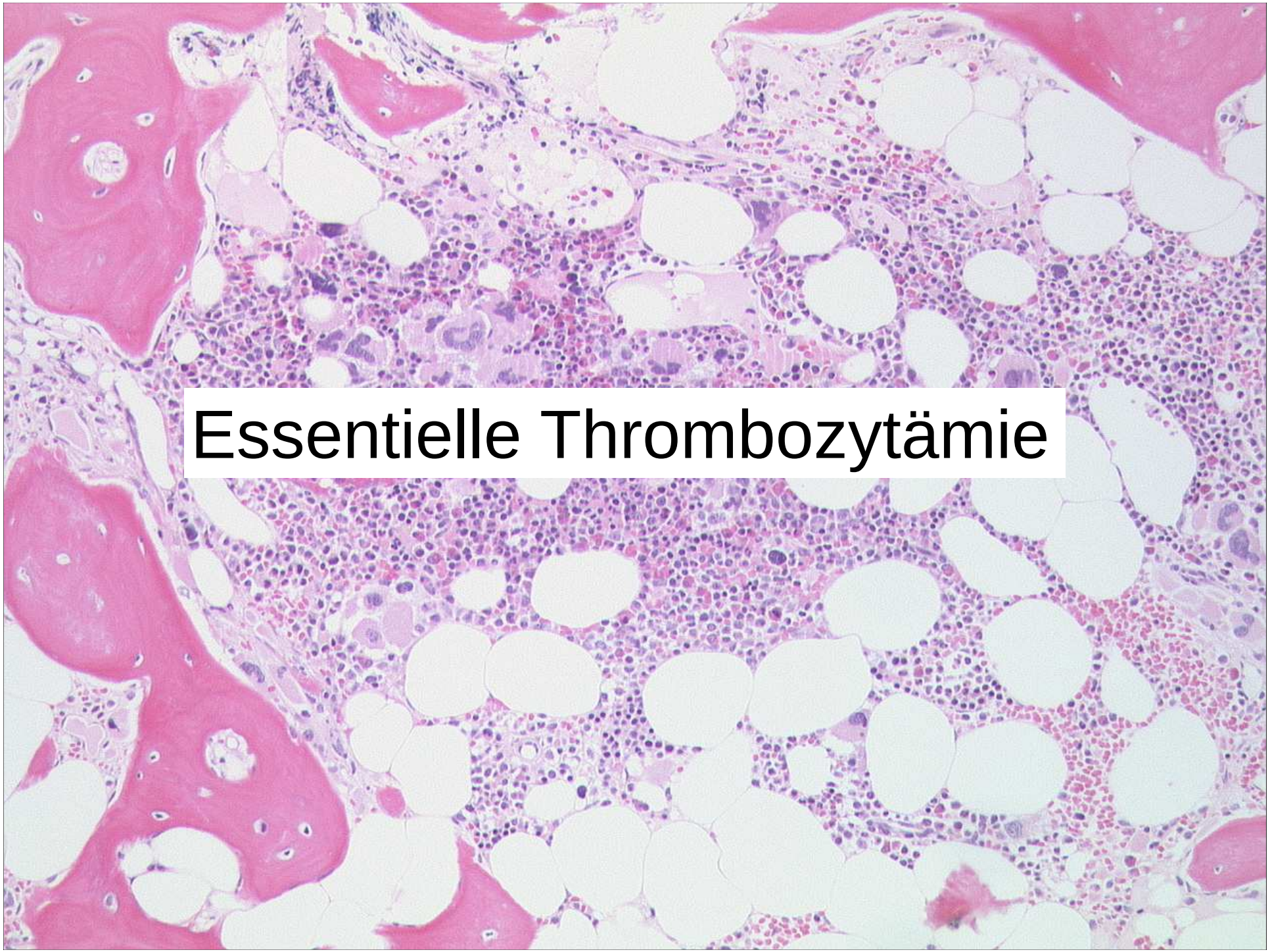
Prophylaxis and management of venous thromboembolism in patients with myeloproliferative neoplasms:

Consensus statement of the Haemostasis Working Party of the German Society of Hematology and Oncology (DGHO),the Austrian Society of Hematology and Oncology (ÖGHO) and Society of Thrombosis and Haemostasis Research (GTH e.V.)

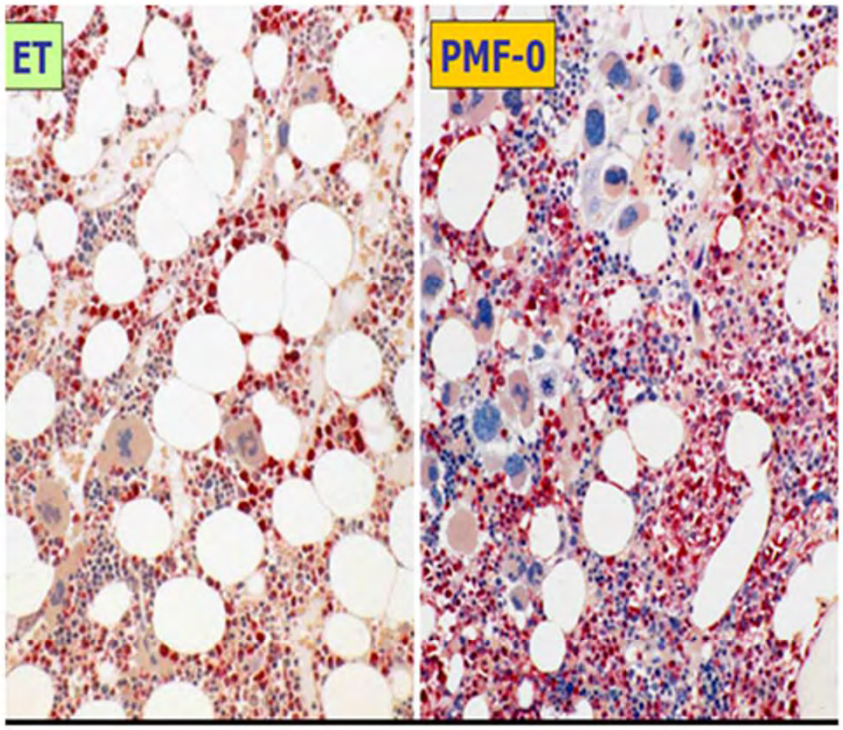
Stephan Kreher, Sebastian Ochsenreither, Ralf U. Trappe, Ingrid Pabinger, Frauke Bergmann, Petro E. Petrides, Steffen Koschmieder, Axel Matzdorff, Andreas Tiede, Martin Griesshammer, Hanno Riess

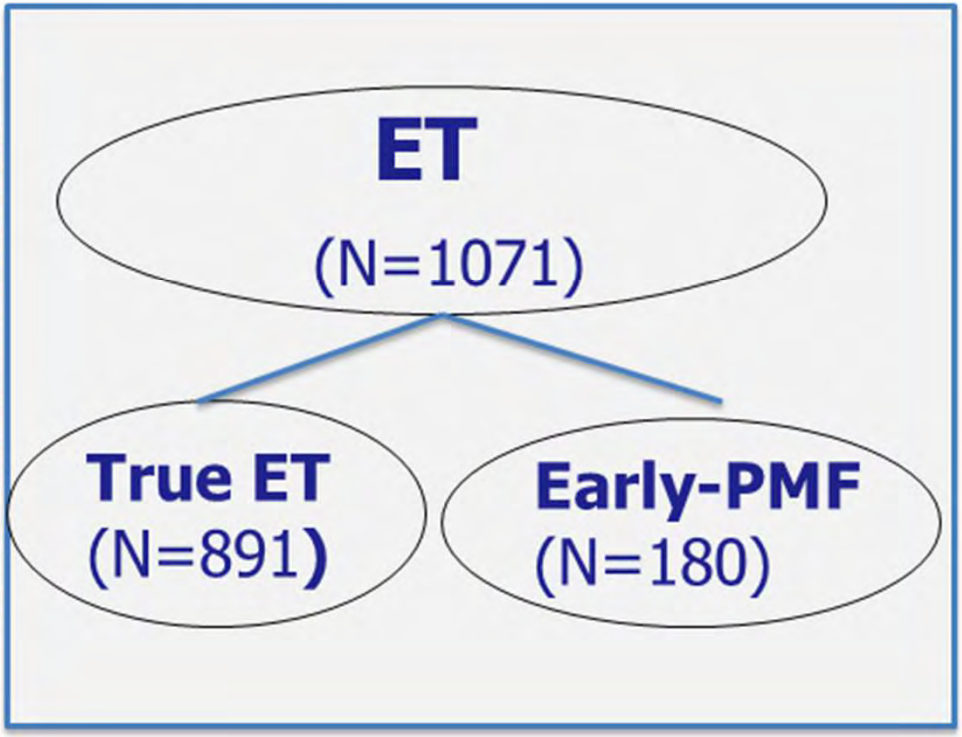


Ann Hematol (2014) 93:1953–1963


Essentielle Thrombozytämie

In ET, presentation and outcomes are influenced by a strictly defined WHO-2008 diagnosis

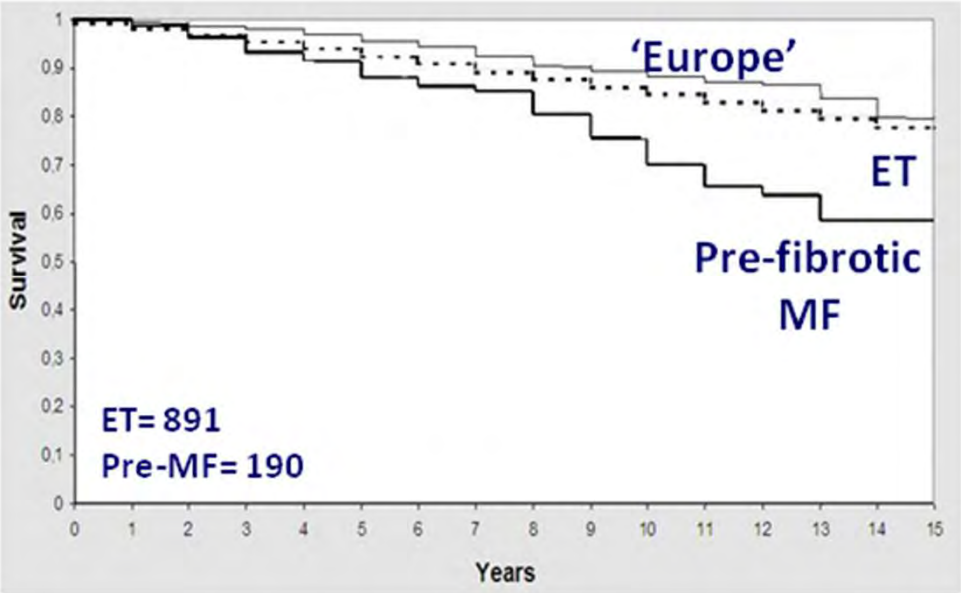




Barbui et al, JCO 2011; Aug 10; 29(23):3179-84

True ET vs early-PMF: prognostic relevance

	Incidence 100 pt-y	
	ET	Pre-MF
Thrombosis	1.7	1.9
Hemorrhage	0.79	1.39
→ overt MF	0.5	1
→ AML	0.1	0.6
Death	1.3	2.7



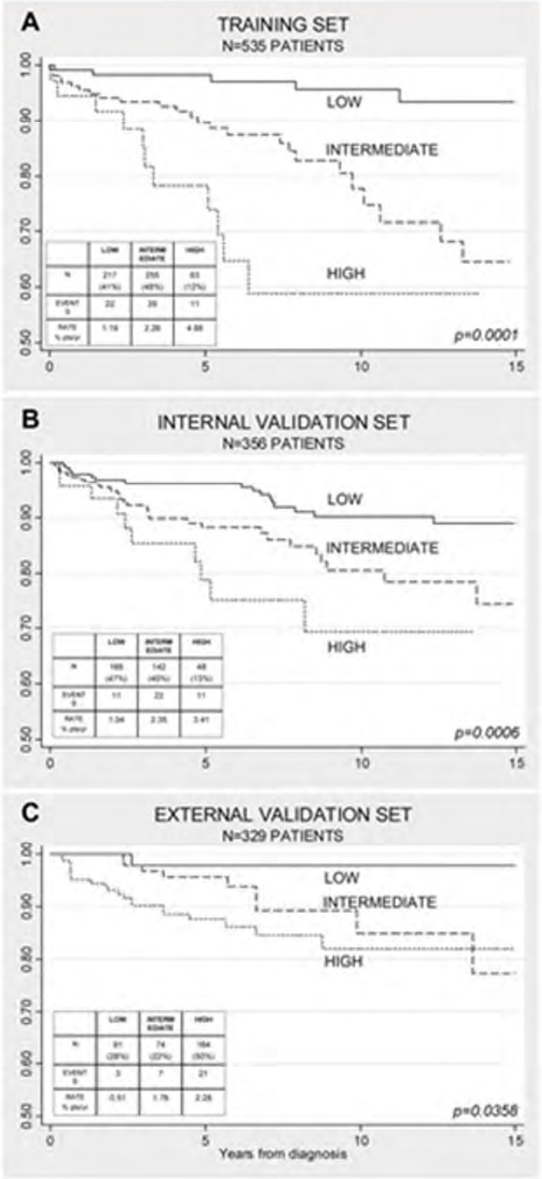
- The survival in pre-fibrotic MF can be reduced compared to «true» ET

Barbui T et al. JCO 2011;23:3179-84; Finazzi G et al. Leukemia 2012;26:717-9

Prediction of thrombosis in 867 WHO-based ET: the IPSET-thrombosis model

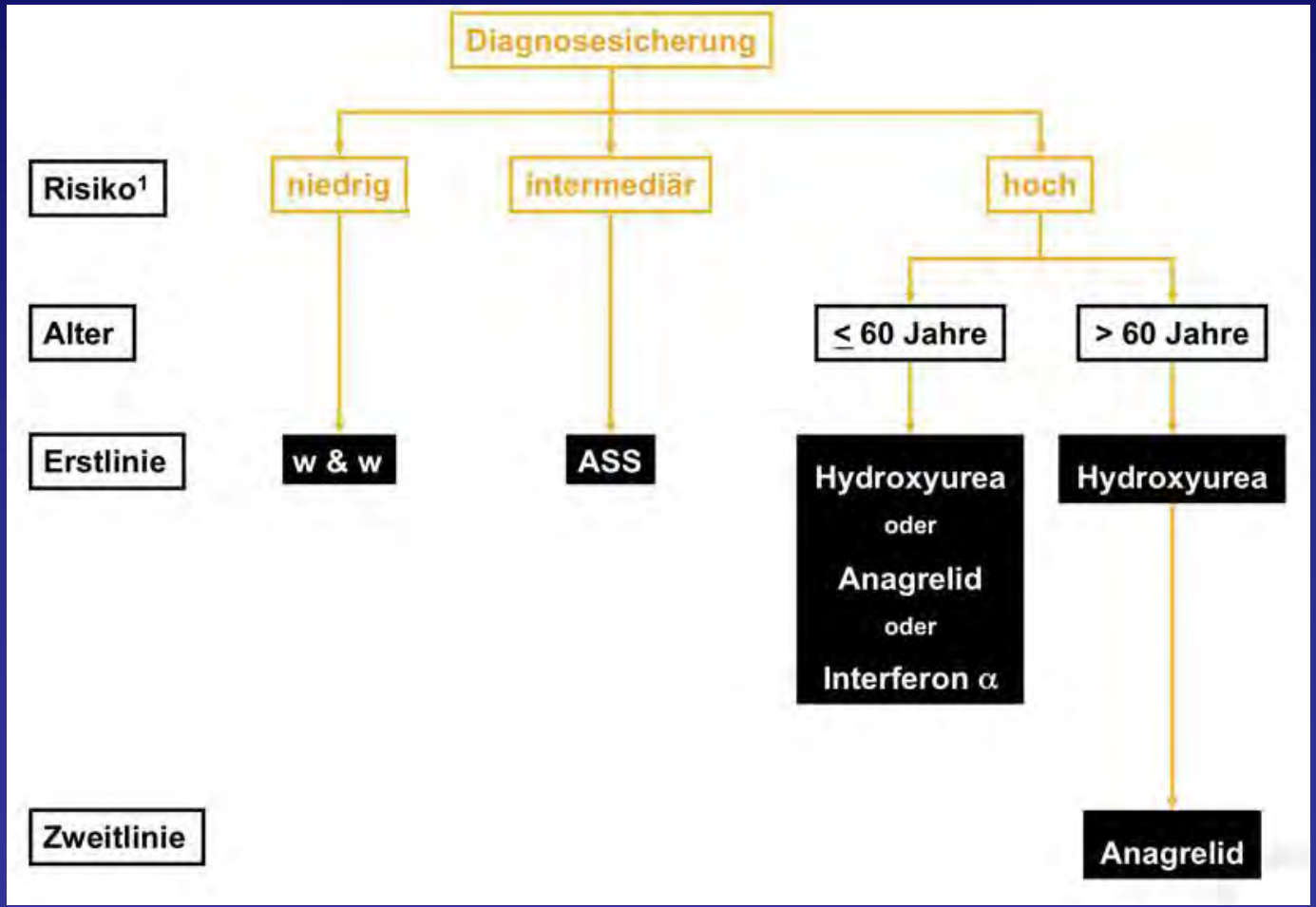
Risk factors	
Age > 60 years	1 point
Cardiovascular risk factors	1 point
Previous thrombosis	2 points
JAK2V617F	2 points

Risk Categories/score	
Low	0-1
Intermediate	2
High	≥ 3



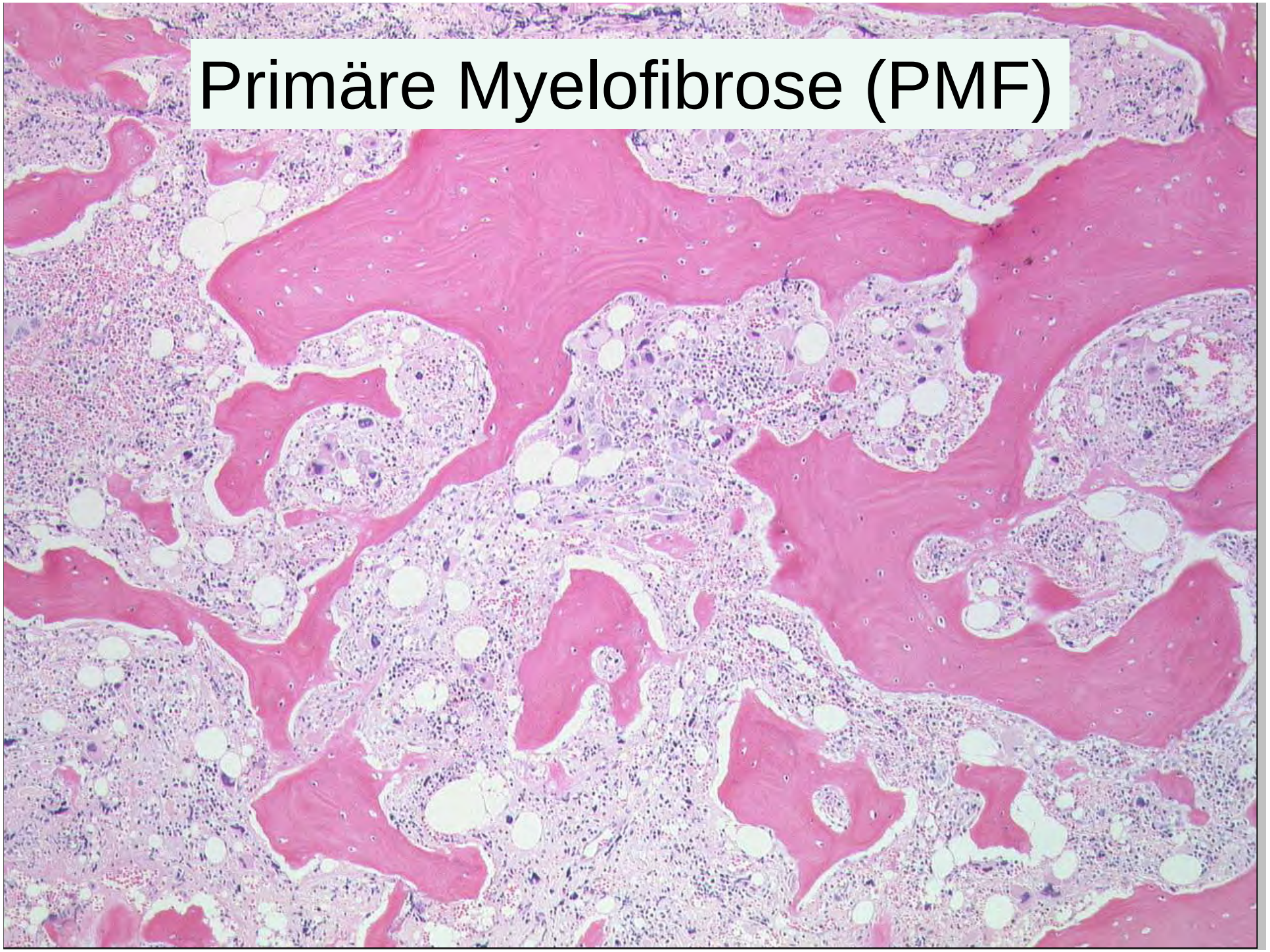
Barbui T, et al. *Blood* 2012; 120:5128-5133.

Behandlungsalgorithmus ET

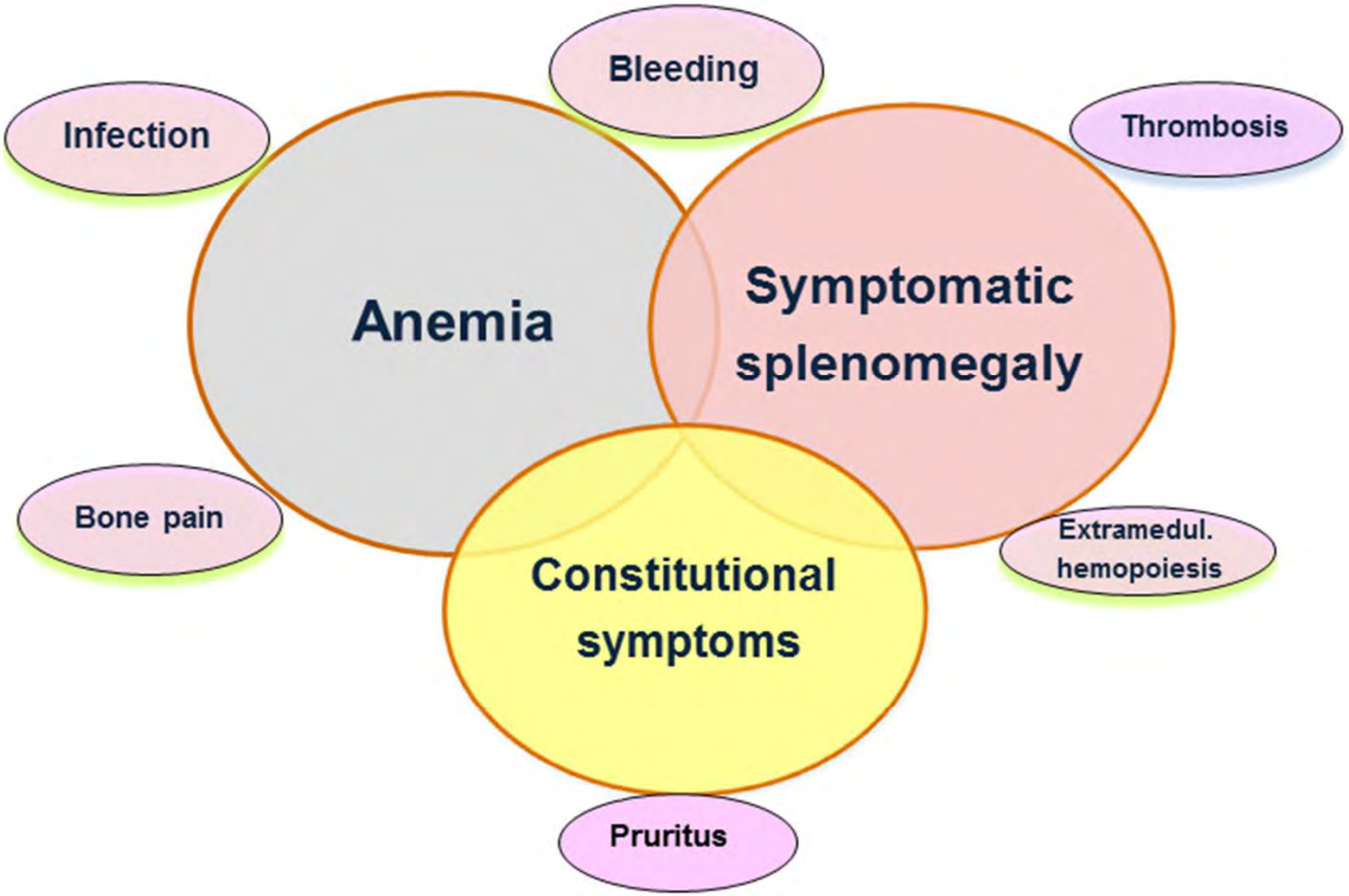


DGHO Leitlinien 2014

Primäre Myelofibrose (PMF)

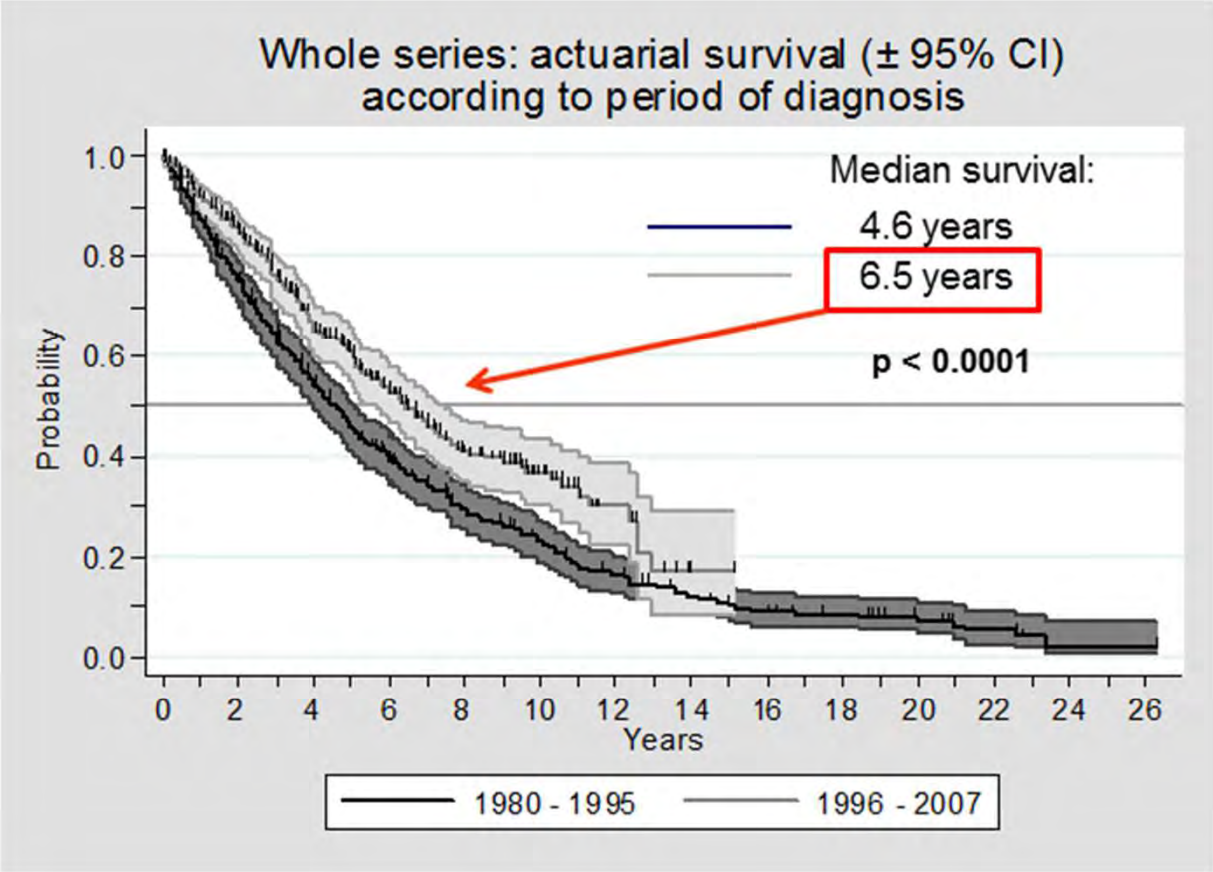


Clinical Manifestations of Myelofibrosis



Cervantes F How I treat myelofibrosis, Blood 2014;124:2635-42

PMF: Survival According to Diagnostic Period (n= 802)



PMF, primary myelofibrosis

Cervantes F *et al.*, JCO 2012; 30:2981-7

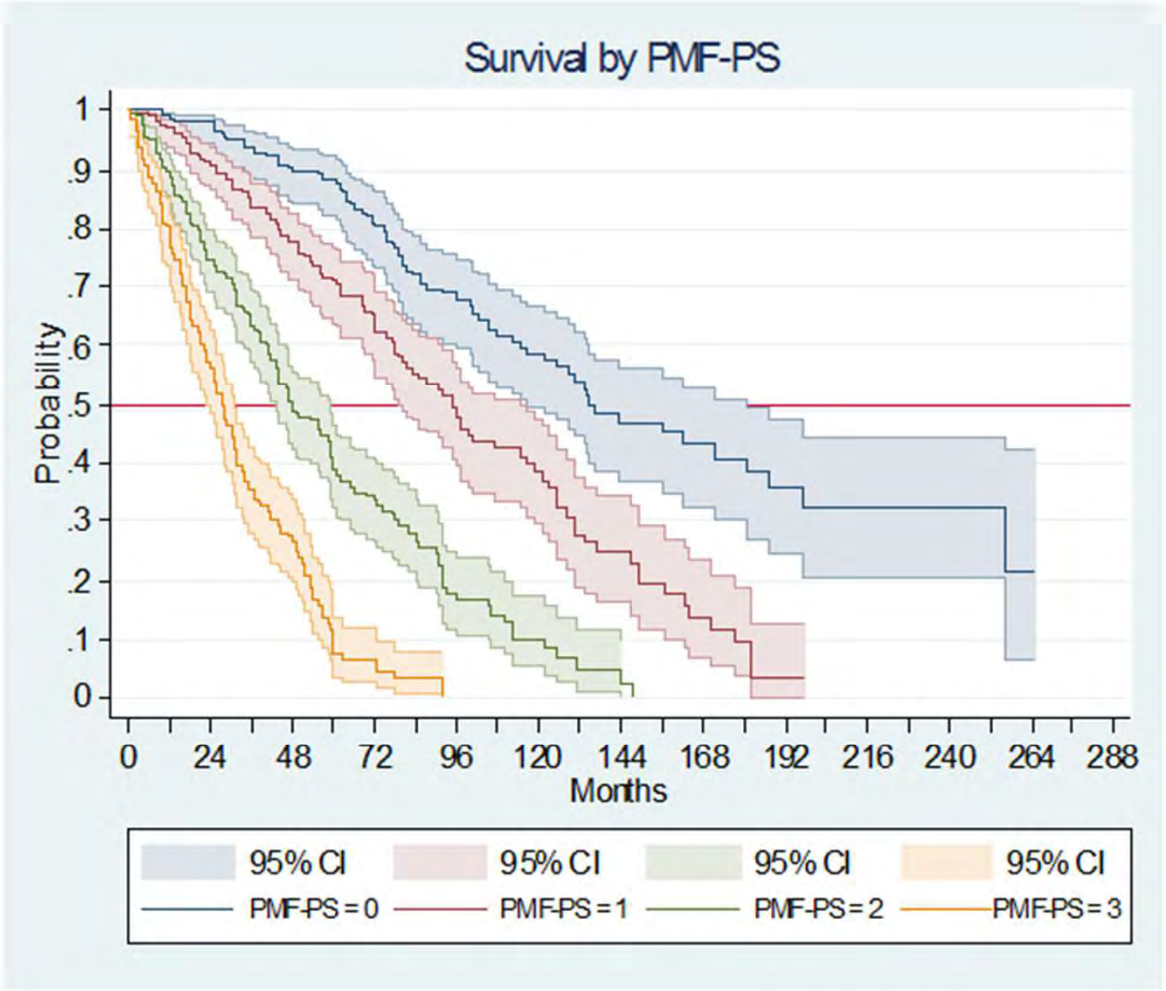
IPSS: Risk Classification of PMF at Presentation

Prognostic factors

- Age >65 years
- Constitutional symptoms
- Hb <10 g/dL
- Leukocytes >25 x 10^9/L
- Blood blasts ≥1%

Risk groups

• Low	0
• Intermediate-1	1
• Intermediate-2	2
• High	≥3



IPSS, international prognostic scoring system

Cervantes F *et al.*, Blood 2009, 113:2895-05

Summary of Current Prognostic Models for PMF

Variable	IPSS	DIPSS	DIPSS-plus
Age >65 yrs.	+	+	
Constitutional symptoms	+	+	
Hb <10 g/dL	+	+	
Leukocytes >25 x 10^9/L	+	+	
Blood blasts ≥1%	+	+	
Platelets <100 x 10^9/L			+
RBC transfusion need			+
Unfavorable karyotype (+8, -7/7q-, -5/5q, i17q, 12p-, 11q23 rearr.)			+
Score	1 point each	1 point each (Hb: 2 points)	DIPSS int-1: 1 point int-2: 2 points high: 3 points Other factors: 1 point

DIPSS, dynamic international prognostic scoring system

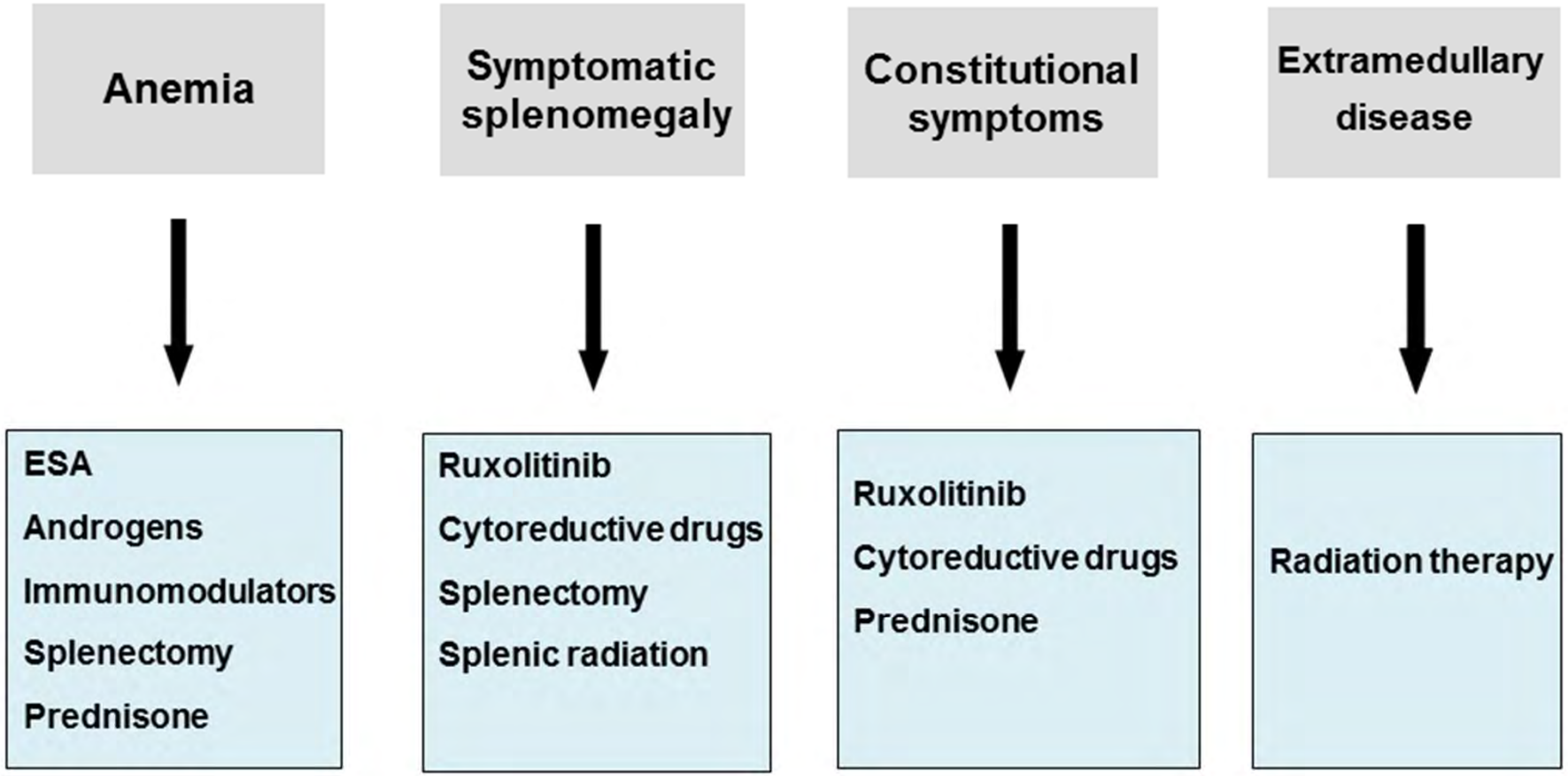
Cervantes F *et al.*, Blood 2009,113:2895; Passamonti F *et al.*, Blood 2010,115:1703; Gangat N *et al.*, JCO 2011, 29:392

MIPSS: Molecular International Prognostic Scoring System for PMF

MULTIVARIATE ANALYSIS			Weighted value
Variables	HR (95% CI)	P	
Age > 60 yrs	3.8 (2.60-5.51)	<0.0001	1.5
Hb < 100 g/L	1.4 (1.01-1.99)	0.04	0.5
Constitutional symptoms	1.5 .(1.13-2.16)	0.007	0.5
PLT < $200x10^9$/L	2.5 (1.77-3.42)	<0.0001	1.0
Triple negativity	3.9 (2.20-6.80)	<0.0001	1.5
JAK2/MPL mutation	1.8 (1.11-2.90)	0.016	0.5
ASXL1 mutation	1.4 (1.06-1.99)	0.02	0.5
SRSF2 mutation	1.7 (1.08-2.58)	0.02	0.5

Vannucchi A *et al.*, ASH 2014, abstract 405

Clinically-adjusted Treatment of Myelofibrosis

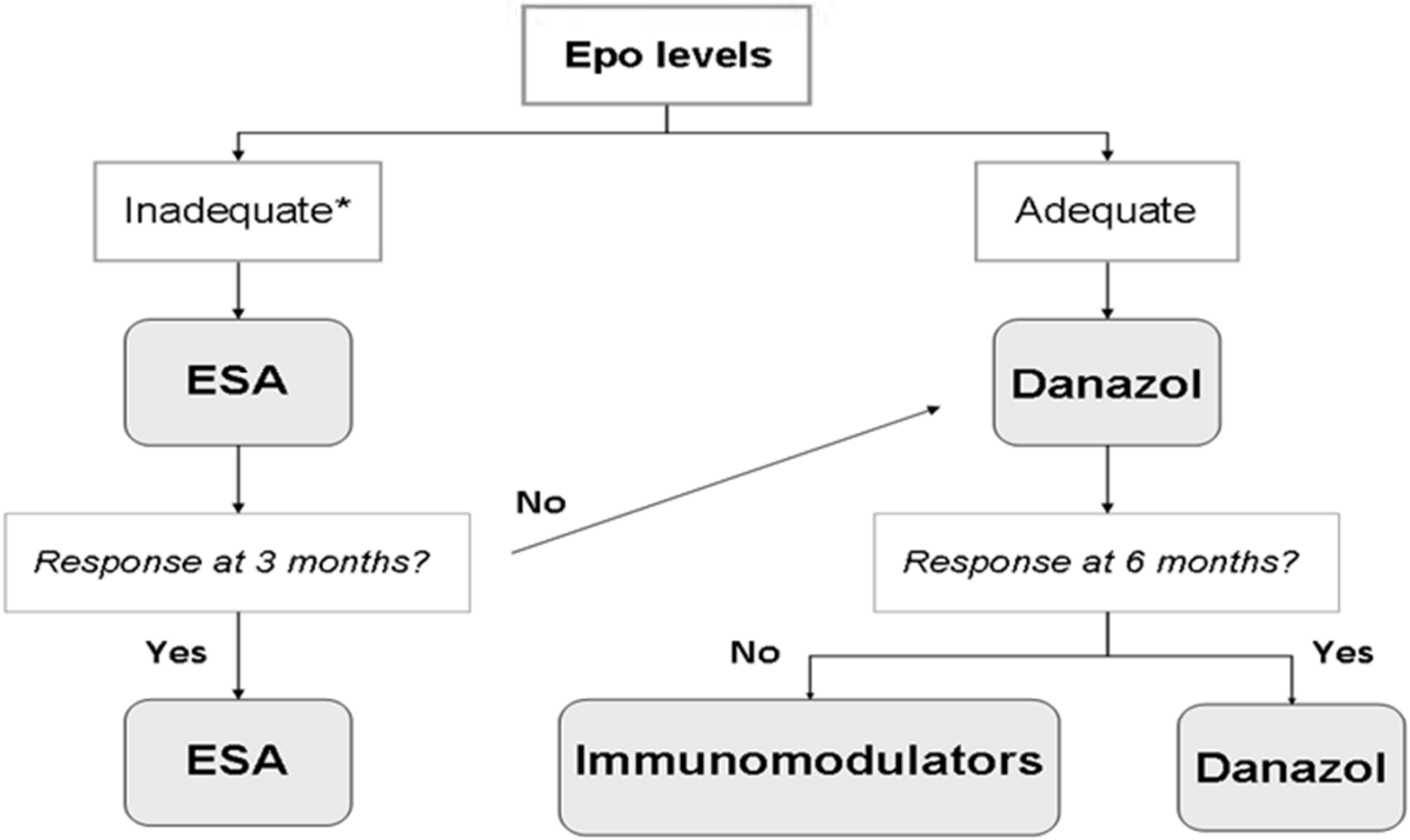


Danazol Treatment of the Anemia of Myelofibrosis (N= 30)

Daily dose:	
Initial	600 mg
Maintenance	200 mg
Response rate	37%
CR	n = 8
PR	n = 3
Median time to response, months (range)	5 (1-9)
Withdrawal due to toxicity	2/30
Durable responses	5/11

Cervantes F *et al.*, Br J Haematol 2005; 129:771-5

Treatment Algorithm for the Anemia of MF



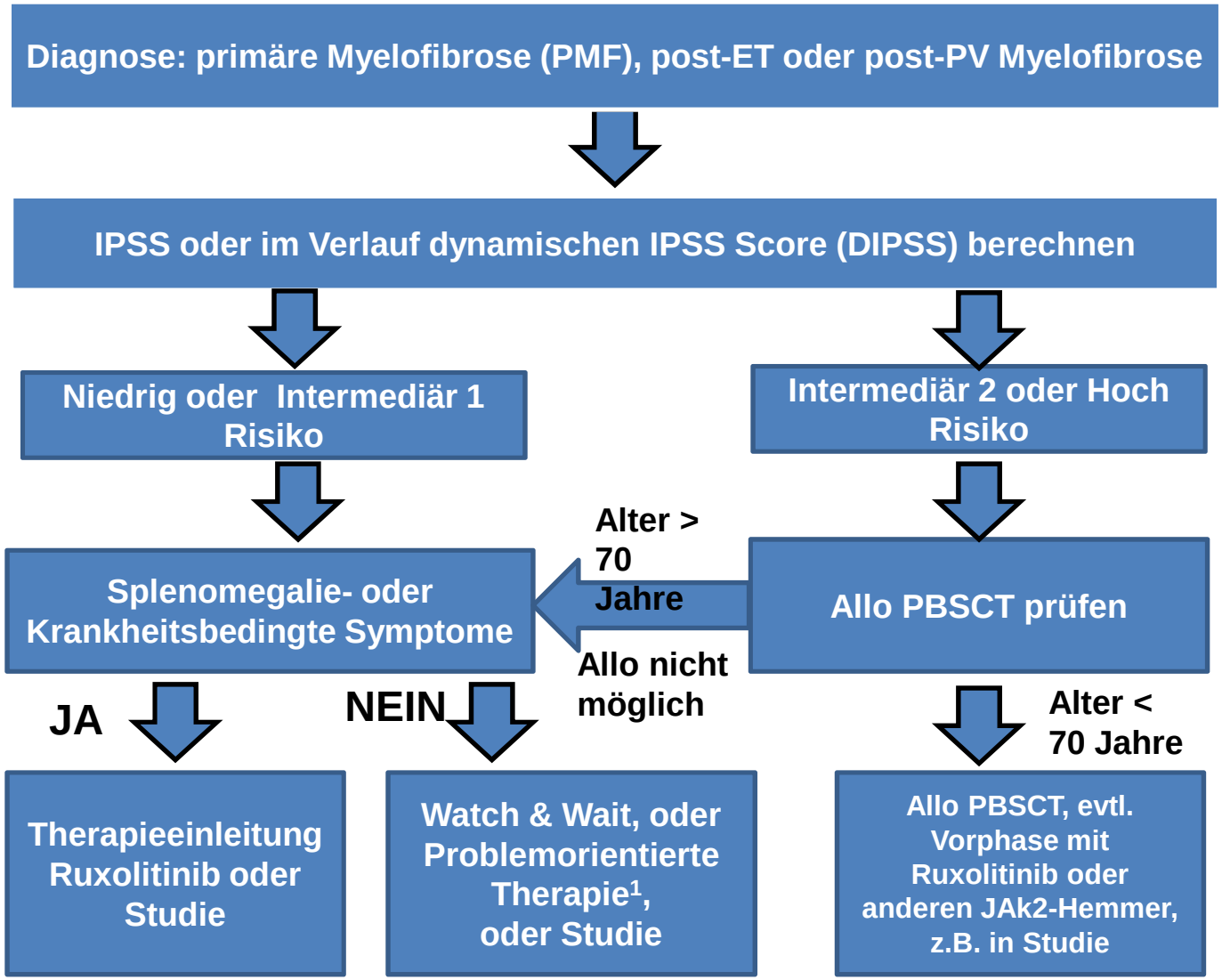
Cervantes F, How I treat myelofibrosis, Blood 2014;124:2635-42

Efficacy of JAK Inhibitors in Myelofibrosis

	Spleen	MF Sympt.	Anemia	Survival effect	JAK2
Ruxolitinib	+	+		+	?
Momelotinib	+	+	+	?	?
Pacritinib	+	+		?	?
AZD-1480	+	+		?	?
NS-018	+	+		?	?

Combination Studies with JAK Inhibitors to Improve Anemia

- ESA
- Danazol
- Lenalidomide
- Pomalidomide
- Azacitidine



[1]Problemorientierte Therapie: Erythropoetin, Hydroxyurea, Steroide, Androgene oder Imide.

DGHO Leitlinien 2014