MEDIZINISCHE UNIVERSITÄT WIEN

Aktuelle Diagnose und Therapieempfehlungen zu MPN

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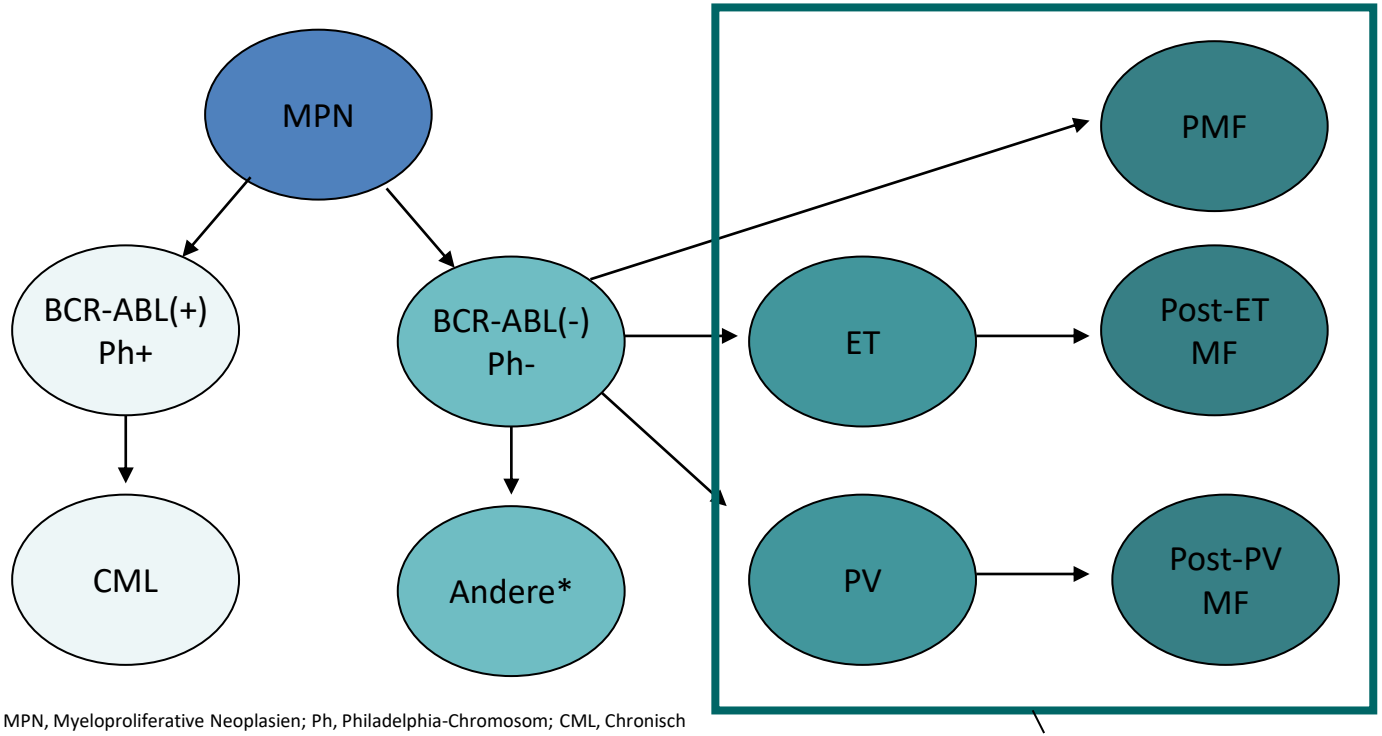
Klassische MPN nach WHO-Klassifikation 2016



MPN, Myeloproliferative Neoplasien; Ph, Philadelphia-Chromosom; CML, Chronisch Myeloische Leukämie; PMF, Primäre Myelofibrose; PV, Polyzythämia vera; ET, Essentielle, Thrombozythämie

* Es gibt weitere von der WHO als MPN klassifizierte Erkrankungen, z. B. Chronische Neutrophilenleukämie, Chronische Eosinophilenleukämie, Hypereosinophiles Syndrom,

Thiele J, Kvasnicka HM. Curr Hematol Malig Rep. 2009;4:33–40.
Tefferi A, Vardiman JW. Leukemia. 2008;22:14–22.

Philadelphia-Chromosom negative MPN

ET
essentielle Thrombozythmämie

Thrombozytose
thrombembolische Ereignisse

PV
Polycythemia vera

Eryzythose
± Thrombozytose
± Leukozytose
thrombembolische Ereignisse
Pruritus

PMF
primäre Myelofibrose

initial Thrombozytose/Leukozytose und Thrombosen möglich
im Verlauf zunehmende Zytopenien
Leukoerythroblastisches Blutbild
Splenomegalie
konstitutionelle Symptome

Management Myeloproliferative Neoplasien

- **Polyzythämia Vera**
- Primäre Myelofibrose
- Essentielle Thrombozythämie

Diagnostik bei Verdacht auf *Polyzythämia vera*

Genaue Erhebung der Anamnese bezüglich:

- **thromboembolischer Komplikationen**
- **Blutungen**
- **Mikrozirkulationsstörungen**
- **Pruritus**

Blue-Toe Snydrome in PV

(Peripheral Microcirculatory Disturbances)

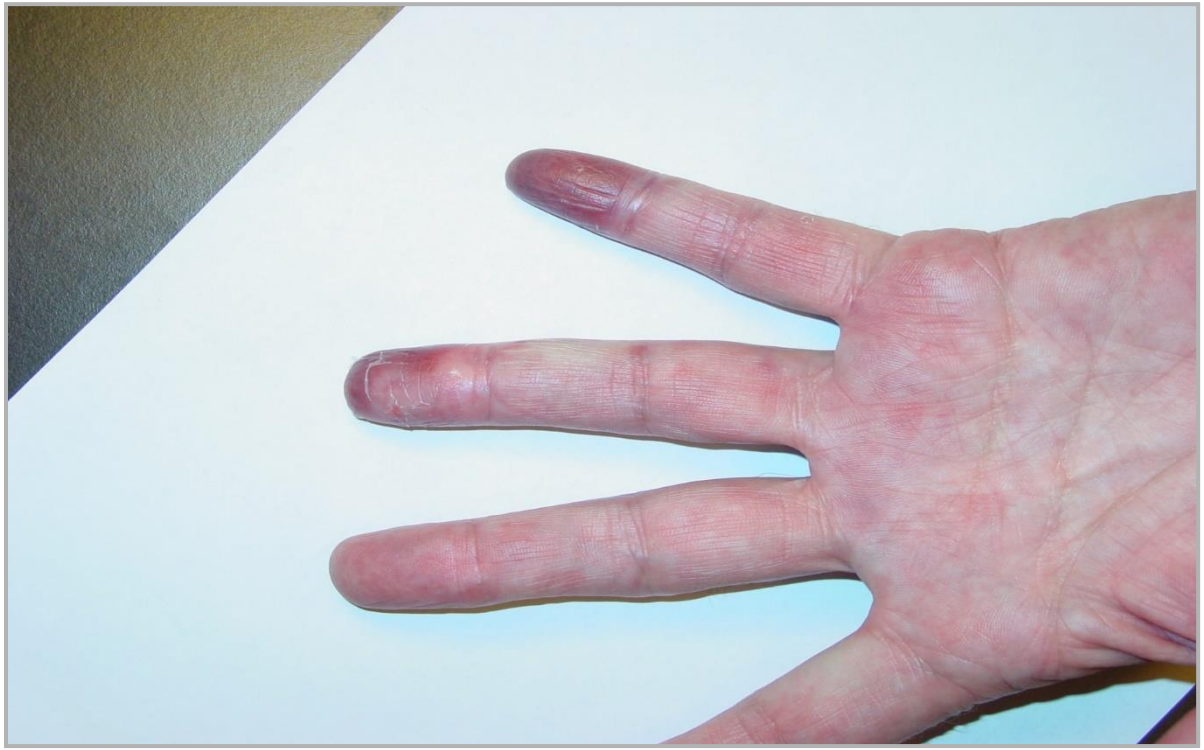


Foto: C. Sillaber

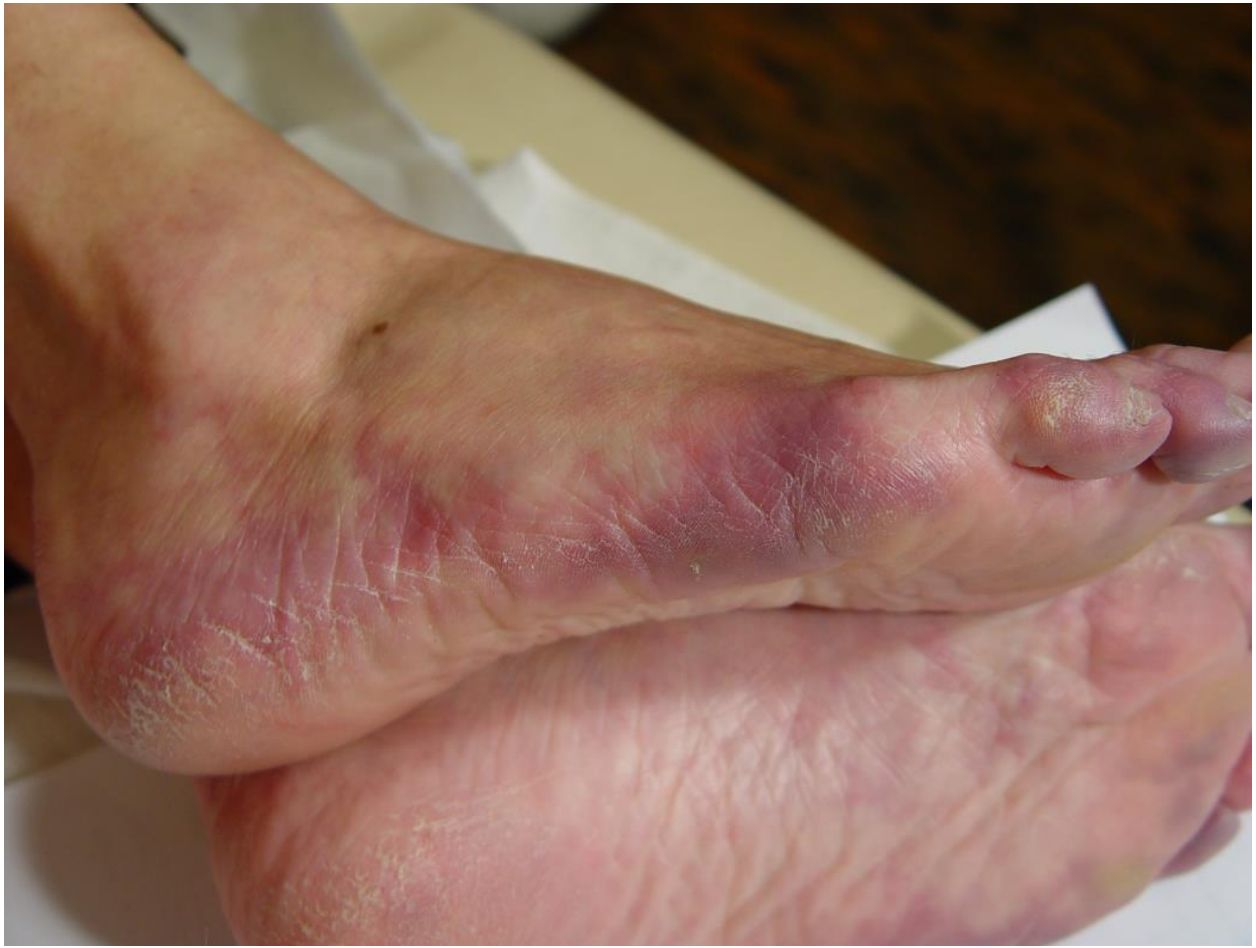


Foto: C. Sillaber

Diagnostik bei Verdacht auf *Polyzythämia Vera*

Ausschluß einer sekundären Polyglobulie

- **BB + Diff., O2-Sättigung**
- **JAK2-Mutation,**
- **EPO-Spiegel, (autonomes BFU-E Wachstum)**

Knochenmarksbiopsie:

- **Histologie**
- **Molekularbiologie (JAK-2, BCR-ABL)**
- **(Stammzellen, autonomes BFU-E Wachstum)**

Ultraschall des Abdomens

- **(mit genauer Angabe der Milzgröße)**

Polycythemia vera (PV)

Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion (WHO 2016)

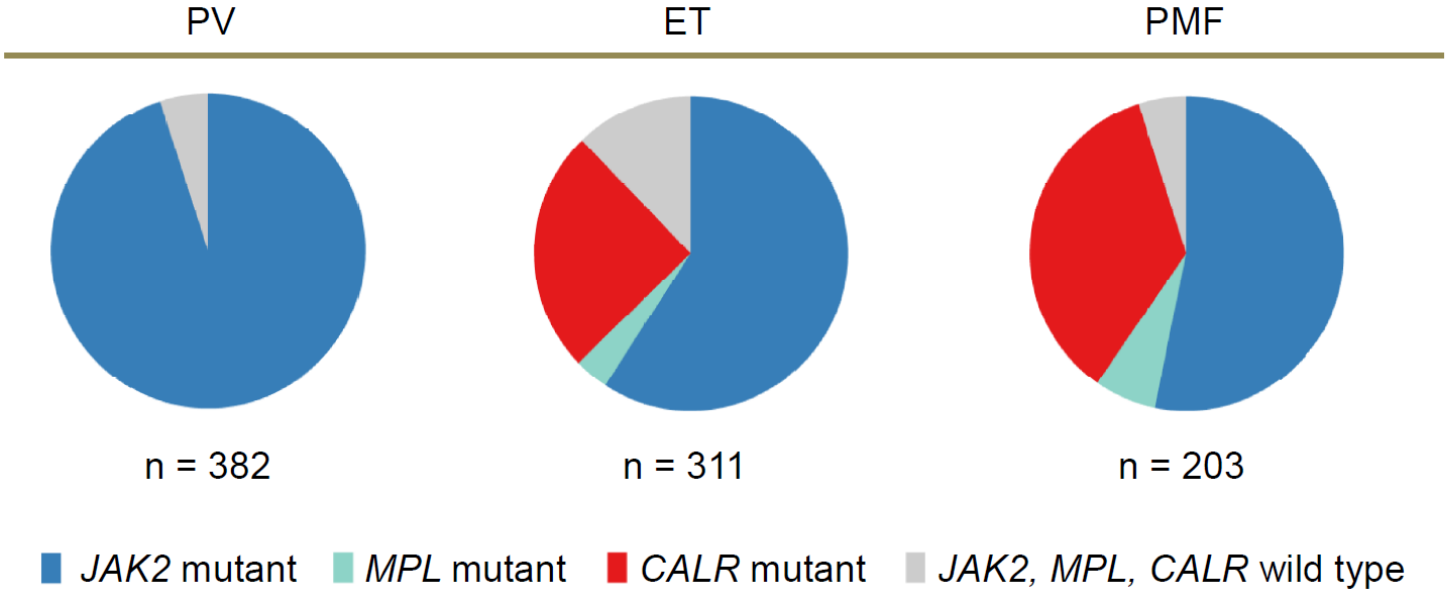
Major criteria

- Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women or Hematocrit > 49% in men, > 48% in women or increased red cell volume
- Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
- Presence of JAK2V617F or JAK2 exon 12 mutation

Minor criteria

- Subnormal serum erythropoietin level

Aufteilung von *JAK2*, *MPL* und *CALR* Mutationen in den drei klassischen MPN-Erkrankungen



bei Verdacht auf MPN --> Abnahme JAK2, MPL, CALR, BCR-ABL aus peripheren Blut

Klinischer Verlauf der Polyzythämia vera

Asymptomatische Phase	Erythrozytotische Phase	Spent Phase KM-Fibrose Leukämie
Erythrozytose Splenomegalie	Erythrozytose Leukozytose Thrombozytose Splenomegalie Thrombose Pruritus	Anämie Thrombozytopenie Leukoerythroblast. Blutbild Riesenmilz Fieber, Nachtschweiß

JAK2-Mutation

Polycythaemia vera

Typical peripheral blood parameters

Patient: M.I., male, 66 years

WBC	13.9 ($x10^9$/L)
RBC	6.37 ($x10^{12}$/L)
Hb	19.9 g/dl
Hct	58.2 %
MCV	91.4 fl
MCH	31.2 pg
Plt	751 ($x10^9$/L)

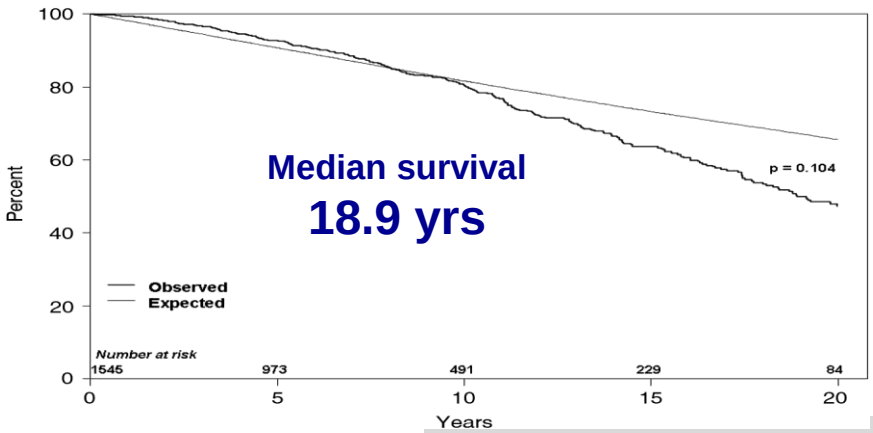
Symptome bei *Polyzythämia Vera*

- *Rötung des Gesichtes*
- *bläuliche Verfärbung der Fingerspitzen, Zehenspitzen oder Ohren*
- *Schwindel, Druck im Kopf*
- *Ohrensausen*
- *Sehstörungen*
- *Bluthochdruck*
- *Thrombosen, Blutgerinnsel*
- *Nasenbluten, sonstige Blutungen*

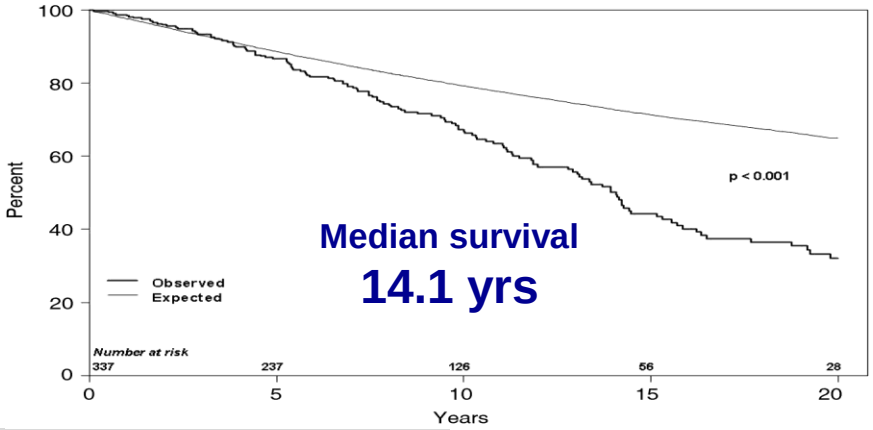
Natural history of PV

Treatment of PV matters

1559 PV patients according to WHO diagnostic criteria



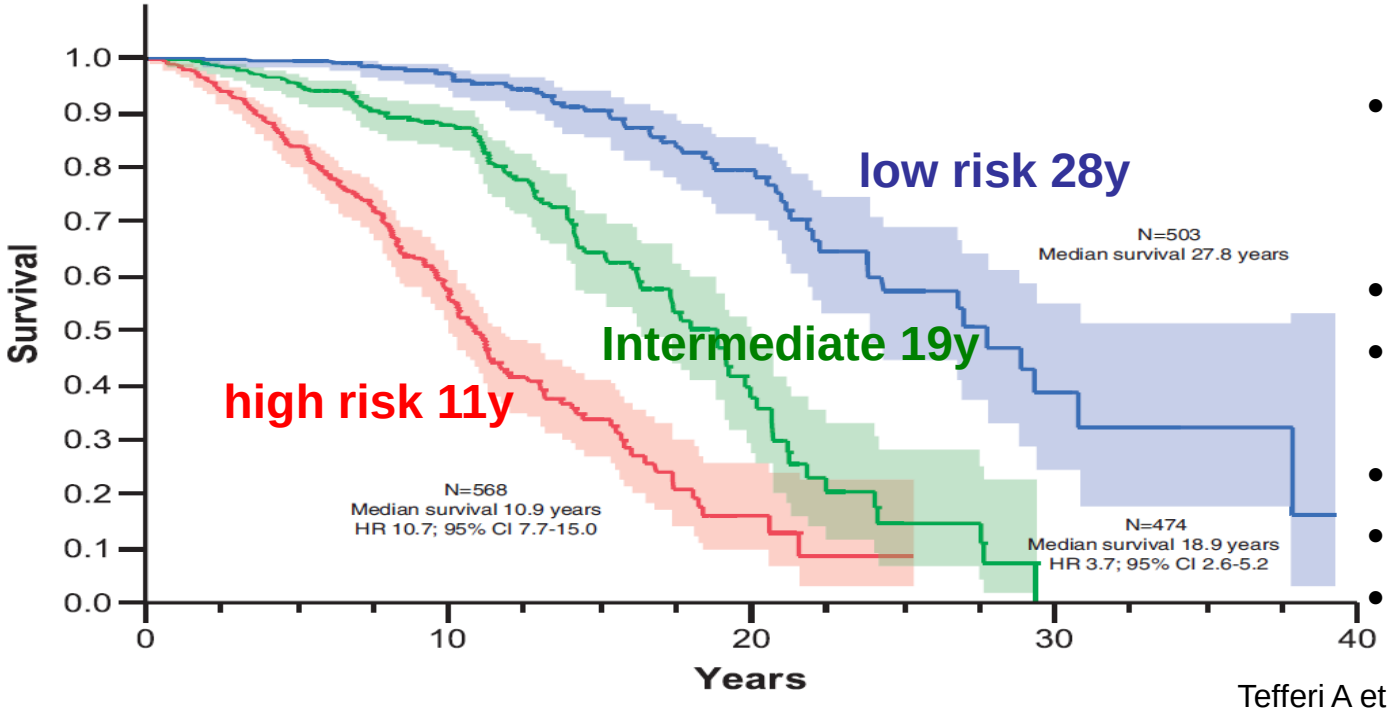
337 PV patients according to WHO diagnostic criteria (Mayo Clinic)



- survival of PV patients compared with expected survival based on individuals of the same age and sex of US pop.

Tefferi A et al. Leukemia 2013;27:1874-1881

Risikostratifiziertes Überleben bei 1545 Patienten mit PV



- ***Age***
  - ≥ 67 years (5 pts)
  - 55-66 years (2 pts)
- ***WBC*** ≥ $15x10^9$/l (1 pt)
- ***Venous thrombosis*** (1 pt)

- Low-risk → 1 pt
- Int.-risk → 2 pts
- High-risk → ≥ 3 pts

Tefferi A et al. Leukemia 2013;27:1874-1881.

Major causes of morbidity and mortality

- arterial and venous complications
- progression to myelofibrosis
- transformation to acute myeloid leukemia

Which patient is at risk?

Risk stratification	age older than 60 yrs	history of thrombosis
LOW	no	no
HIGH	yes	yes
intermediate	no	no

cardiovascular risk factors (hypertension, hypercholesterinemia, diabetes obesity, smoking)

Gangat N et a. BJH 2007 Barbui T et al. Blood Rev 2012
Passamonti F et al. Haematologica 2008
Di Nisio M et al. BJH 2007
Passamonti F et al. Am J Med 2004

Goals of treatment

→ **preventing thrombosis**

→ **preventing or delaying disease transformation**

modification of cardiovascular risk factors

use of aspirin, phlebotomy, cytoreduction

novel interferons ?

Ropeginterferon

→ **relieve symptoms**

JAK 2 inhibitors

Treatment options for PV

- Phlebotomy plus ASA
- Hydroxyurea
- Interferon alpha
- Ruxolitinib

Management of Polycythemia Vera

Age, Vascular events	Low risk	High risk
	Management of cardiovascular risk factors	
	Low dose aspirin	

Barbui T, et al. Leukemia. 2018 May;32(5):1057-1069. Vannucchi AM et al, Annals of Oncology. 2015(S5):v85-v99. McMullin et al. Br J Haematol. 2019; 184(2):176-191.

Management of Polycythemia Vera

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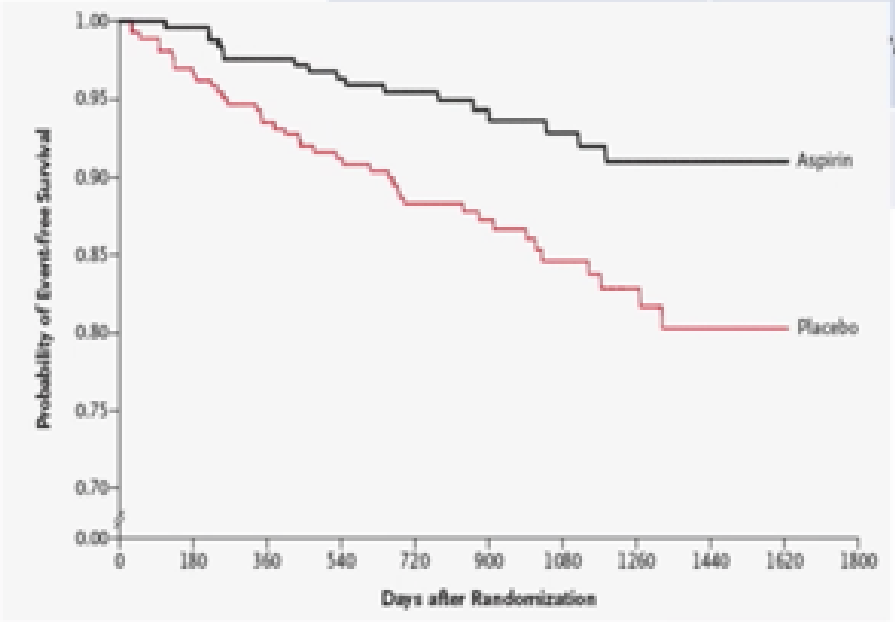
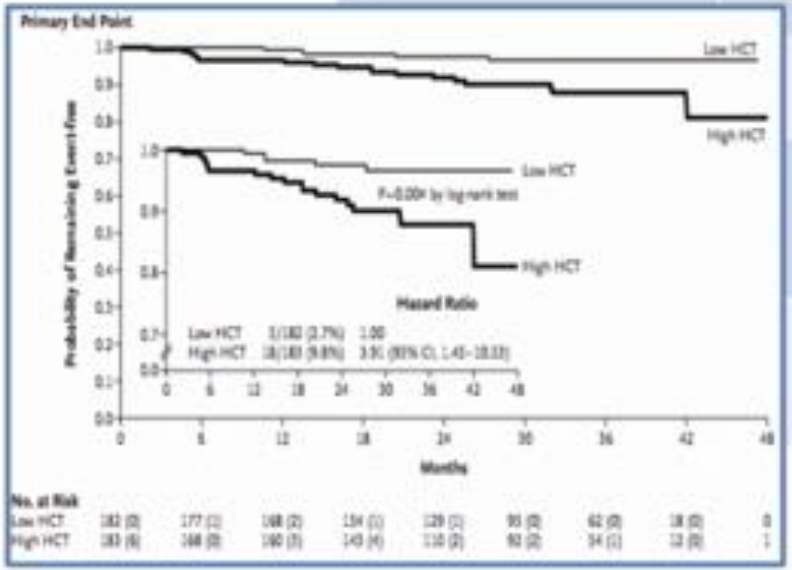
	Low dose aspirin	



Landolfi et al, N Engl J Med. 2004;350(2):114-24

Management of Polycythemia Vera

Age, Vascular events	Low risk	High risk
	Management of cardiovascular risk factors	
	Low dose aspirin	
	Phlebotomies	
	Target Hematocrit <45%	
		Cytoreductive therapy



Marchioli et al. N Engl J Med. 2013;368(1):22-33

Treatment options for PV

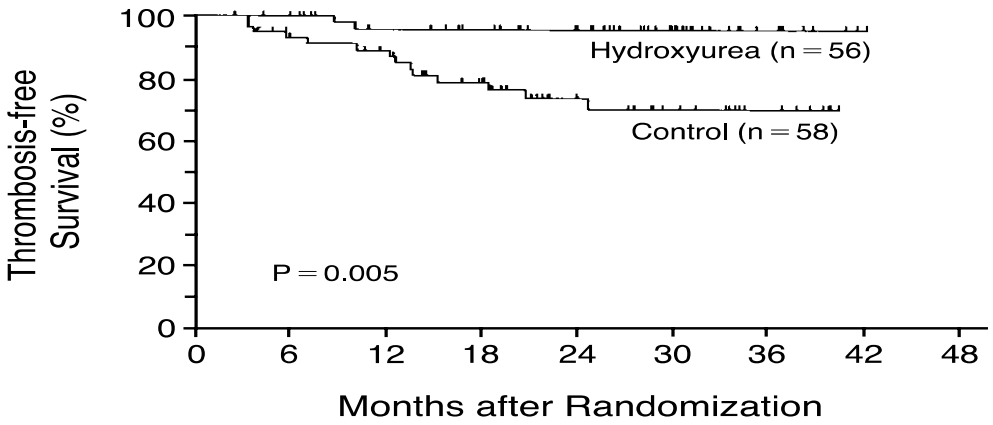
- Phlebotomy plus ASA
- Hydroxyurea
- Interferon alpha
- Ruxolitinib

Key International PV treatment Guidelines

NCCN	ELN	ESMO	BCSH
• Phlebotomy and low dose aspirin (all pts)	• Phlebotomy and low dose aspirin (all pts)	• Phlebotomy and low dose aspirin (all pts)	• Phlebotomy and low-dose aspirin (all patients)
• HU or IFN for high- risk pts	• HU or IFN for high- risk pts	• HU or IFN for high- risk pts	• HU or IFN for high- risk pts
• Ruxolitinib or interferon-α in patients who are intolerant or resistant/ refractory to HU	• Ruxolitinib or interferon-α in patients who are intolerant or resistant/ refractory to HU	• Ruxolitinib may be considered as second line therapy for pts who are resistant/ refractory to HU	• Ruxolitinib or interferon-α in patients who are intolerant or resistant/ refractory to HU
• *Clinical trial*	• *Busulphan*	• *Busulphan, Clinical trial*	• *Busulphan*
Mesa et al., J Natl Compr Canc Netw. 2017	Barbui T, et al. Leukemia. 2018 May;32(5):1057-1069.	Vannucchi AM et al, Annals of Oncology. 2015(55):v85-v99.	McMullin et al. Br J Haematol. 2019; 184(2):176-191.

BCSH, British Committee for Standards in Haematology, ELN, European LeukemiaNet, ESMO, European Society of Molecular Oncology NCCN, National Comprehensive Cancer Network

Hydroxyurea



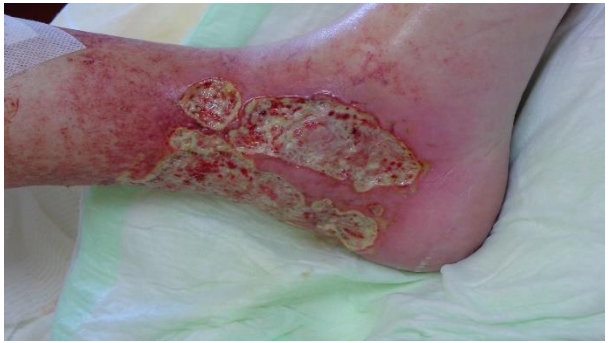
HU vs. untreated control group
– carried out in ET with a significant reduction of the rate of vascular events in the HU arm (increase in secondary malignancies was observed only in those patients treated with HU who had previously been exposed to busulfan)

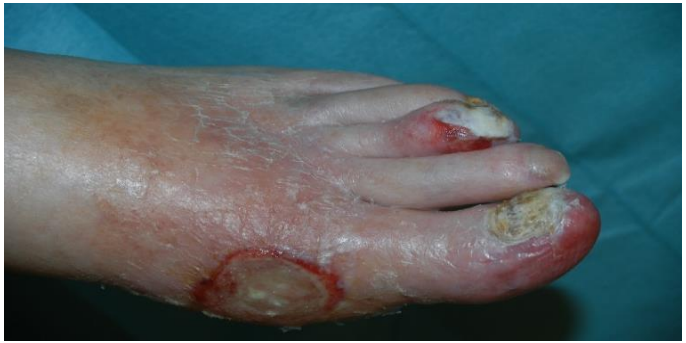
PVSG: 51 pts HU vs. 134 pts. phlebotomy
no significant differences between the 2 groups
acute leukemia (9.8% vs 3.7%), myelofibrosis (7.8 vs 12.7%), total deaths (39.2 vs 55.2%)

Fruchtman SM et al. Semin Hematol 1997;34:17-23.
Cortelazzo S et al. NEJM 1995;332:1132-1136.

HU - problems

- Potential leukemogenic risk ???
  - no controlled studies
- Side effects: skin ulcers, reduction RBCs, GI problems, oral ulcers, hyperkeratosis, actinic keratosis



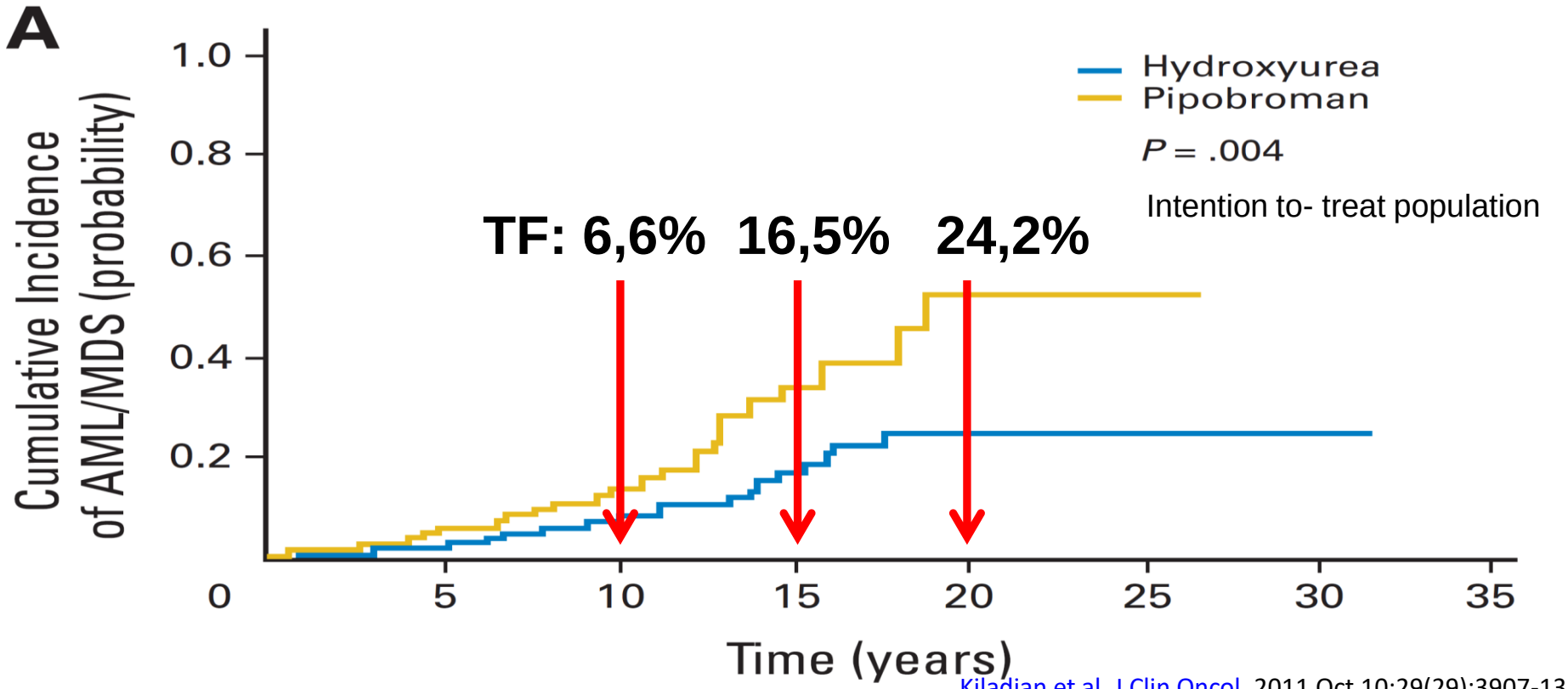


Courtesy of Prof. Griesshammer

Alvarez-Larran A et al. Blood 2012;119:1363-1369

Evolution to AML in Patients treated with hydroxyurea

French Polycythemia Study Group data

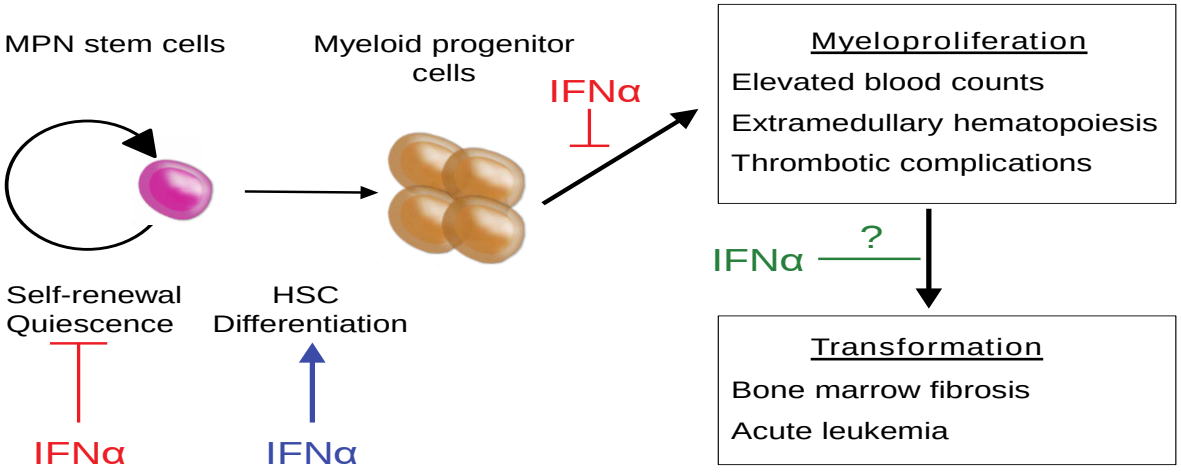


Kiladian et al, J Clin Oncol. 2011 Oct 10;29(29):3907-13.

Treatment options for PV

- Phlebotomy plus ASA
- Hydroxyurea
- Interferon alpha
- Ruxolitinib

Interferon alpha



direct effects on MPN stem cells

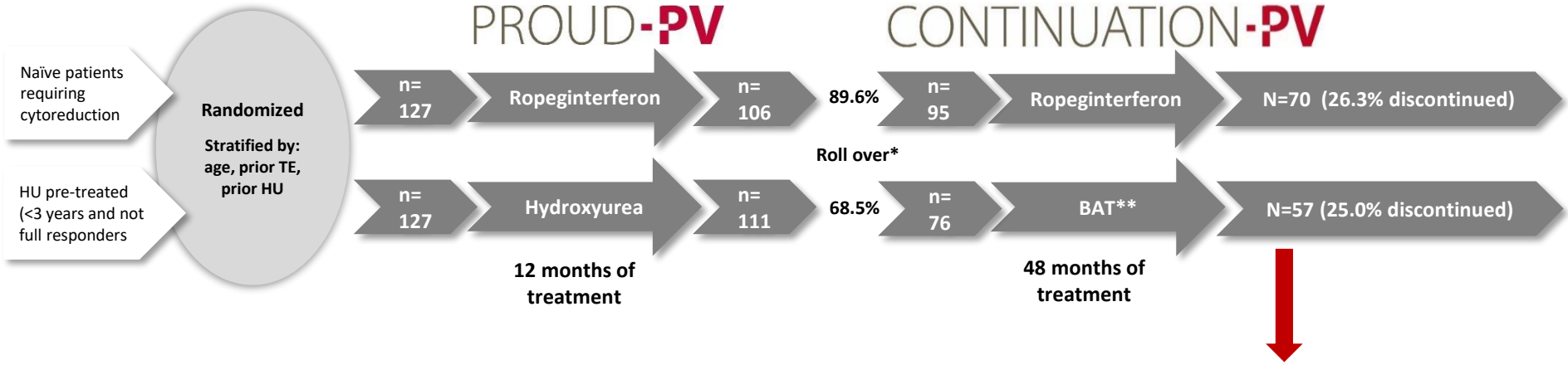
* depletion of long term HSCs (population of rare quiescent cells capable of long term self renewal)
* exit from quiescence
* enforced terminal differentiation

direct effects on downstream effector cells

* reduction in blood counts and extramedullary hematopoiesis

Lane and Mullally Oncotarget 2013;4:500-501.

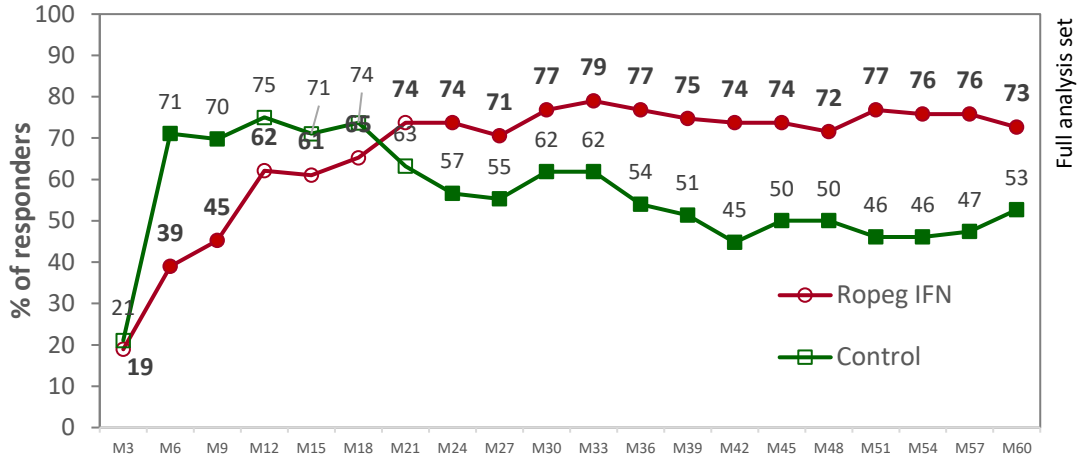
Phase III studies PROUD-PV and CONTINUATION-PV:
Design and patient disposition



* There were no significant differences between patients who entered CONTINUATION-PV study and those who did not roll-over.
** Control group received best available treatment (BAT); 88% of patients received HU as of last available assessment)

60 MONTH INTERIM ANALYSIS:
Efficacy data up to month 60
All safety data up to database lock on 29.05.2020
(up to 6.3 years of treatment overall)

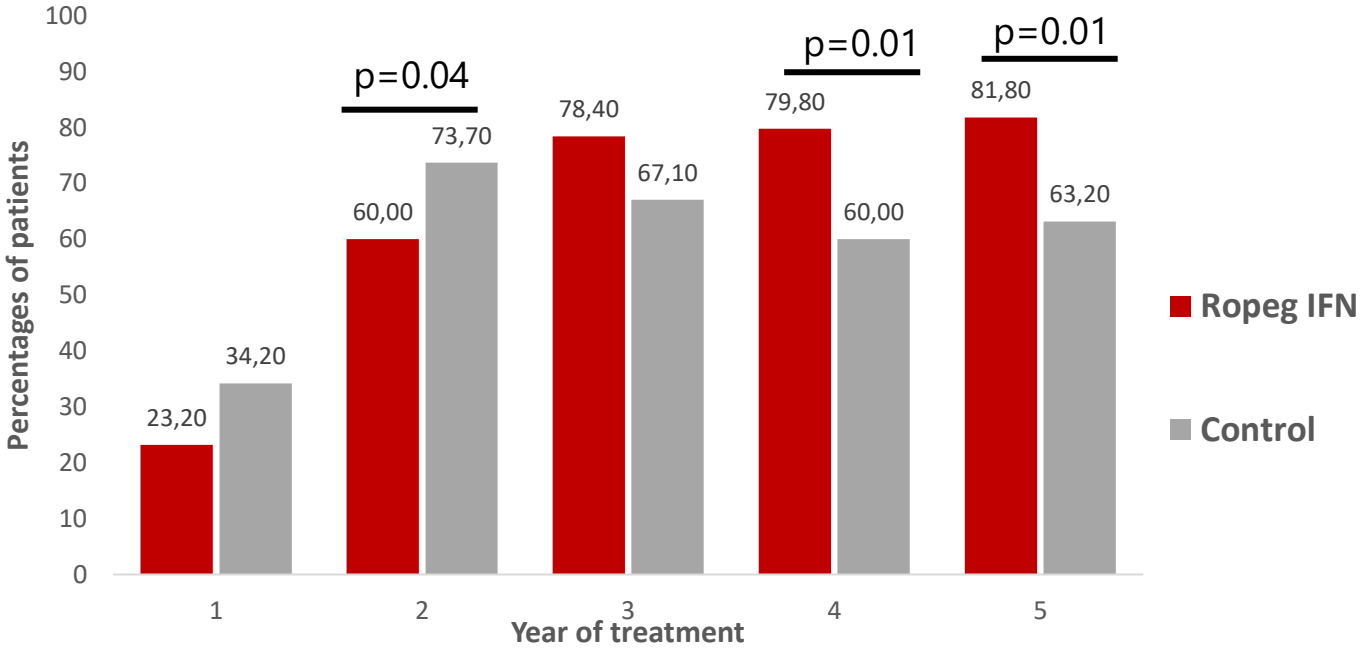
CHR with last observation carried forward (LOCF)



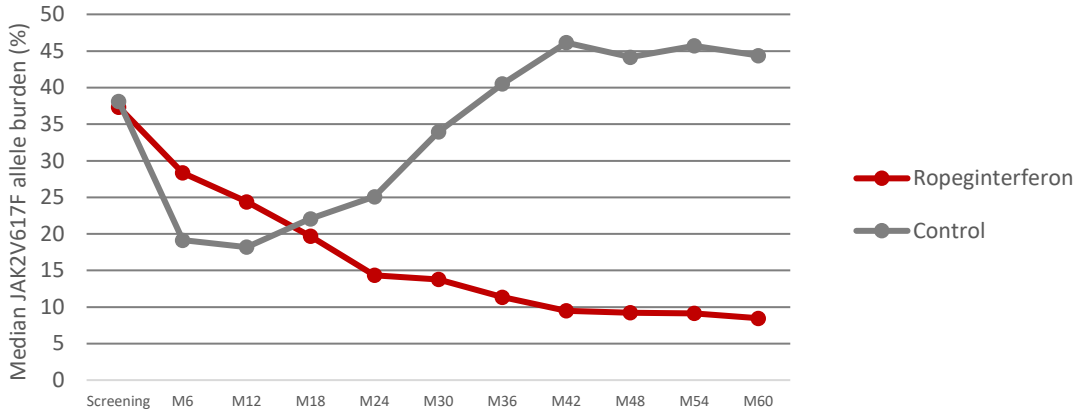
Study Month	Ropeg IFN (N=95)		Control (N=76)		p-value	RR [95% CI] (Ropeg IFN /Control)
	Responder /N	Responder %	Responder/N	Responder %		
MONTH 12 (EOT in PR)	59	62.1%	57	75.0%	0.1	0.85 (0.70 to 1.04
MONTH 24 (LOCF)	70	73.7%	43	56.6%	**0.04**	1.27 (1.02 to 1.60)
MONTH 36 (LOCF)	73	76.8%	41	54.0%	**0.003**	1.43 (1.13 to 1.81)
MONTH 48 (LOCF)	68	71.6%	38	50.0%	**0.004**	1.46 (1.13 to 1.89)
MONTH 60 (LOCF)	69	72.6%	40	52.6%	**0.004**	1.43 (1.12 to 1.81)

Patients who were phlebotomy-free

In the 5th year of treatment, 81.8% of patients in the ropeginterferon alfa-2b arm versus 63.2% in the control arm were phlebotomy-free.



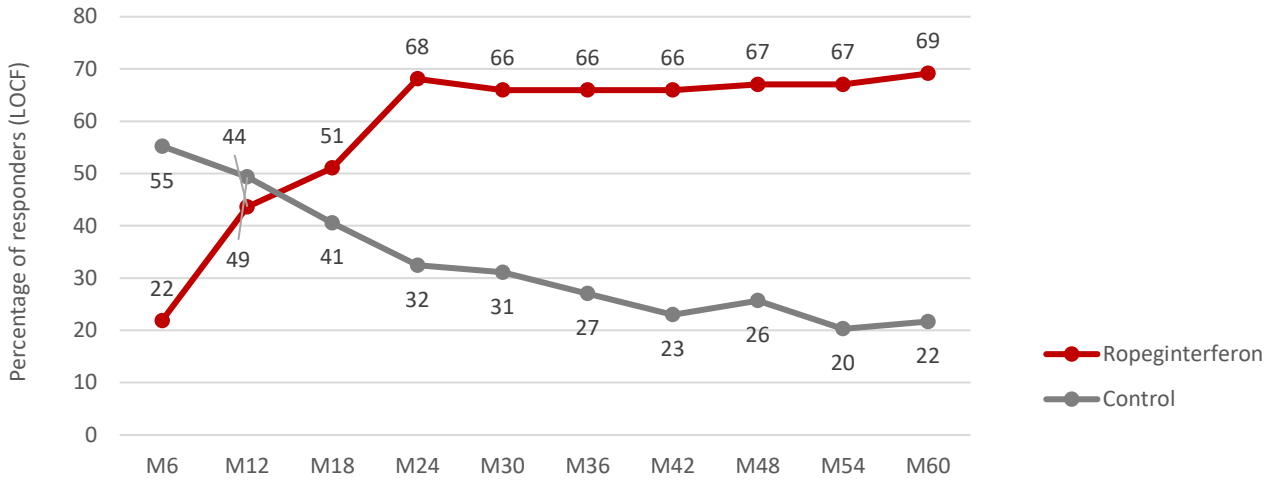
Median *JAK2*V617F allele burden (LOCF)



Study Month	Ropeg IFN (N=95)		Control (N=76)		p-value	RR [95% CI] (Ropeg IFN/Control)
	Mean	Median	Mean	Median		
Baseline	42.8	37.3	42.9	38.1	-	-
MONTH 12	30.2	24.4	24.4	18.2	**0.0244**	6.646 (0.86 to 12.43)
MONTH 24	20.9	14.3	32.4	25.1	**0.0003**	-10.745 (-16.50 to -4.98)
MONTH 36	19.7	11.3	39.3	40.5	**<0.0001**	-18.722 (-24.49 to -12.96)
MONTH 48	19.3	9.2	44.8	44.2	**<0.0001**	-24.582 (-30.35 to -18.82)
MONTH 60)	18.9	8.5	44.0	44.4	**<0.0001**	-23.959 (-29.72 to -18.20)

Full Analysis Set

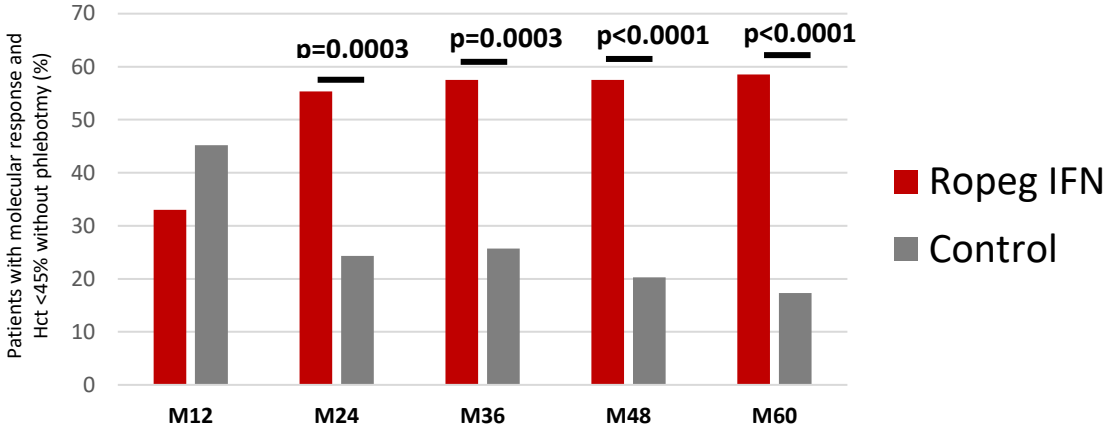
Molecular response (LOCF) according to ELN criteria



Study Month	Ropeg IFN (N=95)		Control (N=76)		p-value	RR [95% CI] (Ropeg IFN/Control)
	Responder/N	Responder %	Responder/N	Responder %		
MONTH 12 (EOT in PR)	41/94	43.6	36/73	49.3	0.3744	0.87 [0.63-1.19]
MONTH 24 (LOCF)	64/94	68.1	24/74	32.4	**0.0001**	2.00 [1.41-2.84]
MONTH 36 (LOCF)	62/94	66.0	20/74	27.0	**<0.0001**	2.31 [1.56-3.43]
MONTH 48 (LOCF)	63/94	67.0	19/74	25.7	**<0.0001**	2.50 [1.67-3.73]
MONTH 60 (LOCF)	65/94	69.1	16/74	21.6	**<0.0001**	3.04 [1.96-4.71]

Full Analysis Set

Combined analysis of Hct<45% without phlebotomy AND molecular response

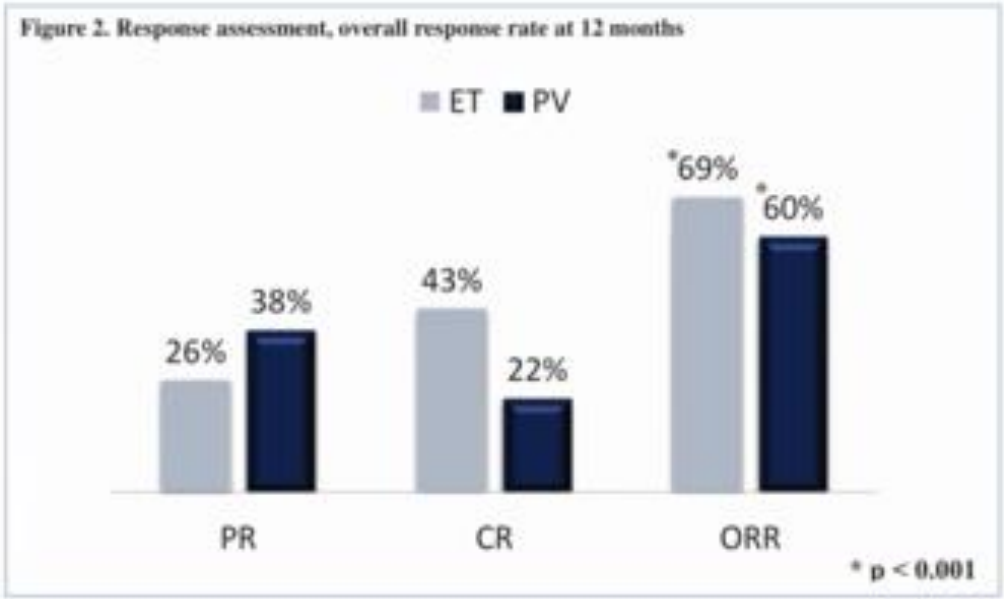


Study Month	Responder/N	Responder %	Responder/N	Responder %	RR [95% CI] (Ropeg IFN/Control)	P-value
	Ropeg IFN (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	31/94	33.0%	33/73	45.2%	0.73 (0.50 to 1.06)	0.0943
MONTH 24 (LOCF)	52/94	55.3%	18/72	24.3%	2.26 (1.46 to 3.50)	**0.0003**
MONTH 36 (LOCF)	54/94	57.5%	19/74	25.7%	2.17 (1.43 to 3.29)	**0.0003**
MONTH 48 (LOCF)	54/94	57.5%	15/74	20.3%	2.79 (1.74 to 4.46)	**<0.0001**
MONTH 60 (LOCF)	55/94	58.5%	13/75	17.3%	3.26 (1.97 to 5.42)	**<0.0001**

Second line therapy:

Switch hydroxyurea / Interferon

Pegylated Interferon Alfa-2a for Polycythemia Vera or Essential Thrombocythemia Resistant or Intolerant to Hydroxyurea.



Yacoub et al., Blood. 2019 Oct 31;134(18):1498-1509

Treatment options for PV

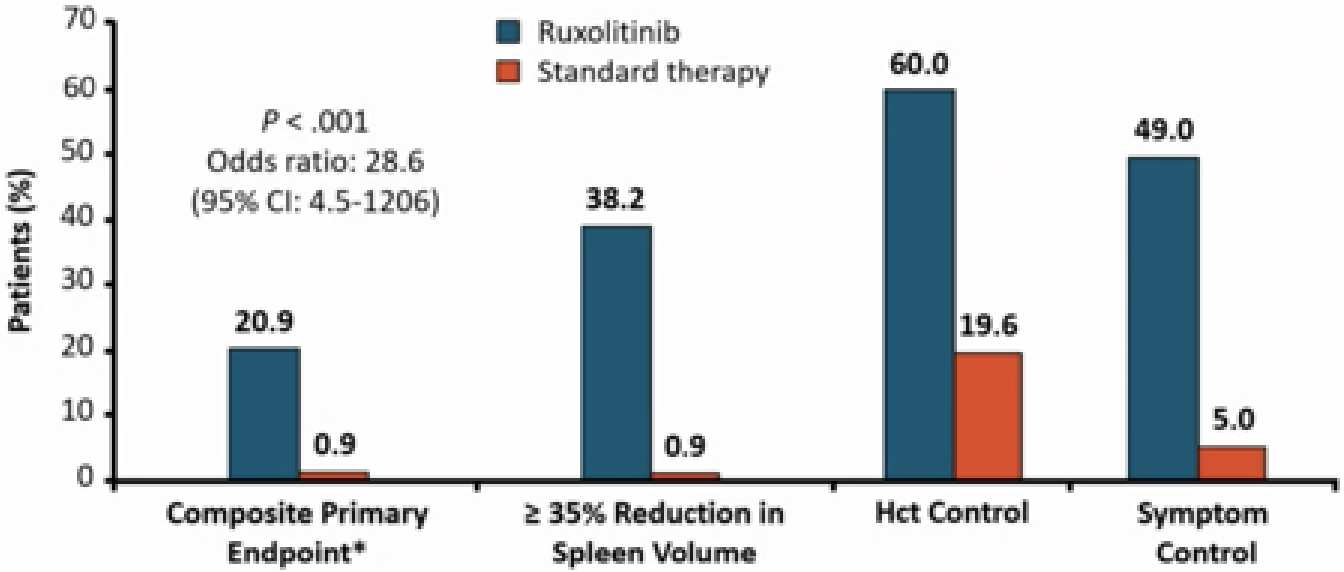
- Phlebotomy plus ASA
- Hydroxyurea
- (Anagrelide + Hydoxyurea)
- Interferon alpha
- Ruxolitinib

Second line therapy:

ruxolitinib

Ruxolitinib is approved to treat patients with polycythaemia vera (PV) who are resistant or intolerant to hydroxyurea (HU)

RESPONSE: Key Efficacy Findings at Wk 32



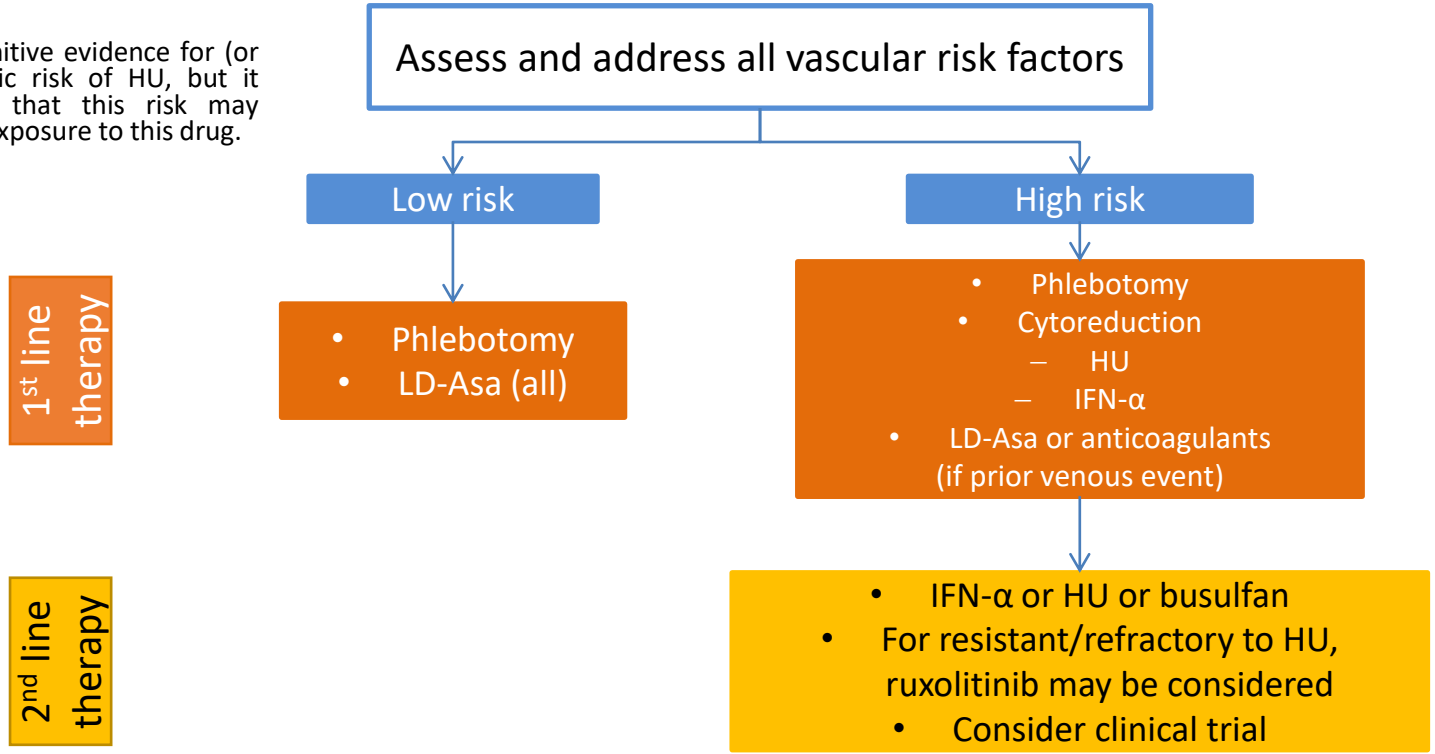
*Proportion with Hct control + spleen volume reduction ≥ 35%.

- Complete hematologic response also significantly improved with ruxolitinib vs standard therapy (23.6% vs 8.9%; *P* = .003)

Vannucchi. NEJM. 2015;372:426.

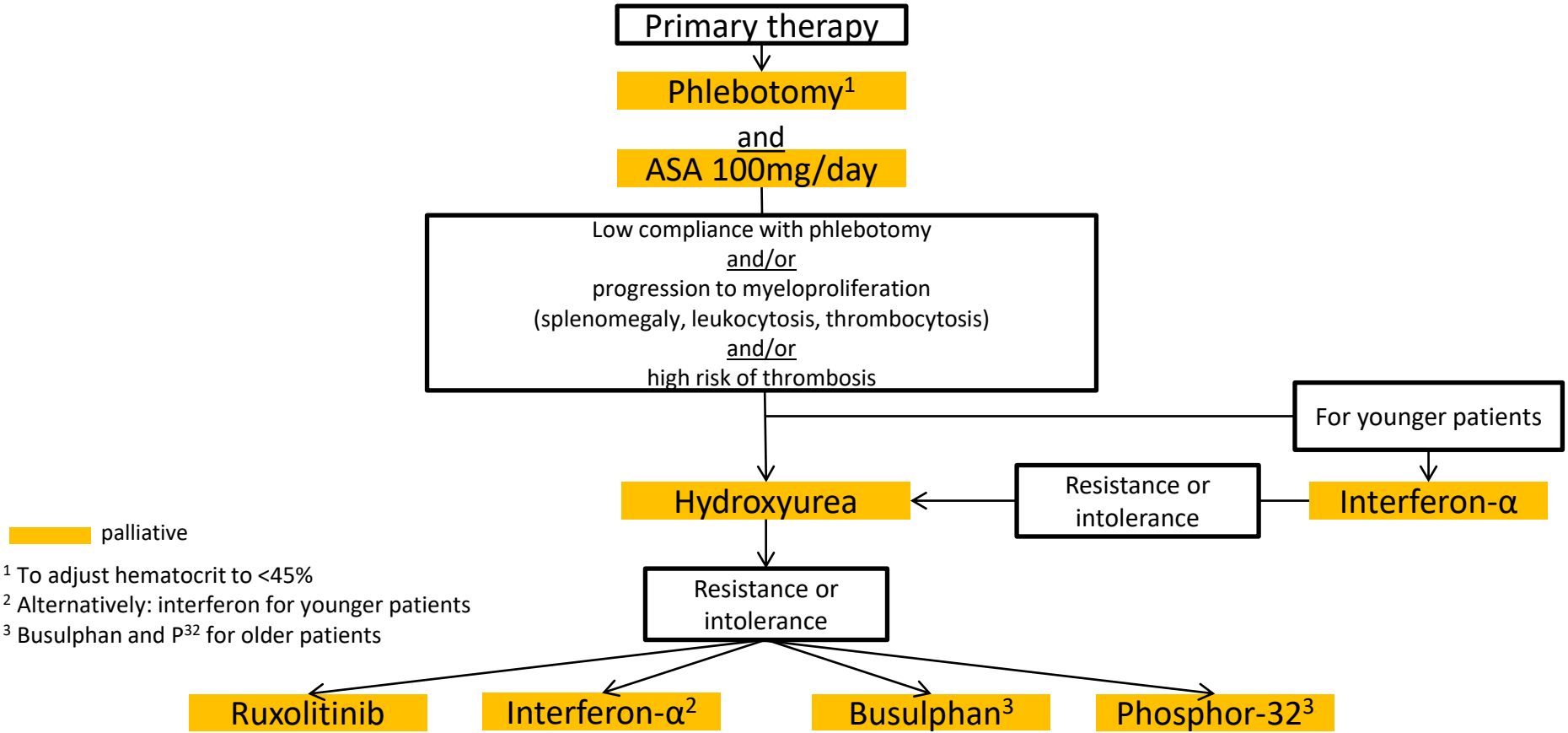
ESMO Clinical practice guidelines for diagnosis, treatment and follow-up of PV

Overall, there is no definitive evidence for (or against) a leukaemogenic risk of HU, but it should be emphasised that this risk may appear after prolonged exposure to this drug.



Vannucchi et al, Annals of Oncology 2015

ELN (DGHO) guidelines for treatment of PV



Austrian consensus on treatment of patients with PV

Low risk
- Age < 60 years
- no history of thrombosis

High risk
- Age > 60 years
  and/or
- history of thrombosis

For all PV patients
- Hkt < 45%
- Aspirin 100mg /d
- stringent control of cardiovascular risk factors

poor tolerance of phlebotomies
progressive splenomegaly
symptomatic disease
progressive thrombocytosis
progressive leukocytosis (> 15 G/l)

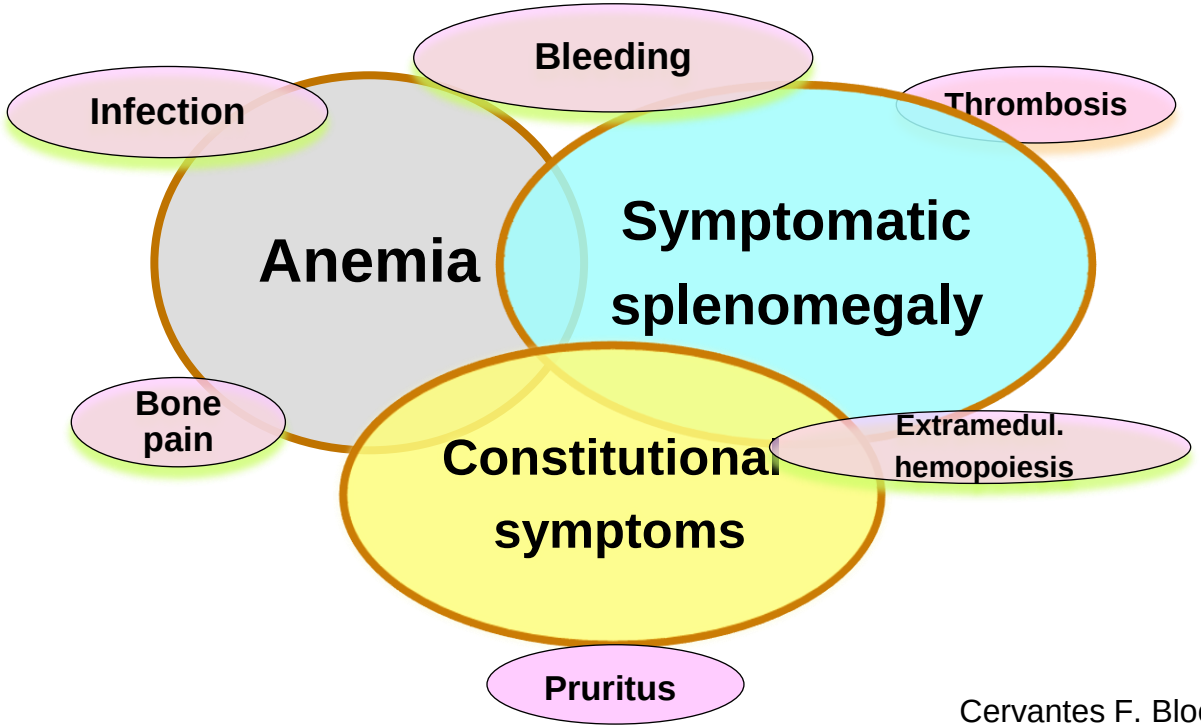
Cytoreductive treatment
- First line:
  - fit patients: **pegylated interferon alpha**
  - patients with major comorbidities or contraindications to IFN: **HU**
- Second line: **Ruxolitinib**

Burgstaller S et al. WiKliWo 2018

Management Myeloproliferative Neoplasien

- Polyzythämia Vera
- **Primäre Myelofibrose**
- Essentielle Thrombozythämie

Clinical Manifestations of Myelofibrosis



Cervantes F. Blood 2014; 124:2635-42.

Myelofibrosis – Development of Risk Scores

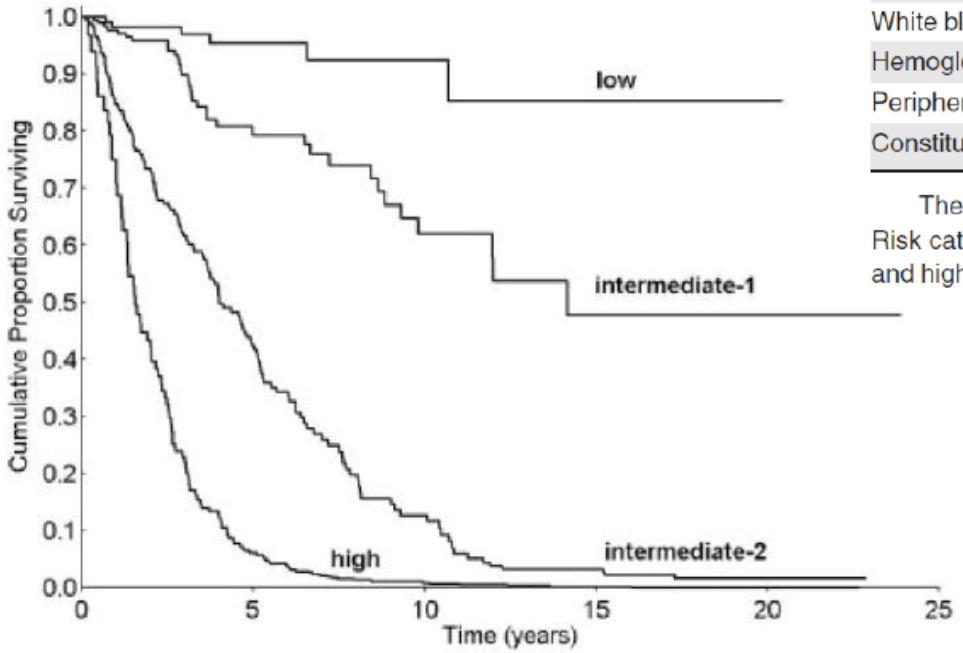
	Lille[+]	IPSS[++]	DIPSS [+++]	aDIPSS [+++]	DIPSS-plus
Anemia	1	1	2	2	2
WBC	1	1	1	1	1
Peripheral Blasts	1	1	1	2	1
Const. symptoms		1	1	2	1
Age		1	1		1
Platelets					1
Cytogenetics					1

[+] Low risk (0 points)
Intermediate risk (1 point)
High risk (2 points)

[++] Low risk (0 points)
Intermediate risk 1 (1 point)
Intermediate risk 2 (2 points)
High risk (≥ 3 points)

[+++] Low risk (0 points)
Intermediate risk 1 (1-2 points)
Intermediate risk 2 (3-4 points)
High risk (≥ 5 points)

PMF – DIPSS score



Prognostic variable	Value 0	1	2
Age, y	≤ 65	> 65	
White blood cell count, $\times 10^9$/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

The risk category is obtained adding up the values of each prognostic variable. Risk categories are defined as low: 0; intermediate-1: 1 or 2; intermediate-2: 3 or 4; and high: 5 or 6.

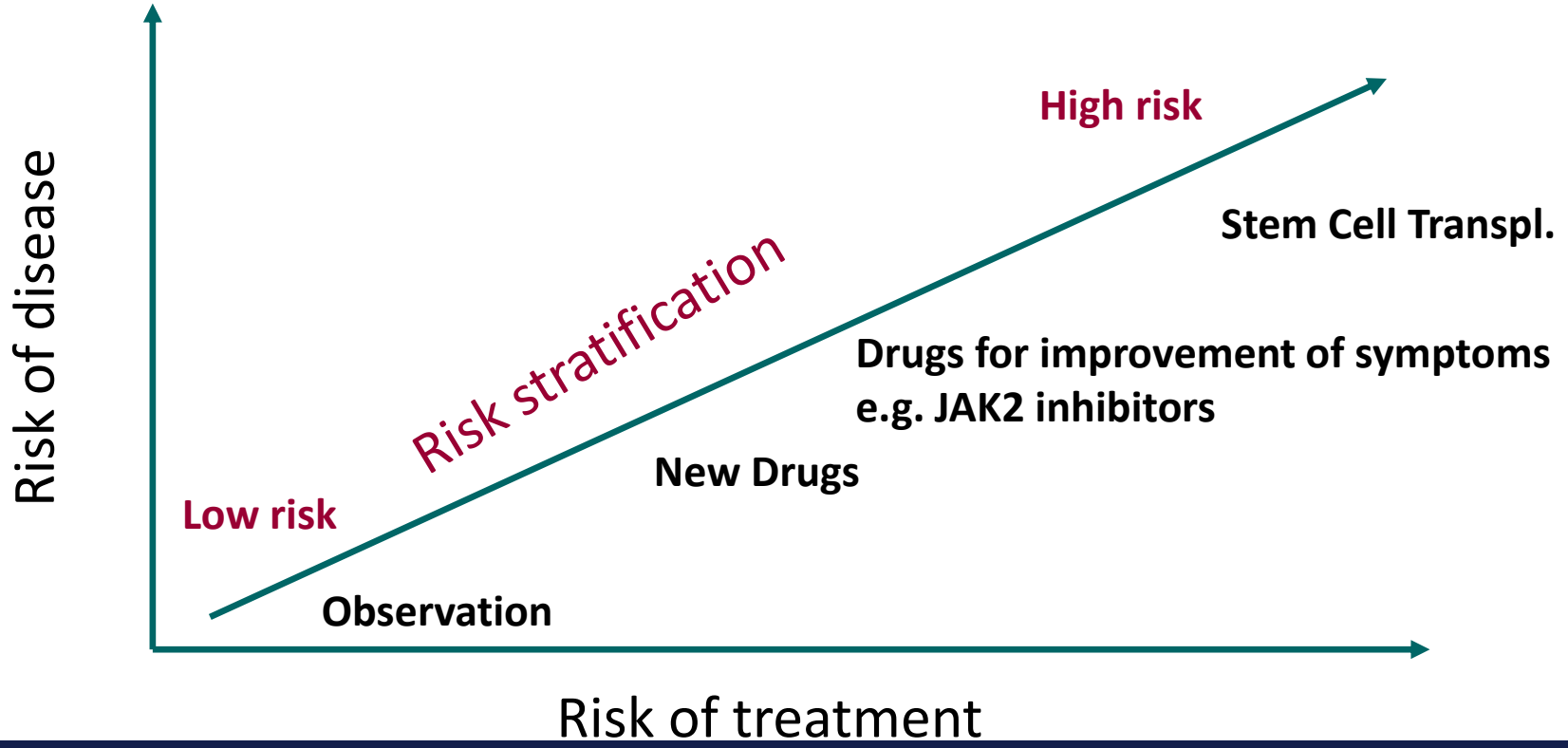
Passamonti F. et al, Blood 2010

Current Goals of Therapy in PMF

- **Main goals are palliation of symptoms and improvement of quality of life.**
- **In selected patients (based on both age and risk group) cure can be considered (Allo-HSCT)**
- **Any potential survival prolongation by a therapy should be balanced with the toxicity and benefit in quality of life**

Barbui T *et al.*, JCO 2011; 29:761-70.

Myelofibrosis - Management



Therapy of Anemia in Myelofibrosis

Therapy	Response	Comments
• **ESA**		
rHuEpo	40%	Responses usually restricted
Darbepoetin	40%	to pts. with inadequate Epo
• **Androgens**		
Danazol	30%	Low response rate in transfusion-dependent anemia
• **Immunomodulators**		
Thalidomide	20-25%	Frequent withdrawal
Lenalidomide	20-30%	due to toxicity
• **Splenectomy**	23%	Associated mortality and morbidity

»

Conventional Therapy of Proliferative Manifestations of MF

Drug	Response	Comments
• **Hydroxyurea** [1]	40%	Usually not profound Median duration1 year
• **Splenectomy** [2]	60-100%	Frequent complications (bleeding, thrombosis, infection)
• **Splenic radiation** [3]	100%	Short-lasting Frequent severe cytopenias

1. Martínez-Trillos A *et al.,* Ann Hematol 2010; 89:1233-7.
2. Tefferi A *et al.,* Blood 2000; 95:2226-33.
3. Elliott MA *et al.,* Br J Haematol 1998; 103:505-11.

Indications of SCT in Myelofibrosis

High and Intermediate-2

All eligible patients

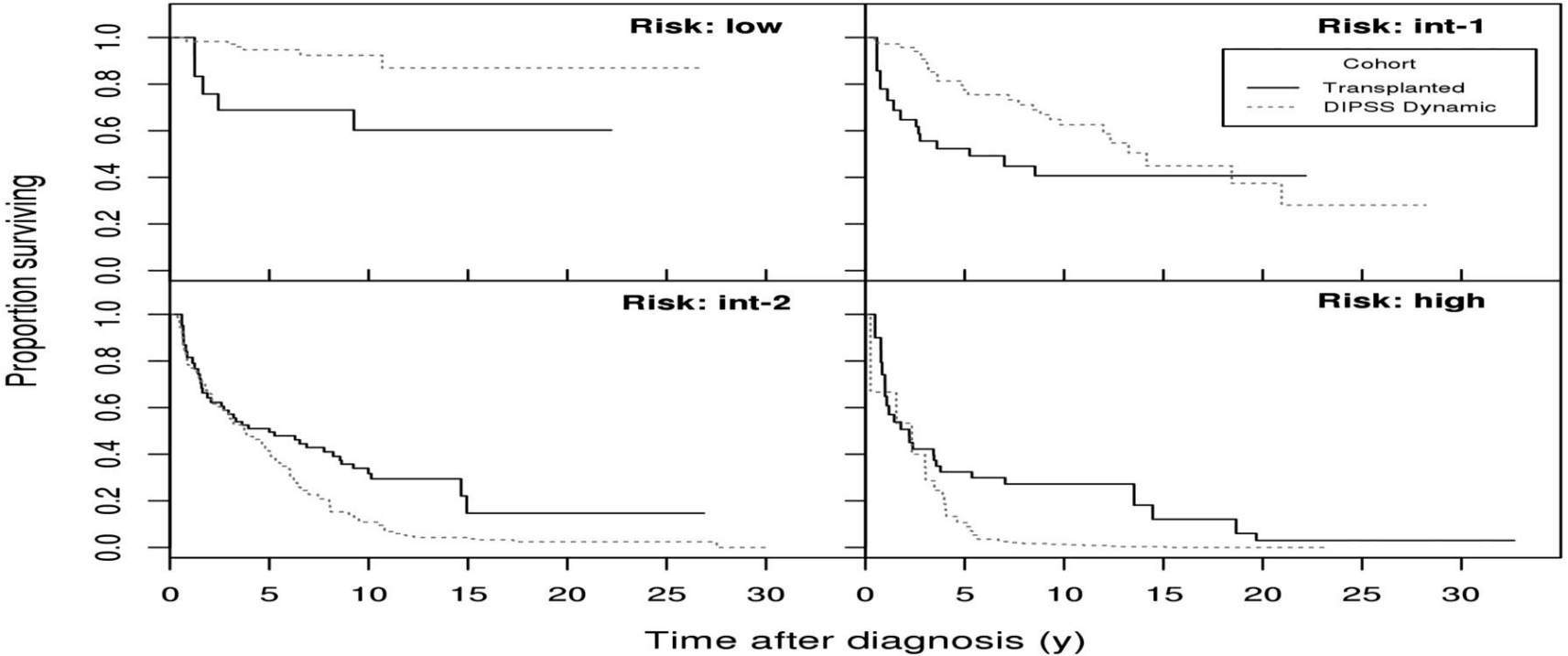
< 70 years

Intermediate-1

- **Age < 65 years**
- **Transfusion-dependent anemia**
- **Refractory anemia**
- **Blood blasts > 2%**
- **Adverse cytogenetics**

Kröger N *et al.,* Leukemia 2015; 29:2126-33.

Survival of DIPSS Groups According to SCT or Conventional Therapy

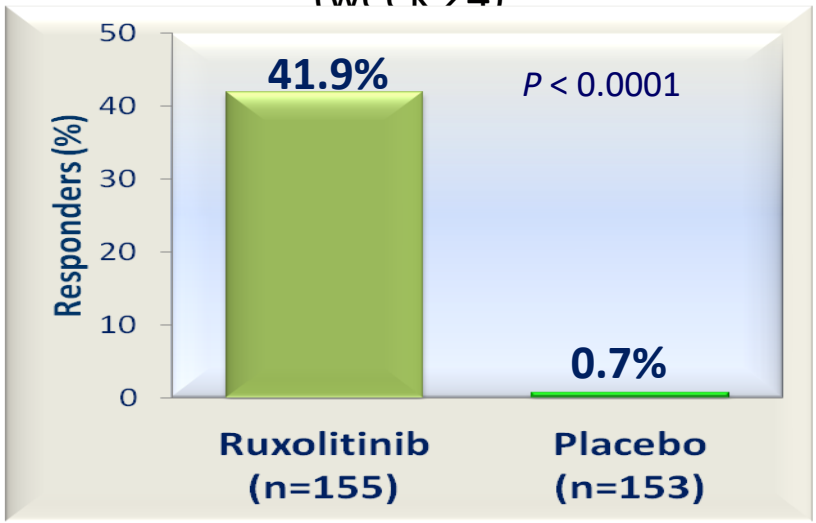


Kröger N *et al*., Blood 2015; 125:3347-50.

Ruxolitinib and Spleen Volume Reduction

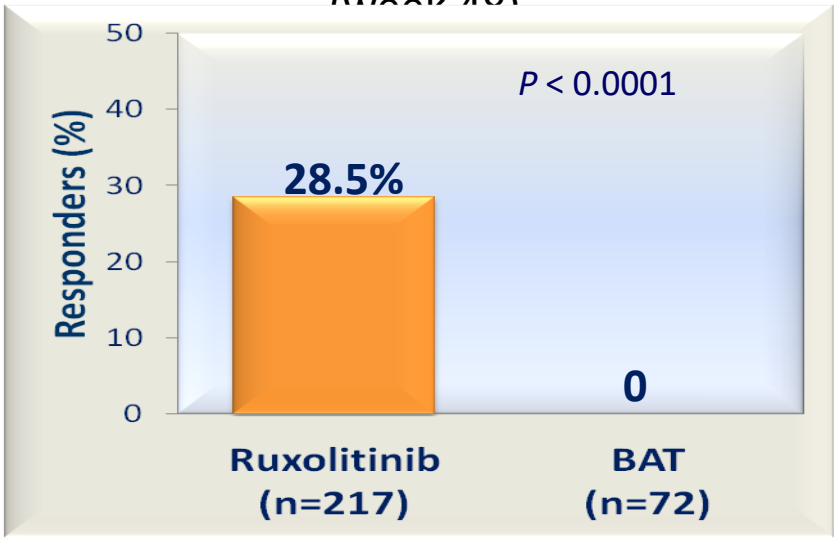
COMFORT-I

(week 24)



COMFORT-II

(week 48)



- **Response: ≥35% reduction of spleen volume by MRI/CT**
- A 35% spleen volume reduction by MRI ≅ **52% reduction in spleen length by palpation**
- It occurred at a median of 12 weeks from treatment start

Verstovsek S *et al*., NEJM 2012; 366:799-07.

Harrison C *et al*., NEJM 2012; 366:787-98.

Impact on Disease Symptoms and QoL

COMFORT-I

(week 24)

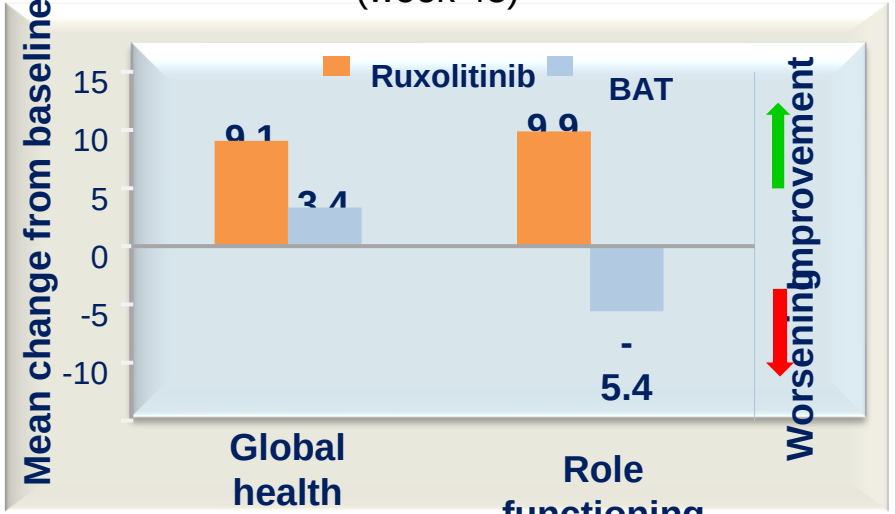
p<0.0001, Chi-square test

Response: % of patients with ≥50% reduction in MSAF Total Symptom Score

Verstovsek S *et al*., NEJM 2012; 366:799-07.

COMFORT-II

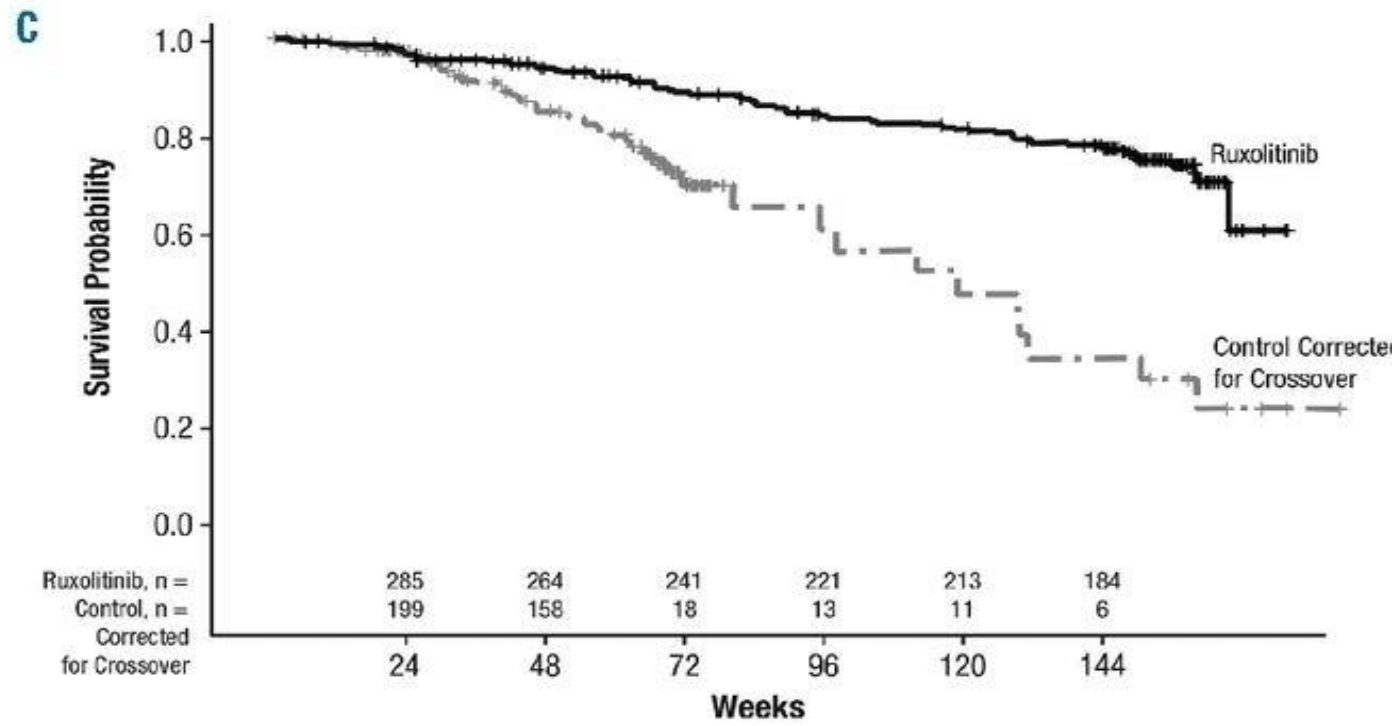
(week 48)



Change in EORTC QLQ-C30 scores at week 48 compared with baseline

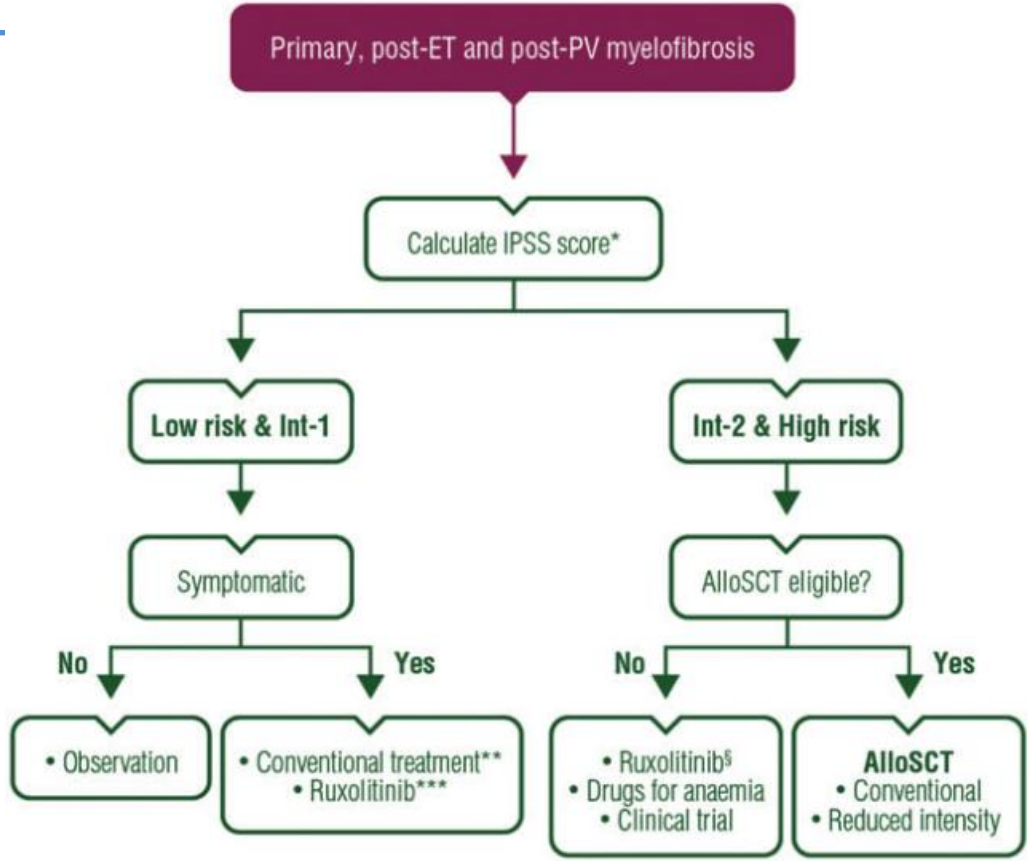
Harrison C *et al*., NEJM 2012; 366:787-98.

Survival of Patients in the COMFORT-I and COMFORT-II Studies Corrected for Crossover from the Control Arms



Vannucchi AM *et al.*, Haematologica 2015;100:1139-45.

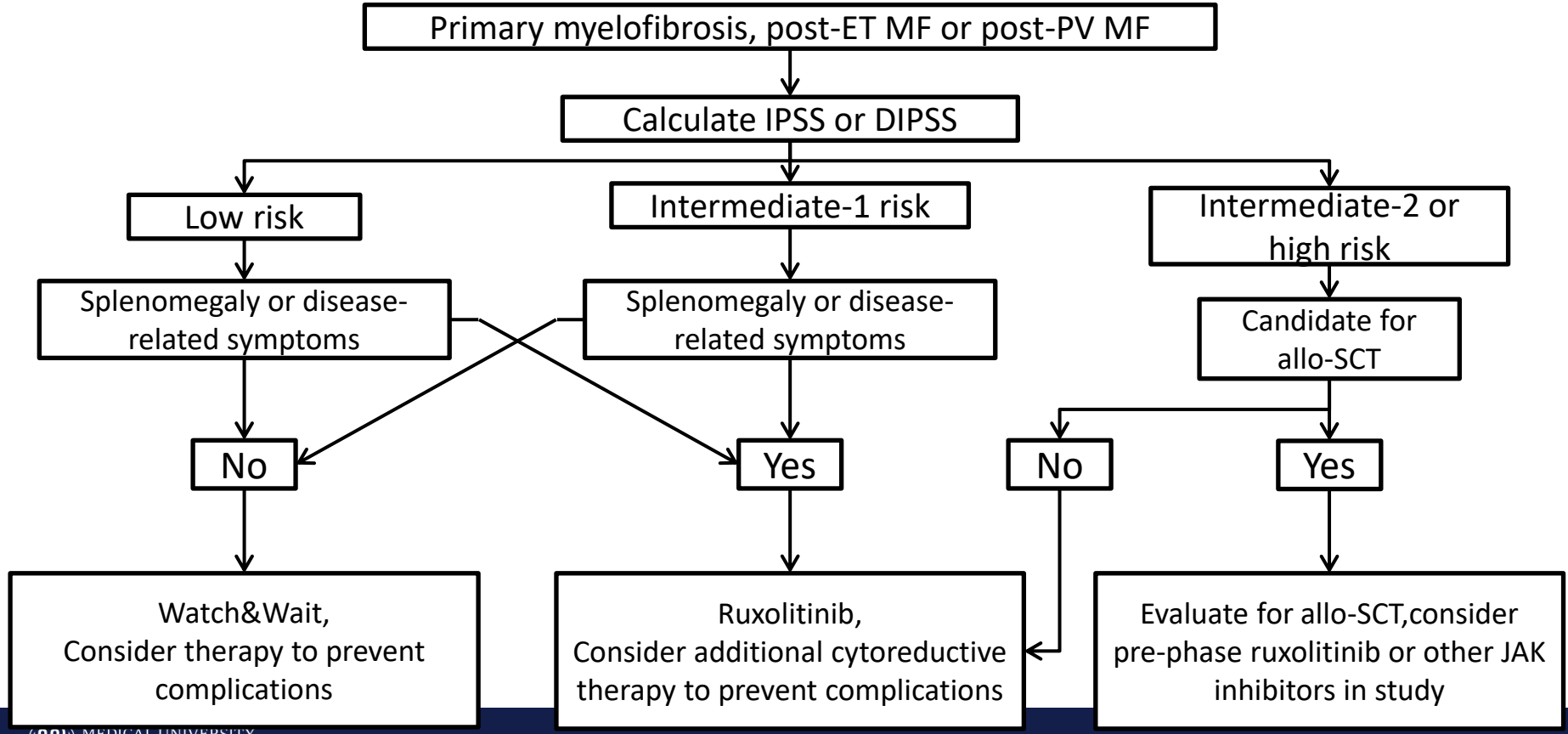
ESMO guidelines for treatment of PMF



* Dynamic IPSS and Dynamic IPSS-plus after diagnosis.
**Hydroxyurea for symptomatic splenomegaly in countries where ruxolitinib is not approved for low-risk patients. If anaemia is the problem, erythropoietin, corticosteroids, danazol, immunomodulators or splenectomy.
***For patients presenting with symptomatic splenomegaly and/or constitutional symptoms if allowed by the label.
§For patients presenting with symptomatic splenomegaly and/or constitutional symptoms. PV, polycythaemia vera; ET, essential thrombocythaemia; LD-Asa, low-dose aspirin; HU, hydroxyurea; INF-α, interferon-α; IPSS, International Prognostic Score System; Int, intermediate; AlloSCT, allogeneic stem cell transplantation.

Vannucchi et al, Ann Oncol 2015

Austrian treatment algorithm for MF patients



Management Myeloproliferative Neoplasien

- Polyzythämia Vera
- Primäre Myelofibrose
- **Essentielle Thrombozythämie**

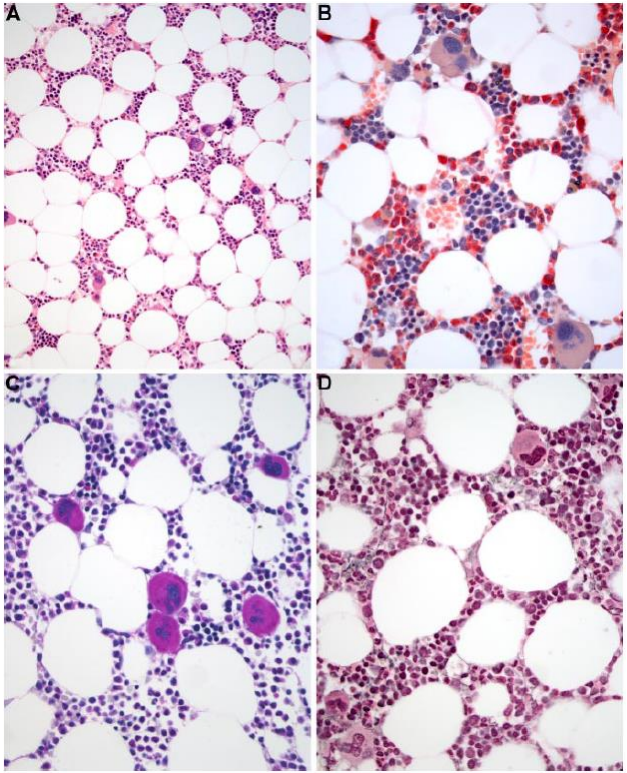
WHO 2016

Barbui et al. Blood Cancer Journal (2015) 5, e337; doi:10.1038/bcj.2015.64
Arber et al. Blood 2016.

Platelet count	A1	≥ 450 x 10^9/l
Bone marrow (BM) histology	A2	BM biopsy showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megacaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers.
Criteria of exclusion	A3	Not meeting WHO criteria for BCR-ABL+CML, PV, PMF, MDS or other myeloid neoplasm.
Clonal genetic abnormality	A4	Presence of JAK2, CALR or MPL mutation
Minor criteria	B	Presence of a clonal marker or absence of evidence for reactive thrombocytosis.
Diagnosis of ET requires	A1-A4 or A1-A3 and one of the B criteria	

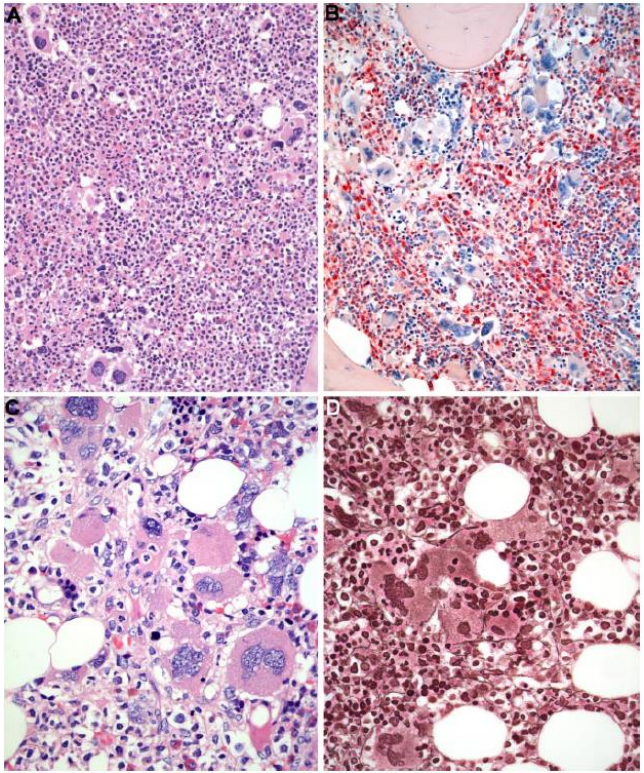
A category: major criteria
B category: minor criteria

WHO-ET vs prePMF: morphologic characteristics



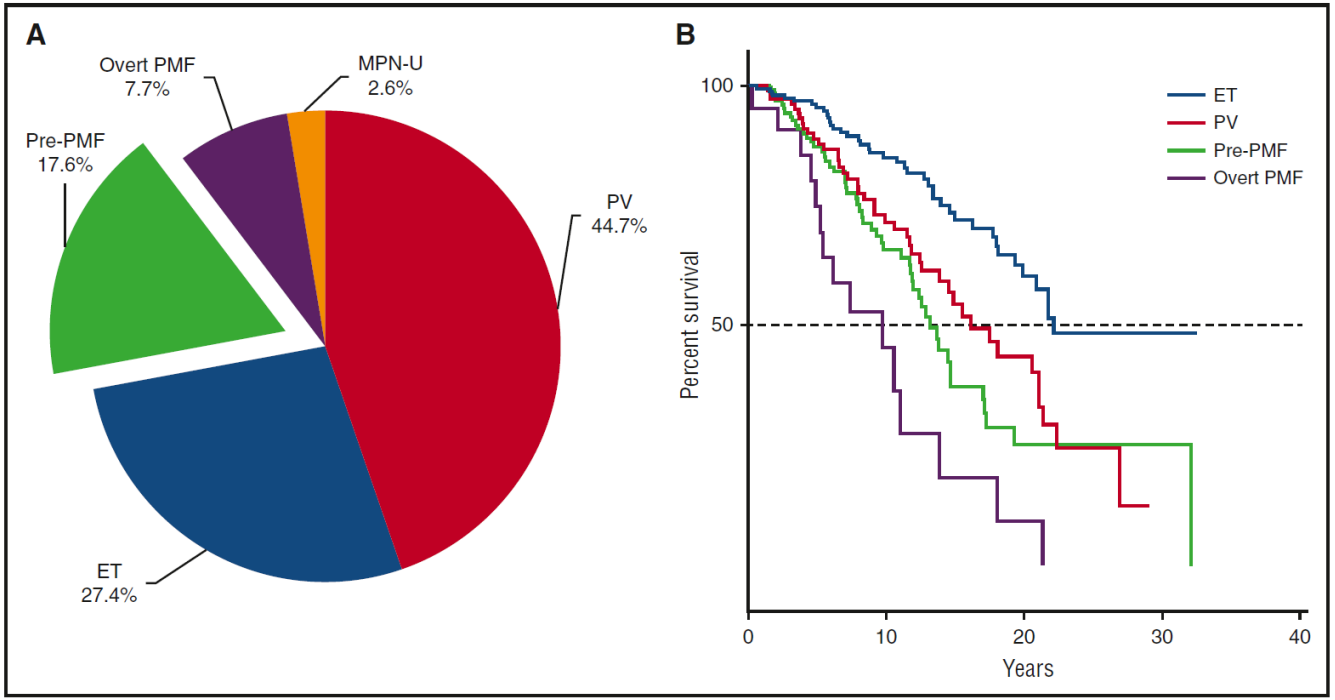
ET

prePMF



A. HE staining
B. Chlor-acetate esterase staining
C. PAS staining
D. Reticulin staining

Thiele et al, Blood 2011



(A) Prevalence and (B) observed survival of pre-PMF as a distinct entity from other MPN (N = 807). Data from the Austrian Reclassification Project.[10] MPN-U, myeloproliferative neoplasm unclassified; PV, polycythemia vera.

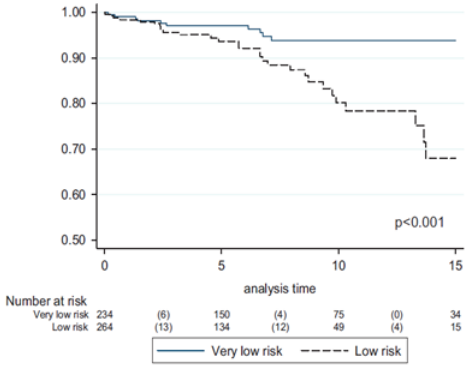
Gisslinger, Blood 2017

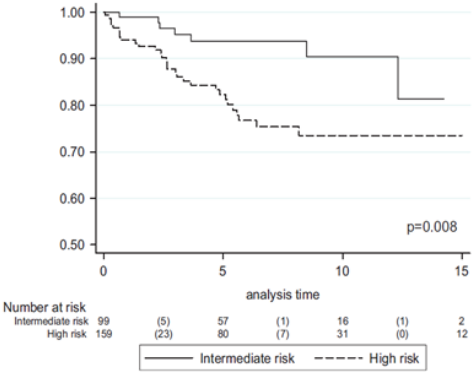
Komplikationen bei Essentieller Thrombozythämie
Zusammenfassung von 687 Patienten aus 11 Studien

- Asymptomatische Patienten: 30,5%
- Arterielle Thrombosen: 23,8%
- Venöse Thrombosen: 5,2%
- Blutungskomplikationen: 19,5%
  - Leichte Blutungen: 15,2%
  - Schwere Blutungen: 4,2%
- Blutungen und Thrombosen: 17,9%
- Mikrozirkulationsstörungen: 47,0%
  - peripher: 28,6%
  - zerebral: 20%

Revised IPSET- thrombosis

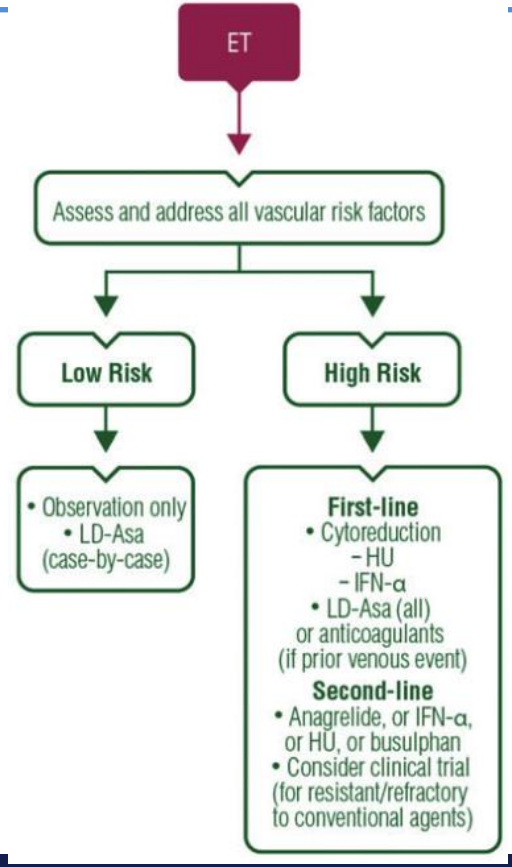
Risk category	Factors
Very low	**No** thrombosis history Age ≤ 60 JAK2 **un**mutated
Low	**No** thrombosis history Age ≤ 60 JAK2 **mutated**
Intermediate	**No** thrombosis history Age > 60 JAK2 **un**mutated
High	**Thrombosis** history or Age > 60 JAK2 **mutated**





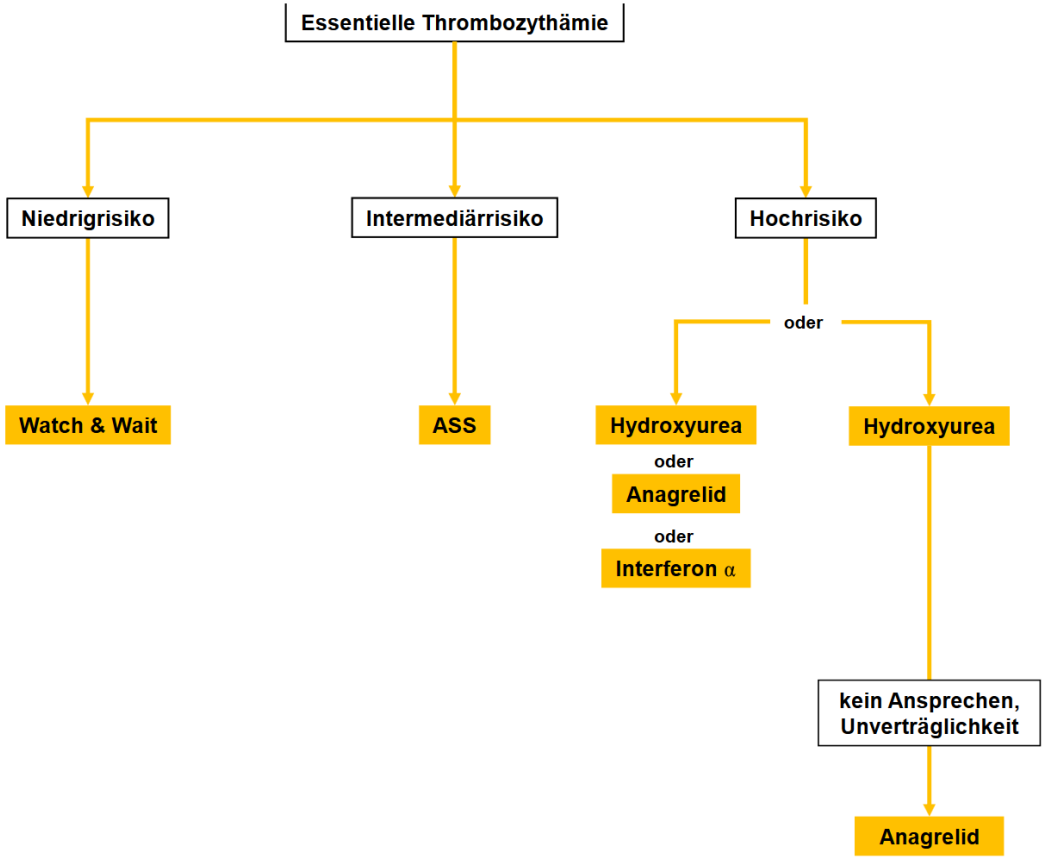
Barbui et al, Blood Cancer J 2015

ESMO guidelines for treatment of ET



Vannucchi et al, Ann Oncol 2015

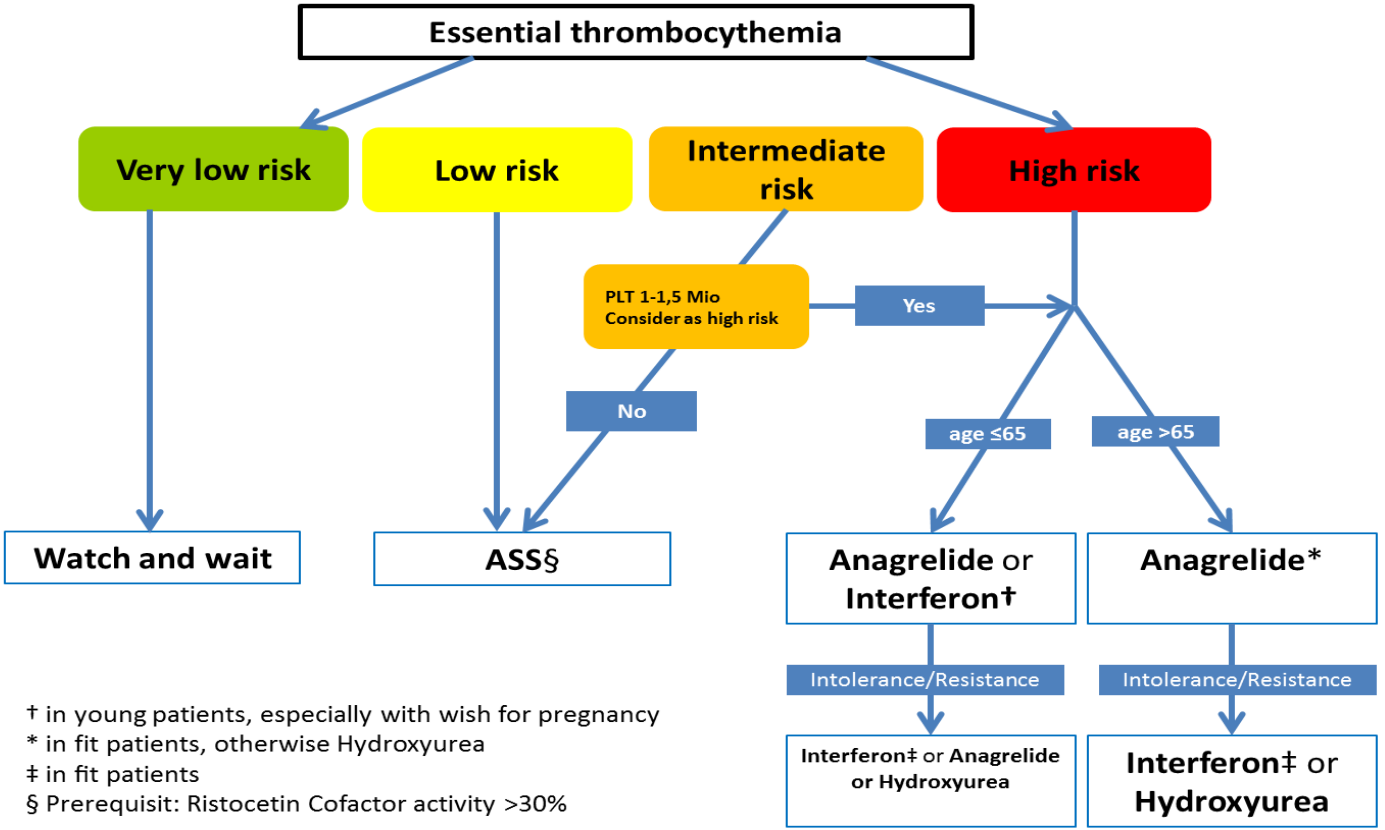
ELN (DGHO) guidelines for treatment of ET



Legende: [1] Risiko - Klassifikation s. Kapitel Kapitel 5.4. Prognostische Faktoren

https://www.onkopedia.com/de/onkopedia/guidelines/essentielle-oder-primaere-thrombozythaemie-et/@@view/html/index.html#ID0ENIAC

Austrian treatment guidelines in ET



† in young patients, especially with wish for pregnancy
* in fit patients, otherwise Hydroxyurea
‡ in fit patients
§ Prerequisit: Ristocetin Cofactor activity >30%

Buxhofer-Ausch et al, Österr. ET Guidelines 2021. WiKliWo

CML - Epidemiologie und Ätiologie

- Epidemiologie:
  - CML: 14% aller Leukämien des Erwachsenalters
  - Inzidenz: 1-2/100.000 (exponentiell mit dem Alter zunehmend)
  - Mittleres Alter bei Diagnose: 45-55a (einige Studien sprechen von über 67a)
  - Geschlechterverhältnis: m:w = 1,4:1
- Ätiologie:
  - Strahlung in hohen Dosen (einzig gesicherter Risikofaktor)
  - Chemische Substanzen als RF nicht verifiziert
  - sonst unbekannt

Klinik – Verlauf und Symptome

- **Chronische Phase (3 - 8a):**
  - allmählicher Anstieg der Leukozytenzahl im Blut und KM
  - Splenomegalie (70 – 95%) mit Druck im li. Oberbauch, Leistungsminderung, Müdigkeit, Nachtschweiß, Gewichtsverlust,...
- **Akzelerationsphase (3 -18m):**
  - rasch steigende Leukozytenzahl, refraktäre Anämie und Thrombozytopenie, zytogenetische Evolution
  - Verschlechterung der Symptome
- **Blastenkrise (3 - 6m):**
  - massive Infiltration des KM mit Blasten und Ausschwemmung ins Blut (2/3 myeloid, 1/3 lymphoid)
  - Schweres Krankheitsgefühl, Myalgien, Athralgien, Knochenschmerzen, Fieber,...

CML - Symptome

• Zufallsbefund (keine Symptome)	20%
• Müdigkeit	33%
• Gewichtsverlust	20%
• Oberbauchbeschwerden	19%
• Schweissausbrüche	15%
• Knochenschmerzen	7%
• Sehstörungen	4%
• Priapismus	2%

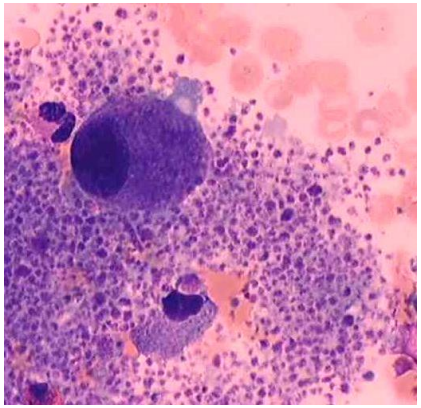
CML - Klinische Befunde

- Milz palpatorisch vergrössert 75%
- Splenomegalie (> 10 cm) 39%
- Vergrösserte Leber 2%

- Keine Lymphadenopathie

Diagnose

- Klinik
- Blutbild:
  - Leukozytose (200.000 - 500.000/µl)
  - Thrombozytose > 450.000/µl
  - Thrombopenie < 150.000/µl
  - Anämie: Hb < 11g/dl



- Differentialblutbild:
  - Linksverschiebung (Promyelozyten u. Myeloblasten)
  - Basophilie
  - Eosinophilie
- Knochenmarksausstrich und -biopsie

BB+Diff. bei CML in chronischer Phase

Komplettes Blutbild				
Erythrozyten	**3.8**	-	4.4-5.8	T/l
Hämoglobin	**10.9**	-	13.5-18.0	g/dl
Hämatokrit	**33.4**	-	40.0-52.0	%
Mittleres Zellvolumen (MCV)	**87.9**		78.0-98.0	fl
Mittleres Zellhämoglobin (MCH)	**28.7**		27.0-33.0	pg
Mittl. Korp. HGB. Konz. (MCHC) Konzentration (MCHC)	**32.6**		32.0-36.0	g/dl
RBC Verteilungsbreite	**17.6**	+	11.0-16.0	%
Thrombozyten	**912**	+	150-350	G/l
Mittleres Thrombozytenvolumen	**10.5**		7.0-13.0	fl
Leukozyten	**147.35**	+	4.0-10.0	G/l
Retikulozytenzählung				
Retikulozyten abs.	**87.8**		32.0-110.0	G/l
Retikulozyten rel.	**2.31**	+	0.7-2.0	%
LFR schwach fluoreszierend (LFR)	**75.0**	-	83.0-97.0	%
MFR mittelstark fluoreszierend (MFR)	**18.6**	+	2.9-15.9	%
HFR stark fluoreszierend (HFR)	**6.4**	+	0.0-1.7	%

Differentialblutbild (manuell)				
Stabkernige z.T. Pelger-Formen	**17**	+	3.0-5.0	%
Segmentkernige	**22**	-	50-75	%
Lymphozyten	**5**	-	25-40	%
Monozyten	**3**		0-12	%
Eosinophile zum Teil unreif	**6**	+	0-4	%
Basophile zum Teil unreif	**13**	+	0.0-1.0	%
Metamyelozyten	**13**			%
Myelozyten	**9**			%
Promyelozyten	**4**			%
Blasten	**8**			%
Normoblasten	**1** 0/100 Leukozyten	+		
Anisozytose	+			
Poikilozytose	. vereinzelt			
Polychromasie	. vereinzelt			
Riesenthrombozyten	. vereinzelt			
Gerinnung				
Normotest	**81**		75-140	%
APTT STA	**39.1**		27.0-41.0	s
Fibrinogen - Clauss	**427**	+	180-390	mg/dl

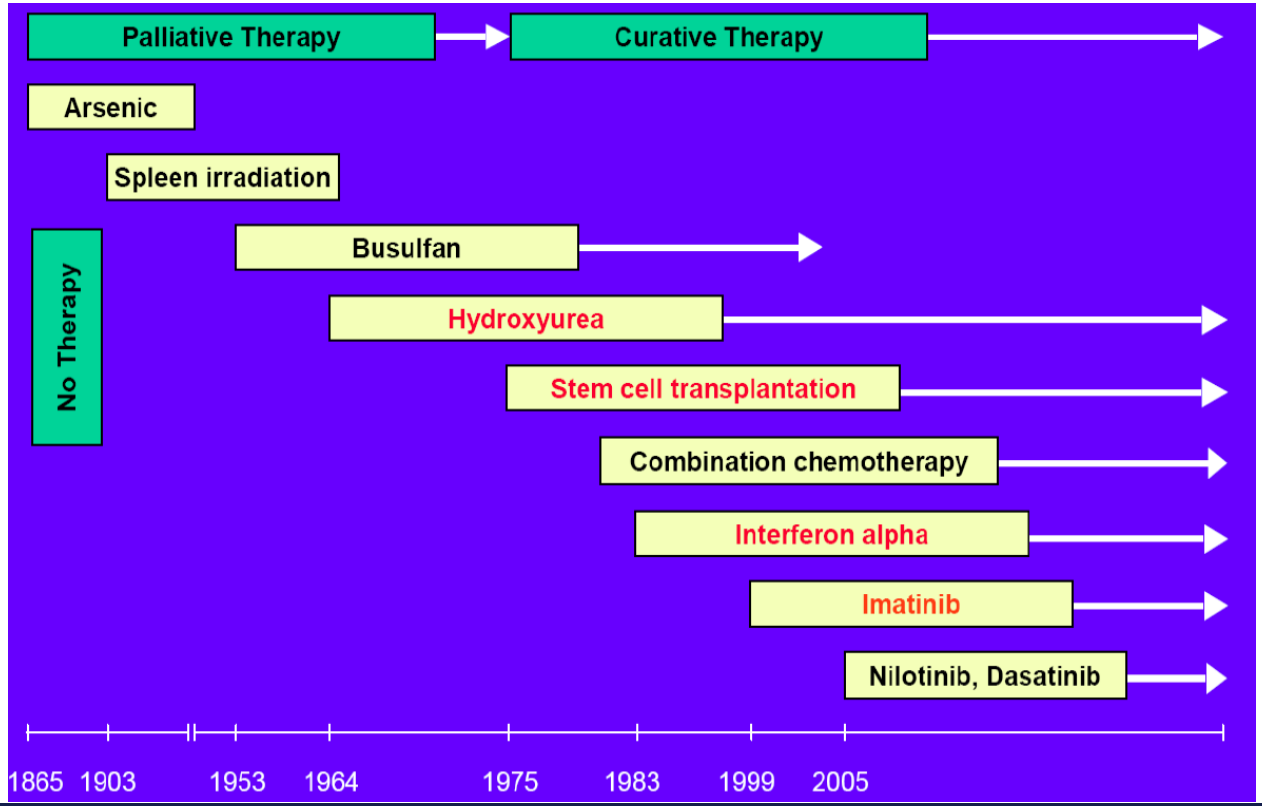
“kontinuierliche Linksverschiebung bis zum Blasten“
absolute Basophilie
absolute Eosinophilie

Philadelphia-Chromosom (Ph)

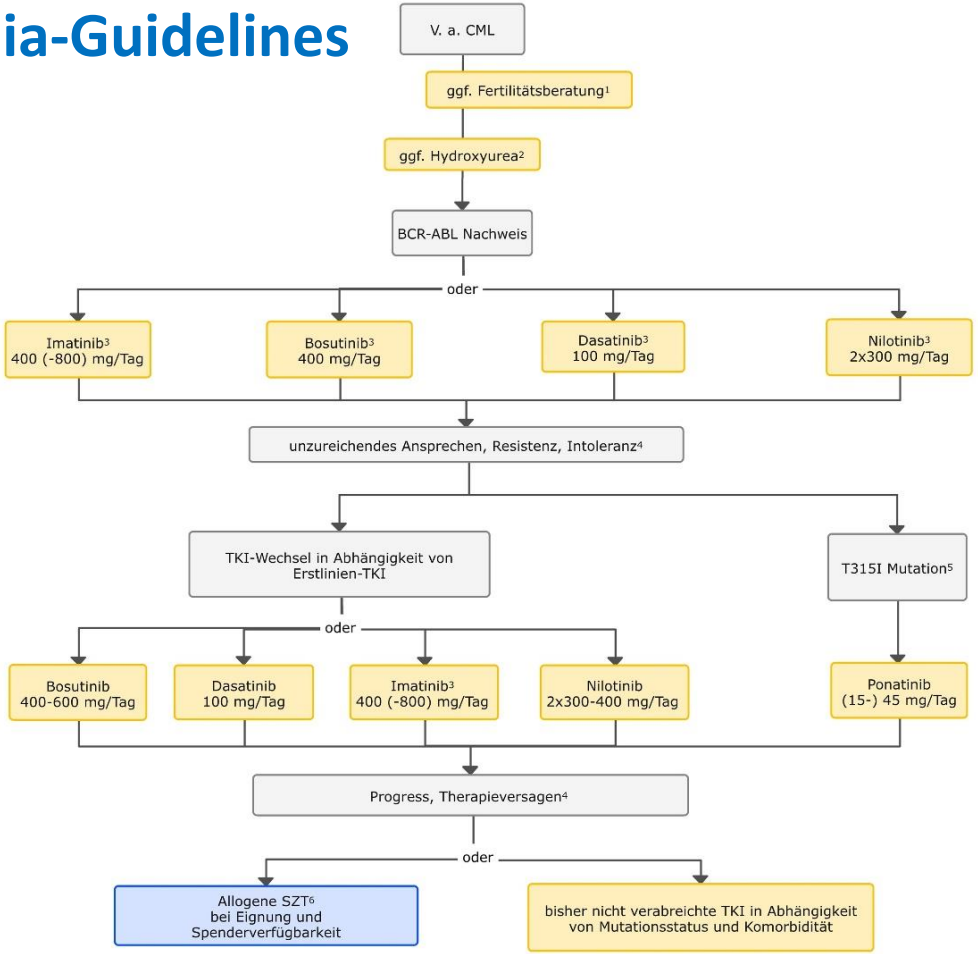
- Ph+ im Zusammenschau mit Blutbild- veränderungen beweisend für CML
- Nachweis
  - zytogenetisch t(9;22) im KM
  - FISH (Fluoreszenz-in-situ-Hybridisierung)
  - Molekularbiologisch (BCR/ABL) KM+PB (97%)
  - Eventuell andere, zusätzliche zytogenetische

- Veränderungen – daher immer KM !

Historische Entwicklung der CML Therapie



aktuelle Onkopedia-Guidelines



charakteristische NW:

Imatinib: GI-Symptome
Dasatinib: Flüssigkeitsretention
Nilotinib: Kardiovask. Ereignisse, Metabolische Verschlechterung
Ponatinib: Thromboembolische Ereignisse
Bosutinib: Lebertox

Danke für die Aufmerksamkeit