WHAT DOES THE FUTURE HOLD IN MPNs?

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Conflict of interest

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Genetic alterations in MPNs

Today: simplified and reliable diagnosis

2014 proposed revision for World Health Organization (WHO) diagnostic criteria for *BCR-ABL1*-negative myeloproliferative neoplasms

	Polycythemia vera (PV)	*Essential thrombocythemia (ET)*	*Primary myelofibrosis (PMF)*
Major criteria			
1	Hemoglobin > 16.5 g/dl (men) > 16 g/dl (women) or hematocrit > 49% (men) > 48% (women)	Platelet count ≥450 x 10^9/l	Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis or
2	BM trilineage myeloproliferation with pleomorphic megakaryocytes	Megakaryocyte proliferation with large and mature morphology	Not meeting WHO criteria for CML, PV, ET, MDS or other myeloid neoplasm
3	Presence of *JAK2* mutation	Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	Presence of *JAK2*, *CALR* or *MPL* mutation
4		Presence of *JAK2*, *CALR* or *MPL* mutation	
Minor criteria			
1	Subnormal serum erythropoietin level	Presence of a clonal marker (e.g. abnormal karyotype) or absence of evidence for reactive thrombocytosis	Presence of a clonal marker (e.g. abnormal karyotype) or absence of evidence for reactive bone marrow fibrosis
2			Presence of anemia or palpable splenomegaly
3			Presence of leukoerythroblastosis or increased lactate dehydrogenase

Adapted from Tefferi A, *et al. Leukemia*. 2014;28:1407-13.

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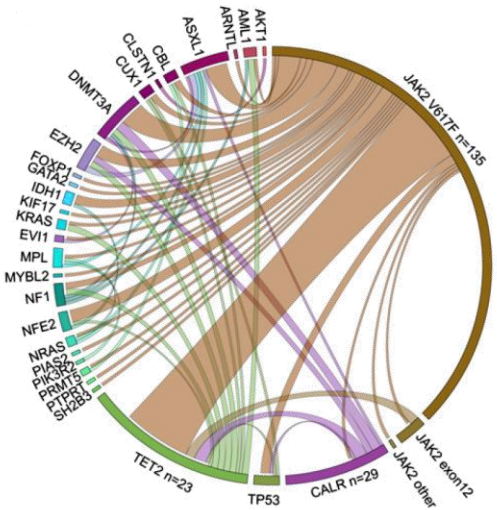
Genetic alterations in MPNs

Tomorrow: a new molecular-based classification?

- PV
- ET
- PMF

- JAK2-pos MPNs
- JAK2-neg MPNs

Concurrence of somatic mutations in the same individual



- Mutational Pattern A: Indolent MPNs
- Mutational Pattern B: Aggressive MPNs

Adapted from Lundberg, P, *et al. Blood*. 2014;123:2220-8

Professor T. Barbui

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The management of thrombosis is driven by the thrombotic risk

Conventional Risk Factors of Thrombosis in ET

Patient Related

Age

Previous thrombosis

Cardiovascular risk factors

Disease Related Risk Factors

Haemaglobin level

Platelet count

JAK2 V617F mutation

Bone marrow reticulin grade

Leukocytosis and inflammation

Barbui T, *et al. Blood.*2013;122:2176-84, Barbui T *et al. Blood.* 2012;120:1528-5133, Carobbio A *et al, Blood.* 2011;117:5857-9,

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IPSET Prognostic model for thrombosis

- **891 patients, followed for 6.2 years**
- Annual rate of thrombosis: 1.9% of patients

- **Model in WHO-defined ET**
  - ***Factors***: age > 60 years (**1 point**), thrombosis history (**2 points**), cardiovascular risk factors (**1 point**), and *JAK2* V617F (**2 points**).
  - ***Model***: Low Risk (LR) if < 2 points; Intermediate Risk (IR) if 2 points; High Risk (HR) if > 2 points
  - ***Risk of thrombosis***: 1.03% patients/year (p/y) (LR), 2.35% p/y (IR) 3.56% p/y (HR)
  - This model better predicts thrombosis than conventional one: 0.95% p/y (LR), 2.86% p/y (HR)

Barbui T. *et al. Blood.* 2012;120:5128-33

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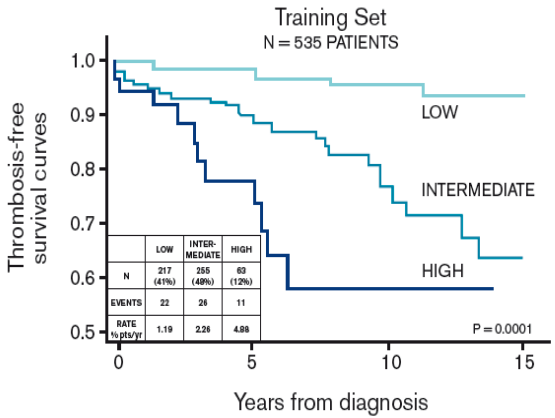
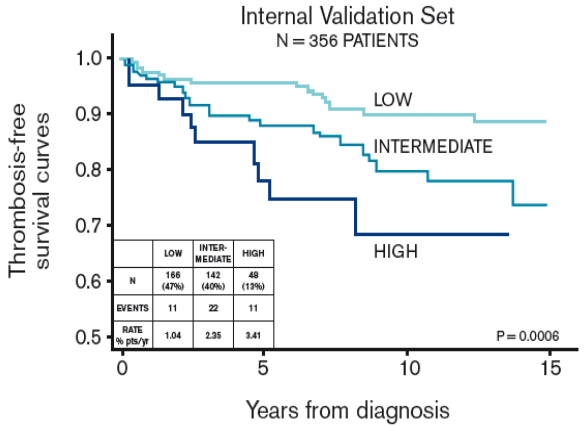
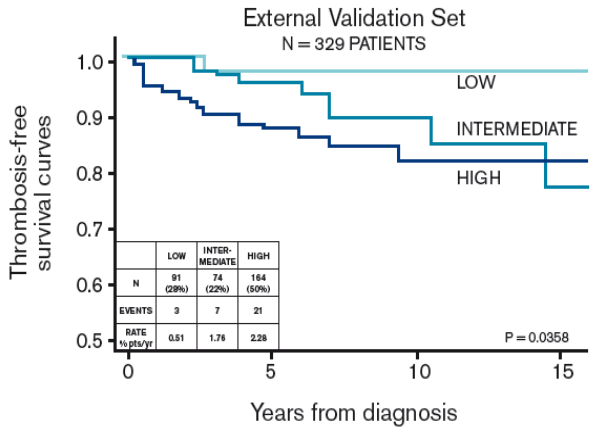
Prognostic model for thrombosis-free survival







HR – Hazard ratio,

Adapted from Barbui T. *et al. Blood.* 2012;120:5128-33

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CALR mutation and IPSET thrombosis

In multivariable models, *CALR* mutation was not associated with the risk of thrombosis:

- All patients:..... HR 0.81 (0.30-2.17), P=0.674
- Low-risk:..... HR 1.01 (0.27-3.81), P=0.987
- Intermediate risk:.....HR 1.80 (0.57-5.72), P=0.317
- The high risk category was not evaluable for the low proportion of *CALR* patients (4%)

Finazzi G, *et al. Blood*. 2014;124:2611-2.

IPSET – International Prognostic Score of thrombosis in WHO Essential Thrombocythaemia

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What does the future hold in MPNs?

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The PAST 10 years

- The 2008 revision of the WHO diagnostic criteria [1]: ***the beginning of a molecular era for MPNs***
- The IWG-MRT diagnostic criteria for post-ET and post-PV myelofibrosis [2]: ***separating the wheat from the chaff***
- The ELN management recommendations [3]: ***highlighting patients' unmet needs***
- ELN criteria for HU resistance/intolerance [4,5]: ***paving the way for alternative treatments***
- ELN & IWG-MRT response criteria for the MPNs [6,7]: ***foreseeing innovative treatments to come***

IWG-MRT – International Working Group-Myeloproliferative Neoplasms Research and Treatment

1 Swerdlow SH, IARC 2008; **2** Barosi G, *et al. Leukemia* 2008; 22:437-8; **3** Barbui T, *et al. J Clin Oncol.* 2011;29:761-70; **4** Barosi G, *Leukemia.* 2007;21:277-8, **5.** Barosi G, *et al. Br J Haematol.* 2010;148:961-3, **6.** Barosi G, *et al. Blood.* 2013;121:4778-81; **7**. Tefferi A, *et al. Blood.* 2013;122:1395-8

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The NEXT 10 years

- The upcoming WHO revised diagnostic criteria [8]: ***CALR,*** [8] ***histology,*** [8] ***and beyond***
- Earlier diagnosis and/or earlier diseases: ***identifying new diagnostic entities*** [9]
- "Old" & new mutations, and disease phenotypes: ***towards molecular-integrated risk scores and new diagnostic tools*** [10]
- "Old" drugs, JAK inhibitors, new upcoming therapies: ***changing the clinical endpoints for drug treatments*** [11]
- The dream of molecular remission [12,13]: ***raising the bar for treatment response criteria***

8. Tefferi A, *et al. Leukemia.* 2014;28:1407-13; **9.** Barbui T, *et al. Leukemia.* 2014;28:1191-5; **10.** Vannucchi AM, *et al. Leukemia.* 2013; 27:1861-9; **11.** Barosi G, *et al. Leukemia.* 2015;29:20-6**; 12.** Kiladjian JJ, *et al. Blood.* 2008;112:3065-71; **13.** Quintas-Cardama A, *et al. Blood.* 2013;122:893-901.

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What does the future hold in MPNs?

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Multidisciplinary approach in MPN

Main changes in the last 10 years

2005 → present: Molecular biology unfolds [1-3]

↓

Teamwork with **molecular biologists**

WHO classification as a key feature of diagnosis [4]

↓

Pathologists are essential players in diagnosis

Patients say: We are here!

↓

Development of MPN **patients associations**

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1. Nangalia J, *et al. N Engl J Med*. 2013;369:2391-2405, 2. Klampfl T, *et al. N Engl J Med.* 2013;369:2379-90,
3. James C, *et al. Nature.* 2005; 434:1144-48, 4. Tefferi A, *et al. Leukemia*. 2014;28:1407-13

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Multidisciplinary approach in MPN

Challenges for the future

Better knowledge of the role of cardiovascular risk factors as key elements in the therapeutic strategy [5]

Involvement of **cardiologists and epidemiologists**

New drugs to prevent the development of myelofibrosis (based on molecular prognostic evidence [5])

Collaboration with **molecular pharmacologists and chemists**

Prospective studies to answer some unmet issues in MPN (eg. Pregnancy [5])

Cooperation of **different medical specialities**

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5. Barosi G, *et al. Leuk Res.* 2014;38:155-160.