



A Case-Based Approach to Topical Issues in MPNs

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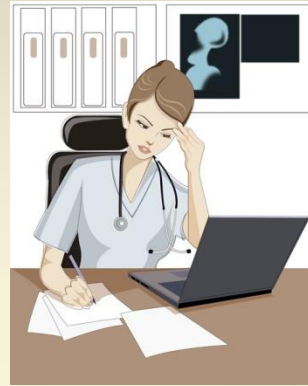
Mayo MPN Patient Conference

February 26, 2010

Elements of the Patient Encounter



Diagnosis &
Relevant Medical
History



Prognosis

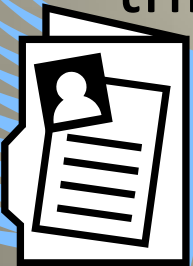


Treatment



Case 1

- Mr. Jones is a 56 year old man presents with increasing fatigue and headaches over the last 6 months. A complete blood count reveals a white blood count of 11.6, hemoglobin 18, hematocrit 54, and platelet count 460,000. A spleen tip is felt on exam. A *JAK2 V617F* mutation is positive. A diagnosis of polycythemia vera is made.
- Q: Mr. Jones asks: Is PV inherited? Will I pass this on to my children?



Swedish Registry Data

➤ The risk of MPN in ~25,000 first degree relatives of 11,000 MPN patients was 5-7 fold higher than in first degree relatives of normal individuals

➤ These familial cases are not explained by inheritance of the *JAK2* V617F mutation

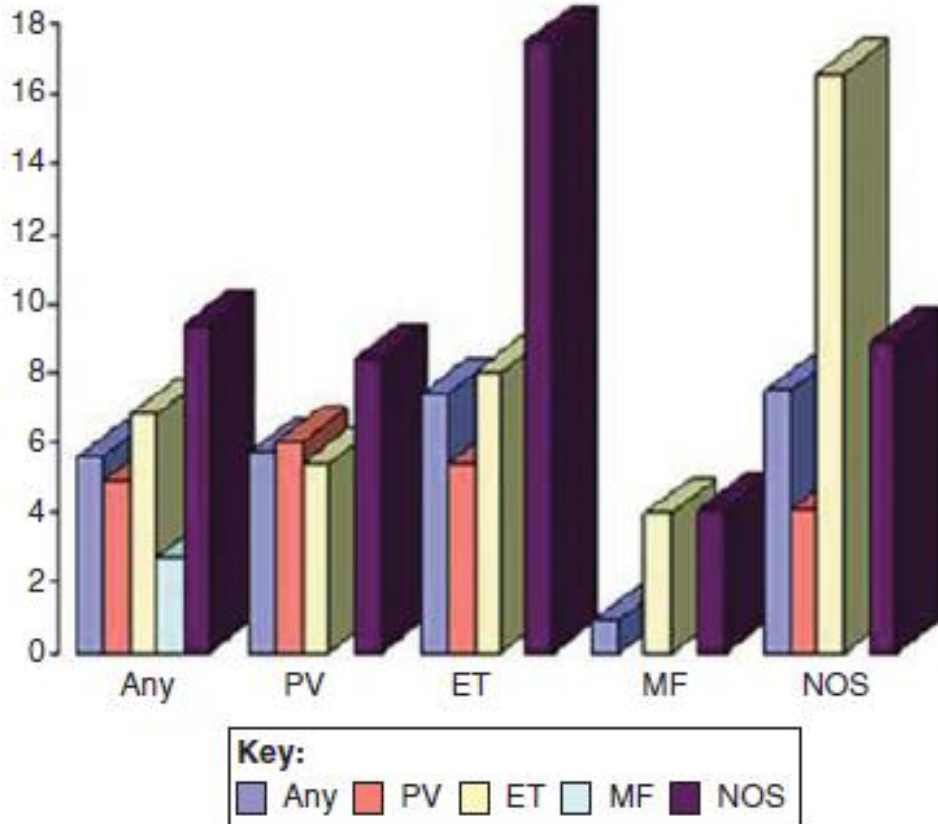
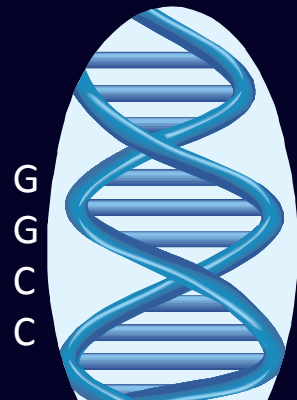


Figure 1

Risk for specific MPNs among first-degree relatives of MPN patients. The bars show relative risk estimates for specific MPNs (given on the x-axis) among first-degree relatives of patients affected with specific MPNs (see key) compared with first-degree relatives of controls.

Background: the 46/1 JAK2 haplotype

- **The 46/1 JAK2 haplotype predisposes JAK2-mutated MPN (PV, ET, PMF) in individuals of European ancestry (Cross, Kralovics, Levine)**
- **JAK2 mutations arise preferentially on 46/1 allele**
- **Odds ratio = 3.7; 46/1 accounts for ~50% of the population attributable risk of developing an MPN**



JAK2 46/1 Haplotype

- The *JAK2* 46/1 haplotype predisposes to both *JAK2* V617F- and MPL-mutated MPNs
- No association between 46/1 and either clinical features or outcome:
 - Age
 - Gender
 - Disease duration
 - WBC count, Hb, platelet count, EPO level, spleen size
 - Survival, arterial or venous thrombosis, hemorrhage, transformation to myelofibrosis or acute leukemia

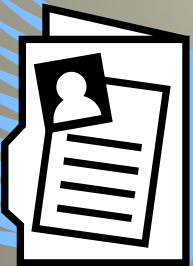
Case 1: Is this inherited?

Will I pass this on to my children?

- The 46/1 haplotype is a heritable DNA variation
- It increases the chance of developing an MPN, but does not guarantee its development
- There is currently no role for screening of the 46/1 haplotype in patients or relatives as it does not alter management

Case 2

- Mrs. Johnson is a 67 year old woman with a 3 month history of progressive fatigue, night sweats, and early satiety. On exam the spleen is enlarged, 12 cm below the left rib cage. A CBC reveals a WBC count of 27,500, hemoglobin 9.2, platelets 110,000, and no circulating blasts. RBC transfusion dependent. Cytogenetics reveals 13q deletion. A bone marrow biopsy reveals myelofibrosis.
- Q: How long am I going to live?
What is the chance of developing acute leukemia?



PMF: Recent Evolving Prognostic Scoring Systems

IPSS

DIPSS

DIPSS Plus

Prognosis in Primary Myelofibrosis

At time of diagnosis

“D”ynamic : during the course of disease

“Plus”: Additionally evaluates the prognostic value of platelet count <100,000, red blood cell transfusion dependence, and unfavorable cytogenetics

IPSS: International Prognostic Scoring System for Primary Myelofibrosis

Table 2. Risk factors at presentation of primary myelofibrosis selected at the stepwise Cox regression model for significant association with shorter survival*

Risk factor	Frequency in the series, %	Hazard ratio (95% CI)	z test	P
Age > 65 y	44.6	1.95 (1.61-2.36)	6.84	< .001
Constitutional symptoms	26.4	1.97 (1.62-2.40)	6.77	< .001
Hb < 10 g/dL	35.2	2.89 (2.46-3.61)	11.24	< .001
WBC count > 25 × 10 ⁹ /L	9.6	2.40 (1.83-3.14)	6.37	< .001
Blood blasts > 1%	36.2	1.80 (1.50-2.17)	6.29	< .001

*In 1001 patients with the 5 variables available.

Table 3. Definition, frequency, and survival of the risk groups of the prognostic scoring system of primary myelofibrosis

Risk group	No. of factors	Proportion of patients, %	Median survival (mo; 95% CI)	Proportion of deaths, %
Low	0	22	135 (117-161)	32
Intermediate-1	1	29	95 (79-114)	50
Intermediate-2	2	28	48 (43-59)	71
High	> 3	21	27 (23-31)	78

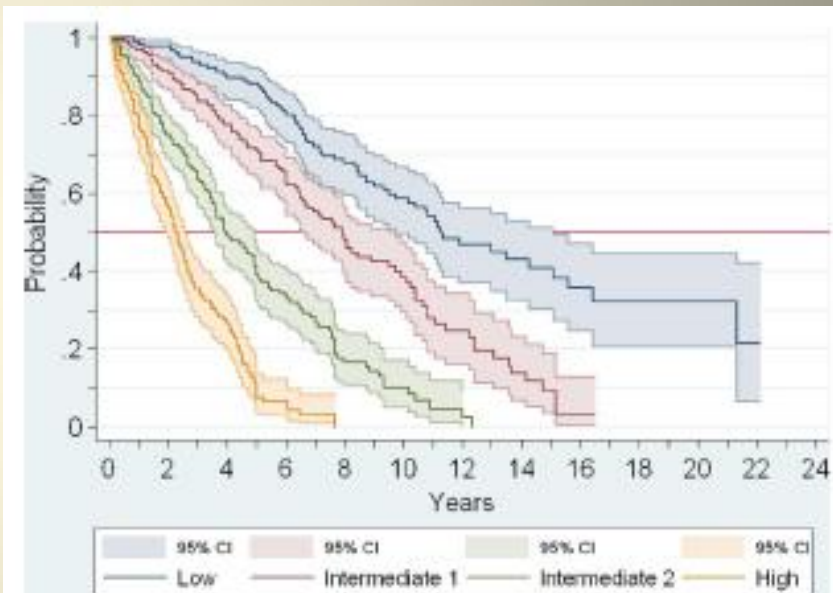


Figure 2. Actuarial survival curves of the 4 risk groups of patients according to the new PMF prognostic system.

DIPSS

Table 3. DIPSS for survival in primary myelofibrosis

Prognostic variable	Value		
	0	1	2
Age, y	≤ 65	> 65	
White blood cell count, ×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.

DIPSS indicates Dynamic International Prognostic Scoring System.

Table 4. Age-adjusted DIPSS for survival in primary myelofibrosis

Prognostic variable	Value		
	0	1	2
White blood cell count, ×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: more than 4.

DIPSS indicates Dynamic International Prognostic Scoring System.

DIPSS Risk Group	# Adverse Points	Median Survival (yrs)
Low risk	0	Not reached
Intermediate-1 risk	1-2	14
Intermediate-2 risk	3-4	4
High risk	5-6	1.5

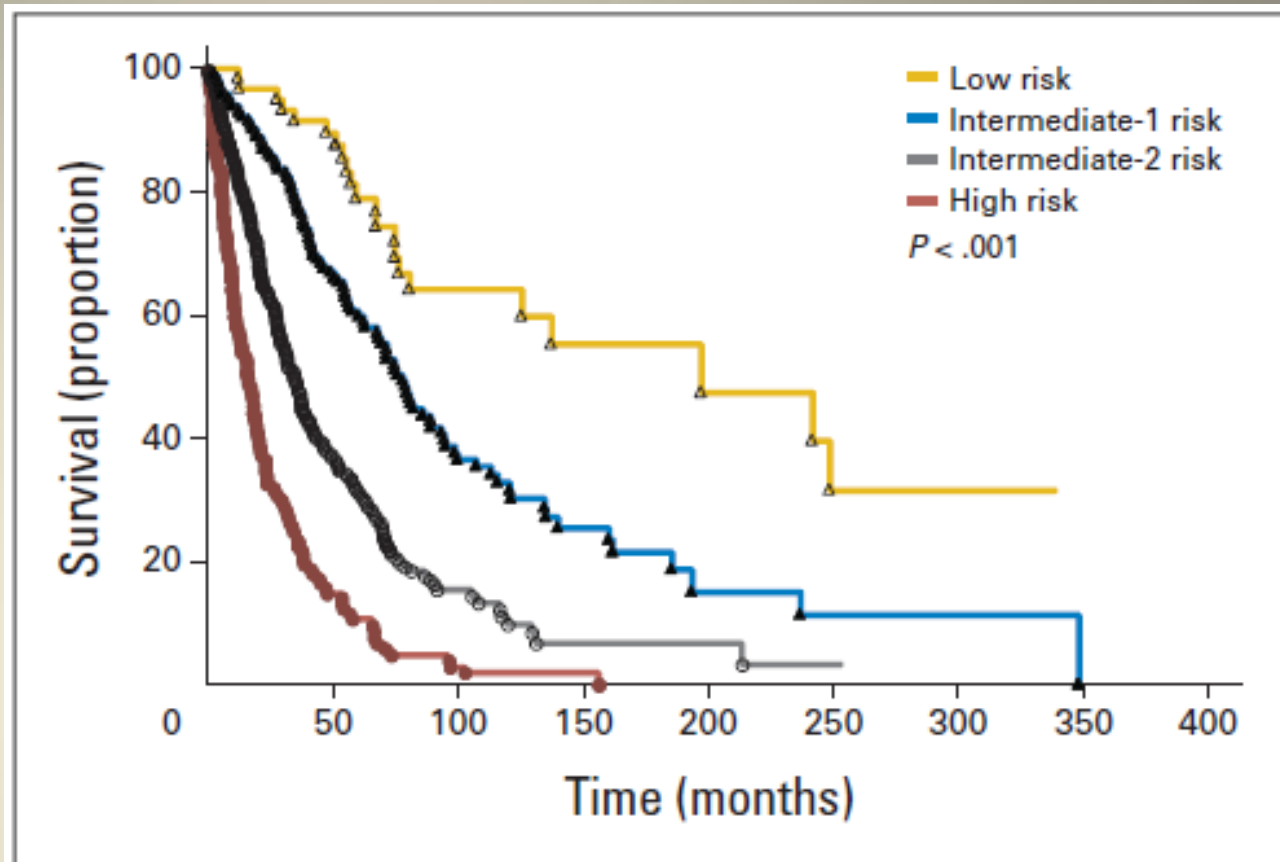
DIPSS Plus

“Plus” Risk Factors (Each adds 1 Adverse Point)

Unfavorable cytogenetics*

Platelet count < 100,000

RBC Transfusion Need



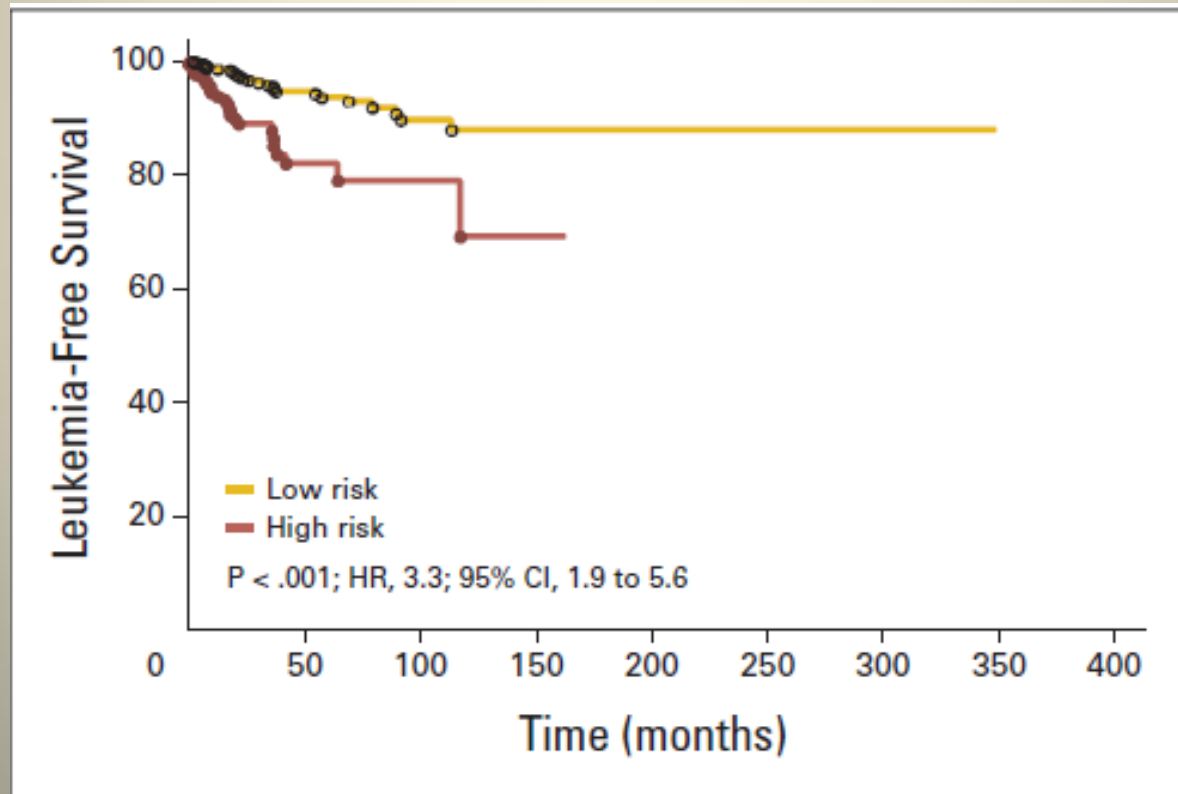
*Unfavorable cytogenetics:
 complex karyotype or sole or two abnormalities that include:

- +8
- 7/7q-
- i(17q)
- 5/5q-
- 12p-
- Inv(3)
- 11q23 rearrangement

DIPSS Plus	# Adverse Points	Median Survival
Low risk	0	185 months (15.4 yrs)
Intermediate-1 risk	1	78 months (6.5 yrs)
Intermediate-2 risk	2-3	35 months (2.9 yrs)
High risk	4-6	16 months (1.3 yrs)

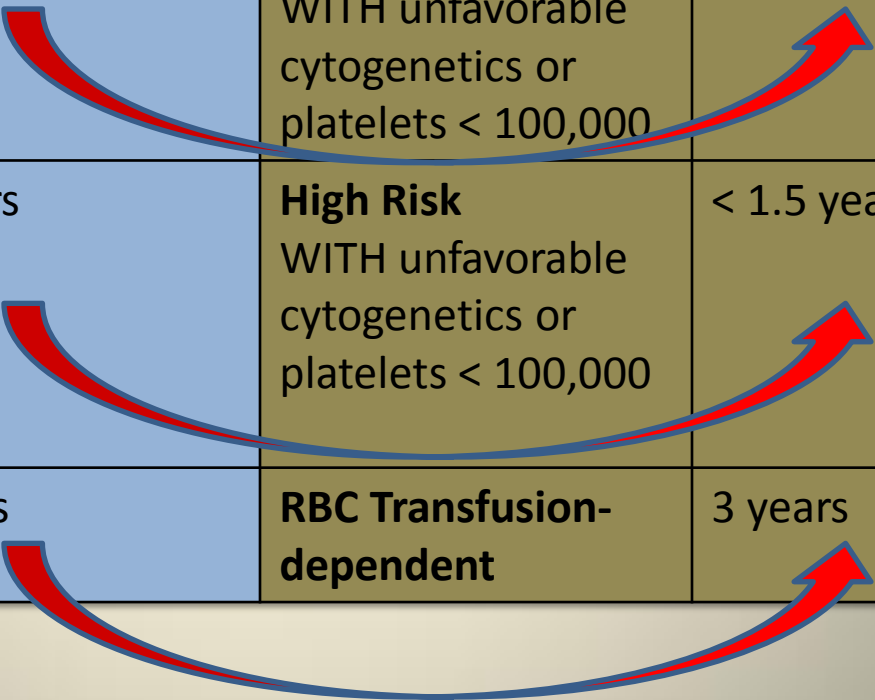
DIPSS Plus: Progression to Acute Leukemia

		5-yr Rate	10-yr Rate
Low-Risk	Favorable cytogenetics AND platelets \geq 100,000	6%	12%
High Risk	Unfavorable cytogenetics OR platelet count < 100,000	18%	31%



Refinement of Prognosis: DIPSS vs DIPSS Plus

DIPSS	Median Survival	DIPSS Plus	Median survival
Low Risk	> 15 years	Low Risk WITH unfavorable cytogenetics or platelets < 100,000	6.5 years
High Risk	~ 3 years	High Risk WITH unfavorable cytogenetics or platelets < 100,000	< 1.5 years
RBC Transfusion- dependent	14 years	RBC Transfusion- dependent	3 years



Case 2: How long am I going to live: What is the chance of developing acute leukemia?

- Age: 67
- WBC count: 27,500
- Hb 9.2, RBC transfusion dependent
- Platelets 110,000
- Constitutional symptoms: fatigue, night sweats
- No peripheral blood blasts
- Cytogenetics: 13q deletion (favorable risk)

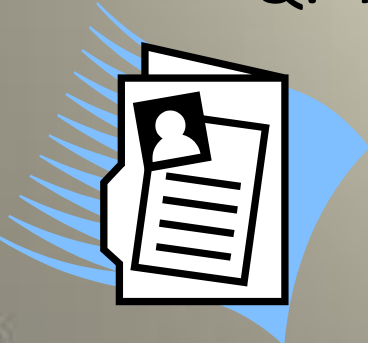
DIPSS Plus

Risk Group: High
Median Survival: 16 months (1.3 yrs)
5-yr rate of leukemia: 6%
10-yr rate of leukemia: 12%

Risk Factor	Adverse Point(s)?
Age >65	1
WBC count >25,000	1
Hb <10	2
Symptoms	1
PB blasts >1%	0
Platelets <100,000	0
Unfavorable Cytogenetics	0
RBC transfusion-dependent	1
Total points	6

Case 3

- Mrs. Adams is found to have a platelet count of 980,000 on a routine health check, and is subsequently referred to a hematologist. On exam, a spleen tip is palpated. The hemoglobin and white blood cell count and differential are normal. The LDH is normal at 150. Reactive causes of an elevated platelet count are excluded. A *JAK2* mutation analysis is positive. The smear reveals large/bizarre platelets without other findings.
- Q: Mrs. Adams asks: Do I need a bone marrow biopsy?



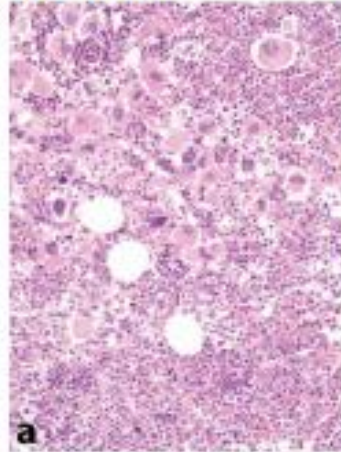
BACKGROUND

- The rationale of the World Health Organization (WHO) diagnostic criteria advocates **bone marrow morphology (BM)** as an integral and most important part,
particularly
- in distinguishing **Essential Thrombocythemia (ET)** from early -prefibrotic **Primary Myelofibrosis (PMF)** that clinically may present like **ET**

Comparative histopathology in early stage PMF and ET

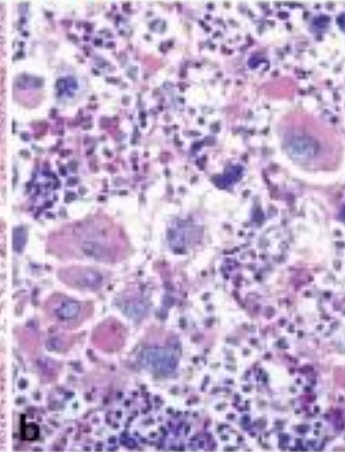


Early-PMF



a

Early-PMF

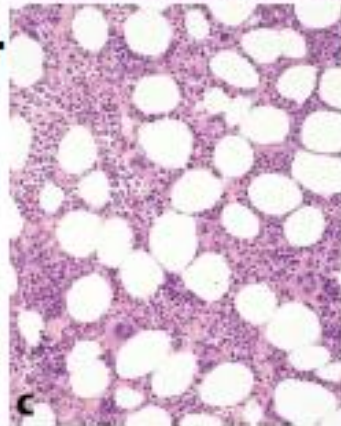


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Early Primary Myelofibrosis

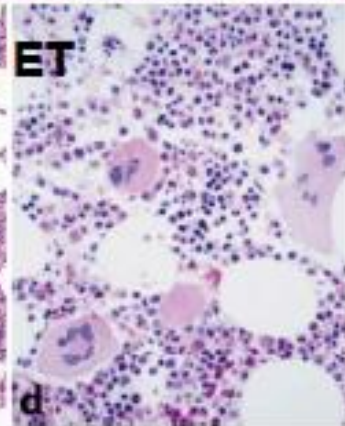
- ✓ prominent clustering of abnormal megakaryocytes
- ✓ hypolobulated / hyperchromatic nuclei
- ✓ Granulocytic proliferation

ET



c

ET



d

Essential Thrombocythemia

- ✓ normocellular
- ✓ Dispersed large to giant megakaryocytes

Study Design

Seven international centers

Inclusion criteria:

local **ET** diagnosis (from 1975 to 2008)
and pre-treatment **Bone Marrow biopsy** obtained at time of
diagnosis (or within 1 year of diagnosis in untreated patients)

1,104 ET patients

WHO 2008 review by

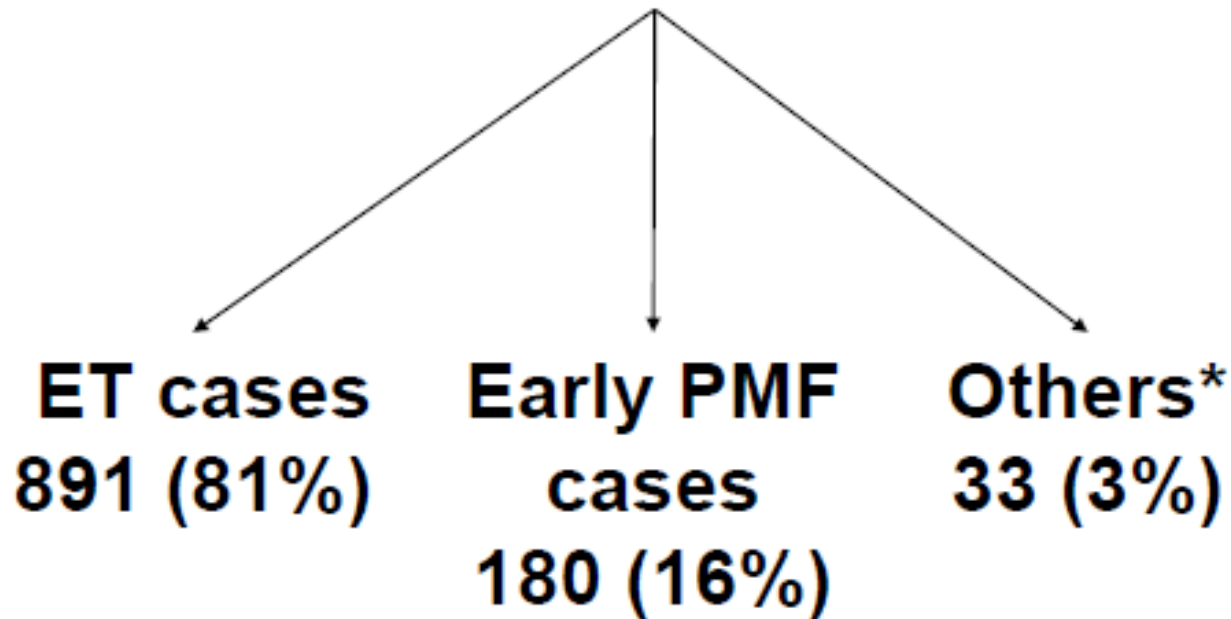
WHO author (JT)

completely blinded to outcome data

True ET

PMF

FINAL ASSIGNMENT



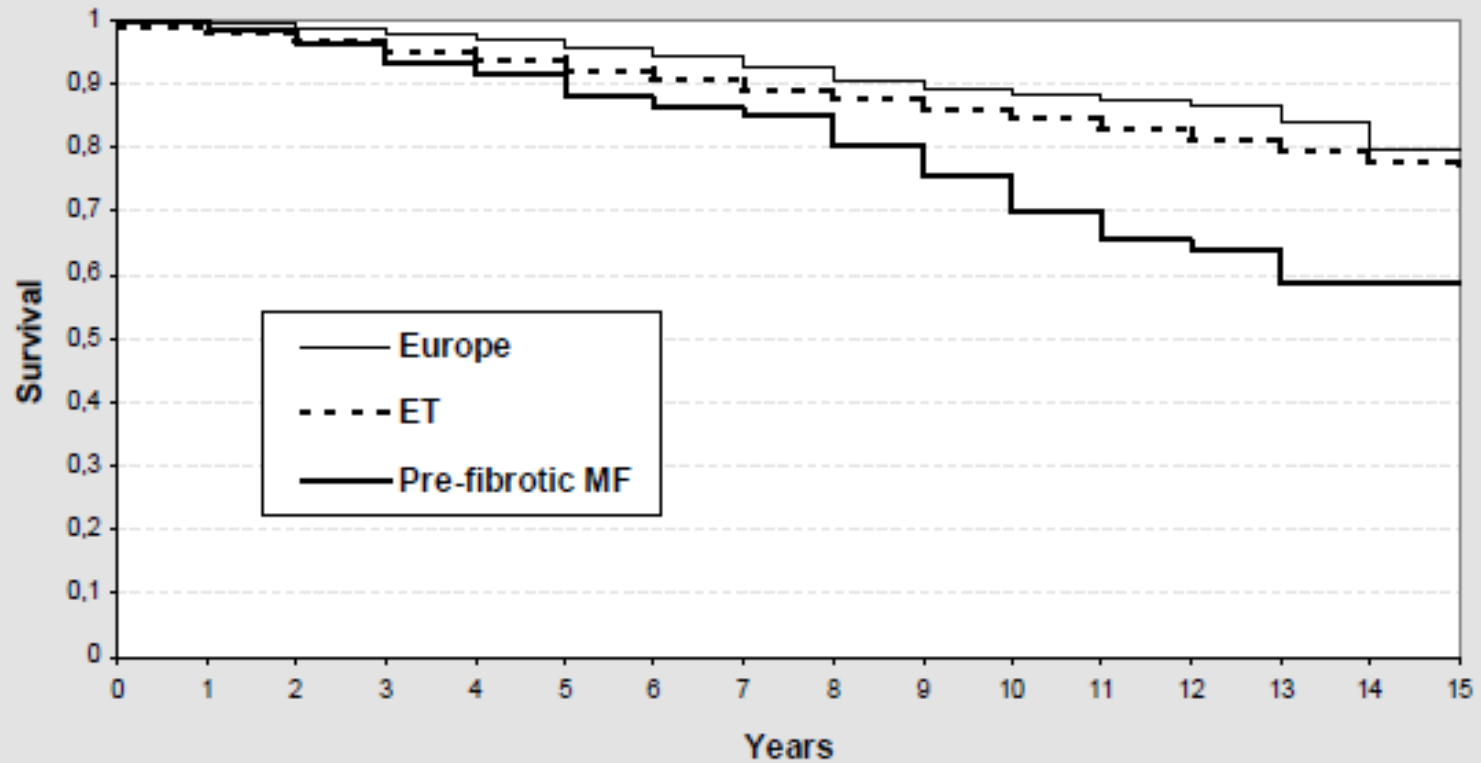
**(were inadequate or reactive cases)*

Disease Complications in Follow-up: ET vs. Pre-fibrotic Myelofibrosis

Complication	Relative Risk for PMF vs ET	P-value
Thrombosis	0.7	0.51 (not statistically significant)
Myelofibrosis	2.0	0.04 (statistically significant)
Acute Leukemia	5.2	0.0012 (statistically significant)
Survival	2.1	0.0002 (statistically significant)

ET and pre-fibrotic MF vs Europe*

Age- and sex-adjusted actuarial survival curves



*EUROSTAT 2008

(crude death rates, all causes of death, EU 27 countries)

Conclusion (1)

- Following an **accurate morphologic diagnosis**, the concept of prefibrotic/early PMF in “ET” **should be acknowledged**
- Clues for considering the possibility of early/prefibrotic PMF are **splenomegaly, elevated serum LDH, anemia, leukocytosis and increased circulating CD34-positive cell count**

Conclusion (2)

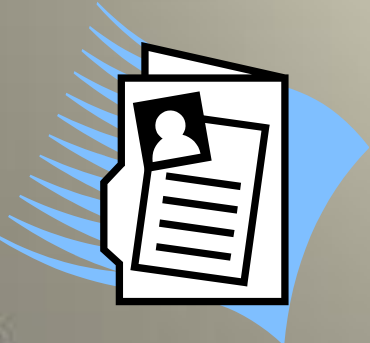
- **In patients with early-PMF** significant higher rates of myelofibrosis, leukemia and death.
- Conversely , **in strictly WHO-defined ET** the rate of these events would be even more favorable than currently assumed : < 1% after 10-15 years (in previous papers 8-10 %)

Case 3: Do I need a bone marrow biopsy?

- Mrs. Adams has a diagnosis of ET and no significant additional findings on blood smear besides increased and large platelets
 - Only a spleen tip is felt
 - The LDH is normal, and there is no co-existing anemia or leukocytosis
 - A CD34 count is not obtained
- In my judgment, a marrow biopsy can be deferred for the current time but should be re-evaluated if one or more of the above findings emerge.

Case 4

- Mr. Thompson is a 63 year old man recently diagnosed with polycythemia vera. A quantitative PCR test is performed showing a 68% *JAK2* V617F mutant allele burden.
- Q: Mr. T asks: What does it mean that my *JAK2* mutation test is at 68%? Is this concerning?



JAK2 V617F and Clinical Correlates

PV patients	JAK2 V617F allele burden (%) ¹				
	1-25	25-50	50-75	75-100	P-value
Hematocrit	53.8	54.2	56.9	57.4	<0.001
White cell count	9.0	10.6	11.7	13.9	<0.001
Platelet count	524	500	483	452	NS

PV patients: 75-100% vs. 1-25% allele burden ¹		
	RR	P-value
Splenomegaly	4.7	<0.001
Requiring chemotherapy	3.1	0.001
Major CV event	7.1	0.003

ET patients ²	JAK2 V617F positive vs. negative		
	Pos	Neg	P-value
Hemoglobin	14.2	13.2	<0.001
White cell count	10.2	8.9	0.008
Platelet count	975,000	1,130,000	0.001

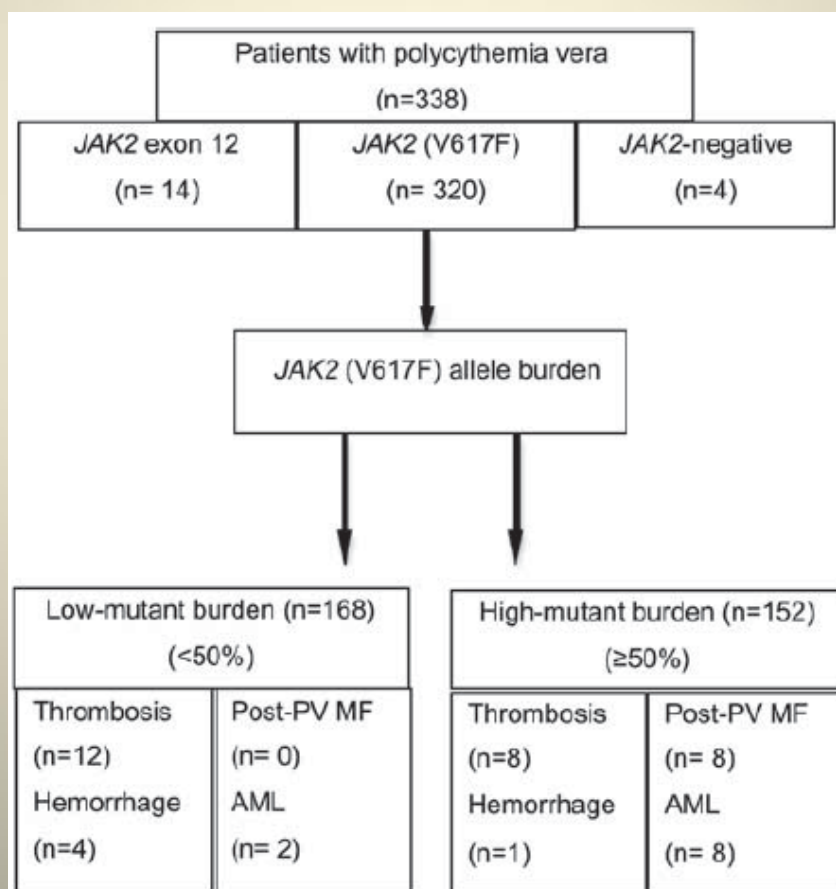
¹ Vannucchi AM et al. Leukemia. 2007. 21:1952-1959.

³ Kittur J et al. Cancer. 2007. 109:2279-2284.

A prospective study of 338 patients with polycythemia vera: the impact of *JAK2* (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications

F Passamonti¹, E Rumi¹, D Pietra¹, C Elena¹, E Boveri², L Arcaini¹, E Roncoroni¹, C Astori¹, M Merli¹, S Boggi¹, C Pascutto¹, M Lazzarino¹ and M Cazzola¹

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**Median
Follow-up
3.2 years**

≥50% JAK2 V617F allele burden in PV

- Higher WBC count
- Greater spleen size
- Lower platelet count

- No effect on:
- Risk of thrombosis, hemorrhage
- Progression to acute leukemia
- Overall survival

Table 3 Multivariable analysis including clinical parameters at *JAK2* assessment in 320 patients with polycythemia vera

Covariates	Events (hazard ratio with 95% confidence interval)			
	Thrombosis	Post-PV MF	Post-PV AML	Survival
Age, years	1.05 (1–1.1) <i>P</i> =0.01	1 (0.9–1.1) <i>P</i> =0.8	1.08 (0.9–1.2) <i>P</i> =0.06	1.1 (1.03–1.2) <i>P</i> =0.002
<i>JAK2</i> mutant allele burden	1 (0.9–1) <i>P</i> =0.8	1.05 (1–1.1) <i>P</i> =0.03	1 (0.9–1) <i>P</i> =0.3	0.99 (0.9–1) <i>P</i> =0.9
Leukocyte count > 11 × 10 ⁹ /l	1.1 (0.4–3.4) <i>P</i> =0.8	0.3 (0.6–1.1) <i>P</i> =0.2	1.6 (0.3–9.3) <i>P</i> =0.6	2.1 (0.6–7.7) <i>P</i> =0.2
Platelet count	1 (0.9–1.0) <i>P</i> =0.9	1 (0.9–1) <i>P</i> =0.6	1 (0.9–1) <i>P</i> =0.4	1 (0.9–1) <i>P</i> =0.3
Hemoglobin level	0.9 (0.7–1.2) <i>P</i> =0.5	1.3 (0.8–2) <i>P</i> =0.2	0.9 (0.6–1.3) <i>P</i> =0.6	0.9 (0.7–1.2) <i>P</i> =0.4
Spleen size	NI	1.1 (0.8–1.3) <i>P</i> =0.4	0.5 (0.1–1.1) <i>P</i> =0.3	0.8 (0.5–1.3) <i>P</i> =0.3
Previous thrombosis	1.9 (0.7–4.9) <i>P</i> =0.1	NI	NI	0.3 (0.1–1.3) <i>P</i> =0.1

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; MF, myelofibrosis; NI: not included as covariate; PV, polycythemia vera.

Increased risk of transformation to post PV myelofibrosis with *JAK2* V617F allele burden $\geq 50\%$

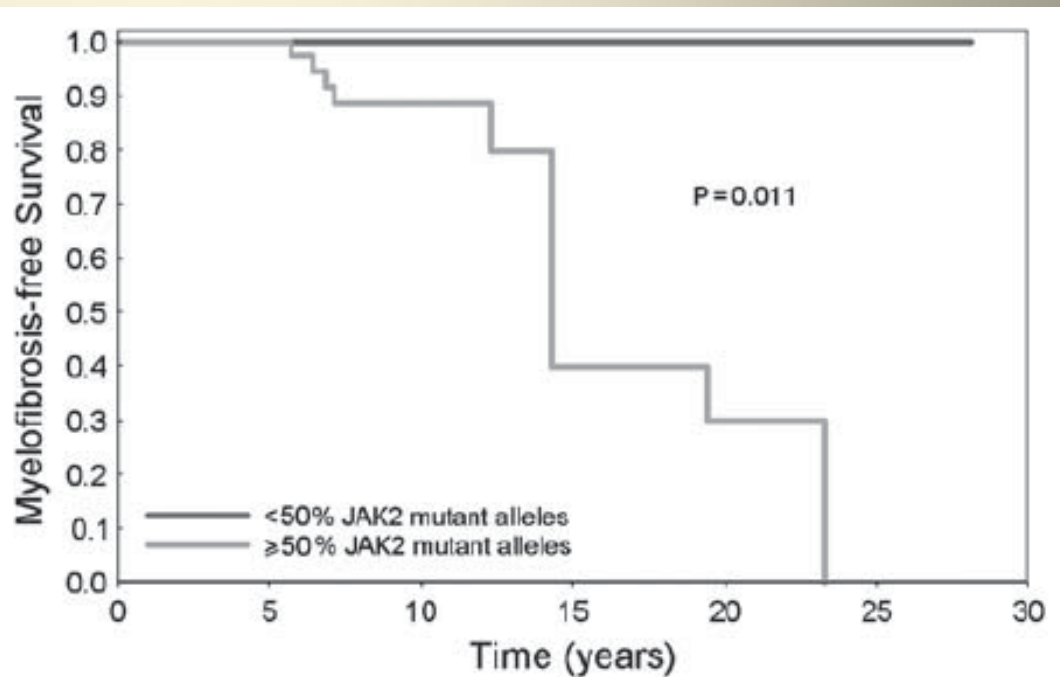
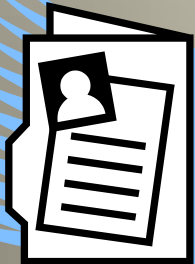


Figure 2 Kaplan–Meier estimate of MF-free survival in 320 patients from diagnosis of PV according to allele burden categories. Observations were left-censored at the time of *JAK2* assessment.

Case 5

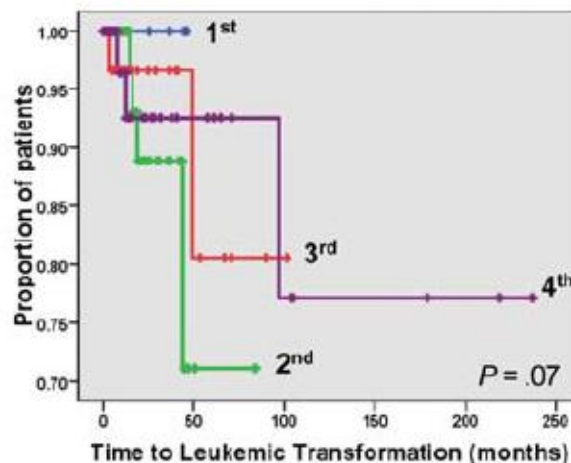
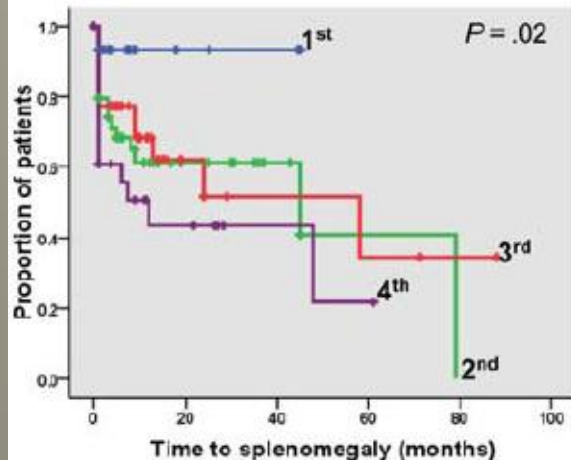
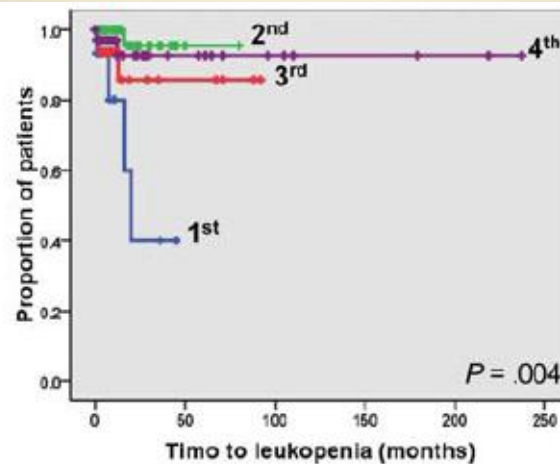
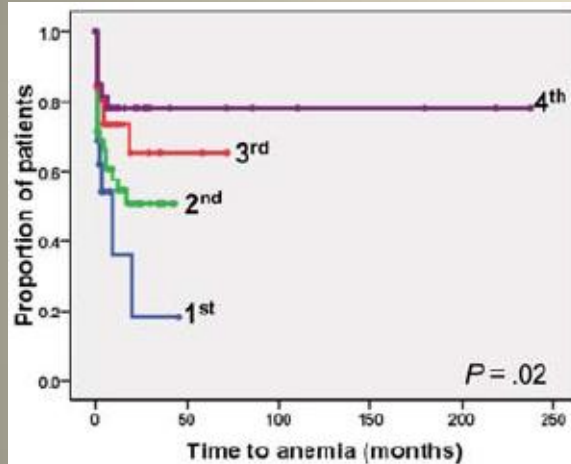
- Mr. Thompson, the recently diagnosed man with polycythemia vera has a friend, Mrs. Huff, who was just diagnosed with primary myelofibrosis. She was found to be *JAK2* V617F positive, but at a low level of 10%
- Q: Mrs. Huff asks: Because my *JAK2* mutation level is low, will I do relatively better?



Identification of patients with poorer survival in primary myelofibrosis based on the burden of *JAK2V617F* mutated allele

Paola Guglielmelli,¹ Giovanni Barosi,² Giorgina Specchia,³ Alessandro Rambaldi,⁴ Francesco Lo Coco,⁵ Elisabetta Antonioli,¹ Lisa Pieri,¹ Alessandro Pancrazzi,¹ Vanessa Ponziani,¹ Federica Delaini,⁴ Giovanni Longo,¹ Emanuele Ammatuna,⁵ Vincenzo Liso,³ Alberto Bosi,¹ Tiziano Barbui,⁴ and Alessandro M. Vannucchi¹

¹Unità Funzionale di Ematologia, Dipartimento di Area Critica, Università di Firenze, and Istituto Toscano Tumori, Firenze; ²Unità di Epidemiologia Clinica, Fondazione Istituti di Ricovero e Cura a Carattere Scientifico, Policlinico S Matteo, Pavia; ³Dipartimento di Ematologia, Università di Bari, Bari; ⁴Divisione di Ematologia, Ospedali Riuniti, Bergamo; and ⁵Dipartimento di Biopatologia e Diagnostica per Immagini, Università Tor Vergata, Rome, Italy

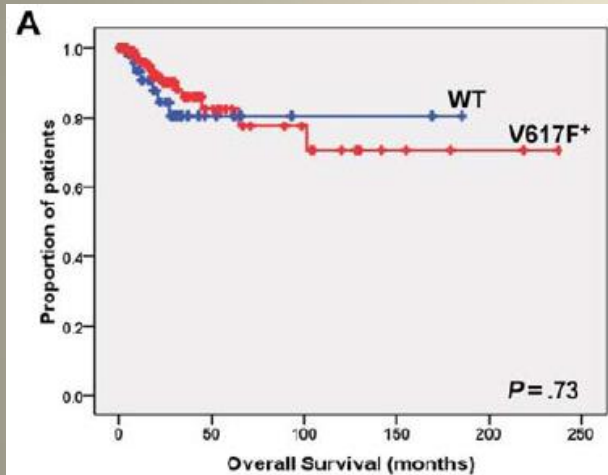


- ✓ Shorter time to anemia and leukopenia
- ✓ Longer time to splenomegaly

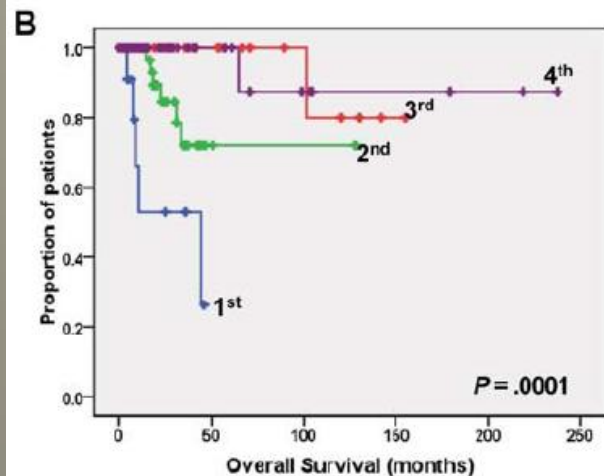
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- Patients with a lower quartile allele burden of *JAK2* V617F (1-25%) exhibited worse survival than:
 - 1) patients with higher allele burdens
 - 2) patient with normal *JAK2*

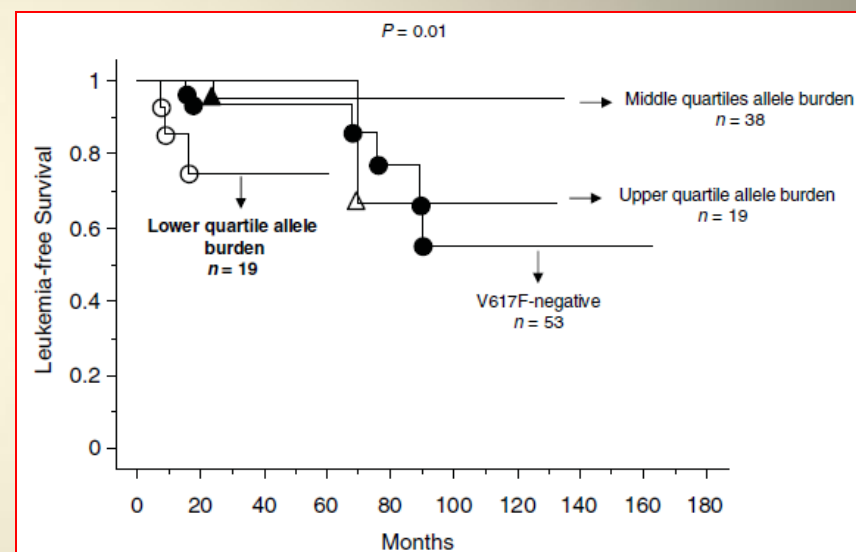
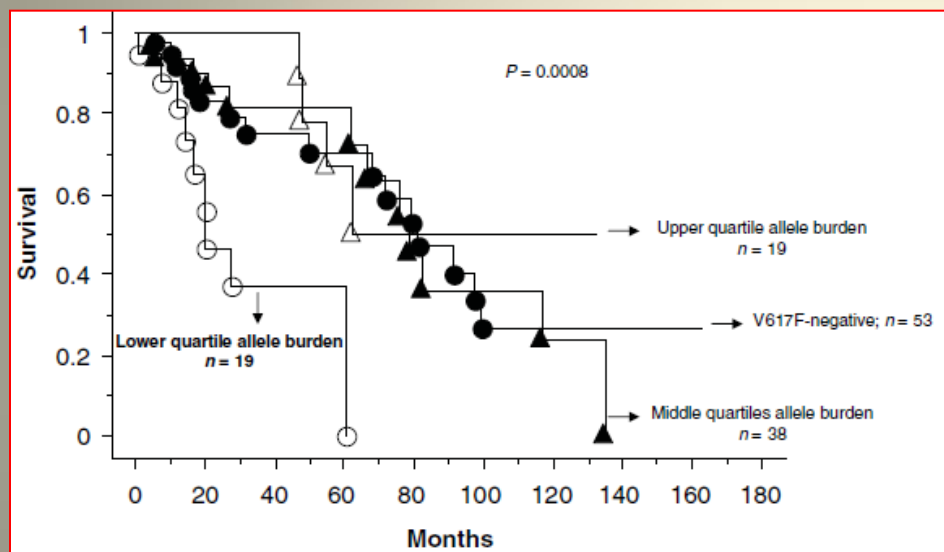


- Deaths were primarily attributed to infection due to low blood counts (marrow failure)

Low *JAK2*V617F allele burden in primary myelofibrosis, compared to either a higher allele burden or unmutated status, is associated with inferior overall and leukemia-free survival

A Tefferi¹, TL Lasho¹, J Huang¹, C Finke¹, RA Mesa¹, CY Li², W Wu³, CA Hanson² and A Pardanani¹

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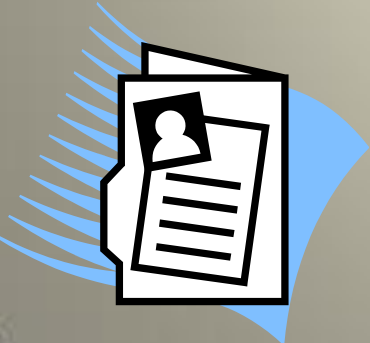
- Low *JAK2* V617F allele burden was associated with decreased overall survival and leukemia-free survival independent of other risk factors
- The survival of higher allele burden patients was not different from patients with normal *JAK2*

Cases 4 & 5: My JAK2 mutation test is at 68%? 10%? What should I do?

- In PV, higher allele burden may lead to a higher rate of (or earlier) post-PV myelofibrosis.
- Two studies now show that in PMF, a low level of *JAK2* V617F is associated with worse survival compared to higher *JAK2* V617F levels or normal *JAK2*
 - Marrow failure/infection vs. leukemia
 - Why should a lower level of *JAK2* V617F lead to worse outcomes?
- There are no established guidelines for making treatment decisions based solely on the *JAK2* mutation level
- Risk stratification in PV and prognostic scoring systems such as IPSS/DIPSS+ for PMF (as well as patient performance status) should guide treatment decisions

Case 6

- Mr. Plaqueta is a 37 year old man with a new diagnosis of essential thrombocythemia. He has never experienced a venous or arterial blood clot. He has no cardiovascular risk factors.
- Q: Mr. P asks: I don't like taking any medications. Do I really need to take aspirin?



Risk-Adapted Therapy for PV and ET

Polycythemia vera

Risk group	Age \geq 60 or history of thrombosis	Treatment
Low	No	Low-dose aspirin + phlebotomy
High [^]	Yes	Low-dose aspirin + phlebotomy + hydroxyurea

Essential thrombocythemia

Risk group	Age \geq 60 or history of thrombosis	Treatment
Low	No	Low-dose aspirin
High [^]	Yes	Low-dose aspirin + hydroxyurea

[^]Extreme thrombocytosis (> 1 - 1.5 million) is a potential risk factor for bleeding and is considered to be a high-risk feature (consider screening for aVWD before starting ASA)

Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia

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N=300 patients	Observation (n=102)	Anti-platelet therapy (n=198)	Statistical significance
Person-yrs of follow-up	802	848	
Rates of thrombosis	21.2/1000 person- yrs	17.7/1000 person-yrs	No difference

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Ant-platelet therapy was specifically useful in two settings:

- Reduction in rate of venous thrombosis in ET patients with *JAK2* V617F
- Reduction in rate of arterial thrombosis in ET patients with cardiovascular risk factors

- In the remaining low-risk patients, anti-platelet therapy was not effective in altering the rate of thrombosis . Observation alone in these individuals may be an adequate option.
- Increased major bleeding in patients with a platelet count > 1,000,000

Case 6: Do I really need aspirin for my low risk ET?

- This is a retrospective study; although compelling, a prospective study with long-term follow-up would be useful
 - ? Is such a study high enough priority
- Subgroups to consider holding or deferring use of aspirin:
 - Low risk ET patients without either the *JAK2* mutation or associated cardiovascular risk factor(s) [more data needed]
 - Platelet count >1-1.5 million where bleeding may increase
 - Check for an acquired von Willebrand defect

Unproven Statements and Myths

- Hydroxyurea definitely increases the risk of leukemia in patients with MPNs
- The degree of platelet count elevation correlates with the risk of thrombosis
- JAK inhibitors are only available to, and are effective in patients with the *JAK2* V617F mutation
- JAK inhibitors can cure myelofibrosis
- The Chicago Cubs can win the World Series

Thank You

Our Patients

Everybody dies, but not everybody lives

- Nicki Minaj, from "Moment 4 Life"