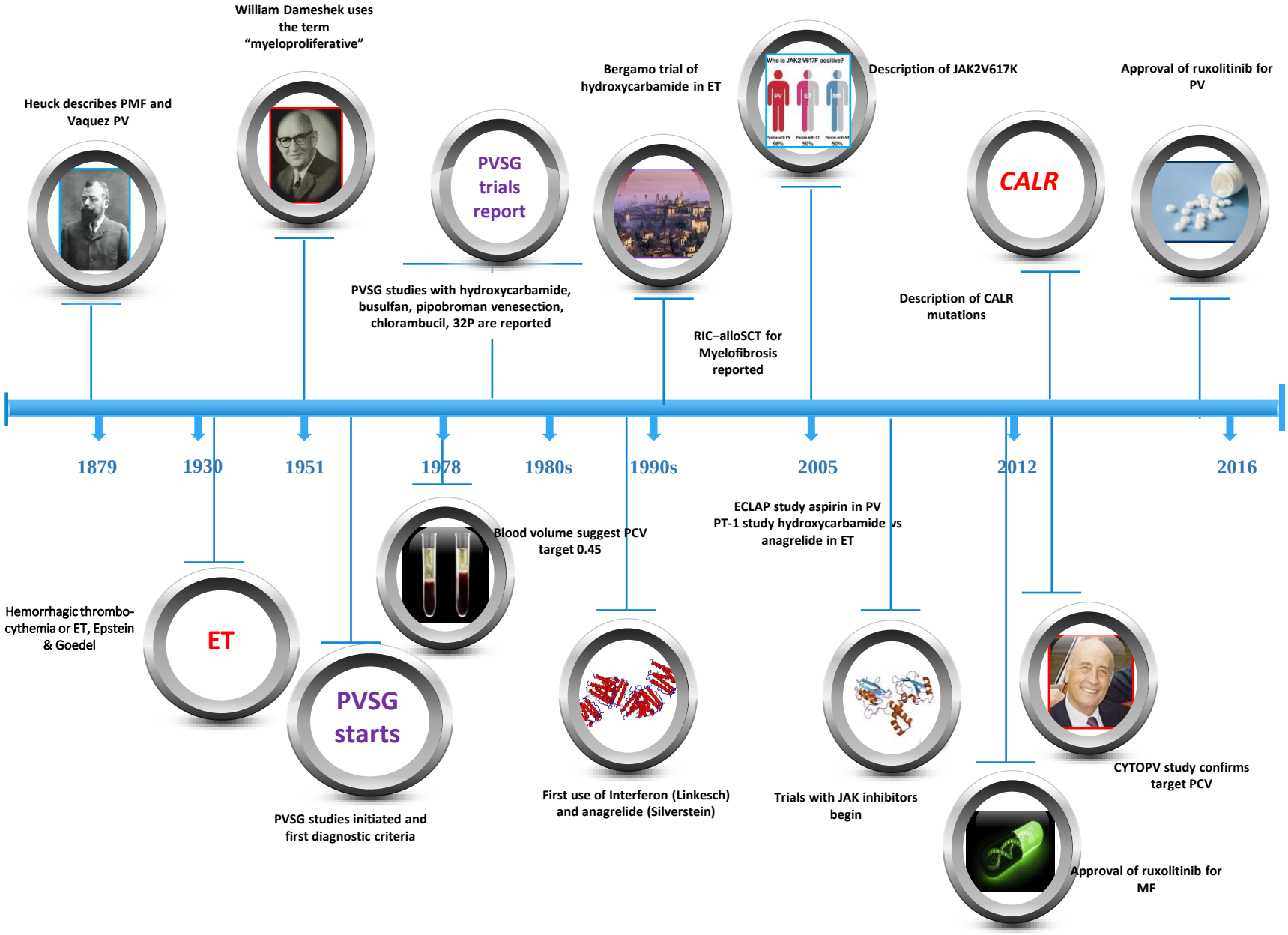
Essential Thrombocythemia: yesterday, today & tomorrow…

Claire Harrison

Guy's and St Thomas' Hospitals London, UK


Heuck describes PMF and Vaquez PV
William Dameshek uses the term "myeloproliferative"
PVSG trials report
PVSG studies with hydroxycarbamide, busulfan, pipobroman venesection, chlorambucil, 32P are reported
Bergamo trial of hydroxycarbamide in ET
RIC–alloSCT for Myelofibrosis reported
Who is JAK2 V617F positive?
PV
ET
MF
Description of JAK2V617K
CALR
Description of CALR mutations
Approval of ruxolitinib for PV
1879
1930
1951
1978
1980s
1990s
2005
2012
2016
Hemorrhagic thrombo-cythemia or ET, Epstein & Goedel
ET
PVSG starts
PVSG studies initiated and first diagnostic criteria
Blood volume suggest PCV target 0.45
First use of Interferon (Linkesch) and anagrelide (Silverstein)
ECLAP study aspirin in PV
PT-1 study hydroxycarbamide vs anagrelide in ET
Trials with JAK inhibitors begin
CYTOPV study confirms target PCV
Approval of ruxolitinib for MF

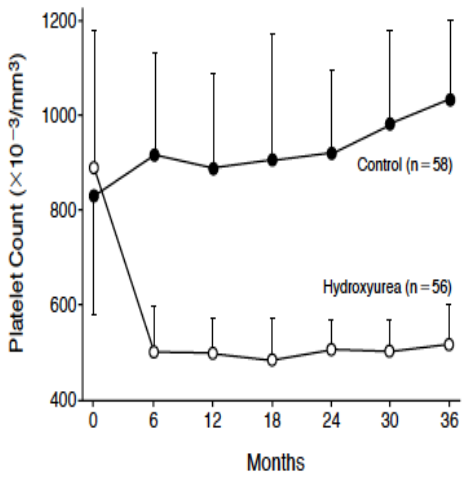
What have we learnt from randomised and other studies in ET?

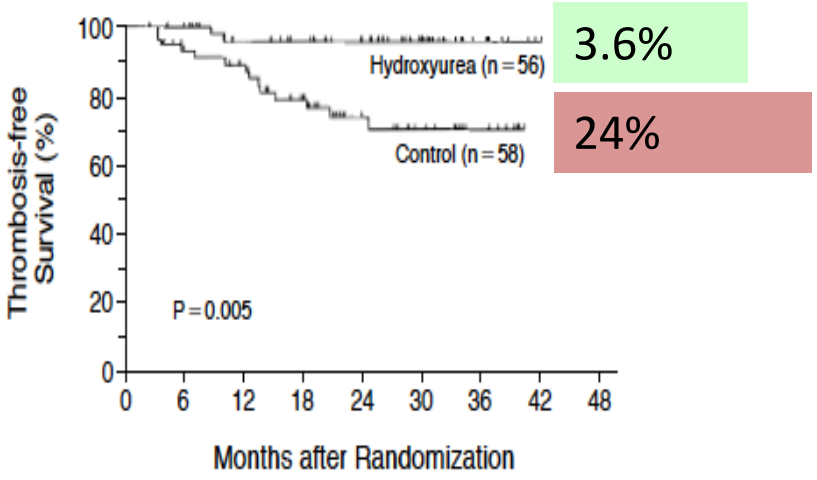
Cytoreduction in high-risk ET

1132 THE NEW ENGLAND JOURNAL OF MEDICINE April 27, 1995

HYDROXYUREA FOR PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA AND A HIGH RISK OF THROMBOSIS

SERGIO CORTELAZZO, M.D., GUIDO FINAZZI, M.D., MARCO RUGGERI, M.D., OSCAR VESTRI, M.D., MONICA GALLI, M.D., FRANCESCO RODEGHIERO, M.D., AND TIZIANO BARBUI, M.D.



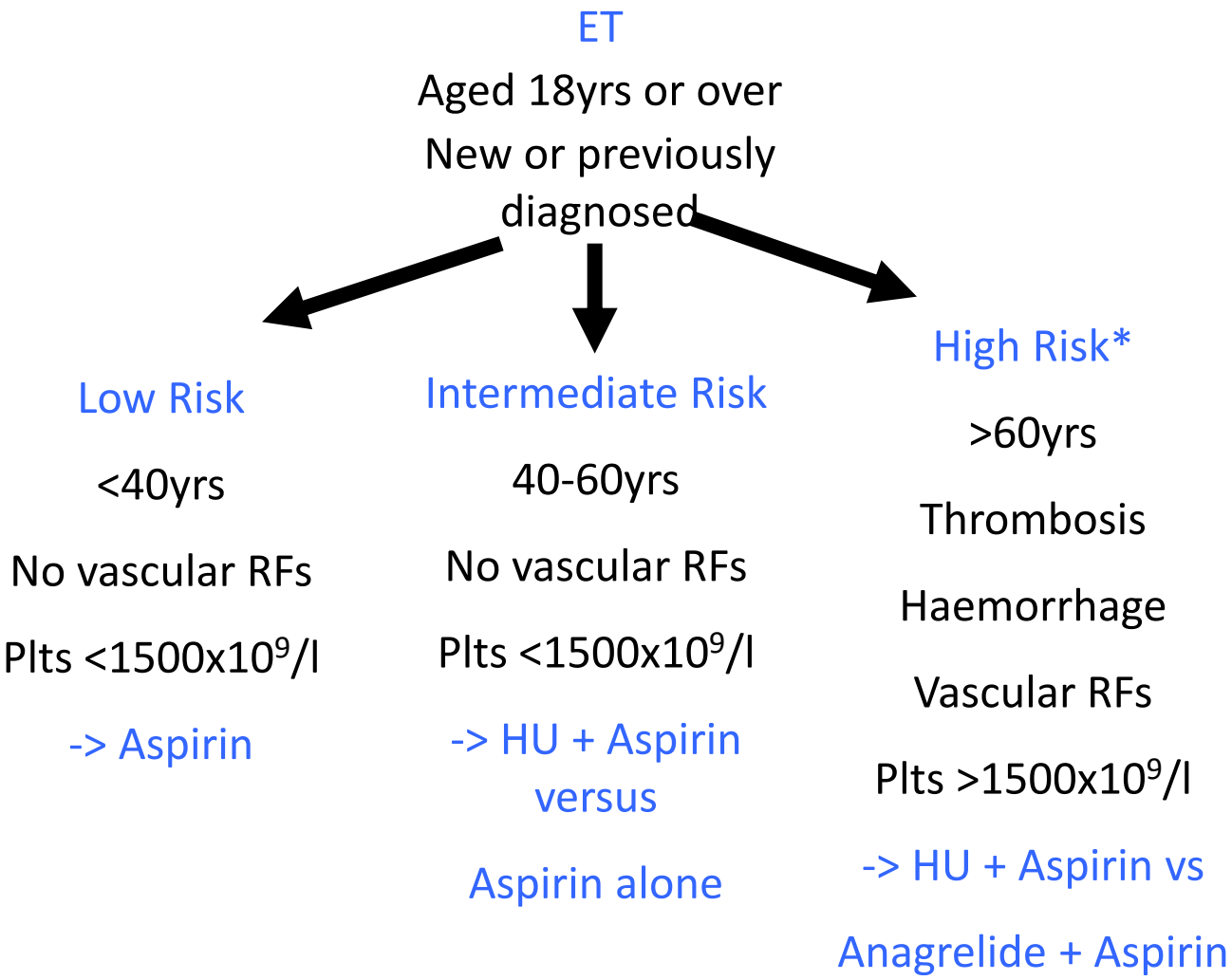


3.6%

24%

- Hydroxyurea (target plts<600) *vs* no hydroxyurea
- Cytoreduction reduces thrombosis in high-risk ET

Primary Thrombocythaemia - 1 Studies (PT1)



HU, Hydroxyurea; RFs, Risk factors of hypertension, diabetes mellitus, ischaemic heart disease
*Harrison et al, NEJM 2005

Choice of cytoreduction: PT1

Hydroxyurea Compared with Anagrelide in High-Risk Essential Thrombocythemia

Claire N. Harrison, M.R.C.P., M.R.C.Path., Peter J. Campbell, F.R.A.C.P., F.R.C.P.A., Georgina Buck, M.Sc., Keith Wheatley, D.Phil., Clare L. East, B.Sc., David Bareford, M.D., F.R.C.P., Bridget S. Wilkins, M.D., F.R.C.Path., Jon D. van der Walt, M.D., F.R.C.Path., John T. Reilly, F.R.C.P., F.R.C.Path., Andrew P. Grigg, F.R.A.C.P., F.R.C.P.A., Paul Revell, M.D., F.R.C.P., Barrie E. Woodcock, F.R.C.P., F.R.C.Path., and Anthony R. Green, F.R.C.Path., F.Med.Sci., for the United Kingdom Medical Research Council Primary Thrombocythemia 1 Study*

N ENGL J MED 353;1 WWW.NEJM.ORG JULY 7, 2005

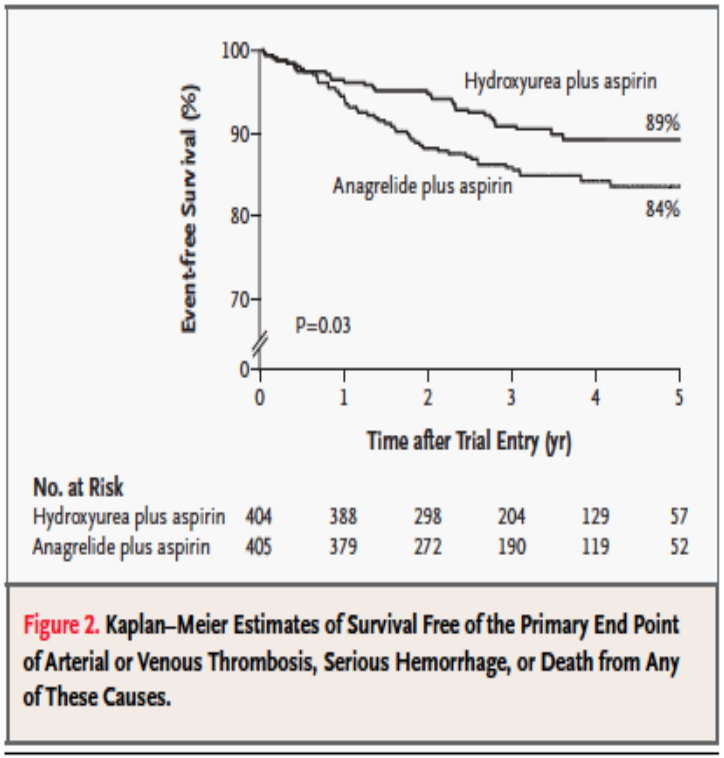


Figure 2. Kaplan–Meier Estimates of Survival Free of the Primary End Point of Arterial or Venous Thrombosis, Serious Hemorrhage, or Death from Any of These Causes.

- 809 high-risk patients randomised to HU or anagrelide
- Target plts<400; equivalent control of platelet count in 2 arms
- Hydroxycarbamide and aspirin appropriate first line in ET

Summary high risk arm of PT-1

- **Equivalent long-term control of platelet count**

- **Anagrelide +aspirin** **- more patients reached 1^0 endpoint**
  - more intolerant of treatment

- **Four other significant differences:**

  Anagrelide +aspirin **- more arterial thrombosis**
  - more myelofibrosis
  - more major hemorrhage

  HU +aspirin **- more venous thrombosis**

✓ Blood counts at diagnosis

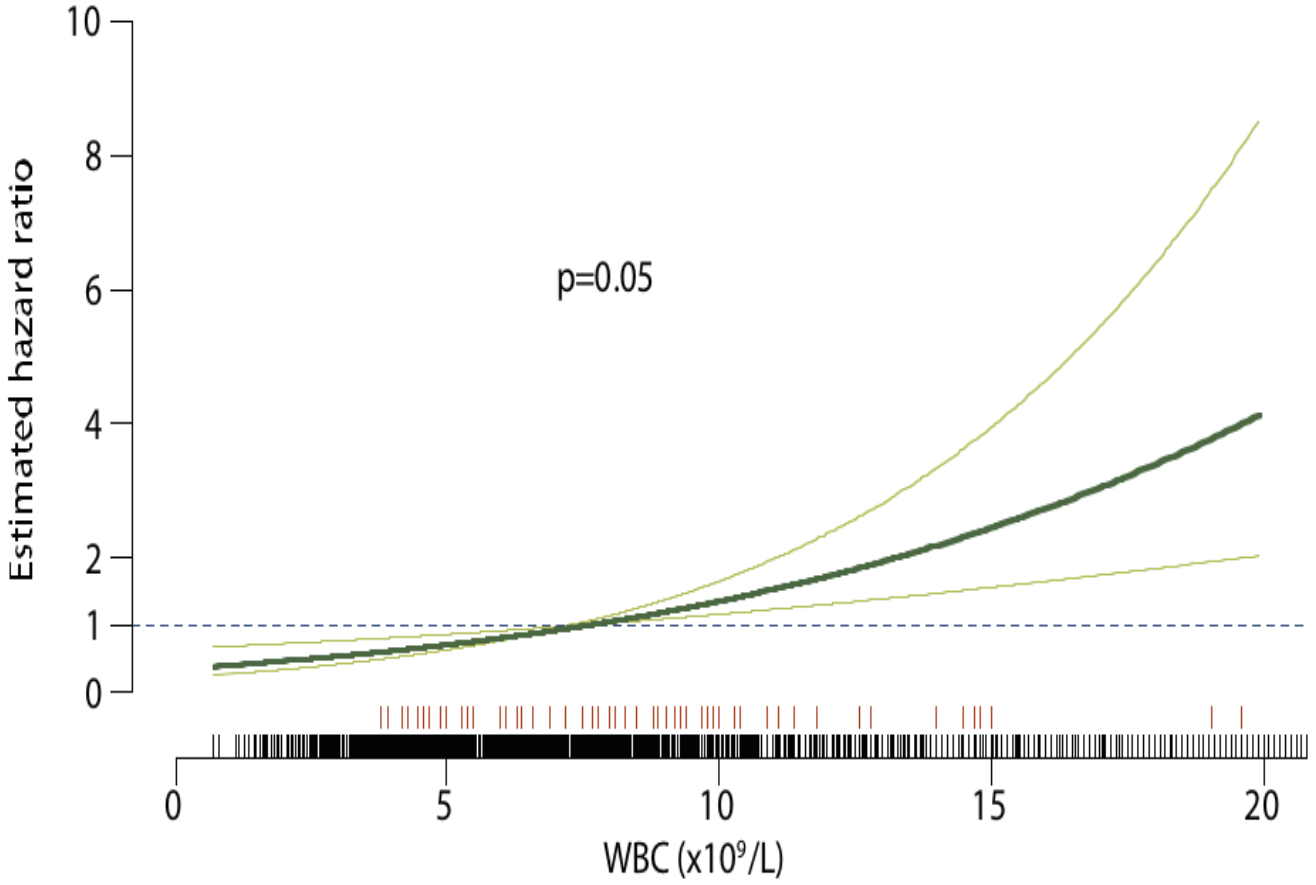
	Platelets	WCC	Hb
Thrombosis	p=0.4	p=0.6	p=1.0
Major hemorrhage	p=0.6	p=0.6	p=0.6
Transformation to Myelofibrosis / AML / MDS	p=0.5	p=0.9	p=0.8

- 21,887 longitudinal blood counts after trial entry

Campbell Blood 2012

- ✓ Blood counts at diagnosis
- ✓ Blood counts during treatment

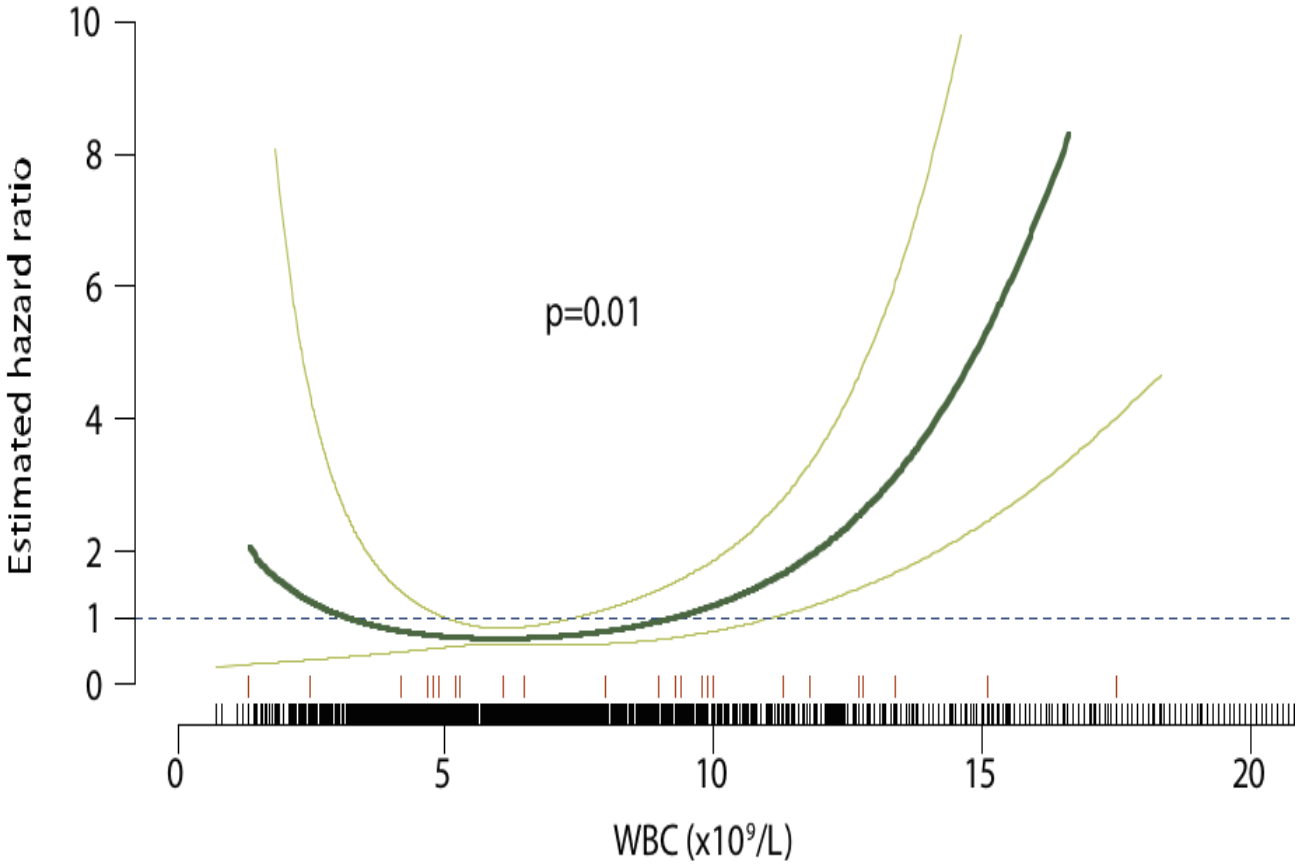
White cell count & thrombosis



Campbell Blood 2012

- ✓ Blood counts at diagnosis
- ✓ Blood counts during treatment

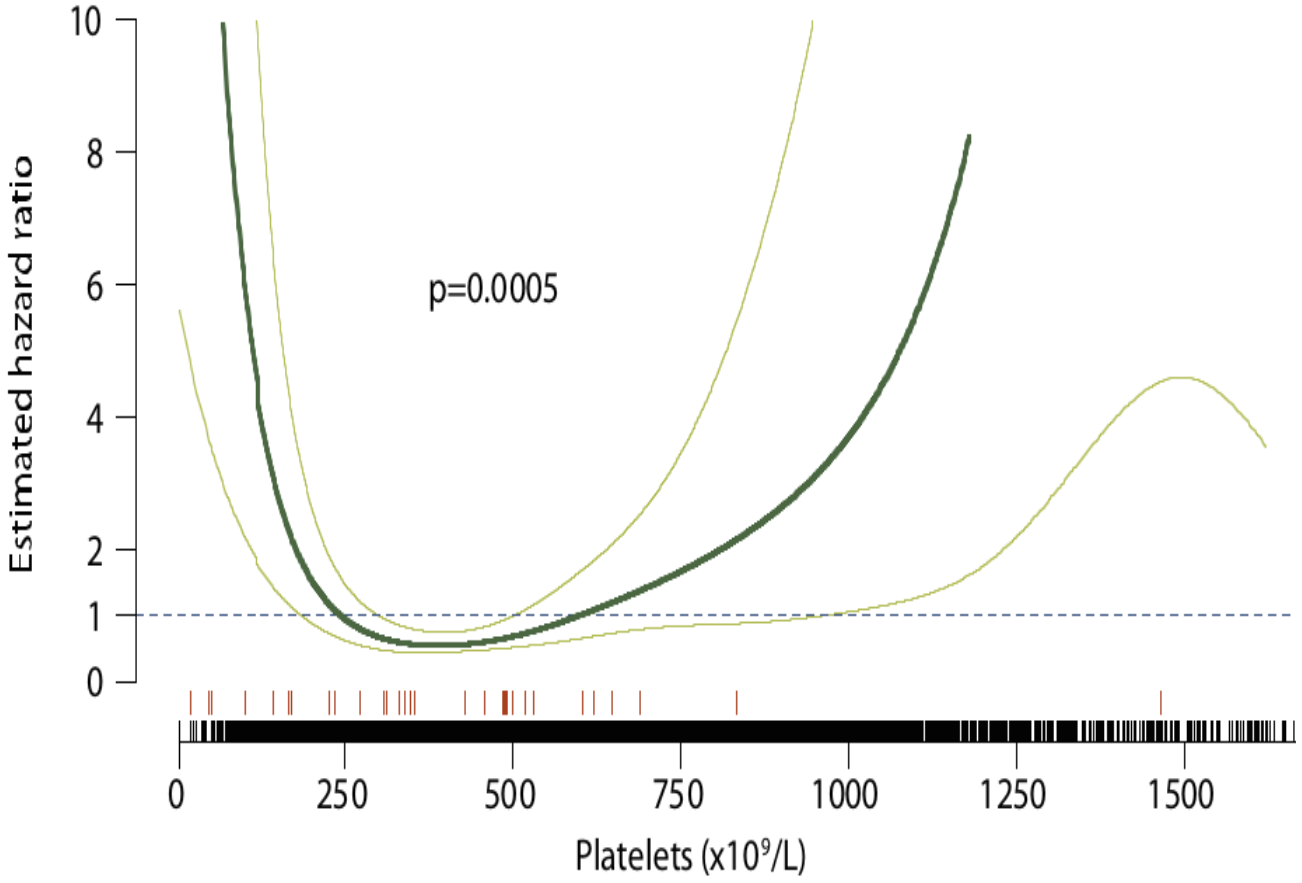
White cell count & major haemorrhage



Campbell Blood 2012

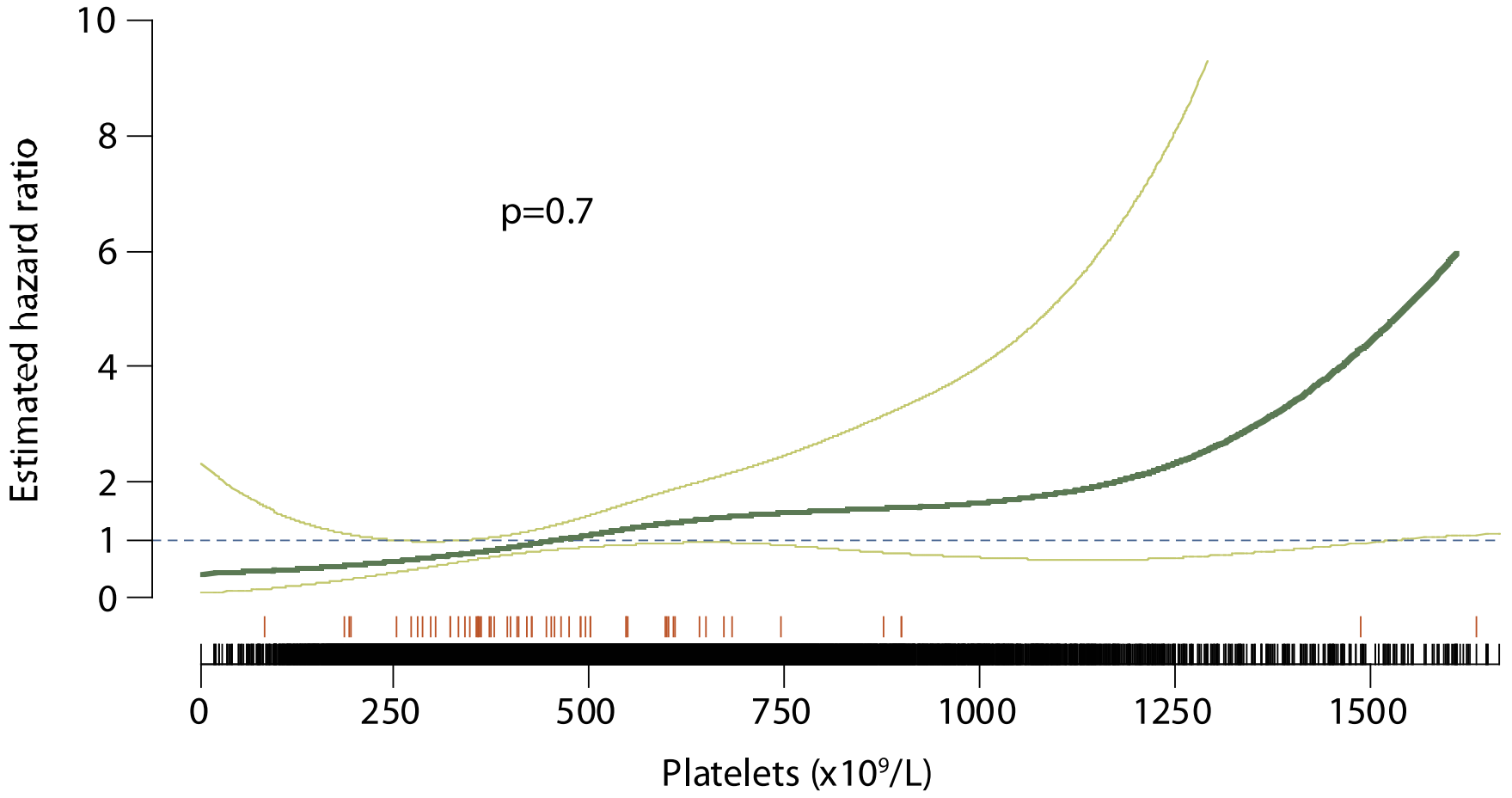
- ✓ Blood counts at diagnosis
- ✓ Blood counts during treatment

Platelet count & major haemorrhage

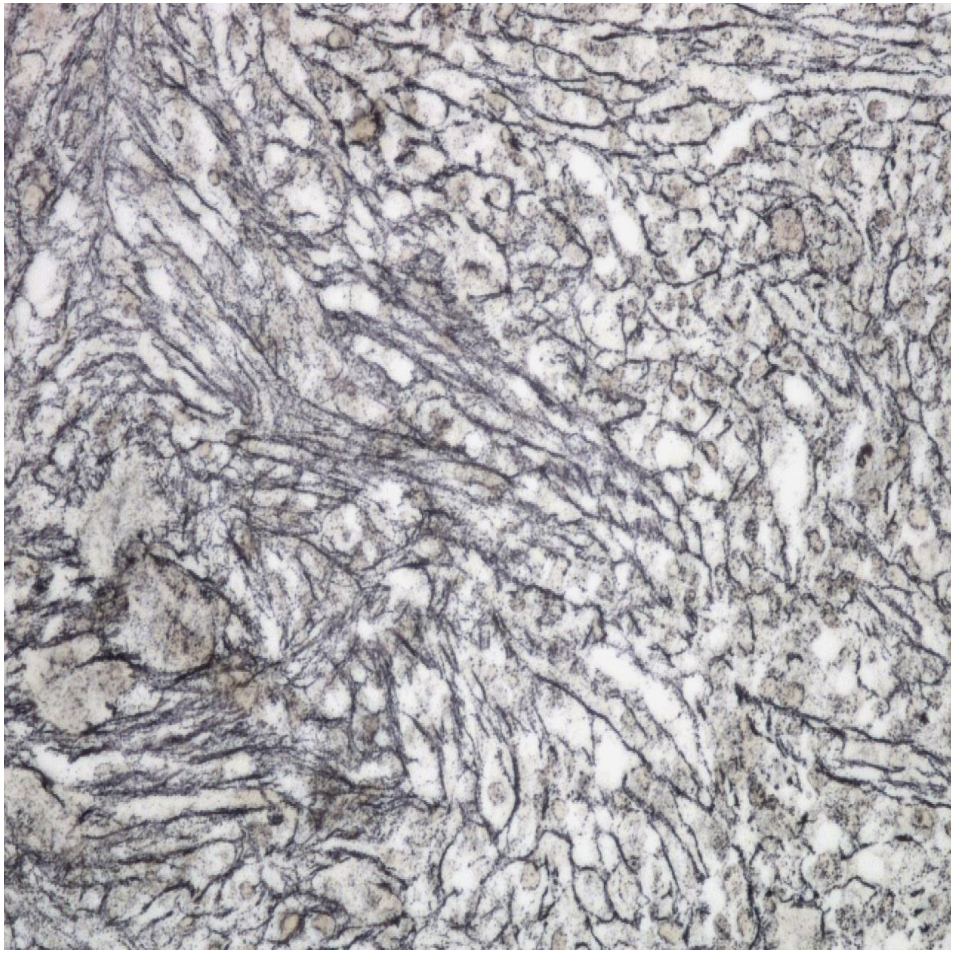


Campbell Blood 2012

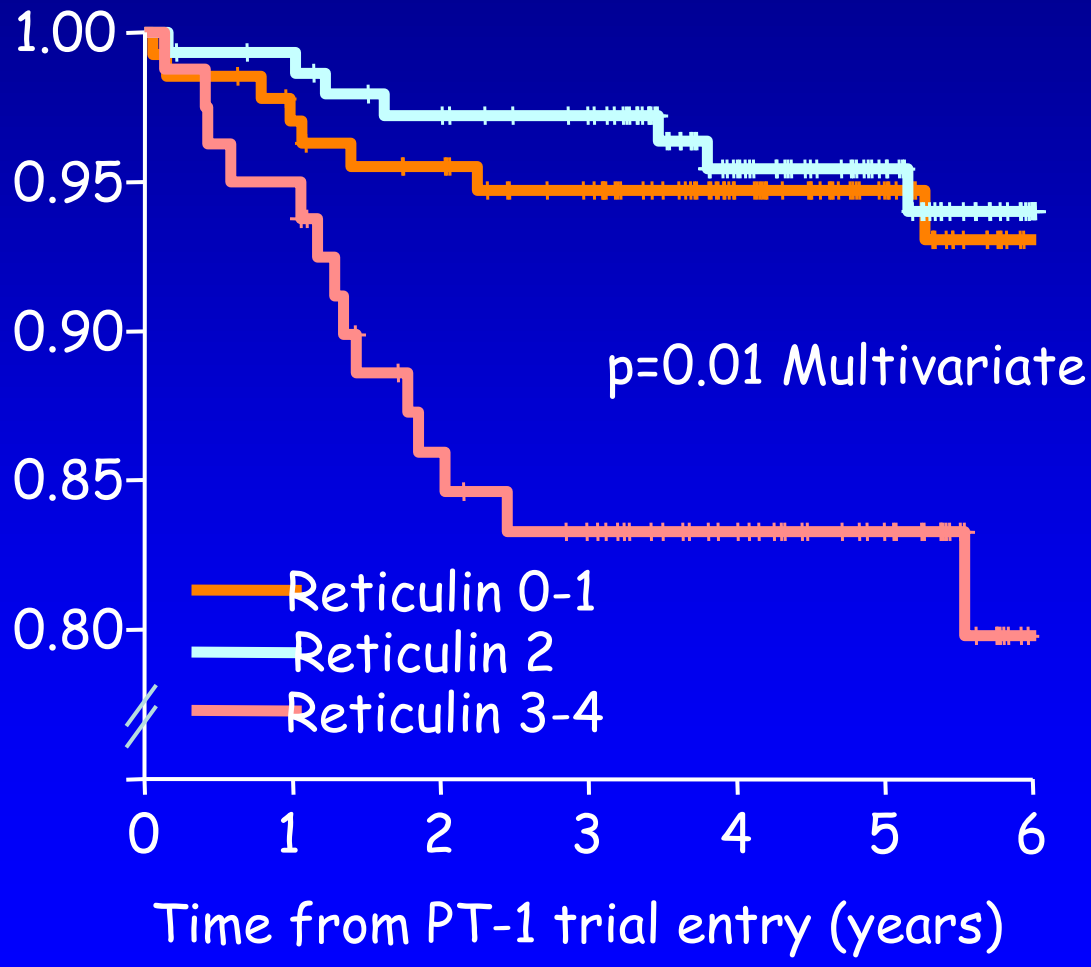
Platelet count does not correlate with thrombosis



- ✓ Blood counts at diagnosis
- ✓ Blood counts during treatment
- ✓ Reticulin fibrosis

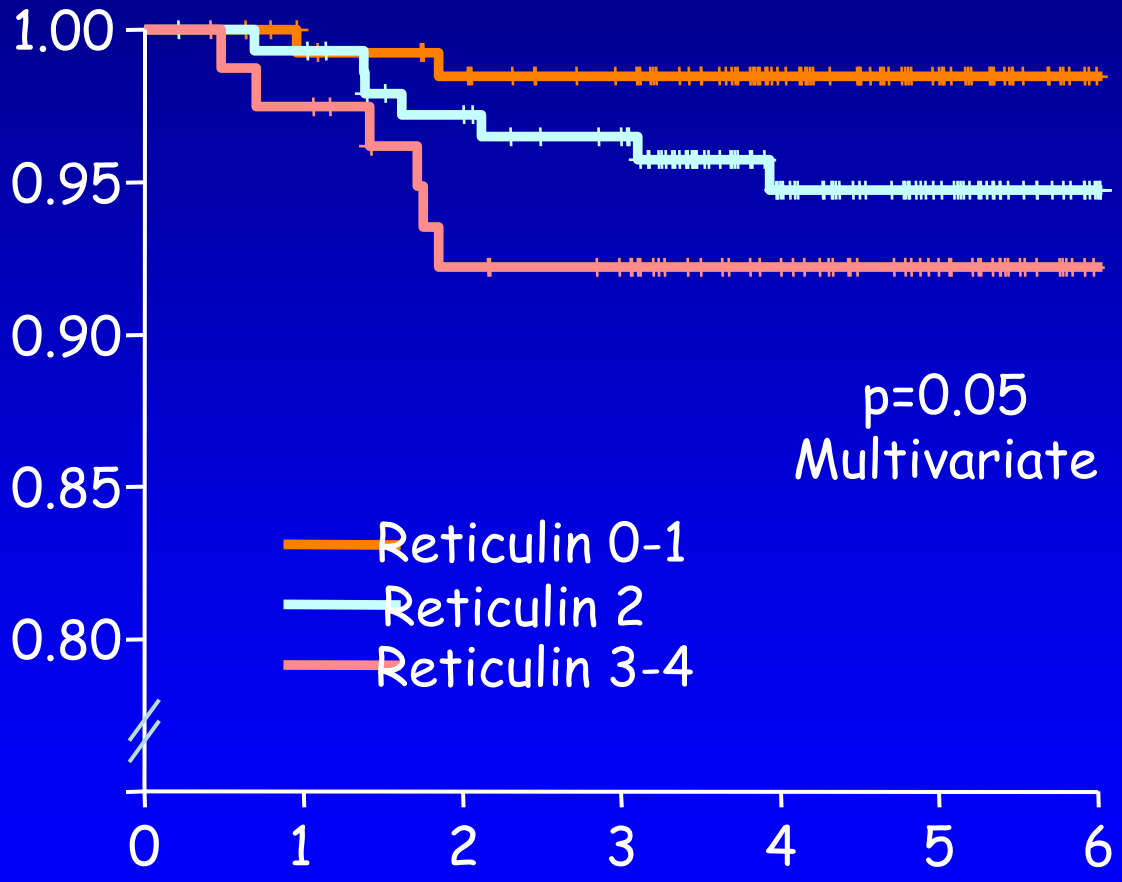


Arterial thrombosis by reticulin in PT-1 trial



Campbell 2009

Major haemorrhage by reticulin in PT-1 trial



Campbell 2009

CLINICAL TRIALS AND OBSERVATIONS

Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial

Heinz Gisslinger,[1] Mirjana Gotic,[2] Jerzy Holowiecki,[3] Miroslav Penka,[4] Juergen Thiele,[5] Hans-Michael Kvasnicka,[6] Robert Kralovics,[1,7] and Petro E. Petrides,[8] for all members of the ANAHYDRET Study Group

[1]Medical University of Vienna, Department of Internal Medicine I, Division of Hematology and Blood Coagulation, Vienna, Austria; [2]Institute of Hematology, Clinical Center of Serbia, Belgrade, Serbia; [3]Silesian Medical University, Department of Hematology and BMT, Katowice, Poland; [4]University Hospital Brno, Department of Clinical Hematology, Brno, Czech Republic; [5]Institute of Pathology, University of Cologne, Cologne, Germany; [6]Department of Pathology, University of Frankfurt/Main, Frankfurt/Main, Germany; [7]Center for Molecular Medicine (CeMM), Austrian Academy of Sciences, Vienna, Austria; and [8]Hematology Oncology Center and Ludwig Maximilians University of Munich Medical School, Munich, Germany

Key Points

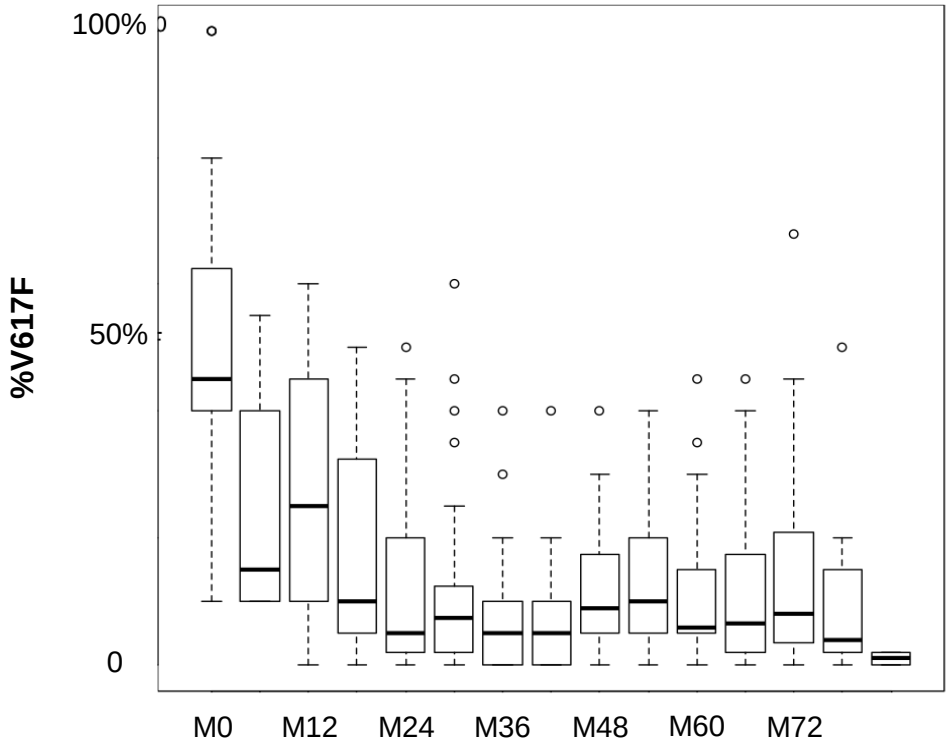
- Noninferiority of anagrelide in comparison with hydroxyurea in WHO-essential thrombocythemia, a phase 3 trial

- A large study of 3700 ET patients in Europe
- Non randomised

- Confirms that anagrelide is less good than HU at preventing arterial thrombosis
- AND there was more MF in anagrelide treated patients
- CONFIRMS risk of skin cancer with HU

What about interferon?

- Molecular response (also seen for *CALR*)

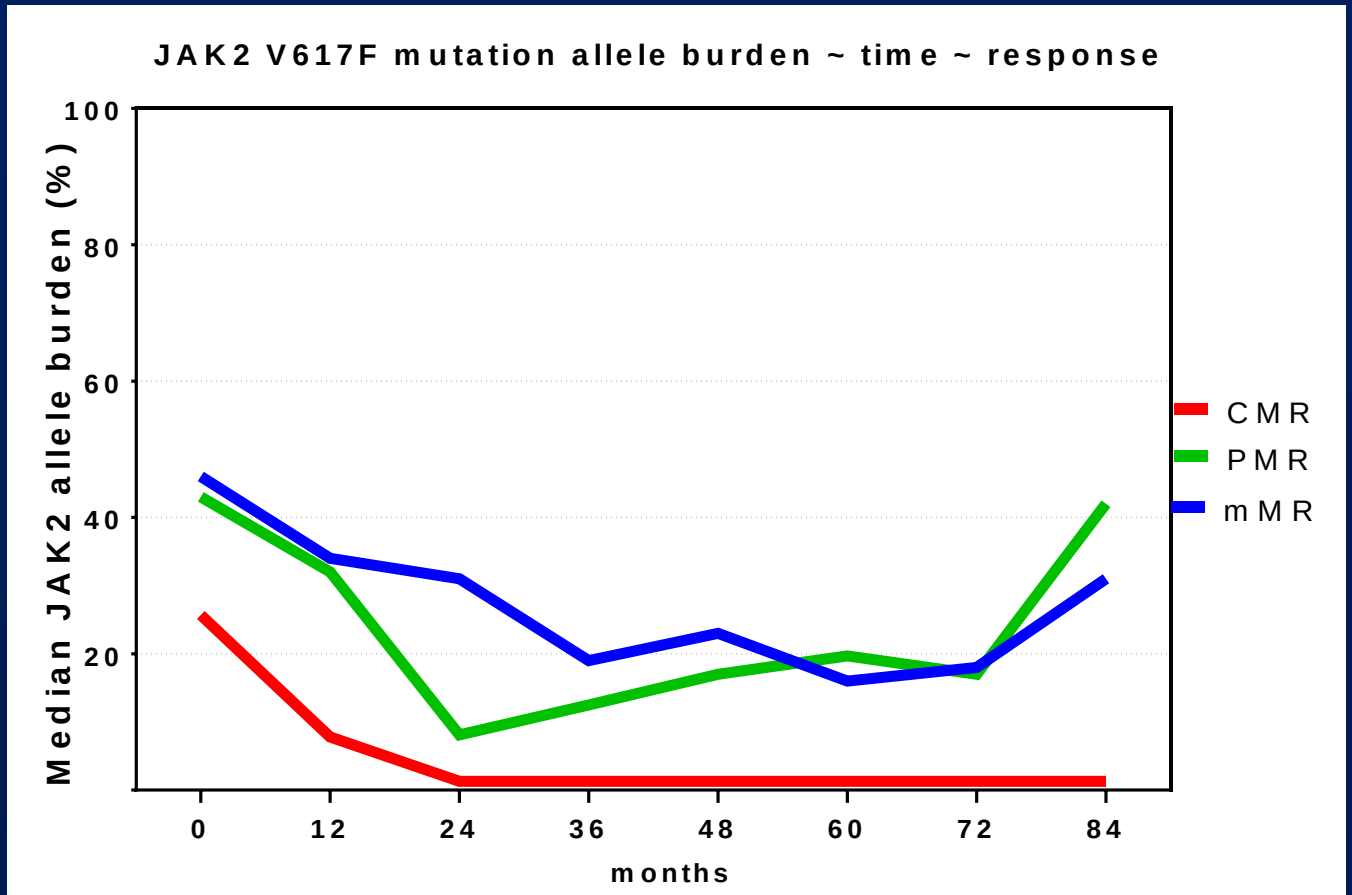


Ongoing Studies of IFNα in PV + ET

- peg-IFNα-2a
  - Phase 2 (MPD-RC 111)
  - Phase 3 (MPD-RC 112) provisional results equivalent responses for BOTH HU and IFN
  - Phase 3 in DK (DALIAH)

- peg-IFNα-2b (ropeginterferon α-2b)
  - Phase 2 completed (PEGINVERA)
  - Phase 3 ompleted (PROUD-PV) HU and IFN equivalent

PEG-IFN2a in ET-PV. Molecular Response in JAK2 V617F+(N=55)



No of evaluable patients on therapy								
CMR	10	10	5	5	7	6	7	7
PMR	20	15	10	9	13	8	10	9
mMR	4	3	3	2	1	1	2	3

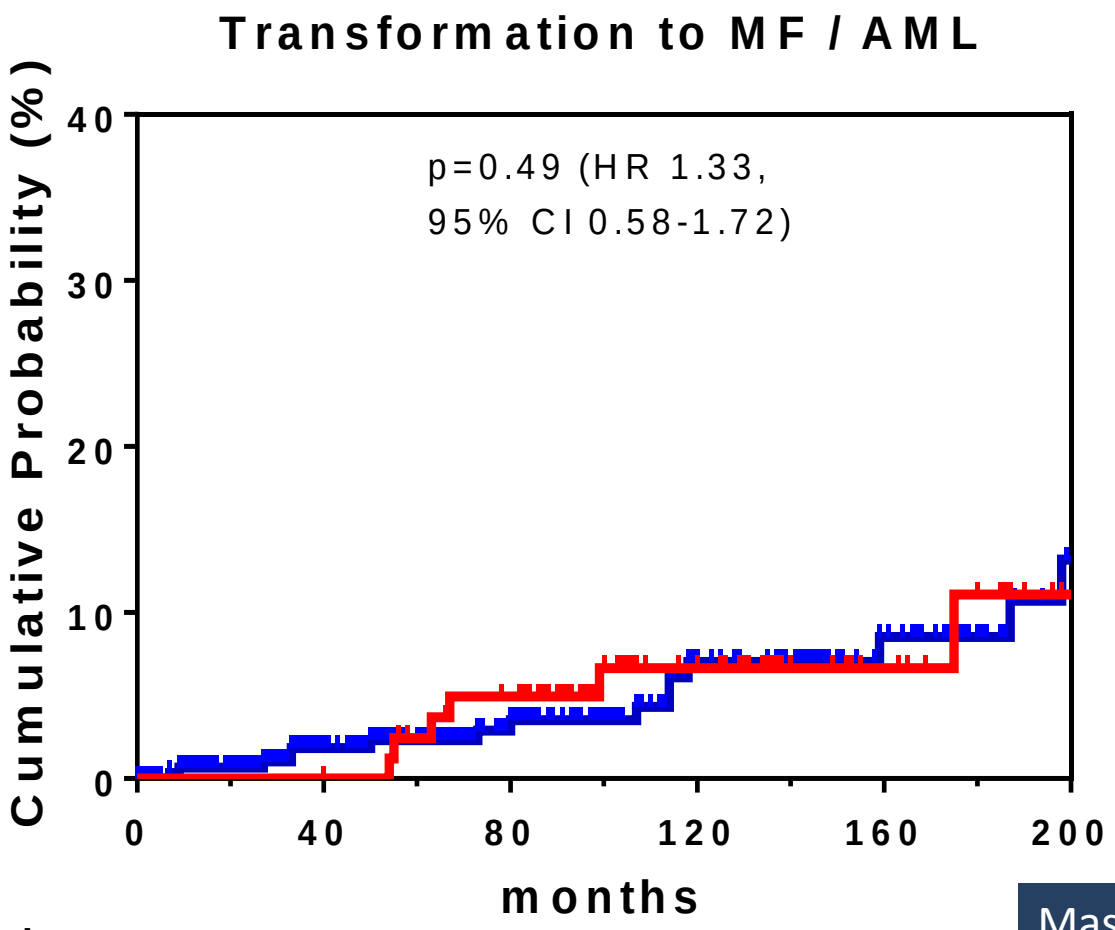
Masarova et. al. ASH 2015

PEG-IFN2a in ET-PV. Vascular Events

	N (%) ; median
• Thromboembolic	8 (10) ; 3 provoked
Venous: PE, DVT, stroke	5 (6)
Arterial: thrombosis	3 (3)
• Bleeding: stroke	1 (1)
• Time to event, mos	38 [14-60]
• Patients in CHR	5 / 9 (56)

Masarova et. al. ASH 2015

PEG-IFN2a in ET-PV. Transformation MF/AML



N at risk						
PEG	83	83	75	46	25	14
Control	352	224	159	97	62	35

Masarova et. al. ASH 2015

MAJIC

TAP
From Leukaemia & Lymphoma Research

- **Population:** Patients with high risk Polycythaemia vera (PV) or Essential Thrombocythaemia (ET) who are intolerant or resistant to Hydroxycarbamide

- **Aim:** To investigate and evaluate the safety and activity (in terms of complete haematological response within one year) of Ruxolitinib in the treatment of patients with PV or ET who have met criteria for resistance or intolerance of hydroxycarbamide (HC) therapy

- Patients are randomised to ruxolitinib or BAT

@CRCTU

PRIMARY ANALYSIS

Primary endpoint - Complete Haematological Response per ELN:

27 (46.6%) of RUX patients
vs 23 (44.2%) BAT patients (χ^2 test p= 0.81).

Partial Haematological Response per ELN:

26 (44.8%) of RUX patients
Vs 27 (51.9%) of BAT patients.

Mean overall MPN-10 TSS & individual symptoms of early satiety & itching during the first 12 months were all significantly lower for RUX vs BAT (all $p<0.05$).

Adverse events in >10% of study population

Adverse Event	RUX Arm (% patients)		BAT Arm (% patients)	Number of patients discontinued
	Grade 3	Grade 4	Grade 3 & 4	
Anemia	19	0	0	2
Neutropenia	2	0	0	0
Thrombocytopenia	5.2	1.7	0	0
Infections	10.3		3.6	2
	Any grade Patients (% patients) [Events]		Any grade Patients(%patients)[Events]	
Thrombotic events*	9 (15.5%) [10]		5 (8.9 %) [5]	5
Hemorrhagic events*	1(1.7 %) [1]		5 (8.9%) [5]	0

*adjusted following central review

Discontinuations due to haematological toxicity

2 RUX patients discontinued for anemia & none for thrombocytopenia.

Transformations

8 RUX vs 3 BAT treated patients developed PET-MF

1 RUX patient developed acute myeloid leukemia.

Deaths

2 in each arm, due to 1 each of multiple organ failure, cerebral hemorrhage - BAT arm, bowel infarction (adhesions), & ischemic cardiomyopathy - RUX arm.

CONCLUSIONS –ET arm of MAJIC STUDY

- Ruxolitinib and BAT were equivalent for primary outcome – complete haematological response. Symptoms improved with ruxolitinib

- Rates of thrombosis and transformation events were similar.
- Molecular responses mainly in ruxolitinib treated patients and include patients with CALR mutations

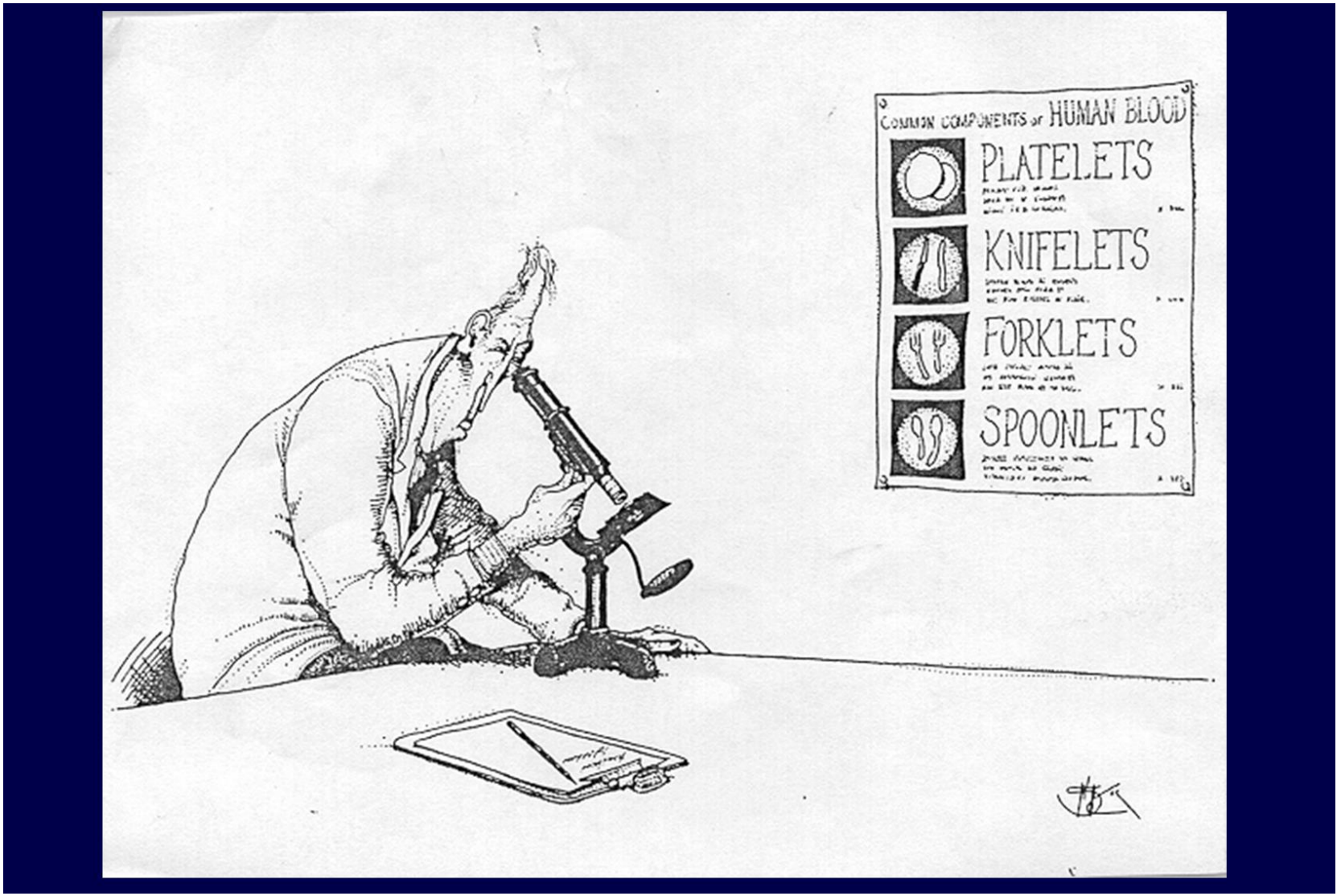
- Ruxolitinib may be an appropriate and safe therapy for ET patients requiring second line treatment. BUT thrombosis and transformation events still occur.

What are we doing today?

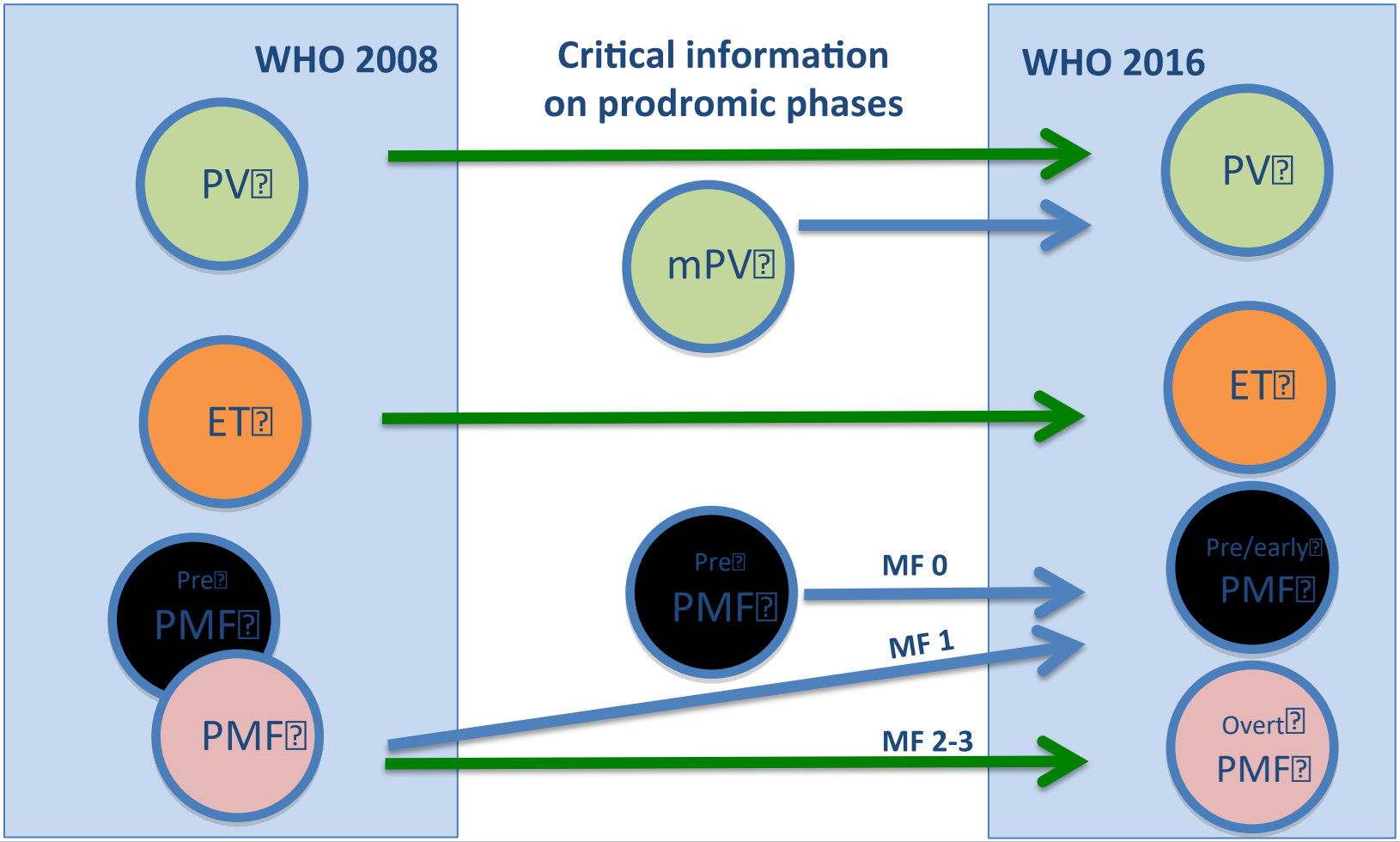
ET today

- Clinical management
  - Diagnostic accuracy
  - Indications for cytoreductive therapy
  - Problems with current therapeutics

Diagnosis is sometimes a challenge



Changes to the WHO diagnostic criteria & recognised entities
FOCUS on ET vs PV as well as vs MF



Clinical Management
Indications for cytoreductive treatment

- Prevention of thromboembolic disease
- Prevention of haemorrhage
- Minimising transformation to AML and MF
- ? Impact on symptoms and quality of life (being assessed in MEASURES study)

- VS
- Balancing risks of medication
- Compliance/ chronic illness management

……..Risk stratification

Management of ET: risk stratification

According to their risk of thrombotic complications

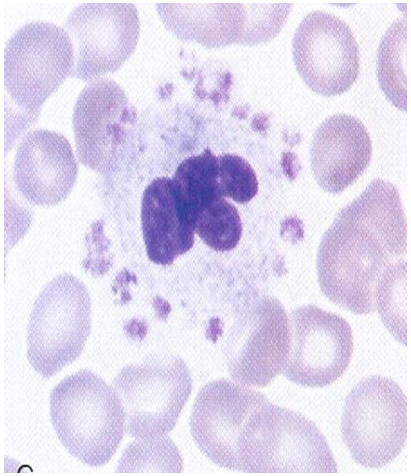
- Key risk factors

Age

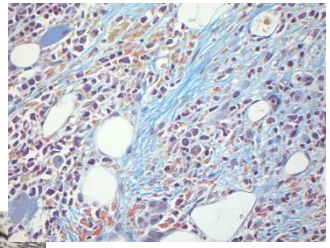
Prior thrombosis (Cortelazzo 1995; BCSH 2010)

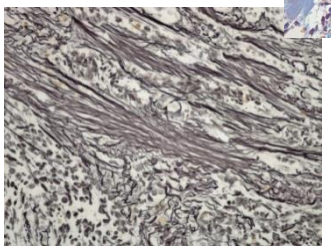
- Microvascular events ONLY thrombotic events if they are severe or resistant to aspirin
- Platelet count *per se* does not correlate with thrombosis but platelets >1500 x 10^9/L an indicator based upon haemorrhagic risk
- <40 years a higher platelet threshold may be reasonable
- The impact of “cardiovascular risk factors” is uncertain

Emerging risk factors



- Leucocyte count
- JAK2V617F allele burden
- CALR mutation
- Reticulin fibrosis

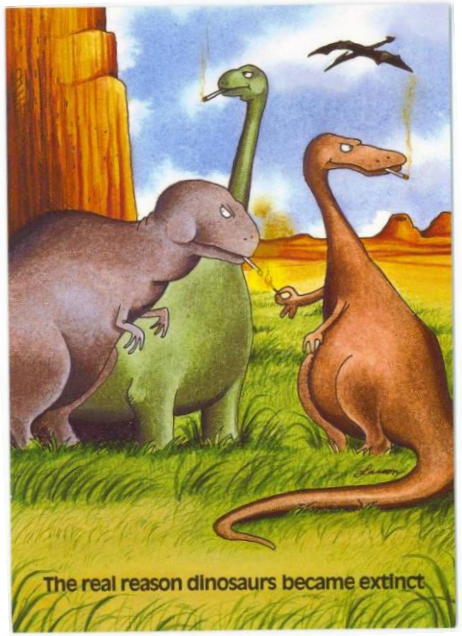


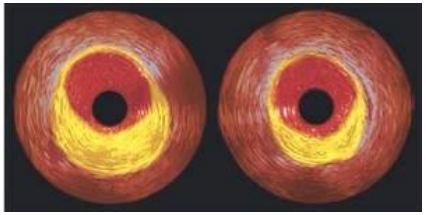


Management of ET the basics

- Aggressively manage all reversible vascular risk factors

Level IV Grade C





- Adults with clinical evidence CHD
- Primary prevention >20% 10 year risk CHD
- Secondary prevention Jan 2006

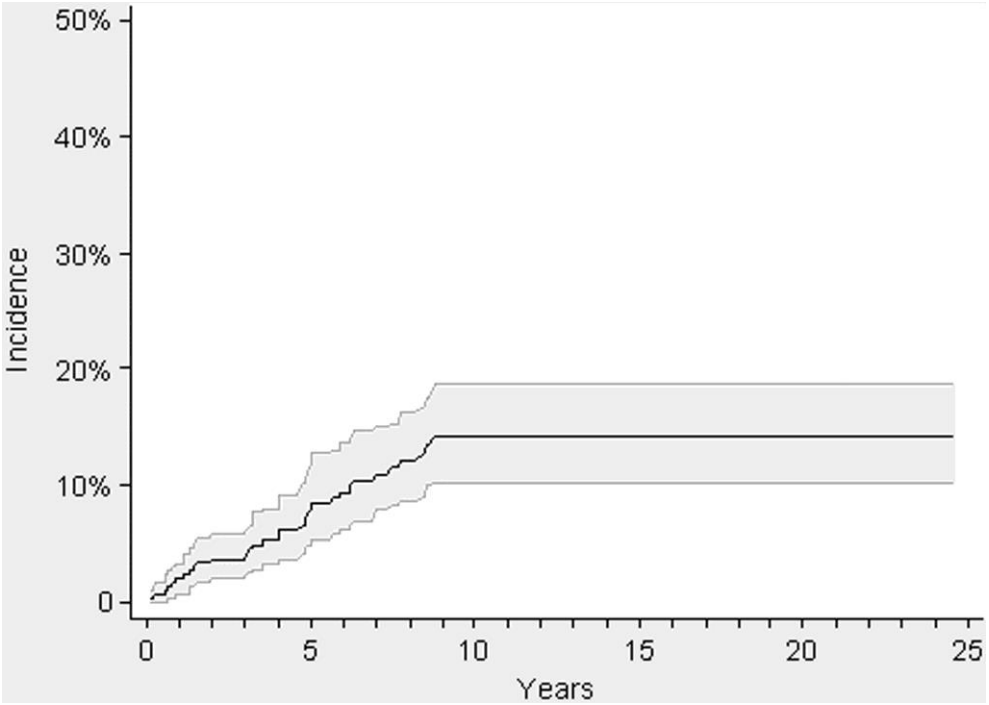
Management recommendations -ET

ASPIRIN MAY NOT BE A PANACEA BUT……..

- Low risk - Aspirin ?
- Intermediate risk - Aspirin + individualised
- High risk - Aspirin and hydroxyurea.
  (Young/ paediatric patients anagrelide or IFN a)
- Refractory/intolerant use non-leukemogenic treatment where possible.

BCSH guidelines Harrison 2010

Cumulative incidence of thrombosis in 300 patients with low-risk ET



RESULTS

- 32 thrombotic events were recorded in 15 and 17 patients of the observation and antiplatelet groups.
- PE resulted in one death.
- No events after 9 years.

- Aspirin protected patients with cardiovascular risk factors against arterial events and those with JAK2V617F against VTE.
- Patients with plts >1000 had increased bleeding on aspirin

The use of aspirin in low-risk ET patients should be reviewed……

Alvarez-Larran, A. et al. 2010

EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

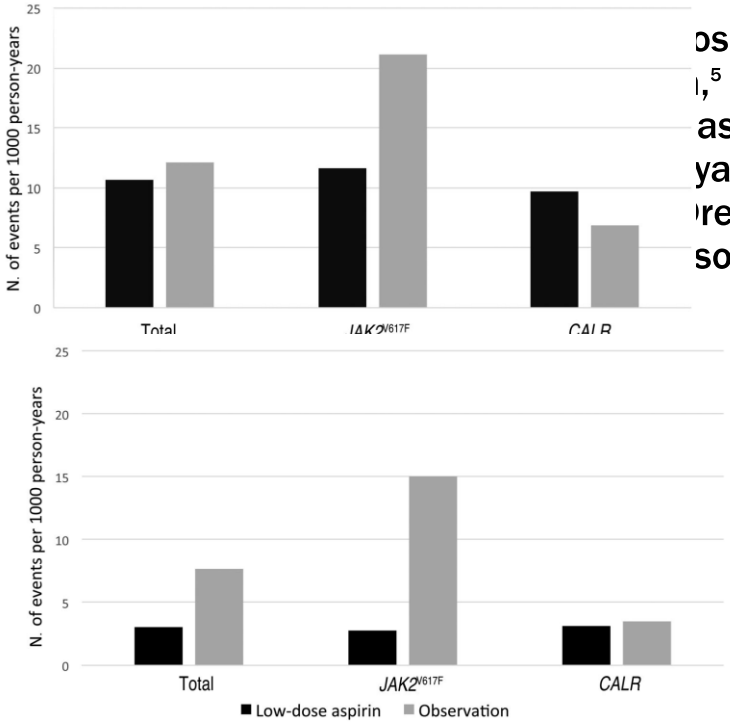
Antiplatelet therapy *versus* observation in low-risk essential thrombocythemia with a *CALR* mutation

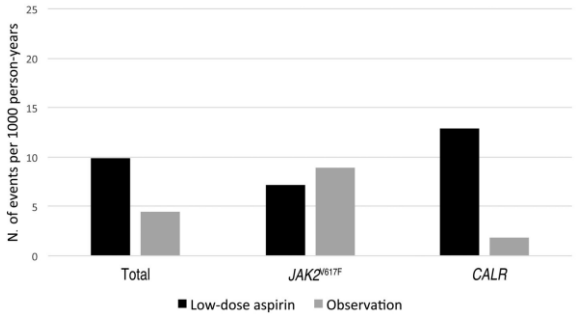
Alberto Alvarez-Larrán,[1] Artu… Hernández-Boluda,[4] Eduardo… Alimam Samah,[6] Martin Grie… Carmen Burgaleta,[10] Jiri Schv… Pere Barba,[14] María Teresa G… Sonja Zweegman,[17] Mary F. M… Francisco Cervantes,[20] Alessa…

Aspirin benefits *JAK2V617F* positive low risk ET for overall and arterial thrombosis

Haematologica 2016
Volume 101(8):926-931

BUT ALSO venous thrombosis

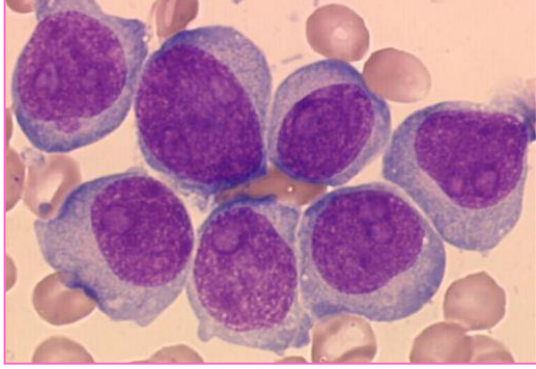




BUT for *CALR* positive low risk ET appears to increase risk of bleeding

	HU	Anagrelide	IFN alpha
Drug class	Antimetabolite	Imidazoquinazolin	Biologic response
Mechanism	Impairs DNA repair	Impairs MK differentiation	Myelosuppressive
Specificity	Affects all	Platelets only	Affects all cells
Onset	3-5 days	6-10 days	3-26 weeks
Side Effects in >10%	Neutropenia anaemia, ulcers pigmentation	Headache, diarrhoea palpitations, fluid retention	Flu-like symptoms alopecia, weight loss
Side Effects in <10%	Leg ulcers, D & V	CCF, arrhythmia's anaemia	Confusion, arthritis depression
Contraindicated In:	Neutropenia pregnancy	CCF, pregnancy	? Safe in pregnancy

Leukaemia and HU



- Concerns have been raised
- Clinical studies give conflicting results

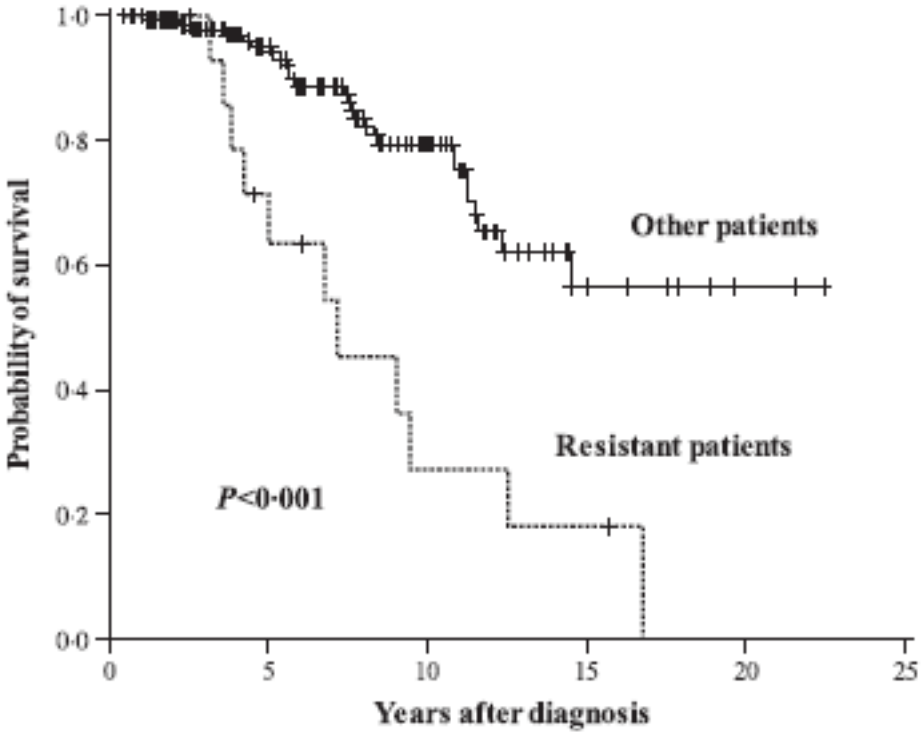
- HU appears not to cause leukemia in patients with sickle cell disease

- It is unclear whether HU alone is leukemogenic; AND, any increased risk is likely to be small and should be balanced against control of thrombohaemorrhagic complications
- Ongoing studies should address this question

Hydroxyurea resistant/intolerant patients

- 166 ET patients followed 1986 -2009 assessed for response/ resistance to HU using ELN criteria (Barosi 2009)
- 33 or 20% fulfilled the ELN criteria Patients with anaemia had worse prognosis 7/15 post ET MF

Criteria	No. of patients	Time to occurrence*
Platelet count >600 × 10^9/l after 3 months with ≥2 g/d of HC	0	–
Platelet count >400 × 10^9/l and leucocytes <2·5 × 10^9/l at any dose	3	97 (27–168)
Platelet count >400 × 10^9/l and Hb <100 g/l at any dose	15	45 (4–171)
Leg ulcers or other unacceptable mucocutaneous toxicity	20	31 (1–115)
HC-related fever	1	32
Any of the above criteria, no. (% of total patients)	33 (20)	



Hernández-Boluda et al 2010

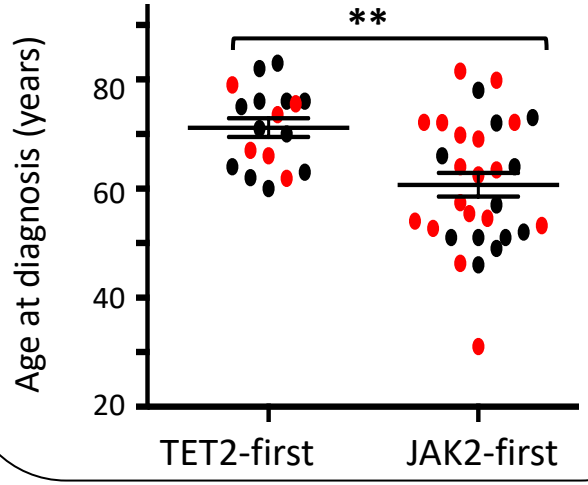
What might we do in the future?

What might we do in the future?

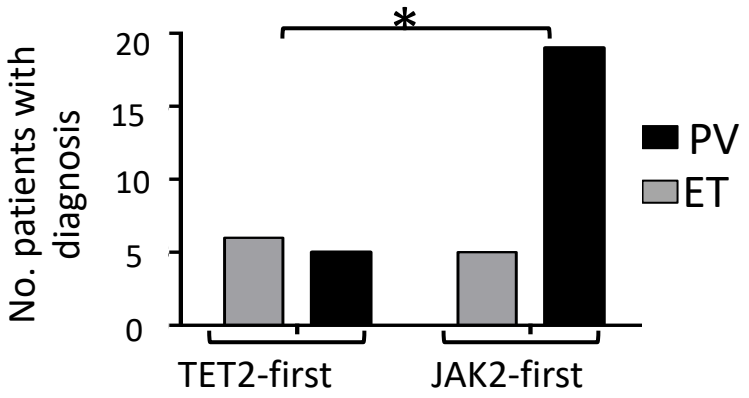
- More individualised therapy

In ET/PV mutation order may matter

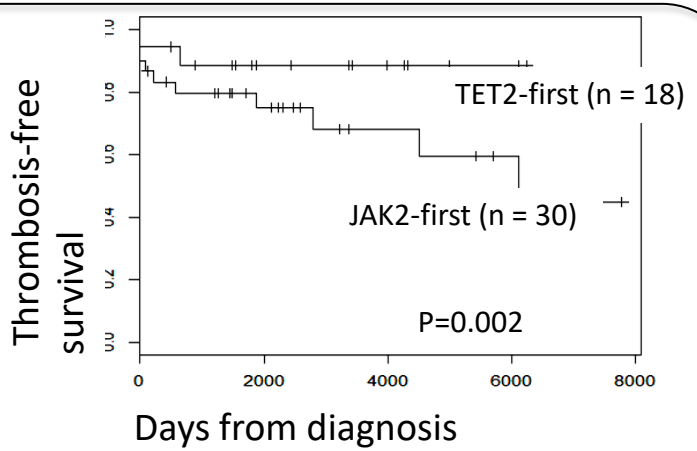
JAK2-first patients present at a younger age



…. are more likely to present as PV



…. and have increased risk of thrombosis (arterial + venous)



JAK2-first cells also more responsive to ruxolitinib

Ortmann CA, et al. *N Engl J Med* 2015;372:601–12.

Phenotypic differences and treatment responses in molecular subgroups of essential thrombocythaemia from analysis of the PT1 cohort

Jyoti Nangalia MB BChir PhD

Authors

J Nangalia, J Grinfeld, AV Jones, AL Godfrey, C MacLean, P Beer, A Bench, FL Nice, BS Wilkins, WN Erber, D Bareford, JJ Kiladjian, NC Cross, MF McMullin, CN Harrison, PJ Campbell, AR Green

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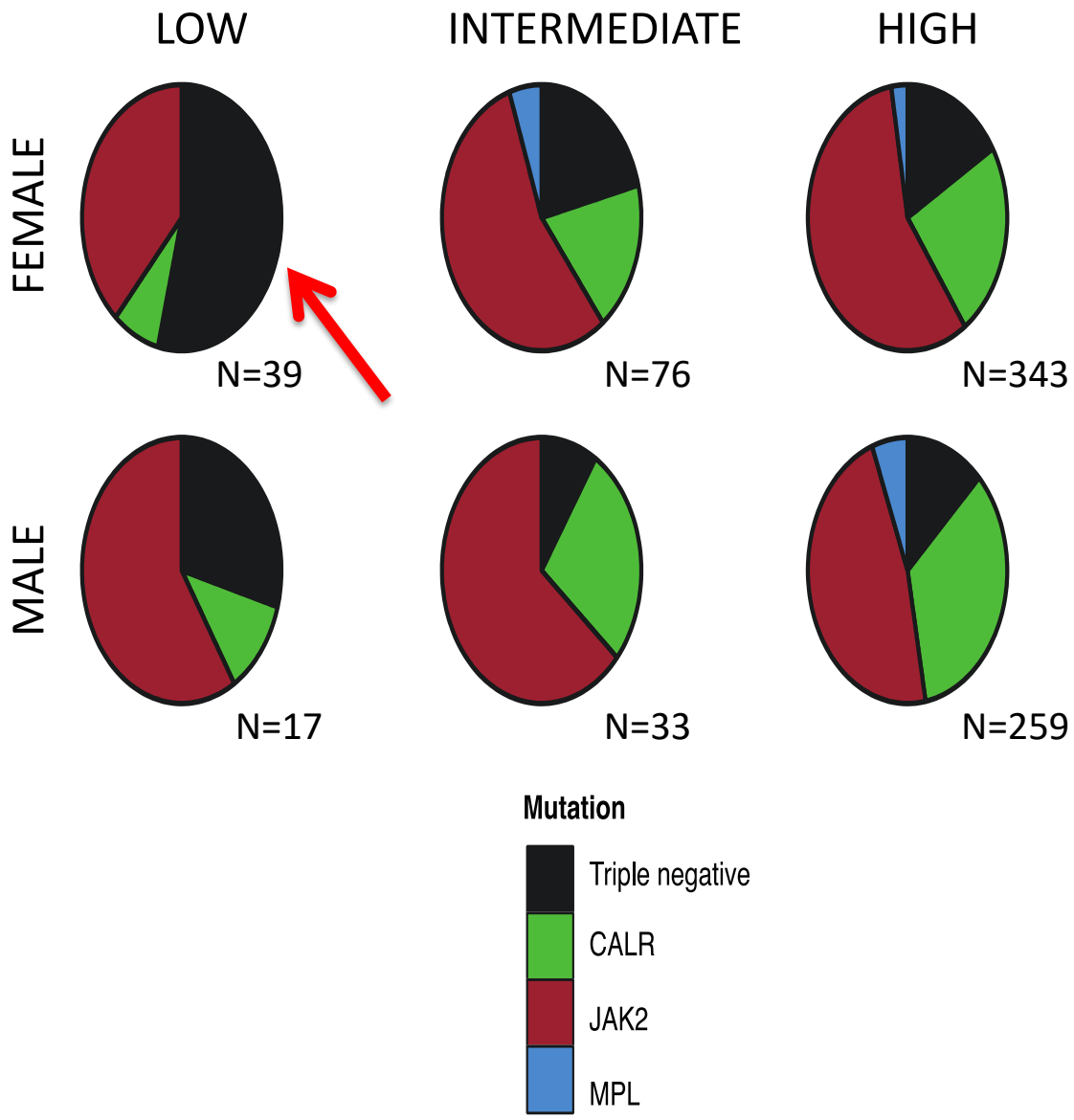
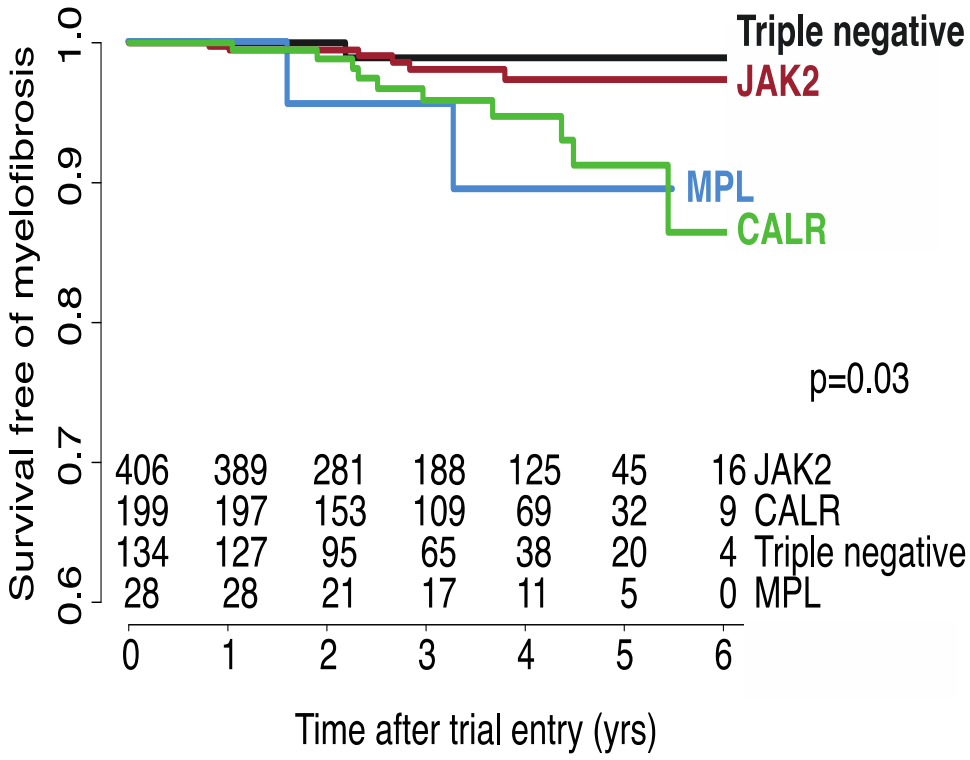
Baseline clinical characteristics



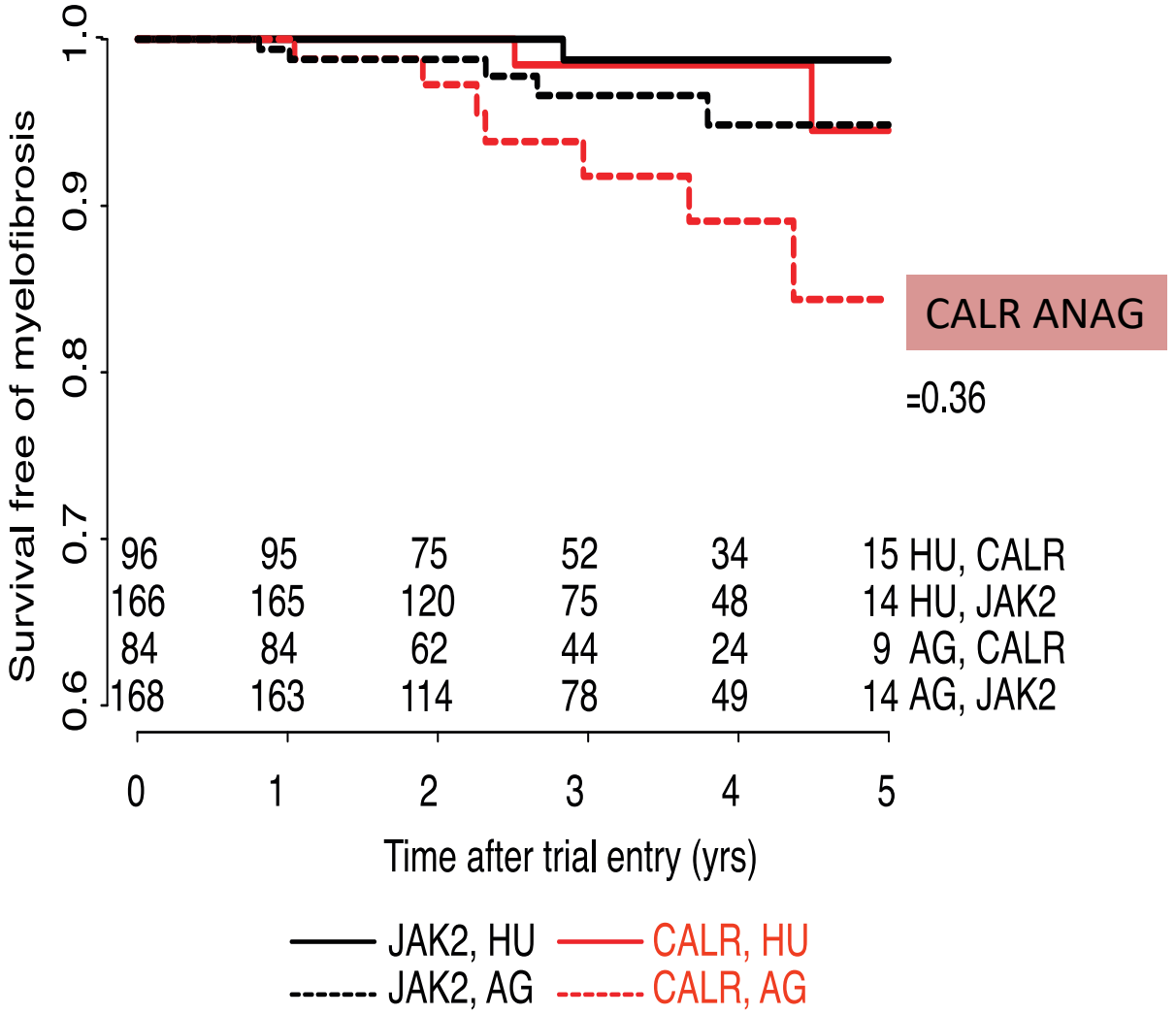
Adverse events in molecular subgroups

- ↑ Venous thromboses and PV transformations in JAK2^{V617F} group
- ↑ MF transformations in CALR-mutated group



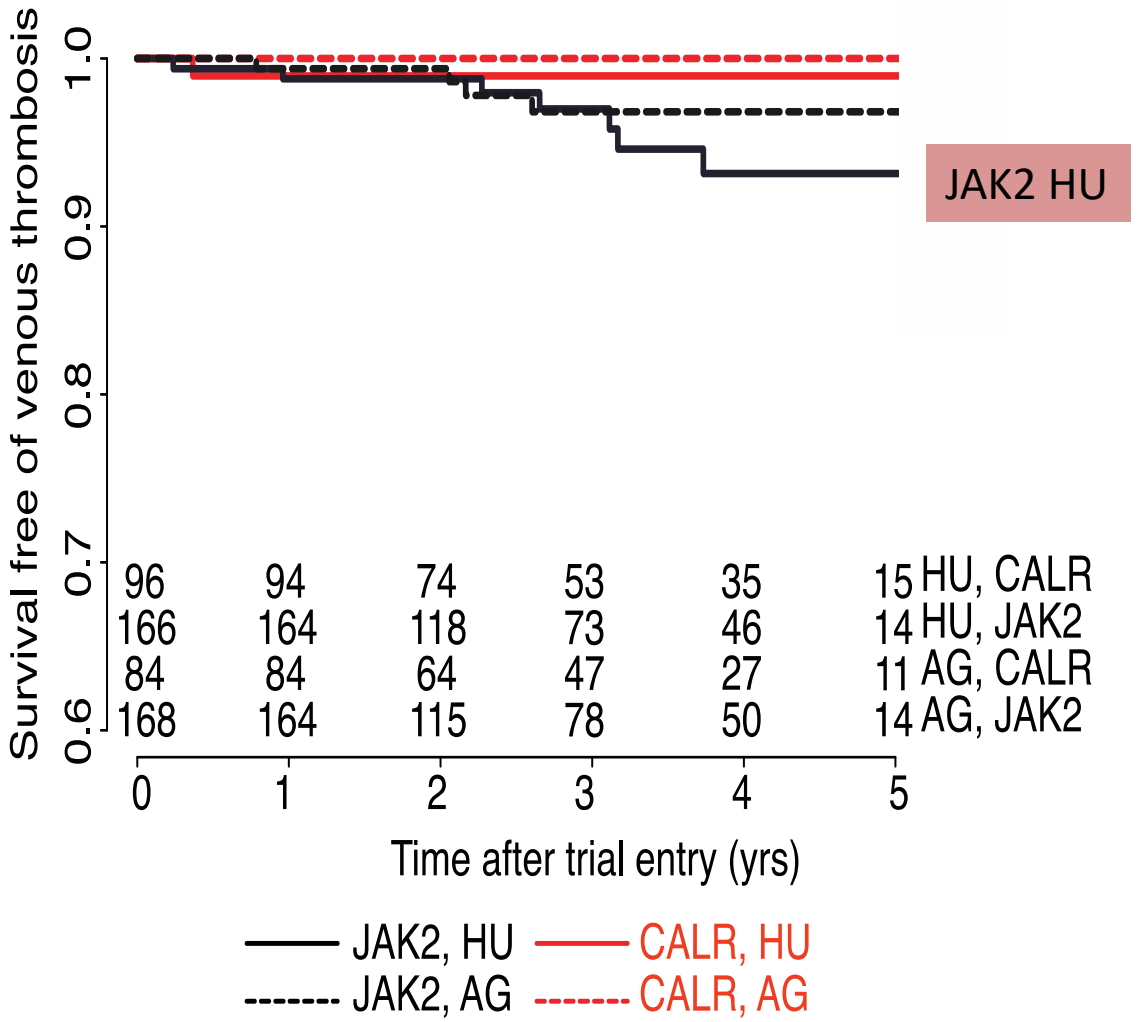
Does treatment with HU or Ag alter adverse outcomes associated with molecular status?

Myelofibrosis

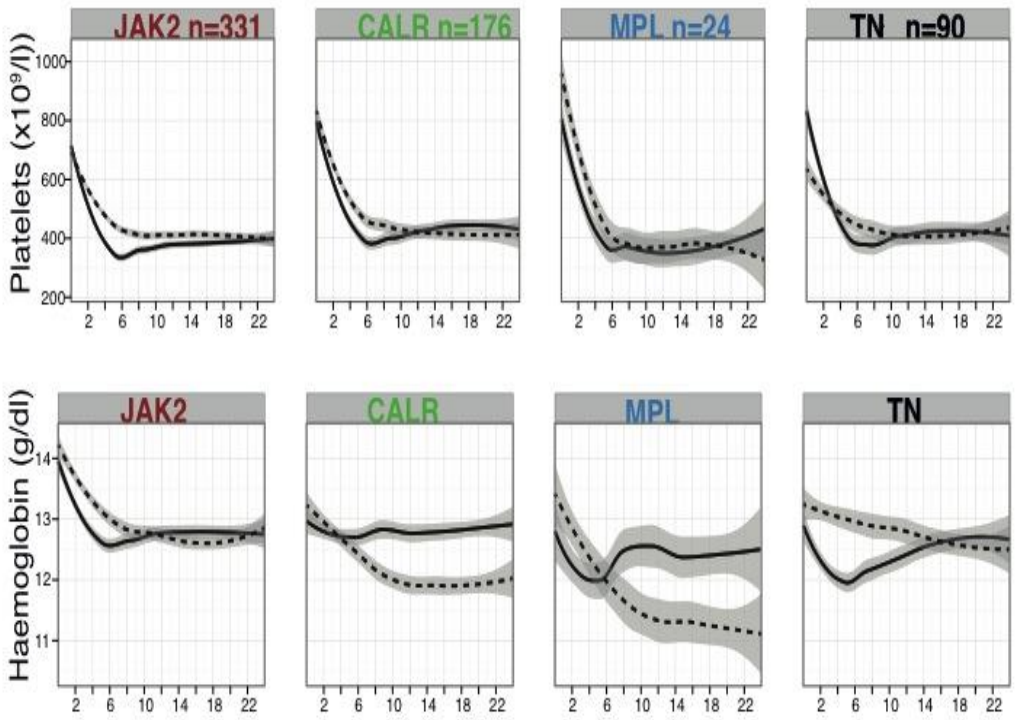


Does treatment with HU or Ag alter adverse outcomes associated with molecular status?

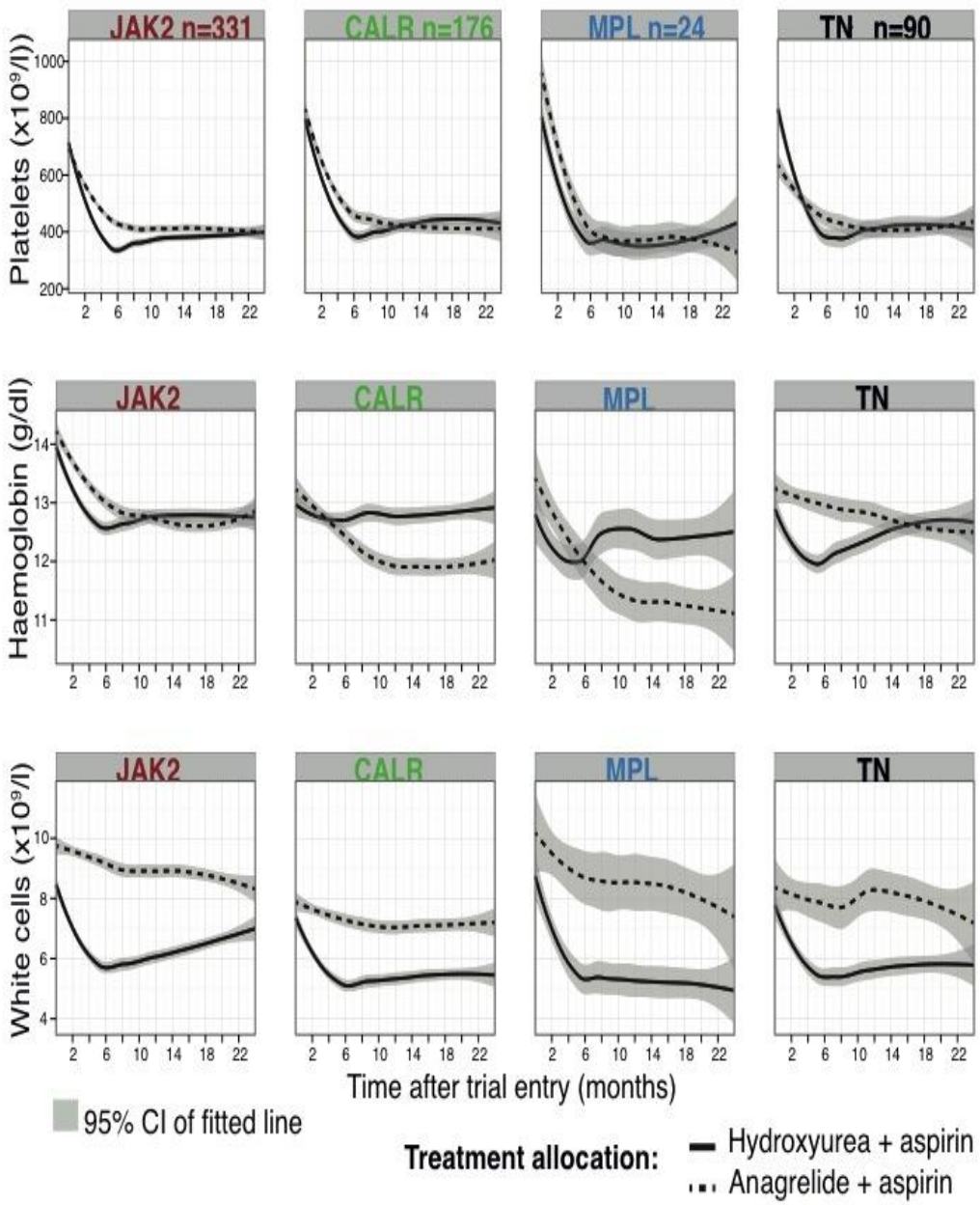
Venous thrombosis



How do molecular subgroups respond to HU or Ag?



How do molecular subgroups respond to HU or Ag?



Summary and conclusions

- Genotype-phenotype analysis of a large prospective cohort in ET identifies 3 distinct subgroups

- CALR-/MPL-mutated ET: share a disease phenotype
  - Thrombocytosis, histology, increased myelofibrosis, treatment responses
  - CALR del52 – some features associated with MF

- JAK2-mutated ET: features resembling PV
  - Higher Hb levels, transformation to PV, venous thromboses

- Some treatments may be better for some genotypes…

What might we do in the future?

- More individualised therapy
- Newer therapies…

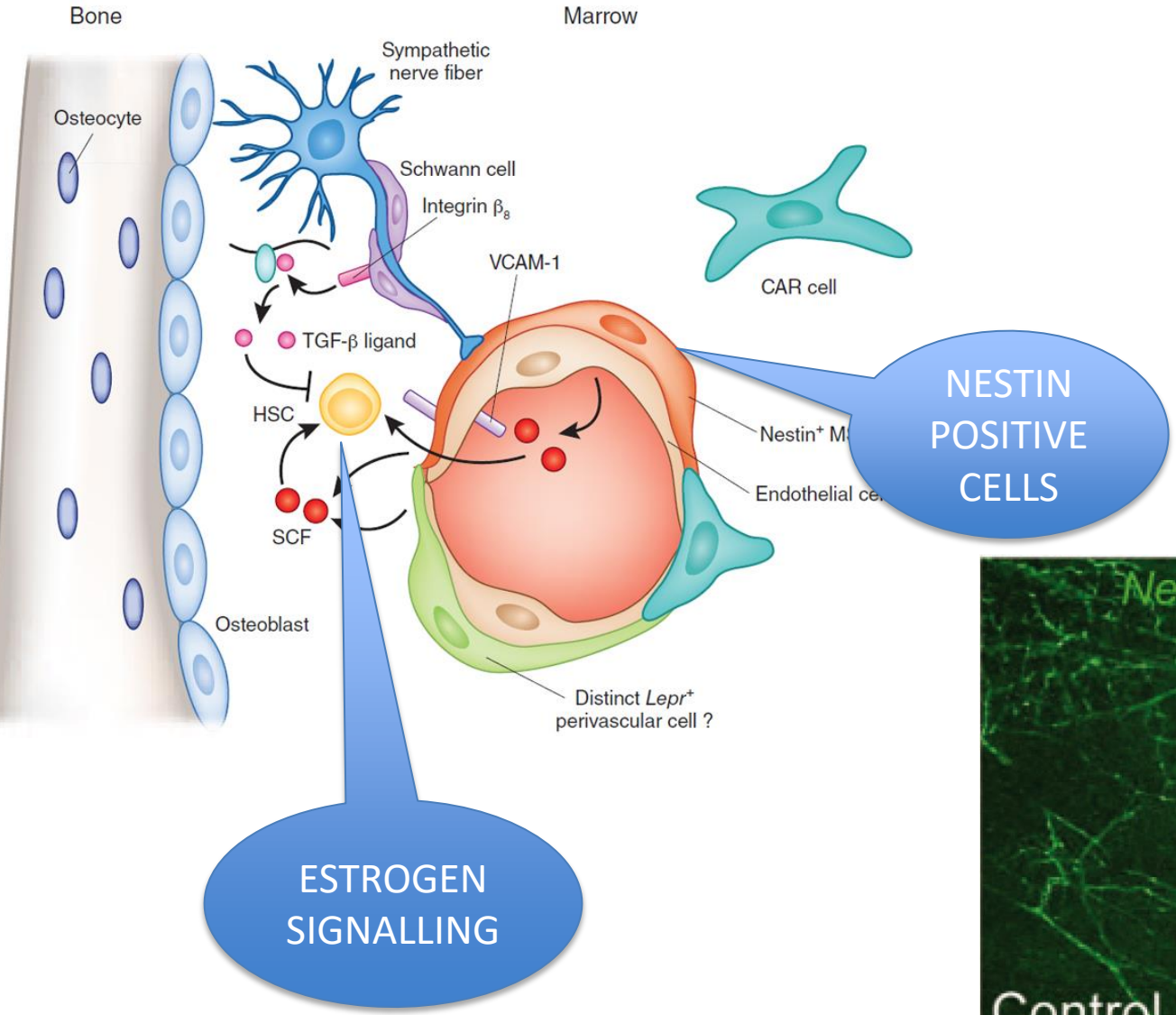
Newer therapies…?

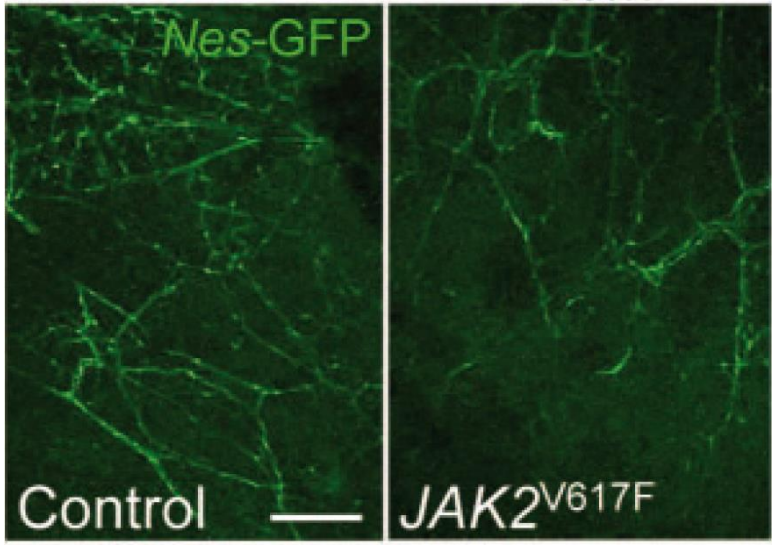
- Gene editing
- CRISPR
- Immunotherapy
  - Too embryonic and “risky” for ET

- Other therapies may effect the stem cell “niche”
  - Mirabegron
  - Tamoxifen

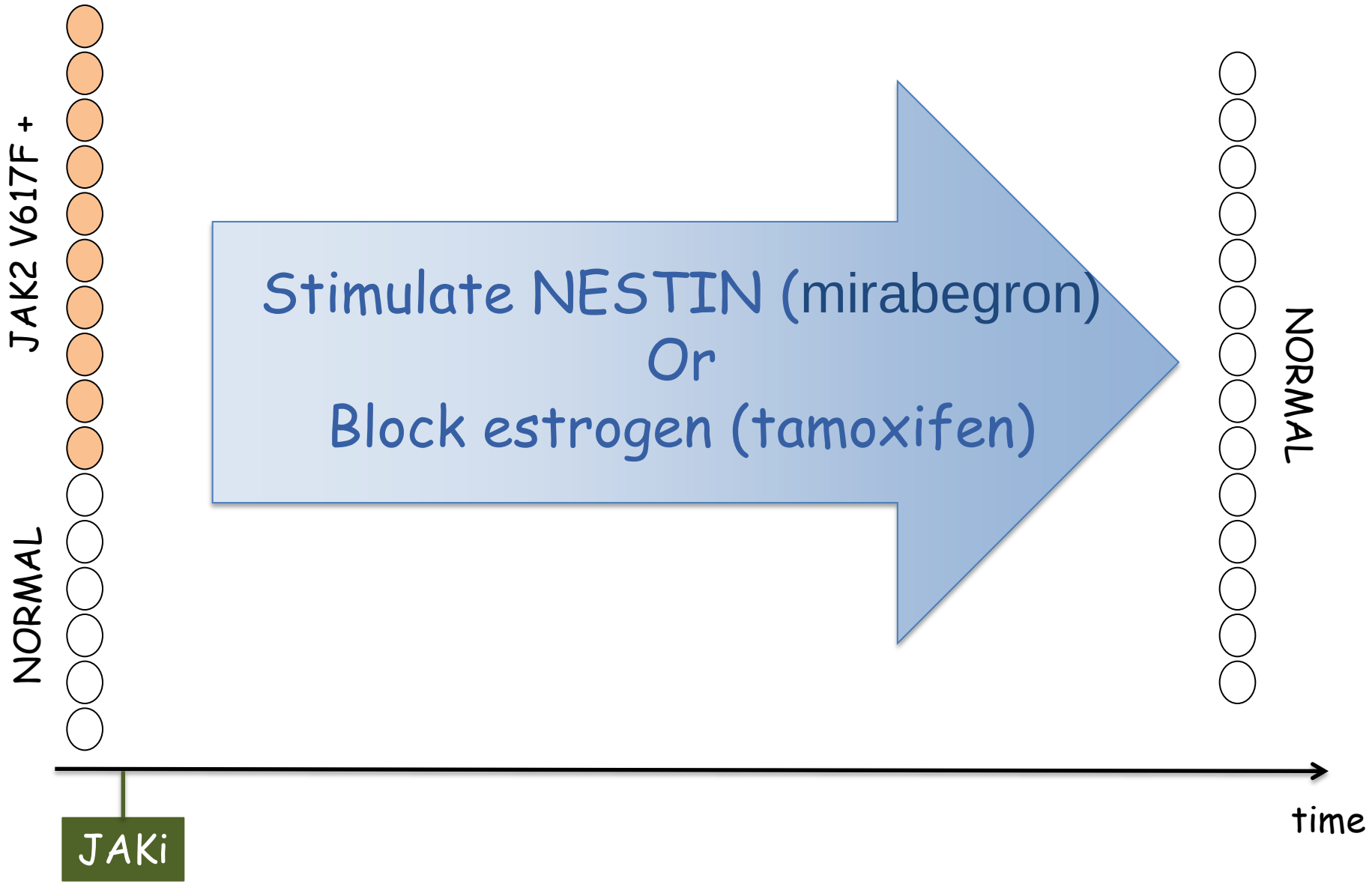
Stem cell niche as a target in MPN

Factors of interest in the stem cell niche



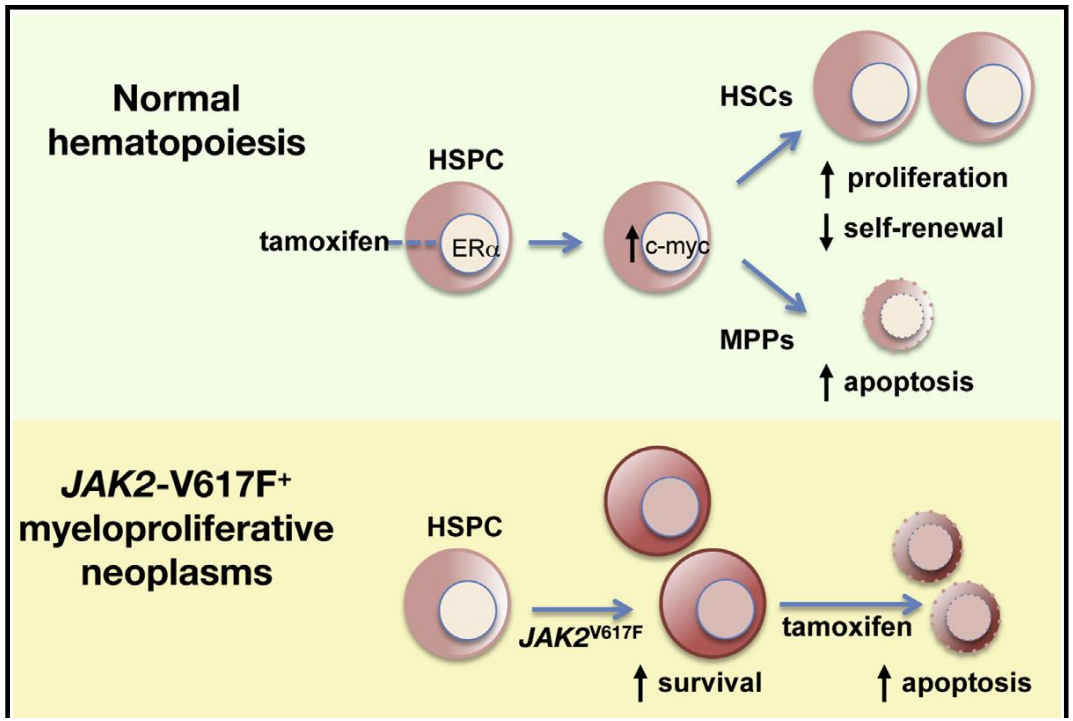


Arranz et al (2014) *Nature*, 512:78–81


JAK2 V617F +
NORMAL
Stimulate NESTIN (mirabegron)
Or
Block estrogen (tamoxifen)
NORMAL
JAKi
time

Cell Stem Cell

Estrogen Signaling Selectively Induces Apoptosis of Hematopoietic Progenitors and Myeloid Neoplasms without Harming Steady-State Hematopoiesis



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Study open in UK to test this

TAMARIN

Effects of the Sympathicomimetic Agonist Mirabegron on Disease Course, Mutant Allele Burden, Marrow Fibrosis, and Nest Stem Cell Niche in Patients with JAK2-Mutated Myeloproliferative Neoplasms: a Prospective Multicenter Phase II Trial SAKK

Beatrice Drexler[1], Jakob R. Passweg[1], Martin Bigler[2], Alexandre PA Theocharides[3], Nathan Cantoni[4], Peter Keller[5], Georg Stuessi[6], Axel Rüfer[7], Rudolf A. Benz[8], Geneviève Favre[9], Alexandar Tzankov[10], Pontus Lundberg[1], Andrea Fuhrer[2], Christine Biaggi[2], Markus G. Manz[3], Mario Bargetzi[4], Simon Mendez-Ferrer[11], and Radek C. Skoda[12] on behalf of the Swiss Group for Clinical Cancer Research (SAKK)

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ABSTRACT

Myeloproliferative neoplasms (MPN) are initiated and maintained by mutated hematopoietic stem cells (HSPC). Bone marrow mesenchymal stem cells expressing the intermediate filament protein nestin (nestin+ MSCs) that are innervated by sympathetic nerve fibers constitute an important component of the stem cell niche and regulate normal HSCs. These nestin+ MSCs are strongly reduced in the bone marrow of JAK2-V617F positive MPN patients and in mice expressing JAK2-V617F due to damage of the sympathetic nerve fibers triggered by cytokines from the mutant cells. In a JAK2-V617F mouse model of MPN, treatment with a beta-3 sympathomimetic agonist corrected the damage inflicted by the MPN clones on their niches and ameliorated the MPN phenotype.[1]

OBJECTIVES

To test the potentially beneficial effect of beta-3 sympathomimetic stimulation on MPN by modulating bone marrow niche cells, we performed a phase II trial with mirabegron, a beta-3 sympathomimetic agonist, which is approved for the treatment of patients with irritable bladder.

METHODS AND PATIENT COHORT

The trial consisted of mirabegron treatment with 25 mg daily during the first week, followed by 50 mg daily for at least 24 weeks. Patients with a cytohistologically confirmed diagnosis of MPN and a JAK2-V617F allele burden >20% in granulocytes at study entry were eligible, if not treated with JAK2 inhibitors or interferon. Reduction of the JAK2-V617F mutant allele burden ≥50% in granulocytes was defined as the primary endpoint. Secondary endpoints included changes in blood counts or MPN related symptoms. As a side study, bone marrow biopsies were quantified for nestin+ MSCs, fibrosis and CD34+ HSPCs. N=39 patients have been accrued in 10 institutions in Switzerland. Eight (21%) had ET, 22 (56%) PV, and 9 (23%) PMF. N=27 (69%) were male, the median age was 62 (Q1-Q3 53-72) years. N=28 (72%) patients had cytoreductive treatment, the remaining patients had antiaggregation, anticoagulation, or phlebotomy.

RESULTS

The primary end
reached by any o
by 24 weeks of tr
the CTCAE scal
considered to be
mean blood cou
treatment. In 20 p
of mirabegron tre
in the nestin+ M
3.27)/mm^2 to 3.
signed-rank test)
median grade of
(p=0.02), were ob
cells from baseli
1.65-5.39).

> Treatment with mirabegrom increased Nestin
>
> But did not markedly reduce the JAK2 allele burden

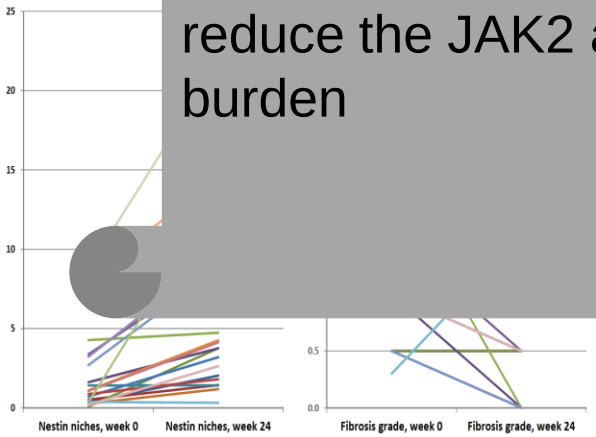
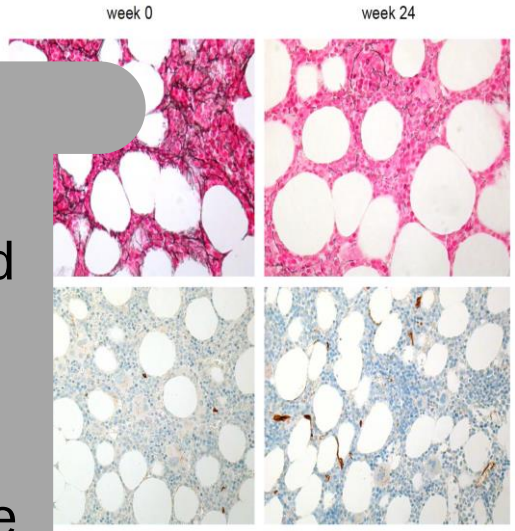


Figure 1: Single patient evolutional curves of the nestin+ mesenchymal cells/mm^2 (left panel) and grade of reticulin fibrosis according to the European consensus on grading bone marrow fibrosis[2] (right panel) at study inclusion and after 24 weeks of mirabegron.

Acknowledgements:
This work was supported by the *Rising Tide Foundation for Clinical Cancer Research*, *Gateway for Cancer Research*, the *Swiss Cancer Research Foundation*, and the *Swiss State Secretariat for Education, Research and Innovation*.



marrow histology of a patient before (week 0) and at the end of
k 24) with mirabegron. Upper panel, reticulin fibers are stained
impregnation (Gömöri). Lower panel, immunohistochemistry
monoclonal antibody against human nestin protein. Note decrease
sis and increase of nestin positive cells (brown staining) after 24
ent. Magnification: 200x

CONCLUSIONS

ympathomimetic agonist mirabegron for 24 weeks failed
he primary endpoint, i.e. to reduce the JAK2-V617F
burden ≥50% in patients with MPN.

A decrease of myelofibrosis and an increase in the nestin+ MSCs in bone marrow were observed.

This data suggest that mirabegron treatment can reverse the damage inflicted by the JAK2-V617F positive MPN clone on the nestin+ stem cell niche.

REFERENCES

1. Arranz et al, Neuropathy of haematopoietic stem cell niche is essential for myeloproliferative neoplasms. Nature 512:78-81, 2014
2. Thiele et al, European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 90: 1128-1132, 2005

Summary

It is important to make an accurate diagnosis we focus on the boundaries with other MPNs

Large studies underpin our current practice but a question remains about IFN vs HU. Recent data is reassuring to patients that these agents are similar at east in the short term.

Increasingly we are likely to use molecular information to tailor our therapies. Eg we may not need to use aspirin in CALR + ET

There are other potential therapy options on the horizon

The landscape is changing

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Pioneering better health for all

With thanks to……

Home team

Deepti Radia, Donal McLornan, Sue Robinson, Yvonne Francis, Claire Woodley, Sam Alimam, Natalia Curto-Garcia

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MPN subgroup

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French MPN Group (FIM)

International collaborators

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Medical Research Council Bloodwise MPN Voice