New Drugs in Hematology

State of the art treatment MPN

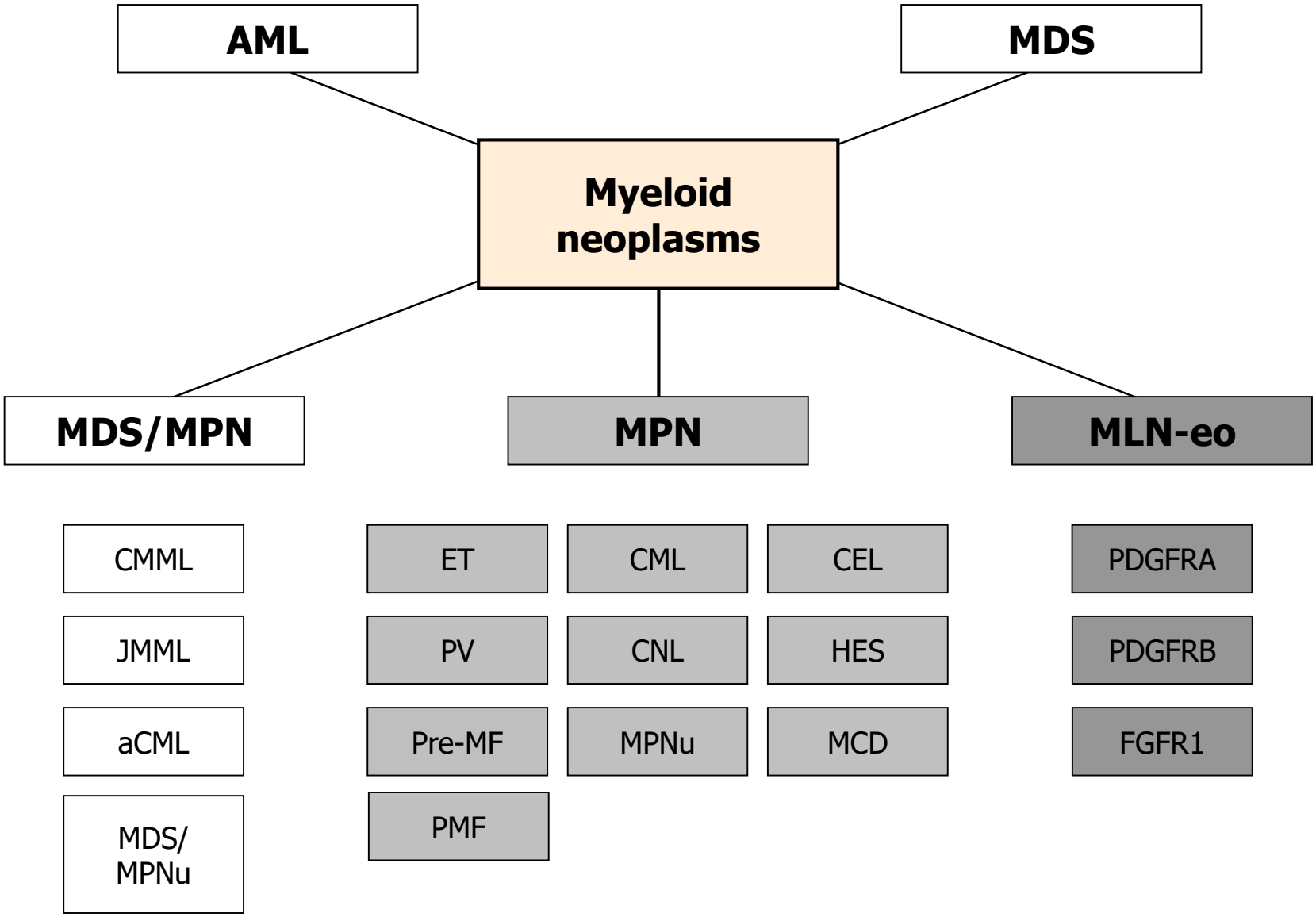
"How has practice changed from a patient perspective?"

Claire Harrison
Guys and St Thomas' Hospital
London

Disclosures:

- Research funding: Novartis and Celgene
- Speaker/Advisory board: Sanofi, Gilead, Novartis, Celgene, CTI, Sierra Oncology, Jannsen, Roche, AOP Pharma

WHO 2016: Myeloid Neoplasms

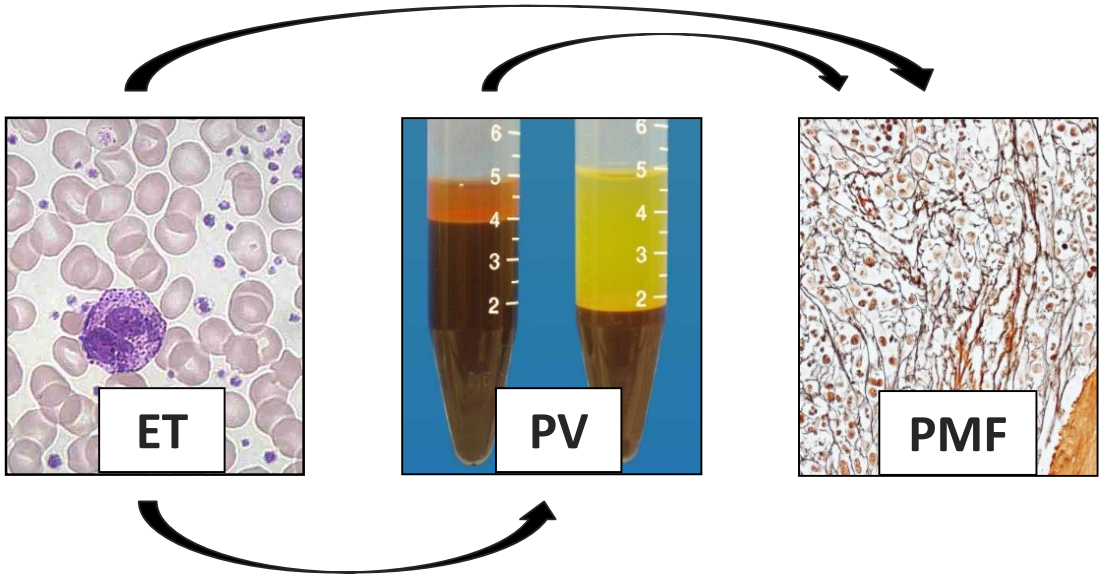


- **Louis Henri Vaquez** (27 August 1860 – 1936) was a French Physician

- In 1892 he was the first to describe **polycythaemia vera** or polycythaemia rubra vera, which is also known as "Osler-Vaquez disease“

- Vaquez described the disease in a 40-year-old male suffering from chronic cyanosis, distended veins, vertigo, dysnea, hepatosplenomegaly, palpitations and marked erythrocytosis

Classifying Different MPNs or Recognizing The Disease Continuum?

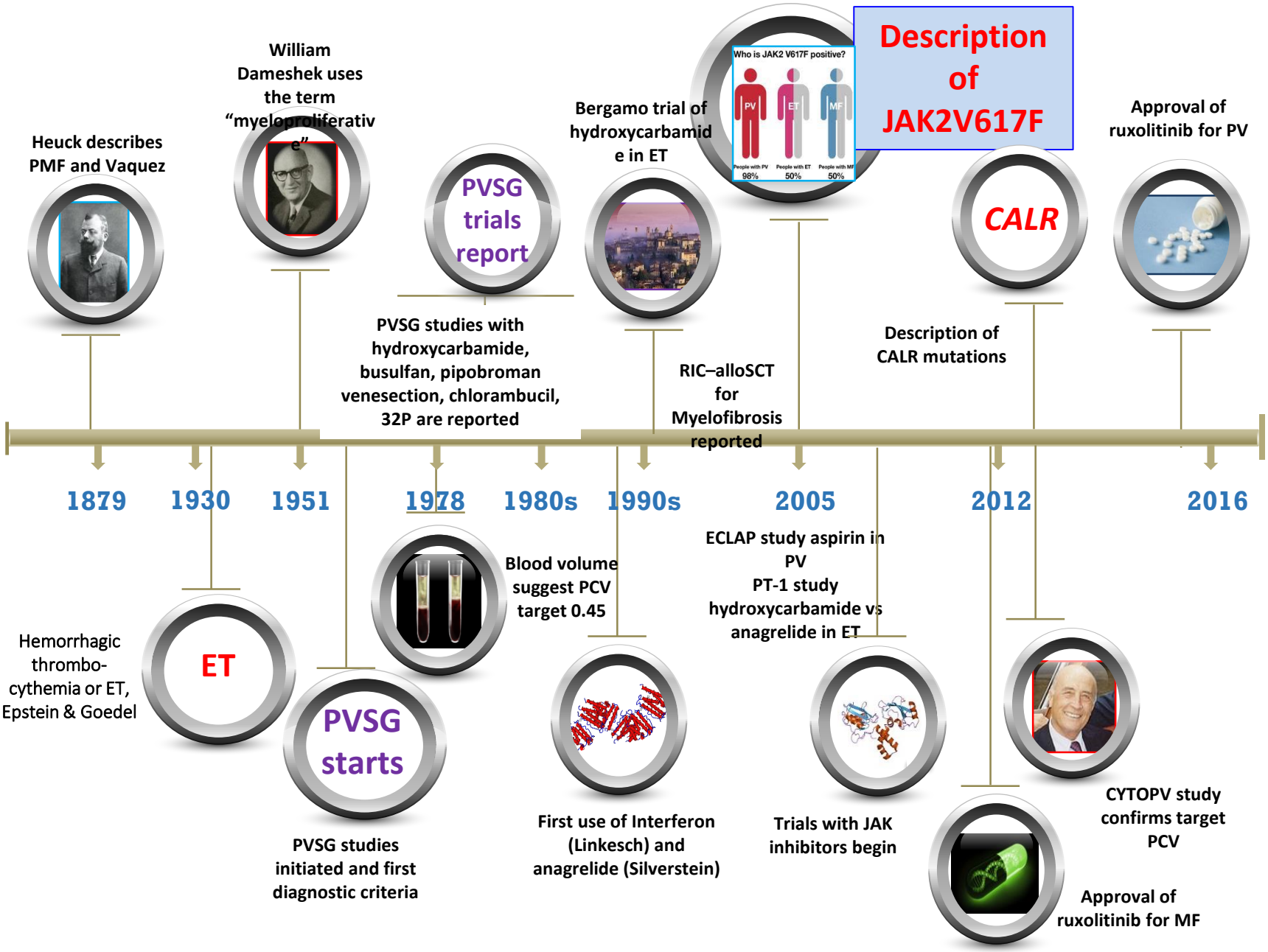


1951

William Dameshek

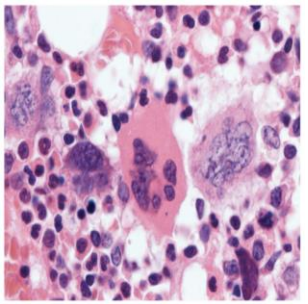
"…we find it difficult to draw any clear-cut dividing lines; in fact, so many "transition forms" exist that one may with equal reasonableness call a single condition by at least two different terms."

Slide courtesy of Jyoti Nangalia, MBBChir, FRCPath.


Heuck describes PMF and Vaquez
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
Who is JAK2 V617F positive?
PV
ET
MF
People with PV 98%
People with ET 50%
People with MF 50%
Description of JAK2V617F
CALR
Description of CALR mutations
Approval of ruxolitinib for PV
RIC–alloSCT for Myelofibrosis reported
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

Patient case:

- 17 year old female from Lebanon. Living in London
- Coincidental finding of thrombocytosis
- Wbc 8 $x10^9$/L; Hb 123g/l; Platelets 1204 $x10^9$/L
- Normal blood film, normal LDH
- No splenomegaly
- Prolonged APTT – factor XI deficiency
- Bone marrow biopsy "consistent with E



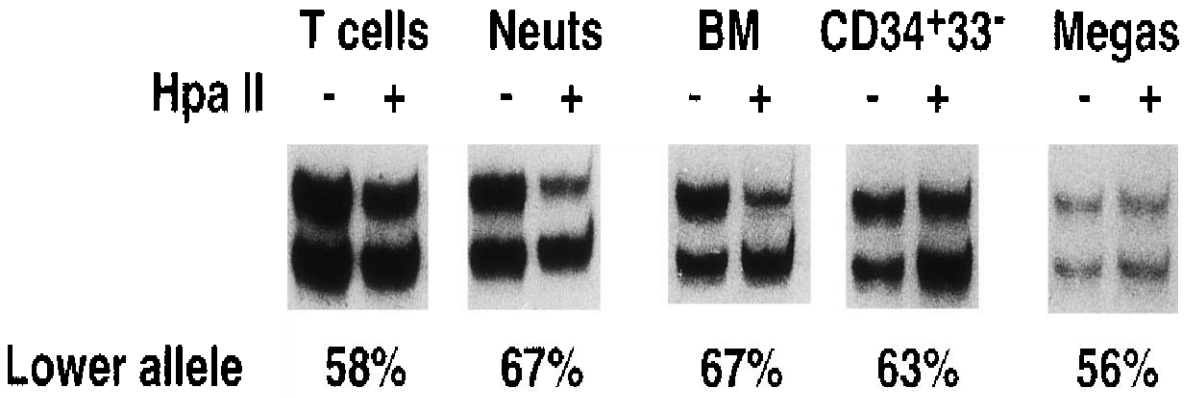
- No treatment
- Seeks second opinion at Mayo clinic
- Ski injury receives anagrelide for surgery

- 4 years later (age 23) gets married
- Wbc 8 $x10^9$/L; Hb 123g/l; Platelets 1534 $x10^9$/L
- Gets pregnant, 3 doses of IFNα miscarriage
- Marriage breaks up

blood®
1999 93: 417-424

A Large Proportion of Patients With a Diagnosis of Essential Thrombocythemia Do Not Have a Clonal Disorder and May Be at Lower Risk of Thrombotic Complications

Claire N. Harrison, Rosemary E. Gale, Samuel J. Machin and David C. Linch



Later found to have a type 2 CALR mutation

Aspirin

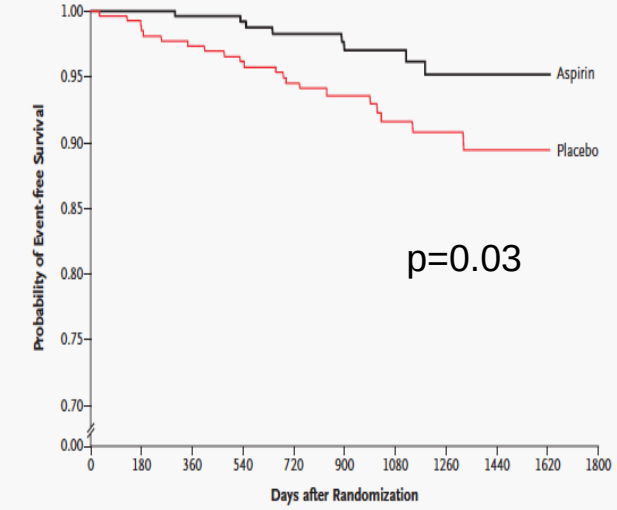
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Low-Dose Aspirin in Polycythemia Vera

Raffaele Landolfi, M.D., Roberto Marchioli, M.D., Jack Kutti, M.D., Heinz Gisslinger, M.D., Gianni Tognoni, M.D., Carlo Patrono, M.D., and Tiziano Barbui, M.D., for the European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators*

N ENGL J MED 350;2 WWW.NEJM.ORG JANUARY 8, 2004



Extrapolated to ET

Low-risk disease

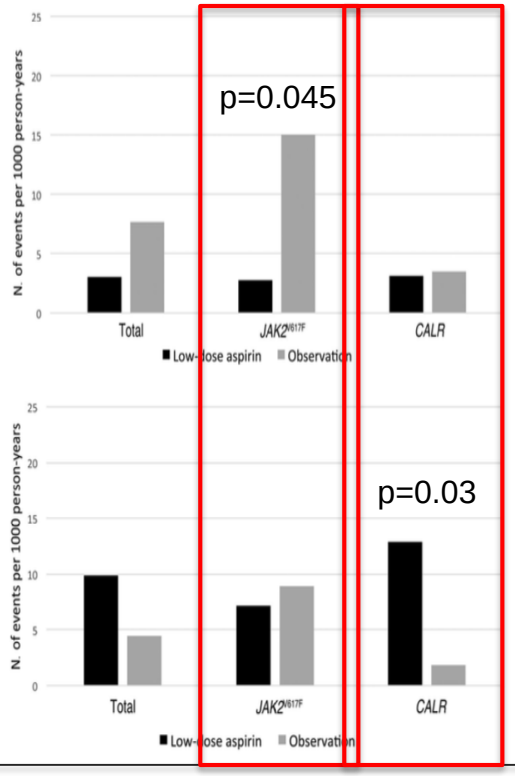
Antiplatelet therapy *versus* observation in low-risk essential thrombocythemia with a *CALR* mutation

Alberto Alvarez-Larrán,[1] Arturo Pereira,[2] Paola Guglielmelli,[3] Juan Carlos Hernández-Boluda,[4] Eduardo Arellano-Rodrigo,[2] Francisca Ferrer-Marín,[5] Alimam Samah,[6] Martin Griesshammer,[7] Ana Kerguelen,[8] Bjorn Andreasson,[9] Carmen Burgaleta,[10] Jiri Schwarz,[11] Valentín García-Gutiérrez,[12] Rosa Ayala,[13] Pere Barba,[14] María Teresa Gómez-Casares,[15] Chiara Paoli,[3] Beatrice Drexler,[16] Sonja Zweegman,[17] Mary F. McMullin,[18] Jan Samuelsson,[19] Claire Harrison,[6] Francisco Cervantes,[20] Alessandro M. Vannucchi,[3] and Carlos Besses[1]

Haematologica 2016
Volume 101(8):926-931

Venous thrombosis

Bleeding

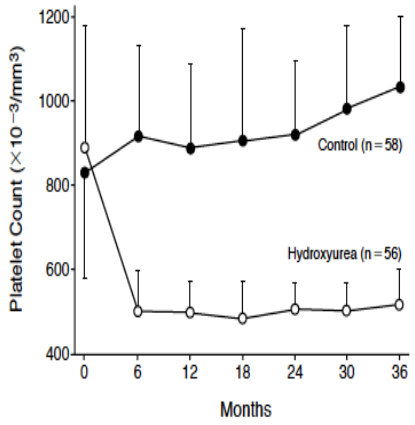


High-risk ET: cytoreduction

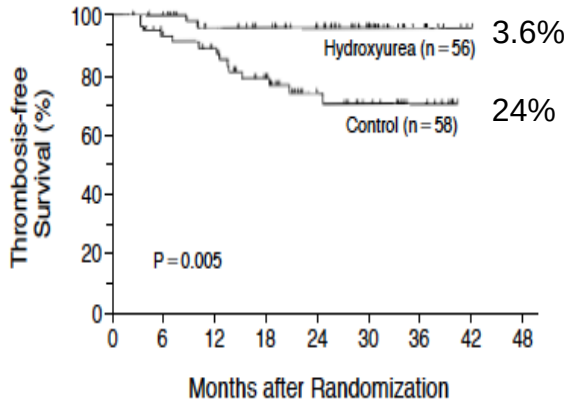
1132 THE NEW ENGLAND JOURNAL OF MEDICINE April 27, 1995

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.



- High risk ET



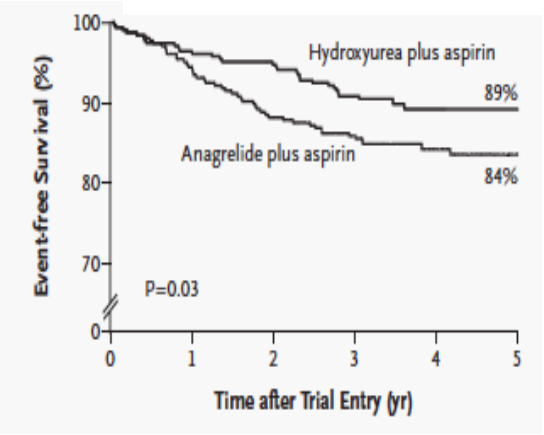
3.6%

24%

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



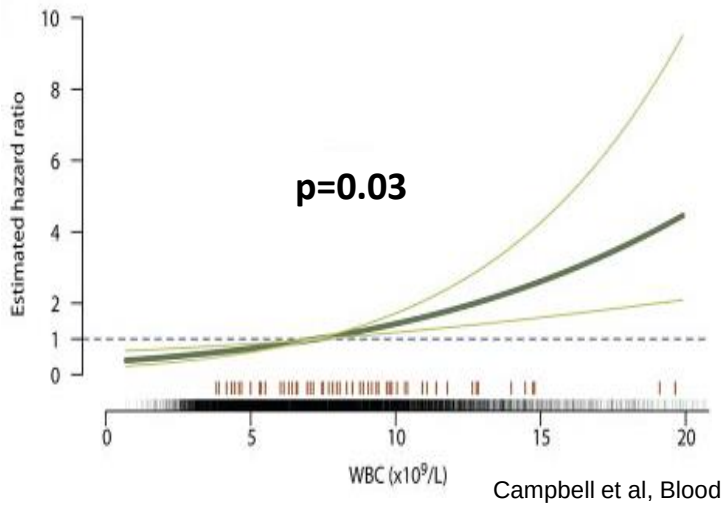
Hydroxycarbamide:

- Fewer MF transformations
- Fewer treatment withdrawals

Anagrelide: second-line

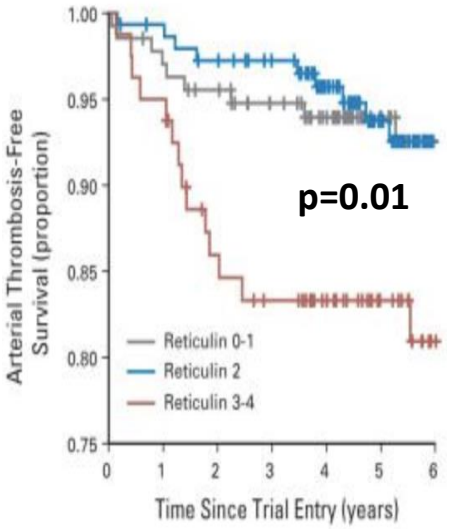
Additional risk factors

White cell count



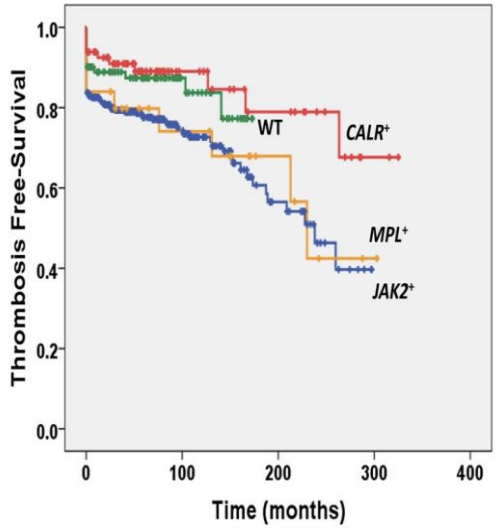
Campbell et al, Blood 2012

Reticulin grade at diagnosis



Campbell et al, JCO 2009

JAK2 V617F vs CALR



Campbell et al, Lancet 2005; Rotunno et al, Blood 2014; Rumi et al, Blood 2014

Cardiovascular risk factors

"IPSET-thrombosis"

Risk factor	HR	Score
Age > 60 y	1.50	1
Cardiovascular risk factors	1.56	1
Previous thrombosis	1.93	2
*JAK2*V617F	2.04	2

Barbui et al, Blood 2012

Back to our case

- Her diagnosis was (very) low-risk ET – perhaps Pre-MF (lacks current WHO 2016 features)
- Traumatised by her diagnosis and the lack of information.
- With other patients and clinicians at GSTT, starts MPN voice

- Gets married again age 38 has an uneventful pregnancy managed with aspirin. By this time there is data published on >300 pregnancies including prospective study from the UK

bjh research paper

Pregnancy outcomes in myeloproliferative neoplasms: UK prospective cohort study

voice

Low-risk ET: cytoreduction?

- No prior data indicating whether cytoreduction beneficial
- “Intermediate risk” arm of PT1:

Age 40 to ≤59 years

No high-risk factors:
- Prior ischaemia or thrombosis
- Prior haemorrhage due to ET
- Hypertension/diabetes on therapy
- Current or previous platelet count
  >1000 x 10^9/L
  (>1500 x 10^9/L May 2004)

15 years
140 centres

Randomisation
1:1, n=382

Hydroxycarbamide + aspirin
Target plts 200 - 400 x 10^9/L

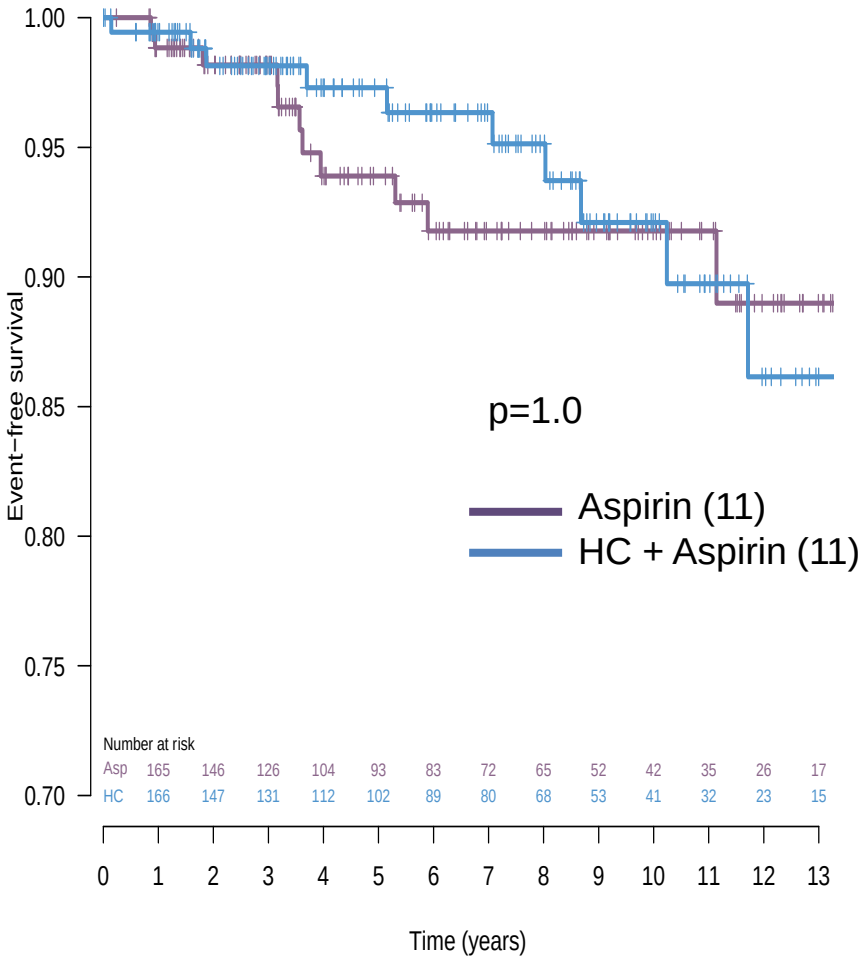
Aspirin alone

Median duration f/u 73 months

Godfrey et al, JCO 2018

Vascular endpoints

Primary: Arterial or venous thrombosis, serious hemorrhage or death from vascular causes

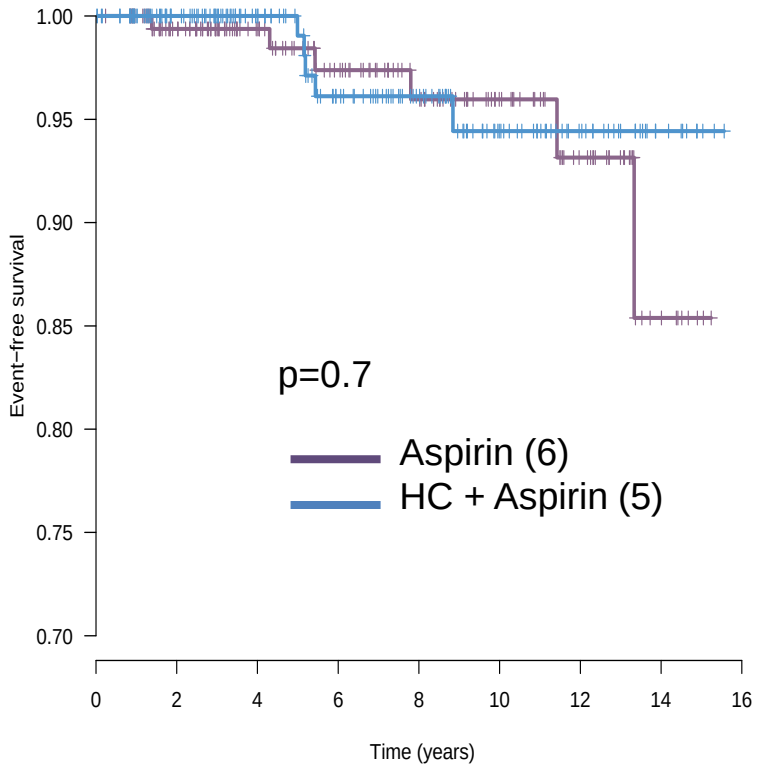


	Aspirin alone (n=176)	HC+ aspirin (n=182)
Arterial thrombosis	7	5
Myocardial infarction	2	0
Ischemic stroke	2	3
Transient ischemic attack	3	1
Small bowel infarction	0	1
Venous thromboembolism	3	4
Deep vein thrombosis	1	3
Pulmonary embolism	2	2
Serious haemorrhage	2	3
Intracranial haemorrhage	1	2
GI haemorrhage	0	1
Post-op major haemorrhage	1	0
Death	7	10
Thrombotic cause	2	2
Hemorrhagic cause	0	1
Hematological cause	2	3
Other cause		

No difference in overall survival

Disease transformation

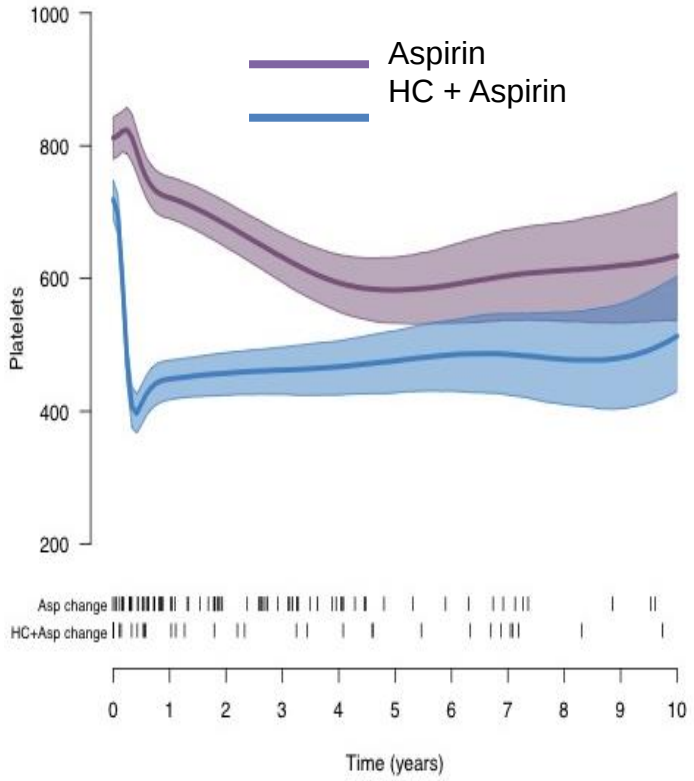
PET-MF, AML or MDS



No difference in non-haematological cancers

Caution in interpreting long-term safety:

- 47% in aspirin alone arm changed therapy
  - Most started HC
  - Reasons: clinical event / symptoms / lack of platelet control / aged 60
- 21% in HC+ aspirin arm changed therapy



Low-risk ET: summary

Age <60

No previous vascular events

Aspirin

- For all?

Who else might need cytoreduction?

- Symptoms: microvascular, disease-related
- Progressive leucocytosis
- Progressive splenomegaly

Treatment target should reflect the indication for cytoreduction

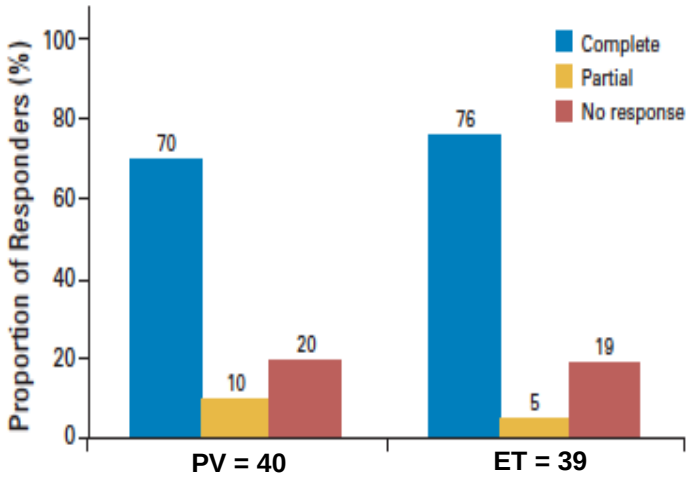
Monitor CV risk

Cytoreduction:

- Pre-emptive addition of hydroxycarbamide to aspirin **did not** reduce vascular events, myelofibrotic or leukemic transformation
- No cytoreduction until another clinical indication arises

Alternatives: pegylated interferon-alfa

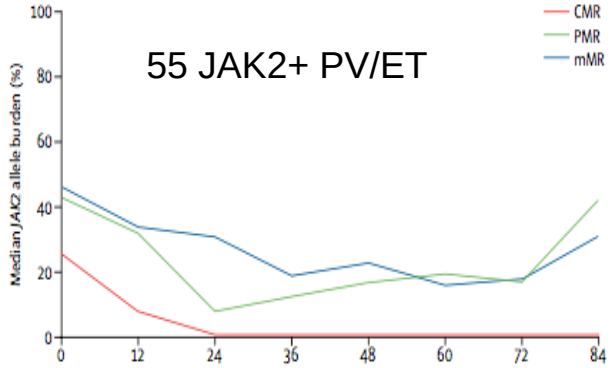
Phase 2



54% molecular response
14% complete MR

38% molecular response
6% complete MR

Responses can be durable:



Quintas-Cardama et al, JCO 2009;
Masarova et al, Lancet Haematol 2017

Phase 3

- MPD-RC 112
  - ➢ Pegylated IFN-α-2a *vs* HC in **PV / ET**
- PROUD/CONTI-PV
  - ➢ Ropeginterferon-α-2b vs HC in **PV**

- Haematological responses ≈ HC
- Good tolerability
- Molecular / histological responses

… but what about long term?

UPDATES DUE AT ASH 2018

Mascarenhas et al, ASH 2016; Gisslinger et al, ASH 2017

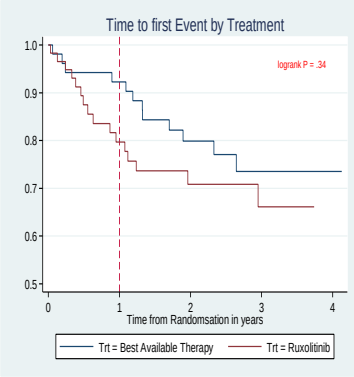
Alternatives for second line therapy: new and old

Ruxolitinib

MAJIC

- 110 ET refractory / intolerant to HC
- Randomised rux *vs* BAT

- No difference in CHR at 1 yr
- No difference in survival
- No difference in transformation, thrombosis or haemorrhage



Harrison et al, Blood 2017

Other second-line agents

- Anagrelide (alone or in combination)
- Busulphan
- Radioactive phosphorus
- Pipobroman
- Imetelstat
  (updates in MF @ ASH 2018)

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

- CONFIRMS anagrelide is less good than HU at preventing arterial thrombosis & bleeding per PT-1
- AND there was more MF in anagrelide treated patients per PT-1
- CONFIRMS risk of skin cancer with HU

Birgegard et al 2018

Alternatives for second line therapy: new and old

Ruxolitinib

MAJIC

- 110 ET refractory / intolerant to HC
- Randomised rux *vs* BAT

- No difference in CHR at 1 yr
- No difference in survival
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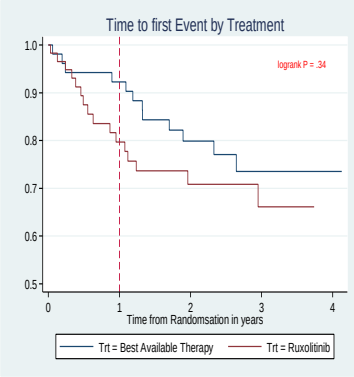


Harrison et al, Blood 2017

Other second-line agents

- Anagrelide (alone or in combination)
- Busulphan
- Radioactive phosphorus
- Pipobroman
- Imetelstat
  (updates in MF @ ASH 2018)

The mutational landscape in hydroxycarbamide-resistant/intolerant essential thrombocythemia treated on the MAJIC-ET study

Jennifer O'Sullivan
Angela Hamblin
Adam Mead

Presented at EHA 2018

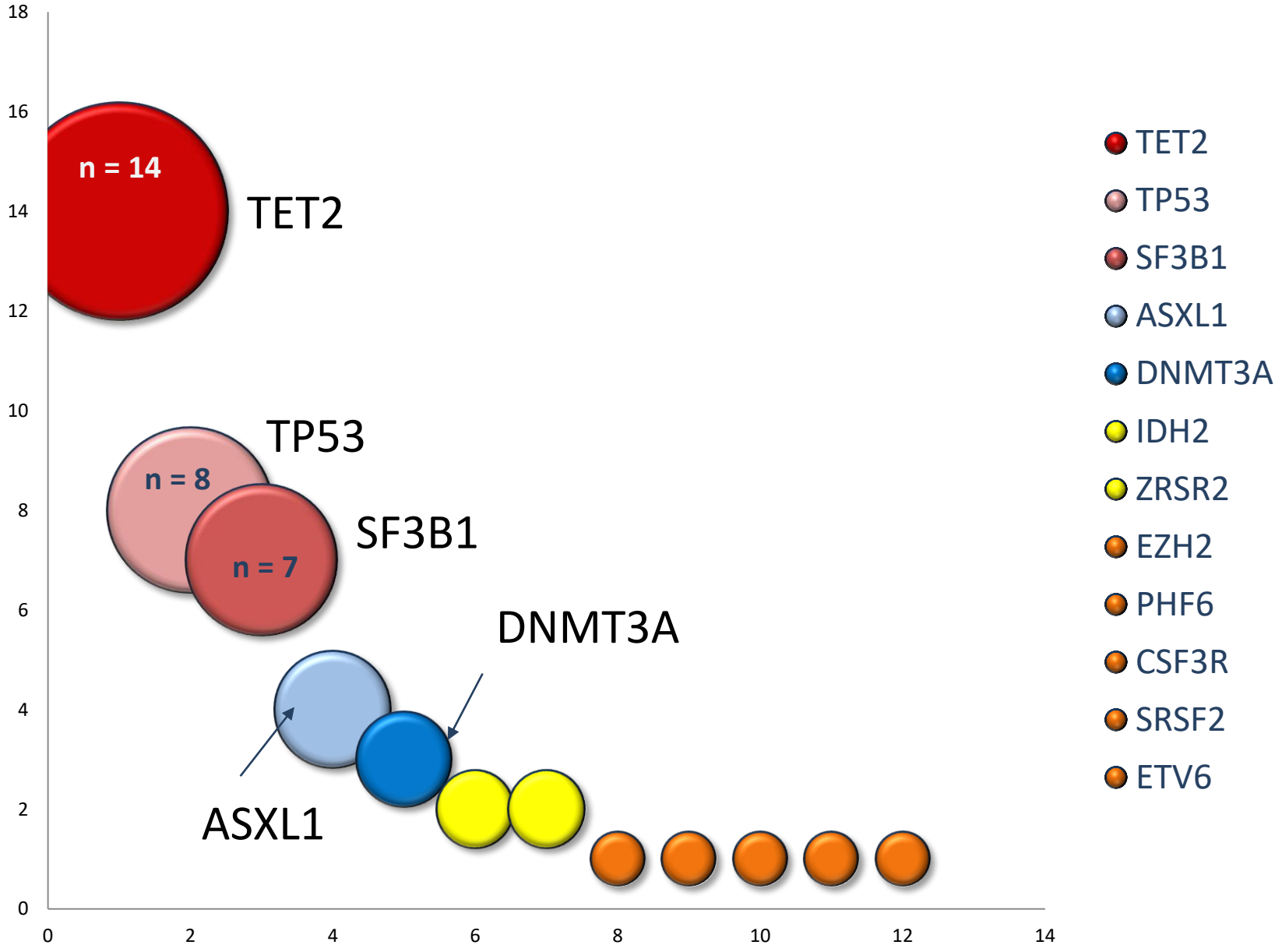
Bloodwise
The blood cancer research charity

Guy's and St Thomas' NHS
NHS Foundation Trust

MAJIC-ET: mutation status

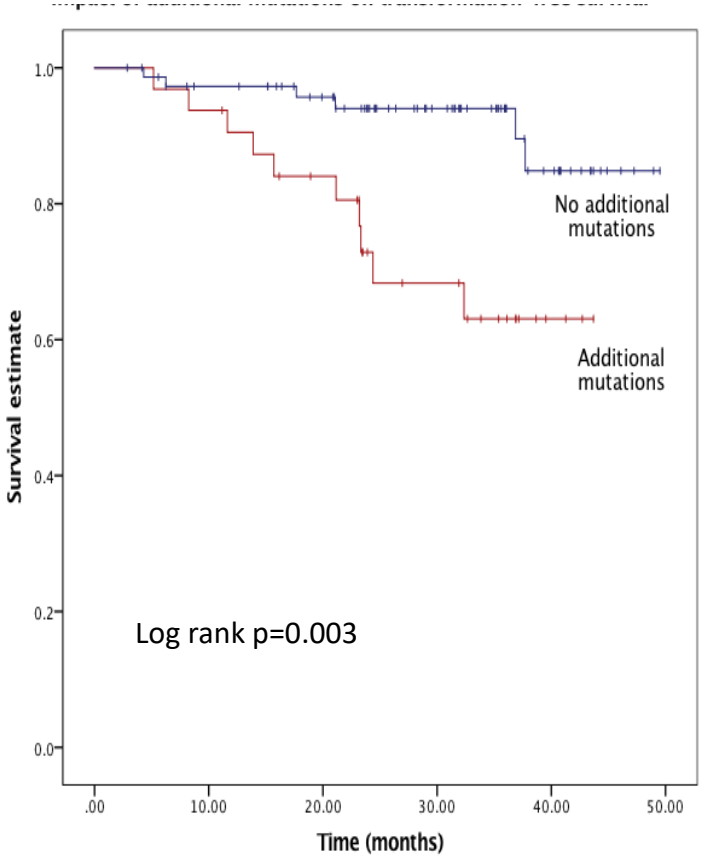
N (%)	BAT (%)	RUX (%)	Overall (%)
Driver mutations			
JAK2	25 (48.1)	28 (49.1)	53 (48.6)
CALR	14 (26.9)	19 (33.3)	33 (30.3)
MPL	3 (5.8)	2 (3.5)	5 (4.6)
Triple negative	10 (19.2)	8 (14)	16 (16.5)
Additional mutations	17 (32.7)	15 (26.8)	32 (29.6)
1	13 (25)	9 (16.1)	22 (20.4)
2	3 (5.8)	5 (8.9)	8 (7.4)
3	1 (1.9)	0	1 (0.9)
4	0	1 (1.9)	1 (0.9)

MAJIC-ET: non-driver mutations



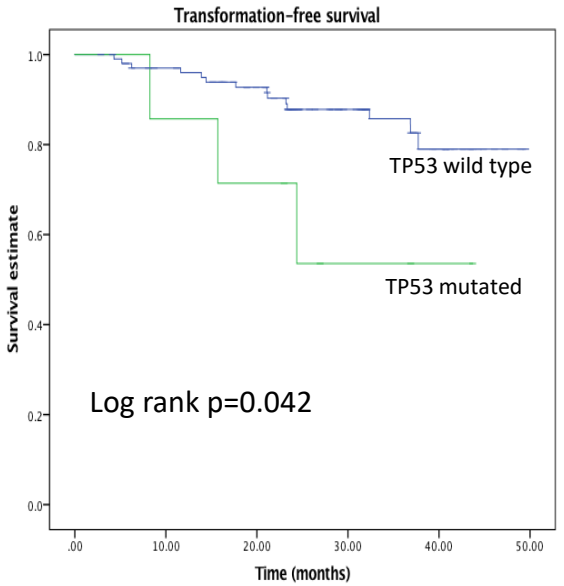
MAJIC-ET: 2-year transformation-free survival

Impact of additional non-driver mutations*

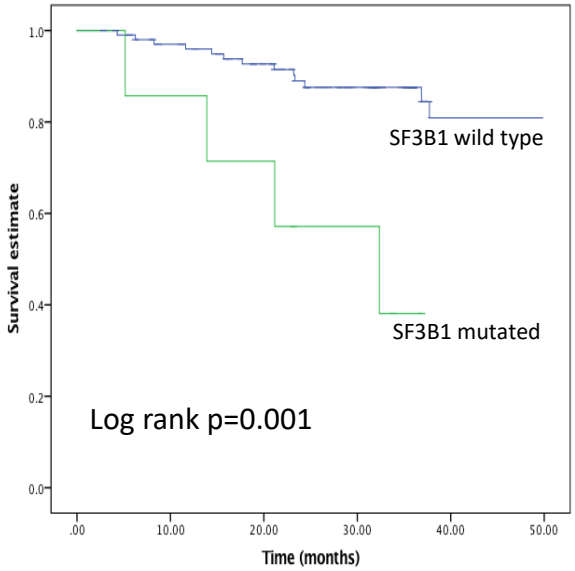


*remains significant for BAT but not RUX patients

TP53



SF3B1



Back to our case

- Age 45 there is a gradual fall of platelets 700 x 10^9/L and Hb 109g/l, leucoerythroblastic film, LDH ⇧, continues to have no symptoms, no splenomegaly
- Marrow shows grade 1 reticulin
- Karyotype is normal
- Now has ASXL1 mutation as well as type 2 CALR .
- ASXL1 is a NEW mutation not present in earlier samples

- Using current criteria we cannot give her a clear diagnosis of PET-MF or overt PMF

- Currently considering options for watch and wait, IFNα, HLA typing siblings……

On-going issues in ET?

Normal platelet count?

<400 - high-risk PT
<600 - Bergamo stu

High platelet count correlates with haemorrhagic but n thrombotic risk

Haematological response?

- What about the HCT for JAK2 positive ET?
- Should we manage JAK2 positive ET as PV?
- What about the leucocyte count? Cut-off?
- What about avoiding the appearance of additional mutations?

- Retrospective study showed no benefit of CR on thrombotic risk or survival

Molecular response?

atients in molecular sponse still have rombotic and ansformation events

ncertain long-term nefit

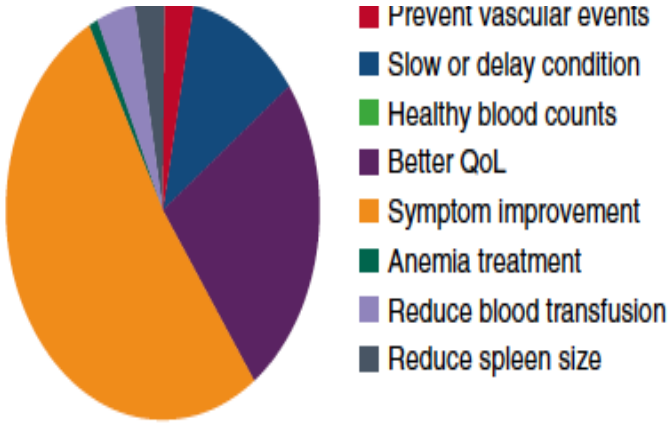
Barosi et al, Blood 2009, 2013;
Hernandez-Boulla et al, B J Haematol 2011

Finding these answers?

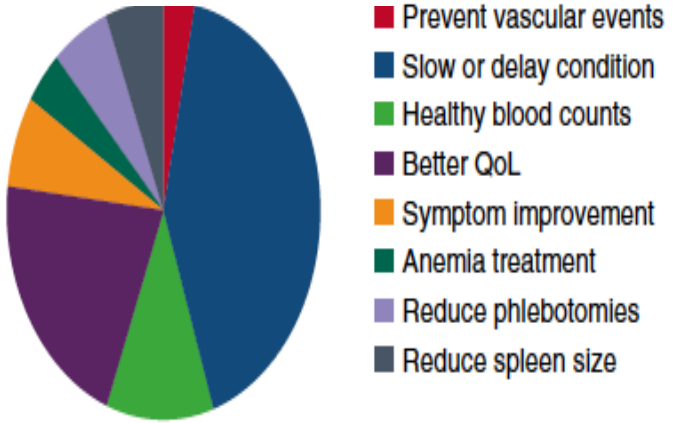
- Only by collaboration (fostered by excellent meetings like this!)
- Long term well designed clinical trials under pinned by excellent science

- Gaps in goals for therapy

Physician



Patient



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Emma Ghibandhi
Christina Yap
Amy Houghton

Mary Frances McMullin
Adam Mead

Ruben Mesa
Robyn Scherber
AmyLou Douek

Tony Green
Peter Campbell
Anna Godfrey
Bridget Wilkins
Jyoti Nangalia
Jacob Grinfeld

PT-1
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Julia Cook
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Keith Wheatley

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Jean-Jacques Kiladjian

Philip Beer
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Wendy Erber
Jon van der Walt

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