Essential Thrombocytopenia: yesterday, today & tomorrow...

Claire Harrison
Guy’s and St Thomas’ Hospitals London, UK
William Dameshek uses the term “myeloproliferative”

Heuck describes PMF and Vaquez PV

PVSG trials report

PVSG studies with hydroxycarbamide, busulfan, pipobroman venesction, chlorambucil, 32P are reported

Blood volume suggest PCV target 0.45

First use of Interferon (Linkesch) and anagrelide (Silverstein)

Trials with JAK inhibitors begin

CYTOPV study confirms target PCV

Approval of ruxolitinib for MF


ET

PVSG starts

PVSG trials report

Description of JAK2V617K

PVSG studies initiated and first diagnostic criteria

ET, Epstein & Goedel

Hemorrhagic thrombocythemia or ET, Epstein & Goedel

Bergamo trial of hydroxycarbamide in ET

Description of CALR mutations

RIC–alloSCT for Myelofibrosis reported

Trials with JAK inhibitors begin

Approval of ruxolitinib for PV

ECLAP study aspirin in PV

PT-1 study hydroxycarbamide vs anagrelide in ET

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

Hydroxyurea (target plts<600) vs no hydroxyurea

Cytoreduction reduces thrombosis in high-risk ET
Primary Thrombocythaemia - 1 Studies (PT1)

ET
Aged 18yrs or over
New or previously diagnosed

- Low Risk
  - <40yrs
  - No vascular RFs
  - Plts <1500x10⁹/l
  - -> Aspirin

- Intermediate Risk
  - 40-60yrs
  - No vascular RFs
  - Plts <1500x10⁹/l
  - -> HU + Aspirin versus
  - Aspirin alone

- High Risk*
  - >60yrs
  - Thrombosis
  - Haemorrhage
  - Vascular RFs
  - Plts >1500x10⁹/l
  - -> HU + Aspirin vs
  - Anagrelide + Aspirin

HU, Hydroxyurea; RFs, Risk factors of hypertension, diabetes mellitus, ischaemic heart disease
*Harrison et al, NEJM 2005
• 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\(^{\text{st}}\) 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

<table>
<thead>
<tr>
<th></th>
<th>Platelets</th>
<th>WCC</th>
<th>Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>p=0.4</td>
<td>p=0.6</td>
<td>p=1.0</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>p=0.6</td>
<td>p=0.6</td>
<td>p=0.6</td>
</tr>
<tr>
<td>Transformation to Myelofibrosis / AML / MDS</td>
<td>p=0.5</td>
<td>p=0.9</td>
<td>p=0.8</td>
</tr>
</tbody>
</table>

• 21,887 longitudinal blood counts after trial entry

Campbell Blood 2012
Blood counts at diagnosis
Blood counts during treatment

White cell count & thrombosis

Estimated hazard ratio

WBC (x10⁹/L)

p=0.05

Campbell Blood 2012
Blood counts at diagnosis
Blood counts during treatment

White cell count & major haemorrhage

Estimated hazard ratio

WBC (x10^9/L)

Campbell Blood 2012
✓ Blood counts at diagnosis
✓ Blood counts during treatment

Platelet count & major haemorrhage

Estimated hazard ratio

$p=0.0005$

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

Reticulin 0-1
Reticulin 2
Reticulin 3-4

p=0.01 Multivariate

Time from PT-1 trial entry (years)

Campbell 2009
Major haemorrhage by reticulin in PT-1 trial

Time from PT-1 trial entry (years)

p=0.05
Multivariate

Reticulin 0-1
Reticulin 2
Reticulin 3-4

Campbell 2009
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

¹Medical University of Vienna, Department of Internal Medicine I, Division of Hematology and Blood Coagulation, Vienna, Austria; ²Institute of Hematology, Clinical Center of Serbia, Belgrade, Serbia; ³Silesian Medical University, Department of Hematology and BMT, Katowice, Poland; ⁴University Hospital Brno, Department of Clinical Hematology, Brno, Czech Republic; ⁵Institute of Pathology, University of Cologne, Cologne, Germany; ⁶Department of Pathology, University of Frankfurt/Main, Frankfurt/Main, Germany; ⁷Center for Molecular Medicine (CeMM), Austrian Academy of Sciences, Vienna, Austria; and ⁸Hematology 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 completed (PROUD-PV) HU and IFN equivalent
PEG-IFN2a in ET-PV. Molecular Response in JAK2 V617F+(N=55)

Masarova et. al. ASH 2015
# PEG-IFN2a in ET-PV. Vascular Events

<table>
<thead>
<tr>
<th>Event Type</th>
<th>N (%) ; median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic</td>
<td>8 (10) ; 3 provoked</td>
</tr>
<tr>
<td>Venous: PE, DVT, stroke</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Arterial: thrombosis</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Bleeding: stroke</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Time to event, mos</td>
<td>38 [14-60]</td>
</tr>
<tr>
<td>Patients in CHR</td>
<td>5 / 9 (56)</td>
</tr>
</tbody>
</table>

Masarova et. al. ASH 2015
PEG-IFN2a in ET-PV. Transformation MF/AML

**Transformation to MF / AML**

<table>
<thead>
<tr>
<th>N at risk</th>
<th>PEG</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>83</td>
<td>352</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>224</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>35</td>
</tr>
</tbody>
</table>

Cumulative Probability (%)

- **PEG**: P = 0.49 (HR 1.33, 95% CI 0.58-1.72)
- **Control**

**Masarova et. al. ASH 2015**
Population: Patients with high risk Polycythemia vera (PV) or Essential Thrombocythemia (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
Primary Analysis

Primary endpoint - Complete Haematological Response per ELN:

27 (46.6%) of RUX patients
vs 23 (44.2%) BAT patients ($\chi^2$ 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 $p<0.05$).
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.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>RUX Arm (% patients)</th>
<th>BAT Arm (% patients)</th>
<th>Number of patients discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 3 &amp; 4</td>
</tr>
<tr>
<td>Anemia</td>
<td>19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5.2</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>10.3</td>
<td>3.6</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic events*</td>
<td>9 (15.5%) [10]</td>
<td>5 (8.9%) [5]</td>
<td>5</td>
</tr>
<tr>
<td>Hemorrhagic events*</td>
<td>1 (1.7%) [1]</td>
<td>5 (8.9%) [5]</td>
<td>0</td>
</tr>
</tbody>
</table>

*adjusted following central review
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
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 $>1500 \times 10^9/L$ 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
Aspirin benefits JAK2V617F positive low risk ET for overall and arterial thrombosis but also venous thrombosis.

BUT for CALR positive low risk ET appears to increase risk of bleeding.
<table>
<thead>
<tr>
<th></th>
<th>HU</th>
<th>Anagrelide</th>
<th>IFN alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
<td>Antimetabolite</td>
<td>Imidazoquinazolin</td>
<td>Biologic response</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Impairs DNA repair</td>
<td>Impairs MK differentiation</td>
<td>Myelosuppressive</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Affects all</td>
<td>Platelets only</td>
<td>Affects all cells</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>3-5 days</td>
<td>6-10 days</td>
<td>3-26 weeks</td>
</tr>
<tr>
<td><strong>Side Effects in &gt;10%</strong></td>
<td>Neutropenia, anaemia, ulcers, palpitations, fluid retention</td>
<td>Headache, diarrhoea, palpitations, fluid retention</td>
<td>Flu-like symptoms alopecia, weight loss</td>
</tr>
<tr>
<td><strong>Side Effects in &lt;10%</strong></td>
<td>Leg ulcers, D &amp; V</td>
<td>CCF, arrhythmia's anaemia</td>
<td>Confusion, arthritis depression</td>
</tr>
<tr>
<td><strong>Contraindicated In:</strong></td>
<td>Neutropenia</td>
<td>CCF, pregnancy</td>
<td>? Safe in pregnancy</td>
</tr>
<tr>
<td></td>
<td>pregnancy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

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

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
Baseline clinical characteristics

**FEMALE**
- **LOW**: N=39
- **INTERMEDIATE**: N=76
- **HIGH**: N=343

**MALE**
- **LOW**: N=17
- **INTERMEDIATE**: N=33
- **HIGH**: N=259

**Mutation**
- Triple negative
- CALR
- JAK2
- MPL
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

Time after trial entry (yrs)

Survival free of myelofibrosis

- JAK2, HU
- CALR, HU
- JAK2, AG
- CALR, AG
Does treatment with HU or Ag alter adverse outcomes associated with molecular status?

Venous thrombosis

Survival free of venous thrombosis

<table>
<thead>
<tr>
<th>Time after trial entry (yrs)</th>
<th>JAK2, HU</th>
<th>CALR, HU</th>
<th>JAK2, AG</th>
<th>CALR, AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>14</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>96</td>
<td>94</td>
<td>84</td>
<td>168</td>
</tr>
<tr>
<td>2</td>
<td>166</td>
<td>164</td>
<td>118</td>
<td>164</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>73</td>
<td>64</td>
<td>115</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>46</td>
<td>47</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>27</td>
<td>27</td>
<td>50</td>
</tr>
</tbody>
</table>
How do molecular subgroups respond to HU or Ag?
How do molecular subgroups respond to HU or Ag?

- Platelets (x10^9/l):
  - JAK2: n=331
  - CALR: n=176
  - MPL: n=24
  - TN: n=90

- Haemoglobin (g/dl):
  - JAK2
  - CALR
  - MPL
  - TN

- White cells (x10^9/l):
  - JAK2
  - CALR
  - MPL
  - TN

Treatment allocation:
- Hydroxyurea + aspirin
- Anagrelide + aspirin

95% CI of fitted line
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

Stimulate NESTIN (mirabegron)  
Or  
Block estrogen (tamoxifen)
Estrogen Signaling Selectively Induces Apoptosis of Hematopoietic Progenitors and Myeloid Neoplasms without Harming Steady-State Hematopoiesis

Authors
Abel Sánchez-Aguilera, Lorena Arranz, ..., Jürg Schwaller, Simón Méndez-Ferrer

Correspondence
abel.sanchez-aguilera@cnic.es (A.S.-A.), smendez@cnic.es (S.M.-F.)

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

Beatrice Drexlert, Jakob R. Passweg1, Martin Bigler1, Alexandre PA Theocharides1, Nathan Cantoni2, Peter Keller2, Georg Stuessi2, Axel Rüfer2, Rudolf A. Benz3, Geneviève Favre3, Alexandar Tzankov10, Pontus Lundberg1, Andrea Fuhrer1, Christine Blagggi2, Markus G. Manz2, Mario Bargetzi2, Simon Mendez-Ferrer11, and Radek C. Skoda12 on behalf of the Swiss Group for Clinical Cancer Research (SAKK)

1Division of Hematology, University Hospital of Basel, Basel, Switzerland; 2Swiss Group for Clinical Cancer Research, Bern, Switzerland; 3Division of Hematology, University Hospital Zurich, Zurich, Switzerland; 4Center of Oncology, Hematology, & Transfusion Medicine, Cantonal Hospital of Aarau, Aarau, Switzerland; 5University Clinic of Hematology and Central Hematology Laboratory, University Hospital Bern, Bern, Switzerland; 6Clinic of Haematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; 7Department Medizin, Luzerner Kantonsspital, Luzern, Switzerland; 8Kantonsspital Muensterlingen, Muensterlingen, CHE; 9Cantonal Hospital Liestal, Liestal, Switzerland; 10Institute of Pathology, University Hospital of Basel, Basel, Switzerland; 11Stem Cell Institute and Department of Haematology, University of Cambridge, and National Health Service Blood and Transplant, Cambridge, United Kingdom; 12Department of Biomedicine, Experimental Hematology, University Hospital Basel, Basel, Switzerland

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.

RESULTS
The primary endpoint was reached by any of the determined parameters by 24 weeks of treatment. The CTCAE scales v3.0 were considered to be beneficial or detrimental for mean blood counts or for marrow fibrosis, respectively. In 20 patients (81%) of mirabegron treated patients compared to the baseline (3.27/mm² to 3.09/mm²; signed-rank test, median grade of 2, p=0.02), the bone cells from baseline had a slight decrease of 1.65-5.39.

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 cytogenetically 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, antiagulation, or phlebotomy.

Figure 1: Single patient evolution curves of the nestin+ mesenchymal cells/mm² (left panel) and grade of reticulin fibrosis according to the European consensus on grading bone marrow fibrosis (right panel) at study inclusion and after 24 weeks of mirabegron treatment.

Figure 2: Bone marrow histology of a patient before (week 0) and at the end of treatment (week 24) with mirabegron. Upper panel, reticulin fibers are stained with Gomori's reticulin (Gombr). Lower panel, immunohistochemistry with monoclonal antibody against human nestin protein. Note decrease in myelofibrosis and increase of nestin positive cells (brown staining) after 24 weeks of treatment. Magnification: 20×.

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.

REFERENCES

Poster presented at ASH 2016
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 least 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
With thanks to……

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

PT-1 team
Tony Green, Peter Campbell, Anna Godfrey, Cathy Maclean Cecily Forsyth, Jean-Jacques Kiladjian
NCRN research network participating clinicians
MPN subgroup

Australasian Leukaemia and Lymphoma Working Party

French MPN Group (FIM)

International collaborators
Ruben Mesa, Alessandro Vannucchi, Serge Verstovse, Radek Skoda, Jean-Jacques Kiladjian, John Mascarenhas, Andreas Reiter

Medical Research Council  Bloodwise  MPN Voice