Malattie mieloproliferative

Fabrizio Pane
CML
Issues for discussion

- Clinical
  - Kinetics parameters for prognosis assessment
  - Clinical updates of ENEST / Dasision / PACE
  - Blast crisis

- Biological
  - CML Stem cells
    - CXCR4 and stromal interactions
    - Epigenomics
    - Stemness determinants
      - Rho kinase
      - ILR2
Time – dependent response assessment parameter

- DEEP MOLECULAR RESPONSE (MR4.5) IS REACHED BY THE MAJORITY OF CML PATIENTS, PREDICTS BETTER SURVIVAL, AND IS ACHIEVED FASTER BY OPTIMIZED HIGH DOSE IMATINIB - RESULTS FROM THE RANDOMIZED CML-STUDY IV
  
  *R. Hehlmann et al*

- INDIVIDUAL EARLY DYNAMICS OF BCR-ABL TRANSCRIPTS, BUT NOT BCR-ABL TRANSCRIPT LEVELS AT BASELINE PREDICT SURVIVAL IN PATIENTS WITH CHRONIC PHASE CML

  *V. Shlyakhto et al*
The value of deep molecular response (MR4.5)  
*R. Hehlmann et al*

- German CML study V (1,524 of 1,551 randomized patients)
- OS 88.2% after a median observation time of 67.5 months
- The cumulative incidence of MR$^{4.5}$ after 9 years was 70%, of confirmed MR$^{4.5}54\%$.
- MR$^{4.5}$ was reached significantly faster with optimized high-dose imatinib than with imatinib 400 mg.
OS according to BCR-ABL at 48 months

MR\(^{4.5}\) predicts OS better than 0.1 – 1% BCR-ABL\(^{IS}\) (= CCR)

<table>
<thead>
<tr>
<th>BCR-ABL(^{IS})</th>
<th>8-y survival</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.0032%</td>
<td>92%</td>
<td>n.s.</td>
</tr>
<tr>
<td>0.0032 – 0.01%</td>
<td>90%</td>
<td>n.s.</td>
</tr>
<tr>
<td>0.01 – 0.1%</td>
<td>88%</td>
<td>n.s.</td>
</tr>
<tr>
<td>0.1 – 1%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>&gt; 1%</td>
<td>78%</td>
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Patients at risk:

<table>
<thead>
<tr>
<th>&lt; 0.0032%</th>
<th>0.0032 – 0.01%</th>
<th>0.01 – 0.1%</th>
<th>0.1 – 1%</th>
<th>&gt; 1%</th>
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<td>198</td>
<td>191</td>
<td>260</td>
<td>55</td>
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<td>163</td>
<td>149</td>
<td>206</td>
<td>41</td>
<td>32</td>
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<td>69</td>
<td>69</td>
<td>106</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>40</td>
<td>41</td>
<td>67</td>
<td>17</td>
<td>8</td>
</tr>
</tbody>
</table>

Survival probability

All patients with primary imatinib, n = 1194

8 years survival

< 0.0032%
0.0032 – 0.01%
0.01 – 0.1%
0.1 – 1%
> 1%
EARLY DYNAMICS OF BCR-ABL TRANSCRIPT
V. Shlyakhto et al

- **Aims:** Evaluation of the prognostic significance of:
  1) BCR-ABL/GUS at diagnosis,
  2) Individual reduction of BCR-ABL/GUS at 3 months
  3) BCR-ABL/GUS at 3 months
  4) the established 10% BCR-ABL/ABL\textsuperscript{IS} landmark

- **Patients:** 408 (350 evaluable)
  Median follow-up was 4.8 years (range 1-10)
  Disease progression: 26 patients (7.4%), 18 of them died (5.1%).
EARLY DYNAMICS OF BCR-ABL TRANSCRIPT

V. Shlyakhto et al

Results:

- Median BCR-ABL/GUS ratio at diagnosis: 15% (0.07 - 107)
  at 3 months: 0.70% (0 - 84) = 0.05 fold decline (1.3 log).

- At diagnosis no prognostic cut-off level could be identified.

- A reduction to the 0.35-fold of the transcript level at diagnosis (0.46 log reduction) best cut-off for OS (HR of 6.4) for OS
  - High-risk group of 64 pts (18% of pts, 8-year PFS 77%, 8-year OS 80%)
  - Good-risk group of 286 pts (82% of pts, 8-year PFS 93%, 8-year OS 94%)

- At 3 months, a 6% cut-off discriminates:
  - High-risk group of 86 pts (25% of pts, 8-year PFS 79%, 8-year OS 83%)
  - Good-risk group of 264 pts (75% of pts, 8-year PFS 93%, 8-year OS 94%)

- The established 10% BCR-ABLIS landmark at 3 months
  - High-risk 88 pts (25% of pts, 8-year PFS 83%, 8-year OS 86%)
  - Good-risk 262 pts (75% of pts, 8-year PFS 92%, 8-year OS 93%)

Highlights from EHA
CML
Potential prognostic variables

- Clinical scores
  - Sokal
  - EURO/Hasford
  - EUTOS

- Biological scores
  - Intrinsic disease variables
  - Measures of disease progression
  - Differences in BCR-ABL inhibition

- Individual measurement of response
  - Cytogenetics: achievement of CCyR by 12 months
  - qRT-PCR: <10% $BCR-ABL^{IS}$ at 3 months
    - MR3.0 $BCR-ABL^{IS}$ at 18 months
  - $BCR-ABL$ mutation analysis

Highlights from EHA
EUTOS risk score

EUTOS score = \([7 \times \text{basophil (\%)}] + [4 \times \text{spleen size (cm)}]\)

Determine risk category and probability of complete cytogenetic response (CCgR) at 18 months:

<table>
<thead>
<tr>
<th>EUTOS SCORE</th>
<th>RISK CATEGORY</th>
<th>PROBABILITY OF CCGR AT 18 MONTHS</th>
<th>5 YEAR PFS</th>
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</thead>
<tbody>
<tr>
<td>(\leq 87)</td>
<td>Low</td>
<td>86%</td>
<td>90%</td>
</tr>
<tr>
<td>&gt; 87</td>
<td>High</td>
<td>66%</td>
<td>82%</td>
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Highlights from EHA
The BCR-ABL transcripts level at 3 mo. (10%) and 6 mo. (10% and 1%) may have a prognostic value greater than the Major Molecular Response.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Study/Reference</th>
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<tbody>
<tr>
<td>IMATINIB</td>
<td>GERMAN CML STUDY IV(1)</td>
</tr>
<tr>
<td></td>
<td>HAMMERSMITH(2)</td>
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<tr>
<td></td>
<td>DASISION(3)</td>
</tr>
<tr>
<td></td>
<td>ENESTnd(4)</td>
</tr>
<tr>
<td>DASATINIB</td>
<td>DASISION(3)</td>
</tr>
<tr>
<td>NILOTINIB</td>
<td>ENESTnd(4)</td>
</tr>
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</table>

3Saglio G et al., ASH 2012; Blood. 2012;120:[abstract 1675].
4Hochhaus A et al., Blood. 2012;120:[abstract 0167].
Outcome by landmark stratification at 3 mo.

<table>
<thead>
<tr>
<th>BCR/ABL @ 3 mo.</th>
<th>Nilo 300 BID</th>
<th></th>
<th>Ima 400 QD</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>MMR by 2yrs</td>
<td>MR\textsuperscript{4.5}</td>
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<td>≤1%</td>
<td>120</td>
<td>89%</td>
<td>50%</td>
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<td>&gt;1% - ≤10%</td>
<td>89</td>
<td>67%</td>
<td>18%</td>
<td>133</td>
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<tr>
<td>&gt;10%</td>
<td>24</td>
<td>29%</td>
<td>4%</td>
<td>88</td>
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<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PFS</th>
<th>OS</th>
<th>n</th>
<th>PFS</th>
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<tr>
<td>≤1%</td>
<td>145</td>
<td>96.5%</td>
<td>98.8%</td>
<td>43</td>
<td>98.5%</td>
<td>100%</td>
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<tr>
<td>&gt;1% - ≤10%</td>
<td>89</td>
<td>95.5%</td>
<td>96.9%</td>
<td>133</td>
<td>95.3%</td>
<td>95.3%</td>
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<tr>
<td>&gt;10%</td>
<td>24</td>
<td>82.9%</td>
<td>86.7%</td>
<td>88</td>
<td>83.8%</td>
<td>84.8%</td>
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Outcome by landmark stratification at 6 mo.

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<th>BCR/ABL @ 6 mo.</th>
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<td></td>
<td>n</td>
<td>PFS</td>
<td>OS</td>
<td>n</td>
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<tr>
<td>≤1%</td>
<td>212</td>
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<td>97.4%</td>
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<td>&gt;1% - ≤10%</td>
<td>37</td>
<td>91.3%</td>
<td>94.1%</td>
<td>87</td>
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<tr>
<td>&gt;10%</td>
<td>6</td>
<td>75%</td>
<td>75%</td>
<td>40</td>
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Chronic Myeloid Leukemia - Clinical

- **Low-titer Abl mutations**
  - ULTRA-DEEP SEQUENCING WITH COMPUTED THRESHOLDS FOR SENSITIVE MUTATION ANALYSIS IN THE KINASE DOMAIN OF BCR-ABL: FOCUSED ON DEEP MUTATION DETECTION IN CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE
    - A Brouckova et al

- **Blast Crisis prediction**
  - IKAROS DELETION AND LEVELS OF FULL-LENGTH TRANSCRIPT ARE CRITICAL FOR CML BLAST CRISIS TRANSFORMATION
    - L. Wang et al
Advantages of ultra-deep as against conventional sequencing for BCR-ABL KD mutation screening

- It allows higher sensitivity conjugated with the possibility to fully characterize the spectrum of minor mutated variants.

- It allows to quantitate mutations following their dynamics over time.

- When multiple mutations fall within the same sequence read, it can accurately resolve the clonal architecture of the mutated populations and how they evolved.
**IKZF1 loss 7p12**

- Zinc-finger transcription factor
- Transcriptional activator and repressor, chromatin remodeling
- Ikaros null mice lack all lymphoid lineages
- Mice heterozygous for a dominant negative Ikaros mutation develop aggressive lymphoproliferative disease
IKAROS deletions are frequent in adult B-ALL result in a unique gene expression pattern

**BCR-ABL-like ALL**
- 10-15% childhood ALL
- Gene expression profile similar to BCR-ABL1 ALL
- IKZF1 alteration
- Poor outcome
- CRLF2 rearrangement

- Mullighan et al. NEJM 2009
- Den Boer et al. Lancet Oncol 2009

**IKZF mutations in adult ALL**
- 28% of B-neg ALL cases
- 65% of BCR-ABL1+

Important emerging features of BCR-ABL-like ALL

- BCR-ABL-like ALL is common
  - Up to 15% of childhood ALL
  - Up to 25% of adult ALL
- Diverse range of alterations that converge on ABL1/JAK/PDGFRB signaling

Diagnosis
- phosphosigaling analysis / expression profiling
- Rapid RNA-seq

Targeted therapy:
- ABL1/PDGFRB – Dasatinib et al
- JAK2 alterations – JAK inhibitors (Ruxolitinib)
BCR-ABL+ve Stem Cells

- The CML epigenome shows dynamic changes in the CD34+ compartment in patients who achieve complete cytogenetic response on tyrosine kinase inhibitors
  
  A Bazeos et al

- The role of rho kinase in the survival of chronic myeloid leukaemia cells
  
  L Mukherjee et al

- Neoplastic stem cells of Ph+ chronic myeloid leukaemia (CML) express the alpha-chain of the IL-2 receptor (CD25)
  
  I Sadovnik et al

- CXCR4 antagonist BKT140 (BL-8040) cooperates with imatinib, effectively abrogating stroma-mediated protection and targeting CML cells in vitro and in vivo
  
  K Beider et al
TKIs hit proliferating Ph+ cells but seem to enhance CXCR4-mediated niche interaction of Ph+ stem cells.
Ph+ Stem cells in Chronic Myeloid Leukemia

Biomarkers of HSCT

* Phenotypic markers very similar (flow cytometry)
  - CD34+, Thy1/CD90+, CD133+, CD38-, CD45RA-, CD71-
  - CD34+CD38−CD123+CD33+
  - Lin−BCR-ABL+CD34−

* Molecular markers
  - BCR-ABL
  - Signaling pathways for self-renewal (Wnt/β-catenin)
  - Apoptosis regulators (proteins of bcl-2 family, inhibitor of apoptosis proteins)
  - ABC transporters (ABCB1↑, ABCG2↑, OCT-1↓)
  - Others (PTEN, TGF-β-FOXO)

Highlights from EHA
MPNs
Issues for discussion

Clinical
- Indications for Jak2 inhibitor treatment in IMF and PV
- Risk stratification for myelofibrosis treatment in the Jak2 inhibitor era
- Novel drugs for MPN treatment
- Prefibrotic IMF
- Allo SCT in IMF

Biological
- New targets
  - Epigenomics
- Resistance to Jak2 Inhibitors
- Determinants for treatment resistance
  - Clonal architecture
  - Resistance to IFN

Highlights from EHA
Ph-ve Myeloproliferative Neoplasias

Updating Clinical Trial with Jak-2 inhibitors

- LONG-TERM OUTCOMES FROM A PHASE 3 STUDY COMPARING RUXOLITINIB WITH BEST AVAILABLE THERAPY (BAT) FOR THE TREATMENT OF MYELOFIBROSIS (MF): A 3-YEAR UPDATE OF COMFORT-II
  
  *A Vannucchi et al*

- UPDATED RESULTS FROM A RANDOMIZED PHASE 2 DOSE-RANGING STUDY OF THE JAK2-SELECTIVE INHIBITOR SAR302503 IN PATIENTS WITH INTERMEDIATE-2 OR HIGH-RISK MYELOFIBROSIS (MF)
  
  *M Talpaz et al*
### The Jak Inhibitors in clinical trials

<table>
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<tr>
<th>Compound</th>
<th>Company</th>
<th>Status</th>
<th>Target / MoA</th>
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<tbody>
<tr>
<td><strong>JAK inhibitors – Autoimmune / Inflammation</strong></td>
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<td></td>
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<tr>
<td>Xeljanz (tofacitinib)</td>
<td>Pfizer</td>
<td>Mktd</td>
<td>JAK1/3 inhibitor</td>
</tr>
<tr>
<td>Baricitinib (INCB28050)</td>
<td>Incyte / Eli Lilly</td>
<td>PhII</td>
<td>JAK1/2 inhibitor</td>
</tr>
<tr>
<td>VX-509</td>
<td>Vertex</td>
<td>PhII</td>
<td>JAK 3 inhibitor</td>
</tr>
<tr>
<td>GLPG0634</td>
<td>Galapagos / Abbott</td>
<td>PhII</td>
<td>JAK1 inhibitor</td>
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<td>JAK inhibitor</td>
</tr>
<tr>
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<td>JAK 1 inhibitor</td>
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<td>Dynamix Pharma (pvt.)</td>
<td>PC</td>
<td>Selective JAK3 inhibitor</td>
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<td>UR-67767</td>
<td>Palau Pharma (Pvt.)</td>
<td>PC</td>
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<td><strong>Hematologic Malignancies</strong></td>
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<td>JAKAFI / JAKAVI (ruxolitinib)</td>
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<td>Pacritinib (SB1518)</td>
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</tr>
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</table>
Association of Jak proteins to cytokine receptors of hematopoietic cells

Highlights from EHA
LONG-TERM OUTCOMES FROM COMFORT-II
A Vannucchi et al

COMFORT I

Patients with MF (N = 309) Randomized 1:1
Ruxolitinib 15 mg BID or 20 mg BID
Placebo BID

Primary Endpoint
- Number of subjects achieving ≥35% reduction in spleen volume from baseline to week 24

Secondary Endpoint
- Proportion of patients with ≥50% reduction in Total Symptom Score (mod. MFSAF v2.0 electronic diary)

COMFORT II

Patients with MF (N = 219) Randomized 2:1
Ruxolitinib 15 mg BID or 20 mg BID
Best available therapy (BAT)

Primary Endpoint
- Number of subjects achieving ≥35% reduction in spleen volume from baseline to week 48

Secondary/Exploratory endpoints
- Changes in functioning and symptoms

Ruxolitinib MTD: 25 mg twice daily or 100 mg once daily with thrombocytopenia as DLT

Highlights from EHA
**LONG-TERM OUTCOMES FROM COMFORT-II**
A Vannucchi et al

**Results:**

- Median follow-up, 151 wk
  - Ruxolitinib arm: 45.2% of pts on treatment.
  - BAT arm: 100% of pts discontinued treatment

- Primary reasons for study discontinuation were AEs (16.4%) and disease progression (15.1%) in the ruxolitinib arm and withdrawal of consent and other (12.3% each) with BAT.
Reductions in spleen volumes were sustained with continued ruxolitinib therapy (median duration not yet reached)

Overall, 51 patients died: 29 (19.9%) in ruxolitinib arm and 22 (30.1%) in BAT arm with a 52% reduction in risk of death in the ruxolitinib arm compared with BAT (HR=0.48; 95% CI, 0.28-0.85; log-rank P=.009)

The estimated probability of being alive at 144 wk was 81% in ruxolitinib arm and 61% in BAT arm.
UPDATED RESULTS FROM THE JAK2-SELECTIVE INHIBITOR SAR302503
*M Talpaz et al*

**Study design**

- **Randomization**
  - Intermediate-2 or high-risk primary MF (IWG-MRT criteria)
  - Post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis according to the 2008 World Health Organization (WHO) criteria

- **Treatment groups**
  - SAR302503 300 mg orally once daily
  - SAR302503 400 mg orally once daily
  - SAR302503 500 mg orally once daily

**Patients who continued to benefit clinically could remain on study until the occurrence of disease progression or unacceptable toxicity.**

1 cycle = 28 days

**Primary endpoint:** % change in spleen volume at EOC 3 by central review assessed by MRI.

**Secondary endpoints:**
- % of patients who achieve ≥35% reduction in spleen volume from baseline.
- To measure improvement in baseline myeloproliferative neoplasm (MPN) associated symptoms.
- Safety (NCI CTCAE v4.03), PK/PD.

EOC, end of cycle; MF, myelofibrosis; MPN-SAF, myeloproliferative neoplasm symptom assessment form; MRI, magnetic resonance imaging; PK/PD, pharmacokinetics/pharmacodynamics.
UPDATED RESULTS FROM THE JAK2-SELECTIVE INHIBITOR SAR302503
M Talpaz et al

Results

- N = 31 patients (300 mg n=10; 400 mg n=10; 500 mg n=11). Risk status was balanced in all but the 300 mg group (70% high risk).
  - JAK2 V617F positive (90%)
  - Blood transfusion independent (81%).
- The median number of cycles was 13 (range 2–17) and 24 patients have been on treatment for >12 months.
- Spleen response rates @ 6 cycles (secondary endpoint)
  - 30% (3/10) in the 300 mg group,
  - 60% (6/10) with 400 mg,
  - 55% (6/11) with 500 mg
- Constitutional symptoms reduction at EOC 3 in all dose groups,
  - Night sweats in 14/15 patients (93%), itching 10/14 (71%), early satiety 10/18 (56%), and abdominal pain 10/18 (56%)
- Adverse reactions: Anemia and diarrhea, (grade 3/4 rates of 58% and 13%, respectively)
  - Thrombocytopenia grade 3/4 =16%.
- Median JAK2 V617F allele burden was 93% at baseline, 87% at EOC 3, and 78% at EOC 6 in 19/26 patients with all available samples.
Ph-ve Myeloproliferative Neoplasias

Updating Clinical Trial with other drugs

- LONG-TERM OUTCOMES IN 62 PATIENTS TREATED WITH PEGYLATED INTERFERON ALPHA2A: EXPERIENCE OF THE FIM.
  
  *J-C Ianotto et al*

- IMETELSTAT: A NOVEL APPROACH WITH ROBUST HEMATOLOGIC AND MOLECULAR RESPONSES IN A PHASE 2 STUDY IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMA (ET) WHO ARE REFRACTORY OR INTOLERANT TO PRIOR THERAPY
  
  *G Baerlocher et al*
Activities of IFNs in MPNs

- Inhibit MK proliferation and TPO-induced MPL signaling
  
  Wang et al. Blood 2000

- Inhibit EEC and endogenous MK colony growth
  

- Induce cytogenetic remission
  

- Reversion from monoclonal to polyclonal patterns of hematopoiesis
  
  Liu et al. Blood 2003
LONG-TERM OUTCOMES IN 62 PATIENTS TREATED WITH PEGYLATED INTERFERON ALPHALPHA2A: EXPERIENCE OF THE FIM J-C Ianotto et al

- 62 patients treated with Peg-Interferon-α2a from December 2006 to April 2011 (33 to 81 years)
- The median duration of the study was 34.5 months for the global population and 26.5 months for patients still on therapy. 37 patients stopped the drug due to evolution of myelofibrosis (43%), cytopenia (16%) or psychiatric side effects (16%).
- Twenty-nine IMF, 19 post-PV and 14 post-ET MF. (JAK2V617F positive = 40).
- Spleen reduction in 46% (with 50% of complete response: CR),
- Constitutional symptoms disappeared in 82%, anaemia was reduced in 64% (91% of CR), platelets abnormalities were reduced in 78% (90% of CR).
- Twenty patients died during the study, almost from GVHd (5), evolution of myelofibrosis (4) or acute leukaemia (4)
- Among the 25 patients still under Peg-Ifn α2a, no CR (no bone marrow biopsy), 40% of PR, 30% of CI and 15% of SD.
MF - Potential ways to improve results

Ruxolitinib combination studies in Myelofibrosis

- Clinicaltrials.gov

<table>
<thead>
<tr>
<th>1. Lenalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Panobinostat</td>
</tr>
<tr>
<td>3. Pomalidomide</td>
</tr>
<tr>
<td>4. Danazol</td>
</tr>
<tr>
<td>5. Interferon</td>
</tr>
</tbody>
</table>

Is combination therapy in our future?

1. Will future treatment for Myelofibrosis more resemble Multiple myeloma (drug cocktail) and less Chronic myeloid leukemia (targeted monotherapy)?

2. Concern for overlapping toxicities with combination treatment
Ph-ve Myeloproliferative Neoplasias Biology

- SYNERGISTIC EFFECT OF RUXOLITINIB AND PANOBINOSTAT TO OVERCOME DRUG RESISTANCE RELATED TO BM STROMA MICROENVIRONMENT IN PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS
  
  B De Angelis et al

- A GENOMEWIDE ASSOCIATION STUDY IDENTIFIES NOVEL LOCI THAT PREDISPOSE TO MYELOPROLIFERATIVE NEOPLASMS
  
  Amy Jones et al

- IDENTIFICATION OF A NOVEL MODE OF KINASE INHIBITOR RESISTANCE IN JAK2: JAK2 INHIBITOR RESISTANCE IS MEDIATED BY THE GENERATION OF 45-KDA JAK2 VARIANT WHICH ALTERS THE KINASE DOMAIN STRUCTURE
  
  S Prasad Gorantla et al

- THE MUTATIONAL LANDSCAPE AND CLONAL ARCHITECTURE OF MPN PATIENTS DETERMINED BY TARGETED NEXT GENERATION SEQUENCING
  
  P Lundberg et al
In Vitro Model Of Stroma Mediated Drugs Activity Modulation

HEL SET2 MPNs patients

Ph− cells

Ruxolitinib Panobinostat

Apoptosis Vitality Proliferation

HEL SET2 MPNs patients

Ph− cells

Ruxolitinib Panobinostat

Apoptosis Vitality Proliferation

HS5/SCM

HS5/SCM = HS5 Stroma Conditioned Media containing BM stroma soluble factors

Highlights from EHA
Sinergic Effect Of Panobinostat and Ruxolitinib to Induce Apoptosis in JAK2 V617F+ SET2 Cells

[Graphs showing the effect of Ruxolitinib (Ruxo) and Panobinostat (Pan) on SET2 cells (RM) and SET2 Cells (HS5/SCM).]

Highlights from EHA

✓ Co-treatment of panobinostat and ruxolitinib strongly synergizes, increasing SET2, regardless HS5/SCM exposition.
Questions for the groups

- Treatment end-points of CML
- Indications for Jak-2 inhibitor treatment in MF
- Transplant in MF