2011 post-ASH meeting
Myeloproliferative neoplasms

L. Knoops
Post ASH: Myeloproliferative neoplasms

CML

Treatment strategies in chronic phase

Treatment of advanced disease

BCR-ABL negative MPNs

Management of PV

Management of myelofibrosis
Post ASH: Myeloproliferative neoplasms

CML

Treatment strategies in chronic phase

Treatment of advanced disease

BCR-ABL negative MPNs

Management of PV

Management of myelofibrosis
CML: treatment strategies in chronic phase

Imatinib
Estimated overall survival at 8 years was 85% (93%, considering only CML related deaths)
<table>
<thead>
<tr>
<th>Year</th>
<th>With Event, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td>4</td>
<td>4.8</td>
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<td>5</td>
<td>1.8</td>
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<tr>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>7</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>0.3</td>
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<tr>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>1.4</td>
</tr>
<tr>
<td>14</td>
<td>1.3</td>
</tr>
<tr>
<td>15</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Event**
- Loss of CHR,
- Loss of MCyR,
- AP/BC,
- Death during treatment

**AP/BC**

IRIS – 8 Year Update – imatinib arm
CML: treatment strategies in chronic phase

Imatinib

Dasatinib, Nilotinib, Others?
ENESTnd – 3 years follow-up

- N = 846
- 217 centers
- 35 countries

Stratification by Sokal risk score

- Nilotinib 400 mg BID (n = 282)
- Nilotinib 400 mg BID (n = 281)
- Imatinib 400 mg QD (n = 283)

Follow-up 5 years

*Saglio G, abstract 452
ENESTnd – cumulative incidence of MMR

% With MMR

- Nilotinib 300 mg BID: 282
- Nilotinib 400 mg BID: 281
- Imatinib 400 mg QD: 283

- By 3 Years
  - Nilotinib 300 mg BID: 73%, P < .0001
  - Nilotinib 400 mg BID: 70%, P < .0001
  - Imatinib 400 mg QD: 53%

Δ 17%-20%
ENESTnd – Progression to AP/BC: Including Events After Discontinuation (ITT Analysis)

- **Nilotinib 300 mg BID:** 9 patients, 3.2% progression to AP/BC
  - Hazard Ratio (HR): 0.5 [0.2, 1.0], \( P = 0.0496 \)
- **Nilotinib 400 mg BID:** 6 patients, 2.1% progression to AP/BC
  - Hazard Ratio (HR): 0.3 [0.1, 0.8], \( P = 0.0076 \)
- **Imatinib 400 mg QD:** 19 patients, 6.7% progression to AP/BC

Saglio G, abstract 452
DASISION – Transformation to AP/BP CML
2 years Follow-up - ASCO

Kantarjian H, ASCO 2011, Abstract 6510

Including follow-up beyond discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg QD</th>
<th>Imatinib 400 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/259</td>
<td>2.3%</td>
<td>5.0%</td>
</tr>
<tr>
<td>13/260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/259</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>15/260</td>
<td></td>
<td>5.8%</td>
</tr>
</tbody>
</table>

Kantarjian H, ASCO 2011, Abstract 6510
BELA - 2 years Follow-up

- **Bosutinib (n=248)**
  - Treatment Failure: 4%
  - Transformation to AP / BP: 2%
  - Diarrhea: 70%

- **Imatinib (n=251)**
  - Treatment Failure: 13%
  - Transformation to AP / BP: 5%
  - Diarrhea: 25%
SPIRIT trial – PegIFN 45 µg / week

Patients (%)

MMR 12 month

- Imatinib + PegIFN 90: 54%
- Imatinib + PegIFN 45: 60%
- Imatinib: 38%

grade 3 / 4 Hematological toxicity

- Imatinib + PegIFN 90: 54%
- Imatinib + PegIFN 45: 27%
- Imatinib: 15%*

* Data from NEJM, 2010
CML: treatment strategies in chronic phase

Imatinib

Dasatinib, Nilotinib, Others?

Fewer progression

Better molecular response

Long term side effects?
CML: treatment strategies in chronic phase

Imatinib

Dasatinib, Nilotinib, Others?

Imatinib

Dasatinib, Nilotinib, Others?
CML: treatment strategies in chronic phase

Diagnosis

- Imatinib
- Dasatinib, Nilotinib, Others?
- Imatinib
  - Dasatinib, Nilotinib, Others?
CML: Molecular response at 3 month is predictive for survival

Dasatinib first line, UK Spirit 2 trial, Marin, Abstract 785

Imatinib and dasatinib first line, DASISION trial, Hochhaus, Abstract 2767

Milojkovic, n = 282, Abstract 1680
CML: treatment strategies in chronic phase

- Imatinib
- Dasatinib, Nilotinib, Others?
CML: treatment strategies in chronic phase

Imatinib

Dasatinib, Nilotinib, Others?

Imatinib

Dasatinib, Nilotinib, Others?
ENESTcmr: major eligibility criteria

- Ph+ CML-CP previously treated with imatinib for ≥ 2 years
- CCyR or blood BCR-ABL<sub>IS</sub> < 1%
- Persistent disease as demonstrated by 2 positive BCR-ABL transcript levels by RQ-PCR performed in the last 9 months
ENESTcmar: study design

N = 207
1:1 randomization stratified by:
• Prior imatinib (≤ 36 mos, > 36 mos) AND
• Prior interferon (None, ≤ 12 mos, > 12 mos)

Nilotinib 400 mg BID

Imatinib continue same dose
4-year study
ENESTcmr: Cumulative incidence of MR\textsuperscript{4.5}

Hazard ratio (95%CI) = 2.3 (1.2, 4.2)

% with MR\textsuperscript{4.5}

Months Since Randomization

Nilotinib n = 94
Imatinib n = 91

P = .008

33.0%
16.5%

12 month follow-up

Hughes T J, Abstract 606
CML: treatment strategies in chronic phase

1. Imatinib
2. Dasatinib, Nilotinib, Others?
3. Imatinib, Dasatinib, Nilotinib, Others?
4. Dasatinib, Nilotinib, Others?
STIM trial: Update on the first 100 patients

- Stop imatinib if CMR for more than 2 years
- Median Follow-up of 2.8 years

<table>
<thead>
<tr>
<th>Molecular relapse</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relapse before 7 m</th>
<th>Late relapse</th>
<th>Some patients had fluctuation in their BCR-ABL level</th>
</tr>
</thead>
</table>
| 58                 | 3 (19, 20, 22 m) | Prognostic factor:  
|                    |              | - Low Sokal score  
|                    |              | - Imatinib duration > 5 years |

All patients responded to rechallenge
CML: treatment strategies in chronic phase

- Imatinib
- Dasatinib, Nilotinib, Others?
- Imatinib, Dasatinib, Nilotinib, Others?
- Dasatinib, Nilotinib, Others?
- Imatinib

DIAGNOSIS
ENESTnd: Cumulative incidence of MR^{4.5}

% With MR^{4.5}

Months Since Randomization

Imatinib 400 mg QD

15%
ENESTnd: Cumulative incidence of MR^{4.5}

By 3 Years
32%, P < .0001
28%, P = .0003
15%

Nilotinib 300 mg BID
Nilotinib 400 mg BID
Imatinib 400 mg QD

Saglio G, abstract 452
ENESTcmr: Cumulative incidence of MR^{4.5}

Hazard ratio (95%CI) = 2.3 (1.2, 4.2)

12 month follow-up

Hughes T J, Abstract 606
Nilotinib or Dasatinib discontinuation

- Nilotinib or Dasatinib (second line n = 31, first line n = 2)
- Stop -inib if CMR for more than 2 years
- N = 33; Median FU of 9 month, Minimal FU 6 month

<table>
<thead>
<tr>
<th>Molecular relapse</th>
<th>Remission</th>
</tr>
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<tbody>
<tr>
<td>8 (24 %)</td>
<td>25 (76 %)</td>
</tr>
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<tr>
<th>Relapse before 6 m</th>
<th>Late relapse</th>
<th>11/15 patients had detectable BCR-ABL below MMR</th>
</tr>
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<tbody>
<tr>
<td>8</td>
<td>0</td>
<td></td>
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</tbody>
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All patients responded to rechallenge
CML: treatment strategies in chronic phase

- Imatinib
- Dasatinib, Nilotinib, Others?
- Imatinib, Dasatinib, Nilotinib, Others?
- Dasatinib, Nilotinib, Others?
- Imatinib
CML

Treatment strategies in chronic phase

Treatment of advanced disease

BCR-ABL negative MPNs

Management of PV

Management of myelofibrosis
PACE trial initial results: Ponatinib

Median FU ≈ 5 month

<table>
<thead>
<tr>
<th></th>
<th>CP-CML</th>
<th>AP-CML</th>
<th>BP-CML Ph+-ALL</th>
</tr>
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<tbody>
<tr>
<td>R/I to dasatinib or nilotinib</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T315I mutation</td>
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PACE trial initial results: Ponatinib

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<tr>
<td>Primary endpoint</td>
<td>MCyR</td>
<td>MaHR</td>
<td>MaHR</td>
</tr>
<tr>
<td>R/I to dasatinib</td>
<td>R/I to dasatinib or nilotinib</td>
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Cortes J, Abstract 109
**PACE trial initial results : Ponatinib**

Median FU ≈ 5 month

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</tr>
<tr>
<td>R/I to</td>
<td>79/191 (41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dasatinib or nilotinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T315I mutation</td>
<td>37/57 (65%)</td>
<td></td>
<td></td>
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<td></td>
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PACE trial initial results: Ponatinib

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</tr>
<tr>
<td>R/I to dasatinib or nilotinib</td>
<td>79/191 (41%)</td>
<td>31/42 (74%)</td>
<td></td>
</tr>
<tr>
<td>T315I mutation</td>
<td>37/57 (65 %)</td>
<td>6/13 (46 %)</td>
<td></td>
</tr>
</tbody>
</table>

Cortes J, Abstract 109
Pareto analysis of taste preferences

<table>
<thead>
<tr>
<th>Category</th>
<th>Tasty</th>
<th>Sour</th>
<th>Sweet</th>
<th>Salty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result 1</td>
<td>80%</td>
<td>10%</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Result 2</td>
<td>75%</td>
<td>15%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Result 3</td>
<td>90%</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Result 4</td>
<td>95%</td>
<td>0%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Cortes J, Abstract 109
# PACE trial initial results: Ponatinib

Median FU ≈ 5 month

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<td>R/I to dasatinib or nilotinib</td>
<td>79/191 (41%)</td>
<td>31/42 (74%)</td>
<td>17/46 (37%)</td>
</tr>
<tr>
<td>T315I mutation</td>
<td>37/57 (65%)</td>
<td>6/13 (46%)</td>
<td>16/43 (37%)</td>
</tr>
</tbody>
</table>

Side effects > 10 %
- thrombocytopenia
- rash
- dry skin
- myalgia
- abdominal pain
- arthralgia

Cortes J, Abstract 109
Post ASH : Myeloproliferative neoplasms

CML

Treatment strategies in chronic phase

Treatment of advanced disease

BCR-ABL negative MPNs

Management of PV

Management of myelofibrosis
Survival and Prognosis Among 1,263 Patients with Polycythemia Vera: An International Study
Survival and Prognosis Among 1,263 Patients with Polycythemia Vera: An International Study

- Older age, Leukocytosis, venous thrombosis and abnormal karyotype = BAD
Survival and Prognosis Among 1,263 Patients with Polycythemia Vera: An International Study

- Older age, Leukocytosis, venous thrombosis and abnormal karyotype = BAD

- Pruritus or thrombocytosis = GOOD
Survival and Prognosis Among 1,263 Patients with Polycythemia Vera: An International Study

- Older age, Leukocytosis, venous thrombosis and abnormal karyotype = BAD

- Pruritus or thrombocytosis = GOOD

- IPSS-PV = age $\geq 70$, age 60-69, WBC $\geq 15,000$ and venous thrombosis
Survival and Prognosis Among 1,263 Patients with Polycythemia Vera: An International Study

- Older age, Leukocytosis, venous thrombosis and abnormal karyotype = BAD

- Pruritus or thrombocytosis = GOOD

- IPSS-PV = age ≥ 70, age 60-69, WBC ≥ 15 000 and venous thrombosis

- 15 year AML risk ≈ 6%
Survival and Prognosis Among 1,263 Patients with Polycythemia Vera: An International Study

- Older age, Leukocytosis, venous thrombosis and abnormal karyotype = BAD

- Pruritus or thrombocytosis = GOOD

- IPSS-PV = age ≥ 70, age 60-69, WBC ≥ 15,000 and venous thrombosis

- 15 year AML risk ≈ 6%

- Post-PV AML is associated with P32/chlorambucil/pipobroman but not Hydroxyurea or Busulfan
PVN1 trial follow-up – phase 2 peg-IFNα-2a

- n = 37, median FU 6.2 years
- 11 (30%) treated
- 26 (70%) stopped
  - 14 (38%) Sustained CR
  - 10 (27%) Toxicity
  - 2 (5%) Other
  - 10 (27%) Still in CR
    - Median FU 2.5 years
PVN1 trial follow-up – phase 2 peg-IFNα-2a

n = 37, median FU 6.2 years

<table>
<thead>
<tr>
<th>Hematological Response</th>
<th>CR</th>
<th>PR</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29 (78%)</td>
<td>4 (11%)</td>
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PVN1 trial follow-up – phase 2 peg-IFNα-2a

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<td>4 (11%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Molecular response</th>
<th>Median JAK2 V617F before</th>
<th>Median JAK2 V617F at 6 years</th>
<th>JAK2 V617F negative at 6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43 %</td>
<td>5 %</td>
<td>8 / 29 (28 %)</td>
</tr>
</tbody>
</table>
Post ASH: Myeloproliferative neoplasms

CML
- Treatment strategies in chronic phase
- Treatment of advanced disease

BCR-ABL negative MPNs

Management of ET – PV

Management of myelofibrosis
PMF or PPV-MF, or PET-MF
Intermediate-2 or High Risk by IWG-MRT
Palpable spleen $\geq 5$ cm
Platelet count $\geq 100 \times 10^9/L$
JAK2 V617F positive or negative

COMFORT-I Study design

Vertovsek S, Abstract 278
Patients with PMF, PPV-MF, or PET-MF with ≥ 2 IWG risk factors

N = 219

Randomize

2:1

Ruxolitinib (INC424)
15 or 20 mg oral bid
n = 146

Best available therapy (BAT)
n = 73

Patients with PMF, PPV-MF, or PET-MF with ≥ 2 IWG risk factors

Patients with progressive disease eligible for crossover

Ruxolitinib Crossover and Extension Phase

Patients with progressive disease eligible for extension phase

Harrison C, Abstract 279
COMFORT-II: Percent change from baseline in spleen volume

At Week 48

Ruxolitinib

$P < .0001$

Primary endpoint

Harrison C, Abstract 279
COMFORT-II: Spleen response across subgroups

Proportion of patients with ≥ 35% reduction in spleen volume at week 48

Harrison C, Abstract 279
COMFORT-II : Change in quality of life scores

EORTC QLQ-C30
Global Health Status/QoL

FACT-LymS

Adjusted Mean Change From Baseline
Week
Ruxolitinib, n = 116
BAT, n = 49
115
102
69
120
120
105
70
Ruxolitinib, n = 115
BAT, n = 43
102
69
120
120
105
70
Ruxolitinib, n = 102
BAT, n = 39
69
27
102
39
69
27

Harrison C, Abstract 795
COMFORT-I: Survival data

HR = 0.50 (0.25–0.98)

$P = .04$

Vertovsek S, Abstract 278
<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Specificity</th>
<th>Abstracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAR302503</td>
<td>Slight decrease in JAK2 V617F allele burden</td>
<td>Pardanani A abstract 3838</td>
</tr>
<tr>
<td>TG101348</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacritinib</td>
<td>Minimal myelosuppression</td>
<td>Komrokji R abstract 282</td>
</tr>
<tr>
<td>SB1518</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYT387</td>
<td>Anemia response</td>
<td>Pardadani A abstract 3849</td>
</tr>
<tr>
<td>Many others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ENESTnd – MMR by 3 years according to Sokal risk

% With MMR

- **Low**
  - Nilotinib 300 mg BID: 77%
  - Imatinib 400 mg QD: 63%
  - $P = .0264$

- **Intermediate**
  - Nilotinib 300 mg BID: 75%
  - Imatinib 400 mg QD: 54%
  - $P = .0020$

- **High**
  - Nilotinib 300 mg BID: 67%
  - Imatinib 400 mg QD: 39%
  - $P = .0004$

Saglio G, abstract 452
ENESTnd – 3-year Safety Update

• Minimal change in myelosuppression since the 2-year analysis
• Minimal change in biochemical abnormalities since the 2-year analysis
  – < 1% increase in lipase or bilirubin elevations, or hyperglycemia in both nilotinib arms
  – No new cases of pancreatitis or hepatic events
  – No patient discontinued due to hyperglycemia
• No QTcF > 500 msec or LVEF < 45% reported in any treatment arm during the study
DCC-2036 : Phase I trial

- ‘Switch pocket’ Tyrosine kinase inhibitor – Non-ATP competitive

- Active against the T315I mutation

- Well tolerated

- Significant activity in advanced CML patients
## Patient Disposition

<table>
<thead>
<tr>
<th>Patients</th>
<th>Ruxolitinib (n = 146)</th>
<th>BAT (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing in randomized treatment phase</td>
<td>91 (62)</td>
<td>31 (42)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>26 (18)</td>
<td>24 (33)</td>
</tr>
<tr>
<td>Discontinued for adverse event(s)</td>
<td>12 (8)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

- 32 patients reported an AEs or SAEs after ruxolitinib treatment discontinuation
- 19 of these 32 patients reported AEs ≤ 2 weeks following discontinuation
  - 6 patients had ≥ 1 symptoms referable to MF including general physical health deterioration (1), pyrexia (2), anorexia (2), fatigue (1), weight decreased (2), night sweats (1) and pruritus (1)
- 3 events were reported as CTCAE grade 3: general physical health deterioration, pyrexia, and fatigue
- Among the remaining patients, there was no pattern of event type or severity