10 YEARS’ EXPERIENCE OF TYROSINE KINASE INHIBITOR THERAPY FOR CML IN OXFORD

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²Department of Haematology, Imperial College Healthcare NHS Trust, London, United Kingdom
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
TKIs in the UK

- **Imatinib**: Development, License, NICE approved
- **Dasatinib**: Development, NICE approved
- **Nilotinib**: Development, NICE approved
- **Bosutinib**: Development, NICE approved
- **Ponatinib**: Development, NICE approved

Timeline:
- 2000
- 2005
- 2010
- 2015

Off patent 2016

Courtesy of SPIRIT2 collaborators
Rationale

• Establish a database for our local cohort
  – Investigate effect of TKI introduction on OS
Rationale

• Establish a database for our local cohort
  – Investigate effect of TKI introduction on OS

• Impending loss of patent for Gleevec/Glivec- cost implications
## Cost: Annual price of TKIs

<table>
<thead>
<tr>
<th>Country</th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>92</td>
<td>115.5</td>
<td>123.5</td>
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<tr>
<td>Germany*</td>
<td>54</td>
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<tr>
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</table>

Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood 2013;121:4439–42
Generic Imatinib is on the horizon

<table>
<thead>
<tr>
<th>Online Pharmacy</th>
<th>Quantity</th>
<th>Price Per Pill or Unit</th>
<th>Total Price</th>
<th>PharmacyChecker Approved?</th>
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<tr>
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<td>Online Pharmacy</td>
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Rationale

• Establish a database for our local cohort
  – Investigate effect of TKI introduction on OS
  – Compare real life data to trial outcomes for TKIs

• Impending loss of patent for Gleevec/Glivec- cost implications

• Pressure to introduce 2\textsuperscript{nd} generation TKIs early
### Response definitions for any TKI first line, and 2nd line in case of intolerance, all patients (CP, AP, and BC)

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal response</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>High risk Major route CCA/Ph+</td>
<td></td>
</tr>
<tr>
<td>3 mos.</td>
<td>BCR-ABL&lt;sub&gt;IS&lt;/sub&gt; ≤10%* Ph+ ≤35% (PCyR)</td>
<td>BCR-ABL&lt;sub&gt;IS&lt;/sub&gt; &gt;10%* Ph+ 36-95%</td>
<td>No CHR* Ph+ &gt;95%</td>
</tr>
<tr>
<td>6 mos.</td>
<td>BCR-ABL&lt;sub&gt;IS&lt;/sub&gt; &lt;1%* Ph+ 0% (CCyR)</td>
<td>BCR-ABL&lt;sub&gt;IS&lt;/sub&gt; 1-10%* Ph+ 1-35%</td>
<td>BCR-ABL&lt;sub&gt;IS&lt;/sub&gt; &gt;10%* Ph+ &gt;35%</td>
</tr>
<tr>
<td>12 mos.</td>
<td>BCR-ABL&lt;sub&gt;IS&lt;/sub&gt; ≤0.1%* (MMR)</td>
<td>BCR-ABL&lt;sub&gt;IS&lt;/sub&gt; 0.1-1%* Ph+ &gt;0%</td>
<td>BCR-ABL&lt;sub&gt;IS&lt;/sub&gt; &gt;1%* Ph+ &gt;0%</td>
</tr>
<tr>
<td>Then, and at any time</td>
<td>MMR or better</td>
<td>CCA/Ph- (-7, or 7q-)</td>
<td>Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+</td>
</tr>
</tbody>
</table>

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

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<table>
<thead>
<tr>
<th>Line</th>
<th>Event</th>
<th>TKI, standard dosage</th>
<th>Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Imatinib 400 mg/qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nilotinib 300 mg/bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dasatinib 100 mg/qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bosutinib 500 mg/qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ponatinib 45 mg/qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Search for</td>
<td>alloSCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLAs type + sibs</td>
<td>unrelated donor</td>
</tr>
</tbody>
</table>

### Chronic phase

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>Baseline</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X²</th>
</tr>
</thead>
<tbody>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Intolerance to 1&lt;sup&gt;st&lt;/sup&gt; TKI</td>
<td>Any other TKI approved 1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure 1&lt;sup&gt;st&lt;/sup&gt; line of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>imatinib</td>
<td>X³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>nilotinib</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>dasatinib</td>
<td>X³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>Intolerance to/failure of two TKI</td>
<td>Any remaining TKI</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Any</td>
<td>T315I mutation</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

### Accelerated or blast phase

<table>
<thead>
<tr>
<th>In newly diagnosed, TKI naïve patients</th>
<th>start with</th>
<th>X³</th>
<th>X⁴</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X⁷</th>
<th>X⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>no optimal response, BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TKI pre-treated patients</td>
<td>Any other TKI</td>
<td>X⁶</td>
<td></td>
<td></td>
<td></td>
<td>X⁷</td>
<td>X⁵</td>
<td></td>
</tr>
</tbody>
</table>

¹ choice of the TKI consider tolerability and safety, and patient characteristics (age, comorbidities).² only in case of baseline warnings (high risk, major route CCA/Ph+).³ 400 mg/bid.⁴ 70 mg/bid or 140 mg/qd.⁵ may be required before SCT to control disease and to make patients eligible to alloSCT.⁶ in case of T315I mutation.⁷ only patients who are eligible for alloSCT, not in case of uncontrolled, resistant BP.⁸ 400 mg bid in failure setting.

qd: Once daily; bid: Twice daily
Updated NCCN guidelines

NCCN Guidelines Version 1.2015
Chronic Myelogenous Leukemia

3-MONTH FOLLOW-UP THERAPY

- Continue same dose of imatinib or nilotinib or dasatinib
- Monitor with QPCR every 3 mo

Clinical trial
or Change therapy to alternate TKI (other than imatinib) or nilotinib or dasatinib

Primary treatment with nilotinib or dasatinib

Evaluate patient compliance and drug-drug interactions
Mutational analysis

Primary treatment with imatinib

Evaluate for HSCT depending on response to TKI therapy

Clinical trial
or Continue same dose of nilotinib or dasatinib

3-month evaluation

- BCR-ABL1 transcripts ≤10% by QPCR (IS) or partial cytogenetic response (PCyR) on bone marrow cytogenetics
- BCR-ABL1 transcripts >10% by QPCR (IS) or lack of PCyR on bone marrow cytogenetics

See CML-3

See 6-Month Evaluation (CML-3)

See 6-Month Evaluation (CML-3)

See CML-7

See CML-7

See CML-8
Emphasis on Early Molecular response (EMR)

- The persistence of BCR-ABL transcript levels >10% at 3 months separated
  - a high-risk group (28% of pts; 5-year OS: 87%)
  - >1–10% BCR-ABLIS (41% of pts; 5-year OS: 94%; P=0.012)
  - < 1% BCR-ABLIS (31% of pts; 5-year OS: 97%; P = 0.004)
Table 1. Five-year overall survival of patients grouped according to molecular response at 3 and 6 months, P-values comparing neighboring groups, hazard ratios comparing with the best or better response group

<table>
<thead>
<tr>
<th>BCR-ABL iso</th>
<th>At 3 months (n = 692)</th>
<th></th>
<th>At 6 months (n = 789)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts (%) 5Y-OS</td>
<td>P-value (log-rank)</td>
<td>Hazard ratio (CI)</td>
<td>Pts (%) 5Y-OS</td>
</tr>
<tr>
<td>≤ 1%</td>
<td>218 (31%)</td>
<td>97.2%</td>
<td>n.s.</td>
<td>498 (63%)</td>
</tr>
<tr>
<td>&gt; 1%–10%</td>
<td>283 (41%)</td>
<td>93.9%</td>
<td>1.5 (0.6–4.0)</td>
<td>196 (25%)</td>
</tr>
<tr>
<td>&gt; 10%</td>
<td>191 (28%)</td>
<td>87.0%</td>
<td>0.012</td>
<td>95 (12%)</td>
</tr>
</tbody>
</table>

| ≤ 1%        | 218 (31%) | 97.2% | 0.049 | 498 (63%) | 96.9% | <0.001 |
| > 1%        | 474 (69%) | 91.0% | 2.3 (1.0–5.6) | 291 (37%) | 89.0% | 3.5 (1.8–6.9) |

| ≤ 10%       | 501 (72%) | 95.2% | <0.001 | 694 (88%) | 94.6% | 0.007 |
| > 10%       | 191 (28%) | 87.0% | 2.7 (1.5–5.1) | 95 (12%) | 87.9% | 2.5 (1.3–5.1) |

Abbreviations: BCR-ABL iso, BCR-ABL transcript ratio according to the international scale; CI, 95% confidence interval; pts, number of patients; 5Y-OS, 5-year overall survival.

- Treatment optimization recommended for patients missing this landmark
Early predictor of outcome

• Transcript levels of more than 9.84% at 3 months had significantly lower 8-year probabilities of OS (56.9% v 93.3%; P = .001), PFS, CCCR, CMR

• A single measurement of BCR-ABL1 transcripts performed at 3 months is the best way to identify patients destined to fare poorly, thereby allowing early clinical intervention
Rationale

• Establish a database for our local cohort
  – Investigate effect of TKI introduction on OS

• Impending loss of patent for Gleevec/Glivec-
  cost implications

• Pressure to introduce 2\textsuperscript{nd} generation TKIs
  early

• Debate regarding superiority of 2\textsuperscript{nd}
  generation TKIs and potential discontinuation
  of therapy
ENESTnd

At 12 months:

- **CCyR**: 80% - 78% vs. 65% (P<0.001)
- **MMR**: 44%-43% vs. 22% (P<0.001)

Kantarjian et al. Blood. 2012;120:1676
• 12 months
  • CCyR (83% vs. 72%, P=0.001)
  • MMR (46% vs. 28%, P<0.0001)
• Responses were achieved in a shorter time (P<0.0001).

### Cytogenetics at 12 months

<table>
<thead>
<tr>
<th></th>
<th>Imatinib (%)</th>
<th>Dasatinib (%)</th>
<th>Difference (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cytogenic response (MCR)</td>
<td>209/406 (51.5)</td>
<td>228/406 (56.2)</td>
<td>(4.7)</td>
<td>0.181*</td>
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<tr>
<td>Complete cytogenic response (CCR)</td>
<td>169/406 (41.6)</td>
<td>217/406 (53.4)</td>
<td>(11.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Missing analyses</td>
<td>181/406 (44.6)</td>
<td>166/406 (40.9)</td>
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</table>

*caution required, missing analyses included in denominator

### 12 month PCR

#### Total Cohort n=812

- **Imatinib** n=406
  - On treatment: 320/406 (78.8%)
  - Off treatment: 80/406 (19.7%)
  - Unknown: 6/406 (1.5%)

- **Dasatinib** n=406
  - On treatment: 344/406 (84.7%)
  - Off treatment: 59/406 (14.5%)
  - Unknown: 3/406 (0.7%)

#### Achieved MR3 Response

- (Imatinib): 175/406 (43.1%)
- (Dasatinib): 237/406 (58.4%)

#### Achieved MR4.5 Response

- (Imatinib): 24/406 (5.9%)
- (Dasatinib): 54/406 (13.3%)

\[ \Delta = 15.3\% \quad p<0.001 \]
\[ \Delta = 7.4\% \quad P=0.001 \]
Partial PCR responses

<table>
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<th>Dasatinib</th>
<th>Totals</th>
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<tbody>
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<td>319</td>
<td>636</td>
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<tr>
<td>PCR &gt; 10% (MR1) at 3 months</td>
<td>66</td>
<td>20</td>
<td>86</td>
</tr>
<tr>
<td>PCR &lt; 10% (MR1) at 3 months</td>
<td>251</td>
<td>299</td>
<td>550</td>
</tr>
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</table>

<table>
<thead>
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<th>Dasatinib</th>
<th>Totals</th>
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<tbody>
<tr>
<td>12 month PCR samples available</td>
<td>210</td>
<td>267</td>
<td>477</td>
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<tr>
<td>PCR &gt; 1% (MR2) at 12 months</td>
<td>20</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>PCR &lt; 1% (MR2) at 12 months</td>
<td>190</td>
<td>257</td>
<td>447</td>
</tr>
</tbody>
</table>

Total with 'less than ideal' progress: 86/317 **27.1%** | 30/319 **9.4%** | 116/636 **18.2%**

Median 3 year follow up: no difference in OS or PFS
Rationale

• Establish a database for our local cohort
  – Investigate effect of TKI introduction on OS

• Impending loss of patent for Gleevec/Glivec- cost implications

• Pressure to introduce 2\textsuperscript{nd} generation TKIs early

• Debate regarding superiority of 2\textsuperscript{nd} generation TKIs and potential discontinuation of therapy
  – Faster response
  – Deeper response
  – Sustained response
## Outcomes of patients with CP CML on Imatinib

<table>
<thead>
<tr>
<th>Study/Source</th>
<th>Imatinib dose, mg</th>
<th>No. of patients</th>
<th>High-risk patients (Sokal/Euro)</th>
<th>OS</th>
<th>PFS</th>
<th>EFS</th>
<th>AT</th>
<th>Follow-up, y</th>
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<tr>
<td>IRIS\textsuperscript{18,19}</td>
<td>400</td>
<td>553</td>
<td>18% (S)</td>
<td>85%</td>
<td>92%</td>
<td>NR</td>
<td>8 y</td>
<td>6 (minimum)</td>
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<tr>
<td>Hammersmith\textsuperscript{21}\textsuperscript{22}</td>
<td>400</td>
<td>204</td>
<td>29% (S)</td>
<td>83%</td>
<td>83%</td>
<td>63%</td>
<td>5 y</td>
<td>3.2 (median)</td>
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<tr>
<td>Houston\textsuperscript{25}</td>
<td>400 (19%) / 800 (81%)</td>
<td>258</td>
<td>8% (S)</td>
<td>97%</td>
<td>92%</td>
<td>NR</td>
<td>5 y</td>
<td>4.4 (median)</td>
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<td>PETHEMA\textsuperscript{27}</td>
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<td>210</td>
<td>16% (S)</td>
<td>97%</td>
<td>94%</td>
<td>71%</td>
<td>5 y</td>
<td>4.2 (median)</td>
</tr>
<tr>
<td>Czech registry\textsuperscript{30}</td>
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<td>22% (S)</td>
<td>88%</td>
<td>90%</td>
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<td>5 y</td>
<td>3.8 (median)</td>
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<td>French SPIRIT\textsuperscript{28}</td>
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<td>319</td>
<td>24% (S)</td>
<td>NR</td>
<td>92%</td>
<td>NR</td>
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<td>NR</td>
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<tr>
<td>GIMEMA\textsuperscript{29}</td>
<td>400 (76%) / 800 (24%)</td>
<td>559</td>
<td>22% (S)</td>
<td>90%</td>
<td>87%</td>
<td>65%</td>
<td>5 y</td>
<td>5.0 (median)</td>
</tr>
<tr>
<td>German CML STUDY IV\textsuperscript{31}</td>
<td>-</td>
<td>1551</td>
<td>12% (E)</td>
<td>88%</td>
<td>88%</td>
<td>NR</td>
<td>6 y</td>
<td>5.8 (median)</td>
</tr>
<tr>
<td>Seoul, St. Mary Hospital\textsuperscript{32}</td>
<td>400 (83%) / 6-800 (17%)</td>
<td>363</td>
<td>22% (S)</td>
<td>94%</td>
<td>98%</td>
<td>NR</td>
<td>7 y</td>
<td>5.3 (median)</td>
</tr>
</tbody>
</table>

EFS, event-free survival, where events are death, progression to AP or BP, failure, and treatment discontinuation for any reason, whichever comes first; med, median; min, minimum; NR, not reported; OS, overall survival; PFS, survival free from progression to AP or BP.

\textsuperscript{*} Imatinib 400 + IFNα (28%), imatinib 800 (27%), imatinib 400 (26%), imatinib 400 + low-dose arabinosyl cytosine (10%), imatinib 400 after IFNα (8%).
What Happened To The Patients After 7 Years?

All randomized to imatinib (n= 553; 100%)

Still receiving study imatinib (n = 332; 60%)
  - In CCR (n = 317; 57%)
  - No CCR (n = 15; 3%)

Discontinued study imatinib* (n = 221; 40%)
  - Safety (n = 43; 8%)
  - Efficacy (n = 82; 15%)
  - Other (n = 96; 17%)
   - Alive (n = 17; 40%)
   - Dead** (n = 26; 60%)
   - Alive (n = 52; 63%)
   - Dead (n = 30; 37%)
   - Alive (n = 81; 84%)
   - Dead (n = 15; 16%)

*Patients may have continued imatinib off study.

**Including primary discontinuation reason 'Death' (n=13)

IRIS 7-Year Update: Conclusions

- Overall Survival 86%
- Event Free Survival 81%; 7% progressed to AP/BC on imatinib
- 40% patients discontinued *study* imatinib
- CCR achieved by 456 of 553 (82%) of patients
  - 17% of those achieving CCR subsequently lost CCR
  - 3% of those achieving CCR progressed to AP/BC
    - Of 456 patients who achieved CCR, 10 (2%) died from CML
    - Time taken to achieve CCR did not correlate with rates of progression to AP/BC
- MMR rates and the depth of molecular responses in patients increase over time
- No new safety issues observed
- Imatinib 400 mg daily confirmed as the standard of care for the initial therapy of chronic-phase CML

SPIRIT-3: answer to these questions?
Rationale

- Establish a database for our local cohort
  - Investigate effect of TKI introduction on OS
  - Compare real life data to trial outcomes for TKIs

- Impending loss of patent for Gleevec/Glivec - cost implications

- Pressure to introduce 2\textsuperscript{nd} generation TKIs early
  - ELN guidelines

- Debate regarding superiority of 2\textsuperscript{nd} generation TKIs and potential discontinuation of therapy

- Compare real life data to trial outcomes for TKIs
Concern that trial data may not reflect real-world outcomes

A population study of imatinib in chronic myeloid leukaemia demonstrates lower efficacy than in clinical trials

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients receiving imatinib from initial diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>12 months</td>
</tr>
<tr>
<td>Number of cases assessable</td>
<td>88</td>
<td>83 (11/20)</td>
</tr>
<tr>
<td>Low</td>
<td>20</td>
<td>55%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>29</td>
<td>24%</td>
</tr>
<tr>
<td>High</td>
<td>28</td>
<td>48%</td>
</tr>
<tr>
<td>No data</td>
<td>11</td>
<td>27%</td>
</tr>
<tr>
<td>Overall CCre</td>
<td>88</td>
<td>40%</td>
</tr>
</tbody>
</table>
Method

Pre-TKI cohort

Newly diagnosed patients 1990-1995

Dates of diagnosis
Confirmation of diagnosis
Dates of death confirmed

As for most UK laboratories, molecular results from our laboratory are not routinely normalised to the international scale (IS)

Post TKI cohort

Newly diagnosed patients 2000-2014

Dates of diagnosis
Confirmation of diagnosis
Dates of death confirmed

Cytogenetic and molecular response benchmarked against ELN guidelines

RQ-PCR <10% at 3 months predictive of CCyR, OS and PFS: data recorded
Results

Patients with CML (n=102)

Pre-TKI cohort (n=26)

Post-TKI cohort (n=76)

Upfront allogeneic transplant (n=10)

Complete molecular remission (n=6)

Upfront TKI (n=66)

TKI post-relapse (n=4)
Baseline Data and Prognostic Scores

Median age
Pre TKI cohort: 52 years (18-86)
Post TKI cohort: 50 years (24-81)

<table>
<thead>
<tr>
<th>Phase of disease at presentation n, (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>65 (98)</td>
</tr>
<tr>
<td>Accelerated</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Blastic</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sokal score, n</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>24</td>
</tr>
<tr>
<td>Intermediate</td>
<td>16</td>
</tr>
<tr>
<td>High</td>
<td>12</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
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</table>

<table>
<thead>
<tr>
<th>Haematological parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WCC x 10^9/L, median (range)</td>
<td>104, (4.1-520)</td>
</tr>
<tr>
<td>Spleen cm below costal margin, median (range)</td>
<td>0, (0-25)</td>
</tr>
<tr>
<td>Platelet count x10^9/L, median (range)</td>
<td>418, (43-2950)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional cytogenetic abnormalities at diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Major route abnormalities (n)</td>
<td>1</td>
</tr>
<tr>
<td>Other variant translocations (n)</td>
<td>3</td>
</tr>
</tbody>
</table>
Patients with CML (n=102)

- Pre-TKI cohort (n=26)
  - Post-TKI cohort (n=76)
    - Upfront TKI (n=66)
      - Upfront allogeneic transplant (n=10)
        - Complete molecular remission (n=6)
        - TKI post-relapse (n=4)
      - Nilotinib (n=6)
      - Dasatinib (n=3)
      - Ponatinib (n=1)
      - Imatinib (n=56)
    - Failure (n=0)
    - Intolerant (n=1)
  - Failure (n=18)
    - Intolerant (n=3)
    - Failure (n=0)
  - Failure (n=0)
    - Intolerant (n=1)
    - Intolerant (n=1)
    - Intolerant (n=1)
    - Failure (n=0)
    - Failure (n=0)
    - Failure (n=0)
  - Failure (n=0)
    - Imatinib (n=1)
    - Dasatinib (n=2)
    - Pontatinib (n=1)
    - Bosutinib (n=1)

- Second line TKI
  - Dasatinib (n=16)
  - Ponatinib (n=1)
  - Bosutinib (n=1)
  - Imatinib (n=1)
  - Nilotinib (n=1)
  - Dasatinib (n=2)
  - Bosutinib (n=1)
  - Ponatinib (n=1)

- Third line TKI
  - Imatinib (n=1)
First line TKI

Imatinib (n=56)
  - Intolerant (n=3)
  - Failure (n=18)

Nilotinib (n=6)
  - Intolerant (n=1)
  - Failure (n=0)

Dasatinib (n=3)
  - Intolerant (n=1)
  - Failure (n=0)

Ponatinib (n=1)
  - Intolerant (n=1)
  - Failure (n=0)

Second line TKI

Dasatinib (n=2)

Nilotinib (n=1)

Dasatinib (n=16)

Ponatinib (n=1)

Bosutinib (n=1)

Failure (n=0)

Third line TKI

Imatinib (n=1)

Bosutinib (n=1)
Overall survival stratified according to TKI cohort
Results-survival

- Dramatic improvement in survival after approval of Imatinib in the UK

- 8 year survival
  - 15% pre-TKI
  - 91% post-TKI

- Median survival
  - 2.3 years (pre-TKI)
  - 'unreached' (post-TKI) (P<0.0001)

- Median follow-up of 4.6 years (post TKI cohort)
  - 4 deaths occurred in the post-TKI cohort- none of which directly related to CML

- 25/26 patients from the pre-TKI cohort have died
  - 1/26 had an allograft and subsequently received TKI therapy upon relapse
Comparable published data

![Graph showing cumulative relative survival over time since diagnosis for different intervals: 1973-1979 (dotted blue), 1980-1986 (dashed red), 1987-1993 (solid gray), 1994-2000 (dashed yellow), and 2001-2008 (solid black). The x-axis represents time since diagnosis in years, and the y-axis represents cumulative relative survival.](image-url)
Benchmarking against ELN guidelines
Outcome of patients according to ELN group

**OPTIMAL RESPONSE (n=18)**
- TKI change: intolerance (n=2)
  - MMR3 (n=16)
  - CMR (n=10)

**WARNING (n=17)**
- TKI change: intolerance (n=1)
- TKI change: inadequate response (n=1)
  - CCyR (n=12)
  - No Accelerated or blast phase
  - MMR3 (n=11)
  - CMR (n=1)

**FAILURE (n=22)**
- TKI change: intolerance (n=2)
- TKI change: inadequate response (n=12)
  - CCyR (n=7)
  - Accelerated or blast phase (n=3)
  - MMR3 (n=2)
  - CMR (n=0)

- 3 patients developed kinase domain mutations
- 5 proceeded to allogeneic transplant (Non-relapse mortality: n=1, CMR: n=4)

CMR: Complete Molecular Response
CCyR: Complete Cytogenetic Response
MMR3: Major Molecular Response
Achievement of CCyR on first TKI
Summary of cytogenetic response rate at or by 12 months in patients treated with imatinib 400mg od/bd

<table>
<thead>
<tr>
<th>STUDY / SOURCE</th>
<th>Imatinib dose, mg</th>
<th>N° of pts</th>
<th>High risk pts (Sokal, Euro)</th>
<th>after 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS15,16</td>
<td>400</td>
<td>553</td>
<td>18% (S)</td>
<td>CCyR 68%</td>
</tr>
<tr>
<td>HAMMERSMITH21</td>
<td>400</td>
<td>224</td>
<td>30% (S)</td>
<td>MMR 18%</td>
</tr>
<tr>
<td>TOPS26</td>
<td>400</td>
<td>157</td>
<td>27% (S)</td>
<td></td>
</tr>
<tr>
<td>FRENCH SPIRIT28</td>
<td>400</td>
<td>159</td>
<td>24% (S)</td>
<td></td>
</tr>
<tr>
<td>ENESTnd25</td>
<td>400</td>
<td>283</td>
<td>28% (S)</td>
<td></td>
</tr>
<tr>
<td>NORTH AMERICA/CANADA33</td>
<td>400</td>
<td>123</td>
<td>28% (S)</td>
<td></td>
</tr>
<tr>
<td>DASISION38</td>
<td>400</td>
<td>260</td>
<td>19% (E)</td>
<td></td>
</tr>
<tr>
<td>BELA34</td>
<td>400</td>
<td>252</td>
<td>18% (S)</td>
<td></td>
</tr>
<tr>
<td>GIMEMA29</td>
<td>400</td>
<td>559</td>
<td>22% (S)</td>
<td></td>
</tr>
<tr>
<td>SEOUL, St. Mary Hospital32</td>
<td>400</td>
<td>363</td>
<td>22% (S)</td>
<td></td>
</tr>
<tr>
<td>GERMAN CML STUDY IV31</td>
<td>400</td>
<td>325</td>
<td>12% (E)</td>
<td></td>
</tr>
<tr>
<td>HOUSTON25</td>
<td>800</td>
<td>258</td>
<td>8% (S)</td>
<td></td>
</tr>
<tr>
<td>TIDEL23</td>
<td>800</td>
<td>103</td>
<td>33% (S)</td>
<td></td>
</tr>
<tr>
<td>TOPS26</td>
<td>800</td>
<td>319</td>
<td>23% (S)</td>
<td></td>
</tr>
<tr>
<td>GERMAN CML STUDY IV31</td>
<td>800</td>
<td>338</td>
<td>14% (E)</td>
<td></td>
</tr>
</tbody>
</table>

* 600-800 mg in 23% of patients

$ 6-800 mg in 17% of patients

# 400 mg in 19% of patients

NR = Not Reported
Subgroups of interest

- **Progressive disease**
  - Accelerated phase (AP) n=2. 1 had allogeneic transplant, 1 continued on first line TKI and in CCyR
  - Blast crisis (BC) n=1: had allogeneic transplant

- **Allogeneic transplants**
  - 5 patients had allogeneic bone marrow transplant after TKI treatment
  - 5/5 met criteria for TKI failure by 6 months post TKI initiation.
  - Non-relapse mortality occurred in 1 patient (severe hepatic graft-versus-host disease)
  - 4 are alive and in CMR
  - Post-transplant TKI therapy was used in 1 patient

- **Pregnancies**
  - 2 patients successfully conceived - no adverse outcomes for mother or baby

- **Clinical trial involvement**
  - 16/66 patients involved in TKI trials

- ** Deaths**
  - 1: allogeneic transplant-related graft-versus-host disease
  - 1: respiratory failure and anasarca whilst receiving Dasatinib therapy
  - 2: unrelated malignancies
Map of all the amino acid substitutions in the Bcr-Abl KD identified in clinical samples from patients reported to be resistant to imatinib in published papers.

Soverini S et al. Blood 2011;118:1208-1215
Conclusions

• First-line TKI therapy has dramatically improved OS in CML

• > 85% of patients treated with first-line Imatinib eventually achieved CCyR
• 38% required switch to second-generation TKI

• ELN defined ‘warning’ at 3 months (and later time-points) predicted an increased risk of subsequent treatment failure
  – many of patients meeting ‘warning’ criteria achieved CCyR and MMR3 with no progression events, including patients who did not switch therapy
  – In line with ELN guidance, this supports close monitoring of this patient group but not routine change of therapy

• Large majority of CML patients treated with first line Imatinib have a favourable outcome
  – more work is required to identify those patients who are destined to fail first-line Imatinib treatment and might therefore benefit from upfront second-generation TKIs

• We are currently extending this analysis across the Thames Valley region, encompassing over 200 patients with CML