Current Monitoring for CML: Goals and Principles

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Department of Leukemia
MD Anderson Cancer Center
Survival in Early Chronic Phase CML

- **93%**
- **84%**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censored for non-CML death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>302</td>
<td>15</td>
</tr>
<tr>
<td>1990-2000</td>
<td>963</td>
<td>425</td>
</tr>
<tr>
<td>1982-1989</td>
<td>364</td>
<td>273</td>
</tr>
<tr>
<td>1975-1981</td>
<td>132</td>
<td>129</td>
</tr>
<tr>
<td>1965-1974</td>
<td>123</td>
<td>123</td>
</tr>
</tbody>
</table>
The Philadelphia Chromosome

Chromosome 22

Chromosome 9

BCR

ABL

m-bcr

M-bcr

μ-bcr

e1

e1', e2', b1, b5

e19

5'

3'

5'

3'

e1a2

b2a2

b3a2

e19a2

p190^{bcr-abl}

p210^{bcr-abl}

p230^{bcr-abl}
## The Significance of Philadelphia Chromosome and BCR-ABL in CML

<table>
<thead>
<tr>
<th>Significance</th>
<th>Implication</th>
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<tbody>
<tr>
<td>Pathophysiology</td>
<td>Disease</td>
</tr>
<tr>
<td>Specificity</td>
<td>Monitoring</td>
</tr>
<tr>
<td>Oncogene addiction</td>
<td>Treatment</td>
</tr>
</tbody>
</table>
Evaluating Response in CML

- Number of leukemic cells

- 10^12
- 10^10
- 10^8
- 10^6
- 10^4
- 10^2
- 1

- Hematologic response
- Cytogenetic response
- Molecular response (Q-PCR)

- CHR
- MCR
- CCR (CG)
- CCR (FISH)

- 3 log reduction
- 4 log reduction
- Limits of detection

- 10
- 12
- 8
- 10
- 6
- 2
- 4

- CML
- CML
Evaluating Response in CML

10^12

CHR
Hydroxyurea

10^10

MCR

Interferon

10^8

CCR (CG)

Imatinib

10^6

CCR (FISH)

3 log reduction

10^4

Limits of detection

Response is surrogate marker for long term outcome

r2b
JC2

Number of leukemic cells
Suggested to change imatinib to TKIs by one reviewer. (However, log reduction was defined by imatinib.) Please comment.
rbloechlinger, 2/28/2011

This is a historical perspective and these levels were established with imatinib so I prefer to keep as is.
jecortes, 2/28/2011
## Definitions of Cytogenetic Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| **CHR**   | WBC <10 x 10⁹/L  
Platelets <450 x 10⁹/L  
PB myelo + metaphyelo <5%  
No PB blasts + promyelo  
PB basophils <20%  |
|           | No extramedullary involvement |
| **Cytogenetic*** | % Ph+ Metaphases  
Complete: 0  
Partial: 1-35  
Minor: 36-95 |

*Based on standard karyotype, 20 metaphases (not FISH)
Molecular Response in CML

• Real time PCR = BCR-ABL/control x 100

• Major molecular response (MMR)
  – BCR-ABL/control <0.1% (IS)
  – 3 log reduction (from standardized baseline)
  – Using reduction from individual baseline not validated

• Complete molecular response (CMR) = PCR negative, sensitivity 4- to 5-log
  – CMR⁴, CMR⁴.⁵, CMR⁵
  – BCR-ABL/control ≤0.0032% (IS)
  – Undetectable
IRIS Study in Chronic Phase CML

- 553 pts randomized to imatinib 400 mg/D; 8-yr follow up
- Annual transformation rate to AP/BP (yrs 4-8): 0.9%, 0.5%, 0%, 0%, 0.4%
- Only 15 pts in CCyR (3%) progressed to AP/BP
- No pts in MMR at 12 mos progressed to AP/BP

<table>
<thead>
<tr>
<th>Outcome at 8 yrs</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>On study</td>
<td>55</td>
</tr>
<tr>
<td>CCyR</td>
<td>83</td>
</tr>
<tr>
<td>MMR</td>
<td>86</td>
</tr>
<tr>
<td>EFS</td>
<td>81</td>
</tr>
<tr>
<td>PFS</td>
<td>92</td>
</tr>
<tr>
<td>OS (CML deaths only)</td>
<td>85 (93)</td>
</tr>
</tbody>
</table>

Deininger et al; Blood 2009; 114: Abst# 1126
Monitoring Procedures in CML

- **CG**: looks at all chromosomes; **but**: tedious; needs metaphases; only 20 cells counted (95% CI CCyR 15%); painful BM

- **FISH**: faster; 200 cells; PB; **but**: false (+) up to 5-10%; no information on other chromosomes

- **PCR**: most sensitive; PB; evaluable in CCyR; predicts for relapse; **but**: not standardized; no information on other chromosomes; variability up to 0.5 log; use 1 source (PB) and 1 reliable lab
IFNα in CML
Survival by CG Response

Kantarjian et al. Cancer 2003; 97: 1033
Peripheral Blood FISH: Excellent Correlation With Bone Marrow FISH

## Correlation Between iFISH and Cytogenetics in CML

<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage FISH +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1%</td>
</tr>
<tr>
<td>CCyR</td>
<td>83</td>
</tr>
<tr>
<td>PCyR</td>
<td>9</td>
</tr>
<tr>
<td>CCyR &amp; MMR</td>
<td>92</td>
</tr>
</tbody>
</table>

Testoni et al, Blood 2009; 114: 4939-43; Testoni et al, ASH 2006, abst #4779
Can PCR Replace Cytogenetic Analysis?

Ross DM et al. Leukemia 2006; 20: 664-70
CG Abnormalities in Ph(-) Cells

• 41 of 261 pts (16%) treated with imatinib
  – +8 (n=8); -5/-7 (n=11); 20q- (n=4); other (n=18)
• Transient in 29/41 (71%)
• 36/41 remain in CG response
  – Major 31, Minor 5
  – 1/41 developed AP CML
• 3 developed MDS⇒AML (-7 in 2, 5q- in 1)
  – 20/41 (49%) G≥3 myelosuppression

CG Abnormalities in Ph-negative Metaphases with IM Frontline Therapy

- 21/258 (9%) patients developed CG abnormalities in Ph-negative metaphases after median 36 mo.
- Most common abnormalities: -Y (n=9; 43%), +8 (n=9; 43%), -7 (n=5; 17%).
- 1 (5%; 0.4% overall) developed AML [-7].

Overall Survival

Progression-Free Survival

Detection of Del Der (9) using the Vysis ES Probe
Prognostic Significance of Deletion of der(9) in CML Patients Treated with Imatinib

- Huntly et al\(^1\) (n=397)
  - Deletion der(9) in 59 (15%)
  - Inferior response rate to imatinib
  - More rapid disease progression
  - Trend for inferior survival

- Quintas-Cardama et al\(^2\) (n=352)
  - Deletion der(9) in 33 (9%)
  - No impact on response, remission duration or survival by MVA

- Castagnetti et al\(^3\) (n=521)
  - Deletion der(9) in 60 (12%)
  - 12 month CCyR rates were 82%/85% and MMR 69%/65%, respectively (with/without del der(9))

\(^3\)Castagnetti et al. JCO 2010; 28; 2748-54
Spectral Karyotyping (SKY)
Evaluation of Molecular Response in CML

- Quantitative-RT-PCR (Q-RT-PCR) detects *bcr-abl* transcripts
IRIS – 5-yr EFS by Molecular Response With Imatinib at 12 Months

% without progression

Estimated rate at 60 months

97%  89%  72%

Event = AP-BP on IM; death any cause on IM; loss of CHR or MCyR; or ↑ WBC.

Baccarani et al. ASH 2006, abs 2138.
Please add definition of EFS to slides

rbloechlinger, 2/28/2011
IRIS – 7-yr EFS by Molecular Response With Imatinib at 12 Months

% Without Event

92%
91%
64%
53%

P = .25

BCR-ABL % (IS) (n=301)

≤ 0.1% (n = 153)
>0.1-1% (n = 90)
>1-10% (n = 36)
>10% (n = 22)

≅≅ ≅≅ ≅≅ ≅≅

CCyR

Months Since Start of Treatment

Event = AP-BP on IM; death any cause on IM; loss of CHR or MCyR; or ↑ WBC.

IRIS - EFS by Molecular Response With Imatinib at 18 Months

Event = AP-BP on IM; death any cause on IM; loss of CHR or MCyR; or ↑ WBC.

Add definition of EFS. Original definition of IRIS does not include loss of CCyR.

Loss of CCyR is now considered an important event, while it was not included in the original definition of EFS. When loss of CCyR is included, MMR becomes important and significant.
## 7-Year Outcome by Molecular Response – All Patients

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Percentage</th>
<th>MMR</th>
<th>No MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EFS</td>
<td>85</td>
</tr>
<tr>
<td>6 mo</td>
<td>TFS</td>
<td>96</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>90</td>
<td>89</td>
</tr>
<tr>
<td>12 mo</td>
<td>EFS</td>
<td>91</td>
<td>79</td>
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<tr>
<td></td>
<td>TFS</td>
<td>99</td>
<td>90</td>
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<tr>
<td></td>
<td>OS</td>
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<td>89</td>
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<tr>
<td>18 mo</td>
<td>EFS</td>
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<td></td>
<td>TFS</td>
<td>99</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>95</td>
<td>90</td>
</tr>
</tbody>
</table>

### 7-Year Outcome by Molecular Response – Only Patients with CCyR

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Percentage</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MMR</td>
<td>No MMR</td>
</tr>
<tr>
<td>EFS</td>
<td>85</td>
<td>93</td>
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<tr>
<td>6 mo</td>
<td></td>
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<tr>
<td>TFS</td>
<td>96</td>
<td>98</td>
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<td>OS</td>
<td>90</td>
<td>93</td>
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<tr>
<td>EFS</td>
<td>91</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TFS</td>
<td>99</td>
<td>96</td>
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<tr>
<td>EFS</td>
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<td>86</td>
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<tr>
<td>18 mo</td>
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<tr>
<td>TFS</td>
<td>99</td>
<td>96</td>
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</tr>
<tr>
<td>OS</td>
<td>95</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

Time to Loss of CCyR by Molecular Response at 18-Months

Significance of CMR in CML After Imatinib Therapy

CMR = complete molecular response.
MMR = major molecular response

Significance of Sustained CMR in CML

- 261 pts treated with frontline imatinib
- Sustained CMR in 32% [undetectable (sensitivity ≥4.5-log) in ≥ 2 consecutive assays over ≥6 mo]
- Median time to sustained CMR 30 mo (6-84 mo)

Event-Free Survival

Transformation-Free Survival

Verma et al. Blood 2009; 114; Abst# 505
Imatinib Treatment Discontinuations
The French Experience

- 69 pts treated with imatinib for ≥3 yrs with CMR (≥5-log ↓) sustained for ≥2 yrs
  - 34 prior IFN, 35 no prior IFN
- Median follow-up 21 mo (11-29 mo)
  - 41 (59%) pts relapsed; all within 7 mo
  - 53% prior IFN, 66% no prior IFN
- Probability of CMR 12 mo after stop: 47% post IFN, 34% no prior IFN
- Peripheral NK cells significantly lower in relapse pts at imatinib discontinuation
- All patients responded after imatinib re-start

Mahon et al. Blood 2009; 114: Abst# 859
Patterns of Transcript Levels After Imatinib

- **Plateau** = $\log_{10}$ of most recent BCR–ABL/ABL ratio was no more than 0.25 'lower' than the $\log_{10}$ of the mean BCR–ABL/ABL ratios measured after 18 months from the start of imatinib.

“We conclude that a rise in BCR-ABL of more than 2-fold can be used as a primary indicator to test patients for BCR-ABL kinase domain mutations.”

Loss of CG CR by ↑ in Transcript Levels

Log increase by lowest transcript level

<table>
<thead>
<tr>
<th>Log increase</th>
<th>MMR</th>
<th>No MMR</th>
<th>MMR</th>
<th>No MMR</th>
<th>MMR</th>
<th>No MMR</th>
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<tbody>
<tr>
<td>&lt;1-log</td>
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<td></td>
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<td></td>
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<tr>
<td>1-2-log</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2log</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>Best Mol Resp</th>
<th>No. lost CG CR (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>MMR</td>
<td>1 (3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>24</td>
<td>No MMR</td>
<td>9 (38)</td>
<td></td>
</tr>
</tbody>
</table>

Half-log Increase in Transcript Levels Predicts relapse in CML

Receiver Operating Characteristic Analysis To Define The Optimal qPCR Trigger

Significance of Rising MRD in CGCR on Imatinib

• 116 pts in durable CGCR on imatinib ≥18 mos had ↑ QPCR ≥0.5 log
• 11/116 (9%) had CML progression
• 10/44 (23%) progression if: loss of MMR or not in MMR and ↑ QPCR ↑ > 1 log

<table>
<thead>
<tr>
<th>Status</th>
<th>↑QPCR</th>
<th>No.</th>
<th>CML progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>Any</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Loss of MMR</td>
<td>0.5-1</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Not in MMR</td>
<td>&lt;1</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

Kantarjian et al. JCO 2009; 27: 3642-9
### Criteria for Failure and Suboptimal Response to Imatinib

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Failure</th>
<th>Suboptimal Response</th>
<th>Optimal</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>Lack or loss of MMR represents suboptimal response; lack of CMR is neither</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Lack or loss of molecular response is not a criterion for failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baccarani et al. JCO 2009; 27: 6041-51
rb10  Suggest to indicate MMR is part of the ELN Optimal Response Criteria  
rbloechlinger, 2/28/2011

JC4  That is not my side of the argument for this debate.  
jecortes, 2/28/2011
What is Not Failure to Therapy in CML

- FISH 1-10%
- No MMR at 12 months
- PCR still positive
- Increasing transcript levels
- Chromosomal abnormalities in Ph-negative metaphases
The Simple Interpretation of Molecular Results

• If it is going down, it is good
• If it is stable, it is OK
• If it is going up, monitor more frequently

– Not a failure by itself

– First, optimize therapy; then:
  – Consider low-risk strategies (e.g., vaccines)
  – Dasatinib, nilotinib?

Reproducibility of CCyR and MMR Across CML Frontline Trial

Median (range)
CCyR: 67 (59-74)
MMR: 27 (15-39)

Mean (95% CI)
CCyR: 67 (63-71)
MMR: 28 (21-35)

Adapted from Baccarani et al. Blood 2010; abst #668
BCR-ABL | Shift to Conversion

3 exchanges of patient samples May 05, April 06, Aug 06

Ref Lab - BCR CF 1.25
Lab 5 - ABL CF 0.239

Ref Lab median 0.78%
Lab 5 median 3.10%
P<0.0001

Important Considerations Regarding Molecular Monitoring in CML

- Maintain same source
- Maintain same lab
  - IS to minimize this problem
- Consider variability of test
- Uniform reporting
- Needs: standardization, speed, access
## So What Do We Get?

<table>
<thead>
<tr>
<th>Response</th>
<th>Translates into:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCyR</td>
<td>Significantly improved survival</td>
</tr>
<tr>
<td>MMR</td>
<td>Improvement in EFS, possible longer duration CCyR</td>
</tr>
<tr>
<td>CMR</td>
<td>Possibility of considering treatment discontinuation (clinical trials only)</td>
</tr>
</tbody>
</table>

Molecular Response is a Measure of Success, Not a Measure of Failure
Mechanisms of Resistance to Imatinib

• Bcr-Abl-Dependent
  – Amplification/overexpression
  – Mutations in Abl
  – Remigration of Bcr-Abl to cytoplasm

• Bcr-Abl-Independent
  – Increased MDR expression
  – Increased alpha-1 acid glycoprotein
  – Overexpression of Src-related kinases

• Quiescent stem cells (Persistence)

Incidence of BCR-ABL Mutations after Imatinib Failure

p = P-loop, b = imatinib binding, c = catalytic domain, a = activation loop

Apperley J. Lancet Oncology 2007; 8: 1018-29
# Methods for Detecting Mutations

<table>
<thead>
<tr>
<th>Technology</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Bias*</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequencing</td>
<td>10-15%</td>
<td>+++</td>
<td>No</td>
<td>+++</td>
</tr>
<tr>
<td>Subcloning and sequencing</td>
<td>5%</td>
<td>+++</td>
<td>No</td>
<td>++</td>
</tr>
<tr>
<td>Denaturing high performance liquid chromatography (D-HPLC)</td>
<td>0.1-10%</td>
<td>++</td>
<td>No</td>
<td>++</td>
</tr>
<tr>
<td>Pyrosequencing</td>
<td>5%</td>
<td>++</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Double-gradient–denaturing-gradient gel electrophoresis (DG-DGGE)</td>
<td>5%</td>
<td>++</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Fluorescent PCR and PNA clamping</td>
<td>0.2%</td>
<td>++</td>
<td>Yes</td>
<td>+</td>
</tr>
<tr>
<td>Allele specific oligonucleotide (ASO)-PCR</td>
<td>0.01%</td>
<td>++</td>
<td>Yes</td>
<td>+</td>
</tr>
</tbody>
</table>
## Sensitivity of Mutations to TKI

### Ba/F3 cell proliferation IC$_{50}$ (nM)

<table>
<thead>
<tr>
<th></th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
</tr>
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<tbody>
<tr>
<td>WT</td>
<td>260</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td>M244V</td>
<td>2000</td>
<td>38</td>
<td>1.3</td>
</tr>
<tr>
<td>G250E</td>
<td>1350</td>
<td>48</td>
<td>1.8</td>
</tr>
<tr>
<td>Q252H</td>
<td>1325</td>
<td>70</td>
<td>3.4</td>
</tr>
<tr>
<td>Y253F</td>
<td>3475</td>
<td>125</td>
<td>1.4</td>
</tr>
<tr>
<td>Y253H</td>
<td>&gt;6400</td>
<td>450</td>
<td>1.3</td>
</tr>
<tr>
<td>E255K</td>
<td>5200</td>
<td>200</td>
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<td>61</td>
<td>125</td>
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<td>&gt;2000</td>
<td>&gt;200</td>
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<td>50</td>
<td>7.4</td>
</tr>
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<td>F359V</td>
<td>1825</td>
<td>175</td>
<td>2.2</td>
</tr>
<tr>
<td>V379I</td>
<td>1630</td>
<td>51</td>
<td>0.8</td>
</tr>
<tr>
<td>H396P</td>
<td>850</td>
<td>41</td>
<td>0.6</td>
</tr>
<tr>
<td>H396R</td>
<td>1750</td>
<td>41</td>
<td>1.3</td>
</tr>
</tbody>
</table>

### Classification:
- **Resistant**
- **Moderately sensitive**
- **Sensitive**

CCyR by Mutations in CML Treated with 2\textsuperscript{nd} Generation TKI after IM Failure

- 86/169 (51\%) pts treated had mutation
  - CP 30/59 (51\%), AP 41/71 (58\%), BP 15/39 (38\%)
- IC50 for dasatinib, nilotinib predictive for response in CP and AP

Chronic Phase

Accelerated Phase

Jabbour et al, Blood 2009; 114: 2037-43
# Inducible Mutations in Mutagenesis Studies with AMN and BMS

- Mutants induced by saturation, selection, or induced (ENU)
- Mutations: imatinib 20, nilotinib 10, dasatinib 9

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>BMS</td>
<td>L248V, Q252H, E255K/V, V299L</td>
</tr>
</tbody>
</table>

Spectrum and frequency of BCR-ABL KD mutations recovered after TKI therapy

- T315I and F359V recovered after treatment with SKI-606

Outcome by Presence of Mutation Prior to Imatinib Exposure

- Mutations in 14 (21%): 10/27 (37%) AP, 5/19 (26%), 0/20 CP

**Mutation Detection by Outcome with Imatinib Therapy CML CP**

- 462 pts treated on TOPS ⇒ 280 mutation assay
- Mutation assay if: no MCyR by 6 m, no MMR at 12 m, loss of any response, progression to AP/BC, ↑ BCR-ABL
- 26 mutations identified in 20 pts (7%)

<table>
<thead>
<tr>
<th>Response</th>
<th>Months</th>
<th>N mutations/tested (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CHR</td>
<td>3</td>
<td>0/22 (0)</td>
</tr>
<tr>
<td>&gt;95% Ph</td>
<td>6</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>No MCyR</td>
<td>12</td>
<td>6/25 (24)</td>
</tr>
<tr>
<td>MCyR, no CCyR</td>
<td>12</td>
<td>3/31 (10)</td>
</tr>
<tr>
<td>No MMR</td>
<td>18</td>
<td>5/101 (5)*</td>
</tr>
<tr>
<td>AP/BP</td>
<td>Any</td>
<td>3/14 (21)</td>
</tr>
<tr>
<td>Loss CHR</td>
<td>Any</td>
<td>7/17 (41)</td>
</tr>
<tr>
<td>Loss MCyR</td>
<td>Any</td>
<td>4/11 (36)</td>
</tr>
<tr>
<td>Loss CCyR</td>
<td>Any</td>
<td>1/8 (13)</td>
</tr>
<tr>
<td>Loss MMR</td>
<td>Any</td>
<td>6/45 (13)</td>
</tr>
</tbody>
</table>

* Failed to achieve CCyR

Branford et al. Blood 2010; Abst# 889
Singificance of KD Mutations in Patients Responding to Imatinib

- 10 of 214 (5%) pts who achieved CCyR had mutation
  - 4 before CCyR
- Median time from mutation to loss CCyR 20.7 months
- Median time from detection of mutation to 2-fold ↑ PCR 12 mo
- KD mutation predictive of loss of CCyR

Analysis of Mutations in CML

• Over emphasized; results produce more false therapeutic leads than benefits
• No role for mutation studies pre-Rx or in imatinib responding patients
• If CG or hematologic relapse, mutations studies may help

- T315I: no role for new TKIs; allo SCT or others (HU, ara-C, HHT, “T315I inhibitors”)
- Nilotinib IC\textsubscript{50}>150nM (e.g. Y253H, E255V, F359V) ⇒ Dasatinib
- Dasatinib IC\textsubscript{50}>3nM (e.g. F317L, V299L) ⇒ Nilotinib

• But: ~50% have no mutations, and no difference or no information for most
## Monitoring Recommendations for CML According to the ELN 2009

<table>
<thead>
<tr>
<th>Objective</th>
<th>Recommended frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td>• Every 2 wk until CHR, then at least every 3 mo or as required</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytogenetic</strong></td>
<td>• At diagnosis, 3 mo, 6 mo and every 6 mo until confirmed CCyR, then every 12 mo if molecular monitoring not assured</td>
</tr>
<tr>
<td></td>
<td>• At failure or unexplained myelosuppression</td>
</tr>
<tr>
<td><strong>Molecular</strong></td>
<td>• Every 3 mo until MMR confirmed, then every 6 mo</td>
</tr>
<tr>
<td><strong>Mutations</strong></td>
<td>• In case of failure or suboptimal response, or before change to 2nd TKI</td>
</tr>
</tbody>
</table>

Baccarani et al. JCO 2009; 27: 6041-51
Approaches to Monitoring in CML

- The conservative approach
  - CG every 6 mo until CCyR, then every 6-12 mo
- The FISHer approach
  - No CG
  - Use FISH to evaluate “molecular” response
- The molecular enthusiast approach
  - PCR only, every 3 months
- The “I-don’t-care-about-any-such-studies” approach
  - CBC only
- The hybrid approach
  - Baseline CG (+FISH? +PCR?)
  - BM (CG) every 6-12 mo until CCyR, then every 1-2 yrs
  - FISH every 3mo until “negative”
  - PCR every 3 mo during 1st yr, then every 6 mo
- Mutations when clinical failure

Kantarjian et al. Blood 2008; 111: 1774-80
Not everything that counts can be counted, and not everything that can be counted counts.

Albert Einstein (1879-1955)
(Sign hanging in Einstein's office at Princeton)
Questions?

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