State of the Art Therapy and Monitoring of CML - 2010

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Grand Rounds
UT Southwestern

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# CML. Historical vs. Modern Perspective

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Historical</th>
<th>Modern</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Course</td>
<td>Fatal</td>
<td>Indolent</td>
</tr>
<tr>
<td>• Prognosis</td>
<td>Poor</td>
<td>Excellent</td>
</tr>
<tr>
<td>• 10-yr survival</td>
<td>10%</td>
<td>84 - 90%</td>
</tr>
<tr>
<td>• Frontline Rx</td>
<td>Allo SCT; IFN-α</td>
<td>Imatinib; nilotinib; dasatinib</td>
</tr>
<tr>
<td>• Second line Rx</td>
<td>?</td>
<td>New TKIs; allo SCT</td>
</tr>
</tbody>
</table>
CML Survival at MDACC. 1965-Present (N=1884)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<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>
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<tr>
<td>1975-1981</td>
<td>132</td>
<td>129</td>
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<tr>
<td>1965-1974</td>
<td>123</td>
<td>123</td>
</tr>
</tbody>
</table>

(censored for non-CML death)
CML in US. The Changing Demographics of CML

Incidence = Mortality = 5,000 = 2%
Plateau prevalence = 5,000 x 100 / 2 = 250,000

alloSCT at Dx
30% of 5,000 = 1,500

alloSCT later
4% resistant 250,000 = 10,000
Why Do We Need Bone Marrow At Dx?

- Assess % of blasts and basos (10-15% have CML transformation at Dx)
- Confirm Ph by CG; detect clonal evolution
- FISH can be falsely positive
- QPCR can be falsely positive or negative
Monitoring CML Course

• Cytogenetics
• Fluorescent in situ hybridization (FISH)
• Quantitative PCR (QPCR): real time, competitive
• Abl mutations
Monitoring CML in Stable CGCR. My (Simple) Approach

• FISH and QPCR q 6 mos (ensure concordance and stability of high quality CGCR; both tests can be false positive or false negative)
• Marrow CG q 2-3 yrs; more often if abnormalities in Ph-negative diploid cells (eg chromosome 5 or 7 abn)
• Mutation analysis only if imatinib failure or change of Rx
• Do not order imatinib plasma levels
## How Do I Use FISH and QPCR Monitoring in CGCR?

<table>
<thead>
<tr>
<th>FISH</th>
<th>QPCR</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>Neg</td>
<td>&lt;0.1%</td>
<td>Excellent response; FU 6 mos</td>
</tr>
<tr>
<td>Pos</td>
<td>&lt;0.1%</td>
<td>FISH and QPCR false + or false -; FU 3 mos</td>
</tr>
<tr>
<td>Neg</td>
<td>&gt;1%</td>
<td>FU 6 mos, FU 3 mos if one log ↑</td>
</tr>
<tr>
<td>Neg</td>
<td>0.1-1%</td>
<td>FU 6 mos, FU 3 mos if one log ↑</td>
</tr>
<tr>
<td>Pos</td>
<td>&gt;1%</td>
<td>Check marrow + CG; ? relapse</td>
</tr>
</tbody>
</table>
Course of CML in CGCR on Imatinib Highly Stable and Predictable

• Historical fear of “sudden blastic transformation”

• On imatinib, sudden transformation may still occur, but: rare, usually in first 2 yrs, usually lymphoid BP in younger pts, usually responsive to HCVAD + TKI

• Closer monitoring in first 2 yrs

• Monitoring in stable durable CGCR Q 6 mo (I like FISH + QPCR – check for concordance)
QPCR Monitoring in CR

- No definite role for pre Rx/pre CR QPCR monitoring
- In CGCR, monitor QPCR Q 3-6 mos
- Use same reliable labs, same source of specimen (PB)
- Aim for QPCR <0.1% = major molecular response
- In CGCR, do not react to QPCR variations in major way

Analysis of Mutations in CML

• If CG or hematologic relapse, mutations studies help
• No role for mutation studies pre-Rx or in imatinib responding patients
• T315I: no role for new TKIs; allo SCT or others (HU, ara-C, HHT, “T315I inhibitors”)
• Nilotinib IC50>150nM : use dasatinib (e.g. P-loop ,Y253H,E255V)
• Dasatinib IC50>3nM : use nilotinib (e.g.F317L)

Therapy of CML in 2010

- Frontline—Imatinib 400 mg/D → 800(?); nilotinib 300-400 mg BID; dasatinib 100 mg/D
- Imatinib failure - Nilotinib, dasatinib, bosutinib
- Allogeneic SCT
- Investigational –T315I inhibitors, (AP24534, DCC2036) omacetaxine, decitabine, TKIs combos
- Combining TKIs + old standards (HU, ara-C)
CML. Survival after Allogeneic BMT

1: Sib + CP1 (N=3,372)
2: Sib + Not CP1 (N=1,141)
3: Other Donor + CP1 (N=1,302)
4: Other Donor + Not CP1 (N=725)
5: All Patients (N=6,548)
CML. Survival after Allogeneic BMT

- 60% survival after 15 years
- 15% mortality over 15 years
- 45% survival at 20 years
CML Survival after Allogeneic BMT

1: Sib + CP1 (N=3,372)
2: Sib + Not CP1 (N=1,141)
3: Other Donor + CP1 (N=1,302)
4: Other Donor + Not CP1 (N=725)
5: All Patients (N=6,548)

Imatinib

60% at 45 years

45% at 20 years
Allo SCT. Second or Third Salvage?

- Imatinib failure in AP, BP: new TKI as bridge to MRD, then allo SCT ASAP
- T315I mutation in any CML phase: AP 24534, other T315I inhibitors, HHT, HU, others as bridge to MRD, then allo SCT ASAP
- Imatinib failure in CP:
  - if IC50 ↑, CE, or no major CG in 12 mos → allo SCT (risk should be reasonable: young, good match)
  - If not → TKI until failure
- Age ≥ 70 yrs or if poor match: may decide to forgo curative allo SCT option for several years of CML control
P190 Ph-positive CML

- 14 of 1292 pts with Ph-positive CML had e1a2/p190 disease
- 5/9 pts presenting in chronic phase progressed to CML BP (4-myeloid 3, lymphoid 1) or CML AP (1)-median follow up 48 mos
- 5 received imatinib frontline; 1 CGCR

<table>
<thead>
<tr>
<th>TKI</th>
<th>Target</th>
<th>Potency vs. IM</th>
<th>Dose (mg/D)</th>
<th>FDA Approval in CML</th>
<th>Unique AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Bcr-Abl</td>
<td>400</td>
<td></td>
<td>post IFN; frontline</td>
<td></td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Bcr-Abl</td>
<td>30 - 50</td>
<td>400 BID</td>
<td>post IM CP, AP</td>
<td>pancreas; LFT; rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>frontline</em></td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Src-Abl</td>
<td>300</td>
<td>100</td>
<td>post IM all phases</td>
<td>↓ PLT; effusions</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Src-Abl</td>
<td>30</td>
<td>500</td>
<td>_ _</td>
<td>diarrhea; LFT</td>
</tr>
</tbody>
</table>
Imatinib Mesylate (STI571; Gleevec)

Phenylaminopyrimidine
Normal Bcr-Abl Signaling

The kinase domain activates a substrate protein, e.g., PI3 kinase, by phosphorylation.
This activated substrate initiates a signaling cascade culminating in cell proliferation and survival.

ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain. This prevents substrate phosphorylation and signaling. A lack of signaling inhibits proliferation and survival.

IRIS - Patient Status at 6 years

**RANDOMIZE**

- **Imatinib**
  - $n = 553$
  - 14 (3%)
- **IFN-\(\alpha\) + Ara-C**
  - $n = 553$
  - 359 (65%)
  - Discontinued study treatment 181 (33%)
- **Crossover**
  - 364 (66%)
  - 13 (2%)

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IRIS Update. Cumulative Best Response

CGCR at 5 yrs 67%

Druker et al. NEJM 355:2408, 2006
IRIS in Chronic Phase CML at 8 Yrs

- 553 pts randomized to imatinib 400 mg/D.
- Transformation to AP/BP at Yr 4-8: 0.9%, 0.5%, 0%, 0%, 0.4%
- Only 15 pts in CGCR (3%) progressed to AP/BP
- No pts in MMR at 12 mos progressed to AP/BP

Outcome at 8 yrs

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

Deininger. Blood 114:abst 1126; 2009
• EFS at 8 years = 81%
  - 1 progression to AP/BC and 2 non-CML related deaths in year 8
• Freedom from progression to AP/BC at 8 years = 92%

Deininger et al; Blood 2009; 114: Abst# 1126
Annual Event Rates on IRIS

- **EFS at 8 years = 81%**
  - 1 progression to AP/BC and 2 non-CML related deaths in year 8
- **Freedom from progression to AP/BC at 8 years = 92%**

Deininger et al; Blood 2009; 114: Abst# 1126
Annual Event Rates on IRIS

• EFS IRIS: Event = AP-BP on imatinib + death any cause on imatinib + loss CHR/MCyR
• PFS IRIS: Progression = AP-BP on imatinib
• Patients off Rx not for event/progression (e.g. toxicity, lost to FU, Pt choice, etc.) are censored at time off TKI = 20% of IRIS pts at 5 years

EFS at 8 years = 81%  - 1 progression to AP/BC and 2 non-CML related deaths in year 8
Freedom from progression to AP/BC at 8 years = 92%

Deininger et al; Blood 2009; 114: Abst# 1126
IRIS 8-Year Update. Outcome After Imatinib

- No CCyR: 53%
- Lost CCyR: 7%
- Lost-regained CCyR: 3%
- CCyR Other: 5%
- Safety: 17%
- Sustained CCyR on study: 15%

Deininger et al; Blood 2009; 114: Abst# 1126
Estimated overall survival at 7 years is 86% (94% considering only CML-related deaths).

CG Abnormalities in Ph-negative Metaphases with IM Frontline Therapy

- 21/258 (9%) patients developed CG abnormalities in Ph-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**

<table>
<thead>
<tr>
<th>Cytogenetic Abnormality</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>237</td>
<td>7</td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>3</td>
</tr>
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</table>

**Progression-Free Survival**

<table>
<thead>
<tr>
<th>Cytogenetic abnormality</th>
<th>Total</th>
<th>No Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>237</td>
<td>21</td>
</tr>
<tr>
<td>YES</td>
<td>21</td>
<td>5</td>
</tr>
</tbody>
</table>

Imatinib and Pregnancy

• 180 women, outcome available in 125 (69%)

• Outcomes:
  – 50% normal infants
  – 28% elective termination (3 abnormalities)
  – 12 infants (9%) with abnormalities
    – 3/12 similar complex malformations (exomphalos, kidneys, bones)

• Conclusion: Women on imatinib should be advised not to become pregnant

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

STIM Study. Relapses

40 pts relapsed (loss of CMR) within the first 6 mos; one pt relapsed at M7.

## Sensitivity of Mutations to TKI

### IC50-Fold Increase

<table>
<thead>
<tr>
<th></th>
<th>Imatinib</th>
<th>Bosutinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
</tr>
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<tbody>
<tr>
<td><strong>WT</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>L248V</td>
<td>3.54</td>
<td>2.97</td>
<td>5.11</td>
<td>2.80</td>
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<tr>
<td>G250E</td>
<td>6.86</td>
<td>4.31</td>
<td>4.45</td>
<td>4.56</td>
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<tr>
<td>Q252H</td>
<td>1.39</td>
<td>0.31</td>
<td>3.05</td>
<td>2.64</td>
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<tr>
<td>Y253F</td>
<td>3.58</td>
<td>0.96</td>
<td>1.58</td>
<td>3.23</td>
</tr>
<tr>
<td>E255K</td>
<td>6.02</td>
<td>9.47</td>
<td>5.61</td>
<td>6.69</td>
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<tr>
<td>E255V</td>
<td><strong>16.99</strong></td>
<td>5.53</td>
<td>3.44</td>
<td><strong>10.31</strong></td>
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<tr>
<td>D276G</td>
<td>2.18</td>
<td>0.60</td>
<td>1.44</td>
<td>2.00</td>
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<tr>
<td>E279K</td>
<td>3.55</td>
<td>0.95</td>
<td>1.64</td>
<td>2.05</td>
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<tr>
<td>V299L</td>
<td>1.54</td>
<td>26.10</td>
<td>8.65</td>
<td>1.34</td>
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<tr>
<td>T315I</td>
<td><strong>17.50</strong></td>
<td>45.42</td>
<td>75.03</td>
<td><strong>39.41</strong></td>
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<tr>
<td>F317L</td>
<td>2.60</td>
<td>2.42</td>
<td>4.46</td>
<td>2.22</td>
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<tr>
<td>M351T</td>
<td>1.76</td>
<td>0.70</td>
<td>0.88</td>
<td>0.44</td>
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<tr>
<td>F359V</td>
<td>2.86</td>
<td>0.93</td>
<td>1.49</td>
<td>5.16</td>
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<td>0.47</td>
<td>2.21</td>
<td>2.33</td>
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<td>H396P</td>
<td>2.43</td>
<td>0.43</td>
<td>1.07</td>
<td>2.41</td>
</tr>
<tr>
<td>H396R</td>
<td>3.91</td>
<td>0.81</td>
<td>1.63</td>
<td>3.10</td>
</tr>
<tr>
<td>G398R</td>
<td>0.35</td>
<td>1.16</td>
<td>0.69</td>
<td>0.49</td>
</tr>
<tr>
<td>F486S</td>
<td>8.10</td>
<td>2.31</td>
<td>3.04</td>
<td>1.85</td>
</tr>
</tbody>
</table>

*Redaelli. 2008*  
Highly Resistant / Resistant / Sensitive
CML. Criteria For Failure On Imatinib

- No CG response at 6 mos (Ph 100%)
- No major CG response at 12 mos (Ph>35%)
- No CGCR in Year 2+
- CG relapse or hematologic relapse
- Not failure criteria
  - suboptimal CG response
  - QPCR ↑ in CGCR

Chemical Structures of Approved BCR-ABL Tyrosine Kinase Inhibitors

Imatinib

Nilotinib

Dasatinib
# Phase II Studies of Dasatinib After Imatinib Failure

## Percent by Disease Stage

<table>
<thead>
<tr>
<th>Response</th>
<th>CP n=387</th>
<th>AP n=174</th>
<th>MyBP n=109</th>
<th>LyBP n=48</th>
<th>ALL n=46</th>
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</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>91</td>
<td>64</td>
<td>50</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>CHR</td>
<td>91</td>
<td>50</td>
<td>26</td>
<td>29</td>
<td>35</td>
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<tr>
<td>NEL</td>
<td>-</td>
<td>14</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>62</td>
<td>40</td>
<td>47</td>
<td>58</td>
<td>62</td>
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<tr>
<td>Complete</td>
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<td>54</td>
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<tr>
<td>Partial</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>2</td>
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Dasatinib in CML Chronic Phase After Imatinib Failure (START-C)

- 387 pts; IM resistance 74%; median CML duration 61 mos; dasatinib 70 mg BID

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>91</td>
</tr>
<tr>
<td>CG major/CR</td>
<td>62/53</td>
</tr>
<tr>
<td>MMR</td>
<td>47</td>
</tr>
<tr>
<td>24-mo PFS/Surv.</td>
<td>80/94</td>
</tr>
</tbody>
</table>

- Dose reductions 73%; median dose 101mg/D; grade 3-4 ↓ plts/PMN 48%; pleural effusions 26% (severe 9%)

Dasatinib in Chronic Phase CML Post IM Failure. PFS

% not progressed

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>IM resistant</th>
<th>IM intolerant</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>488</td>
<td>389</td>
<td>99</td>
</tr>
<tr>
<td>12 months</td>
<td>91%</td>
<td>89%</td>
<td>98%</td>
</tr>
<tr>
<td>24 months</td>
<td>81%</td>
<td>78%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Dasatinib 100 mg QD in CML-CP

662 treated

670 randomized

CML-CP with
• resistance
• suboptimal response
• intolerance to imatinib

100 mg

100 mg once daily (n=165)

50 mg BID (n=167)

140 mg once daily (n=163)

70 mg BID (n=167)

Overall Survival With Dasatinib After Imatinib Failure

Shah et al. Hematologica 2010 [E-pub ahead of print]

Median age: 56 yrs
Median time from Dx: 55 mo

100 mg once daily: 24-month overall survival = 91%

<table>
<thead>
<tr>
<th>Dosage</th>
<th>n</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg once daily</td>
<td>167</td>
<td>96%</td>
<td>91% (86–96)</td>
</tr>
<tr>
<td>70 mg BID</td>
<td>168</td>
<td>94%</td>
<td>88% (82–93)</td>
</tr>
<tr>
<td>140 mg once daily</td>
<td>167</td>
<td>96%</td>
<td>94% (90–97)</td>
</tr>
<tr>
<td>50 mg BID</td>
<td>168</td>
<td>96%</td>
<td>90% (86–95)</td>
</tr>
</tbody>
</table>
Nilotinib in CML-CP. Chemical Structures

Imatinib

Nilotinib
Nilotinib in CML Chronic Phase Post Imatinib Failure

- 321 pts with imatinib resistance (71%) or intolerance (29%)
- Median age 58 yrs; median exposure 19 mo
- Nilotinib 400 mg PO BID ≥ 6 mos
- Outcome
  - CHR: 85%
  - MCyR / CCyR: 59 / 44%
    - Resistant: 56 / 41%
    - Intolerant: 66 / 51%
  - 24-month OS / PFS: 87 / 64%
- Median dose intensity 789 mg/d
- Grade 3-4 ↓ plts 31%, neut 31%; lipase elevation 17% (pancreatitis <1%), bilirubin 8%

Nilotinib in CML Chronic Phase. Survival and PFS

Summary of Bosutinib - Preclinical Activity

- Orally bioavailable
- Potent dual Src/Abl inhibitor
- Minimal inhibitory activity against PDGFR and c-KIT
- Inhibits Bcr-Abl signaling in CML cells
- Active against imatinib-resistant mutants of Bcr-Abl, except T315I

Bosutinib in CML post-imatinib failure

- 294 pts; bosutinib 400-600 mg in phase I, 500 mg in phase II
- Median age 52 yrs; median CML 4 yrs; median prior imatinib 2.3 yrs; imatinib resistance 69%; mutations 45%
- CHR 78%; CG major 58%; CGCR 46%; MMR 49%; CMR 30%
- Estimated 12-mo survival 95%

Bosutinib in CP CML (2nd Line)

Overall Survival

Probability of OS (%)

Time to death (months)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median OS</th>
<th>Patients who died, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM resistant</td>
<td>191</td>
<td>Not reached</td>
<td>20 (10)</td>
</tr>
<tr>
<td>IM intolerant</td>
<td>81</td>
<td>Not reached</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

Cortes. JCO 28 (15S): abst 6502, 2010
Nilotinib vs Imatinib in Newly Dx CML.
Endpoints and Design

- Primary: MMR at 12 mos
- Secondary: CCyR by 12 mos
- Other: time/duration of MMR and CGCR, EFS, PFS, time to AP/BP, OS

Newly Diagnosed CML-CP:
- N = 846
- 217 centers; 35 countries

Stratification by Sokal risk; MMR defined as ≤ 0.1% BCR-ABL/ABL ratio) on International Scale

Nilotinib vs Imatinib in Newly Dx CML-CP (ENESTnd). Primary Endpoint - MMR Rate at 12 Months (ITT Population)

P < .0001

Patients with MMR (%)

44
43
22

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

Nilotinib vs Imatinib in CML-CP (ENESTnd). Confirmed CCyR Rates by 12 Months

Larson. JCO 28: abstr 6501; 2010
Nilotinib vs Imatinib in CML-CP (ENESTnd). Progression to AP/BC

4 patients who achieved CCyR on imatinib progressed to AP/BC

* ITT Population, median follow-up of 18.5 months
** P values are based on log-rank test stratified by Sokal risk group vs imatinib for time to AP/BC.

Larson. JCO 28: abstr 6501; 2010
## Nilotinib vs Imatinib in CML-CP (ENESTnd). Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Nilotinib 300 (n = 282)</th>
<th>Nilotinib 400 (n = 281)</th>
<th>Imatinib 400 (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number deaths</td>
<td>5</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>CML-unrelated</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CML-related (after SCT)</td>
<td>2 (1)</td>
<td>1 (0)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Estimated 18-mo OS</td>
<td>98.5%</td>
<td>99.3%</td>
<td>96.9%</td>
</tr>
<tr>
<td>Stratified log-rank test vs. imatinib</td>
<td>0.28</td>
<td>0.03</td>
<td>-</td>
</tr>
</tbody>
</table>

Larson. JCO 28: abstr 6501; 2010
Nilotinib vs Imatinib in CML-CP (ENESTnd). Grade 3/4 Myelosuppression

% of Patients

Nilotinib vs Imatinib in CML-CP (ENESTnd). Grade 3/4 Myelosuppression

- Anemia
  - Nilotinib 300 mg BID: 4
  - Nilotinib 400 mg BID: 4
  - Imatinib 400 mg QD: 5

- Neutropenia
  - Nilotinib 300 mg BID: 12
  - Nilotinib 400 mg BID: 10
  - Imatinib 400 mg QD: 20

- Thrombocytopenia
  - Nilotinib 300 mg BID: 10
  - Nilotinib 400 mg BID: 12
  - Imatinib 400 mg QD: 9

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

Larson. JCO 28: abstr 6501; 2010
Nilotinib vs Imatinib in CML-CP (ENESTnd). Study Drug-Related Adverse Events (≥10% in Any Group)

<table>
<thead>
<tr>
<th>% of patients treated</th>
<th>Nilotinib 300 mg BID N = 279</th>
<th>Nilotinib 400 mg BID N = 277</th>
<th>Imatinib 400 mg QD N = 280</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>&lt;1</td>
<td>20</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>7</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>&lt;1</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>&lt;1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Rash</td>
<td>32</td>
<td>&lt;1</td>
<td>37</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Pruritus</td>
<td>15</td>
<td>&lt;1</td>
<td>13</td>
</tr>
<tr>
<td>Alopecia</td>
<td>8</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10</td>
<td>&lt;1</td>
<td>10</td>
</tr>
</tbody>
</table>

Larson. JCO 28: abstr 6501; 2010
Dasatinib Versus Imatinib Study In Treatment-naïve CML: DASISION (CA180-056). Design

- N=519
- 108 centers
- 26 countries

Randomized*

Dasatinib 100 mg QD (n=259)
Imatinib 400 mg QD (n=260)

Follow-up 5 years

*Stratified by Hasford risk score

- Primary endpoint: Confirmed CCyR by 12 months
- Secondary/other endpoints: Rates of CCyR and MMR; times to confirmed CCyR, CCyR and MMR; time in confirmed CCyR and CCyR; PFS; overall survival

DASISION: First-Line Dasatinib vs. Imatinib in CML-CP. CCyR Rate by 12 Mos (ITT)

Confirmed CCyR by 12 months

- Dasatinib 100 mg QD: 83%
- Imatinib 400 mg QD: 72%

P = 0.0011

Confirmed CCyR by 12 months

- Dasatinib 100 mg QD: 77%
- Imatinib 400 mg QD: 66%

P = 0.0067

DASISION: First-Line Dasatinib vs. Imatinib in CML-CP. MMR Rates (ITT)

DASISION: First-Line Dasatinib vs. Imatinib in CML-CP. 12-mos MMR Rates by Hasford Risk

No patient who achieved MMR progressed to accelerated or blast phase

2 patients who achieved CCyR progressed to accelerated or blast phase (1 with dasatinib, 1 with imatinib)

DASISION: First-Line Dasatinib vs. Imatinib in CML-CP. Forest Plots Comparing Differences in AE Rates

- Anemia, grade 3/4
- Neutropenia, grade 3/4
- Thrombocytopenia, grade 3/4
- Myalgia*
- Nausea
- Vomiting
- Rash
- Diarrhea
- Fatigue
- Headache
- Fluid retention
- Superficial edema
- Pleural effusion

Rate difference (dasatinib–imatinib) with exact 95% CI

*Myalgia = myalgia, muscle inflammation and MSK pains

## Frontline Rx with Imatinib vs. Second Generation TKIs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Imatinib</th>
<th>2\textsuperscript{nd} TKIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>excellent</td>
<td>even better</td>
</tr>
<tr>
<td>%12-mo CGCR</td>
<td>65-70</td>
<td>80-85</td>
</tr>
<tr>
<td>MMR</td>
<td>20-25</td>
<td>40-45</td>
</tr>
<tr>
<td>AP- BP</td>
<td>3.5</td>
<td>0.4-2</td>
</tr>
<tr>
<td>Tolerances</td>
<td>excellent</td>
<td>even better</td>
</tr>
<tr>
<td>Follow up (yrs)</td>
<td>10</td>
<td>6-7</td>
</tr>
<tr>
<td>Cost ($/yr)</td>
<td>54,000</td>
<td>90,000 – 96,000</td>
</tr>
</tbody>
</table>
## Inhibition of Bcr-Abl

<table>
<thead>
<tr>
<th>ATP-binding</th>
<th>T315I-active</th>
<th>Non-kinase Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bcr-Abl</td>
<td>Abl &amp; Src</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>AP24534</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Bosutinib</td>
<td>DCC-2036</td>
</tr>
<tr>
<td>INNO-406</td>
<td></td>
<td>XL228</td>
</tr>
<tr>
<td>PHA-739358</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KW-2449</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
AP24534 – Summary of Preclinical Profile

• Potent inhibitor of native Bcr-Abl, T315I, and other mutants
• Once-daily oral dosing effective in multiple mouse models
• Inhibits emergence of resistance in mutagenesis screen
• Induces apoptosis within 24 hrs (BCR-ABL with or without mutations)

O’Hare . Cancer Cell 16:401-12, 2009
**AP24534 (T315I inhibitor) in CML**

- Oral multi-kinase inhibitor, active against WT and mutants BCR-ABL including T315I
- 48 pts; AP 2-60 mg daily; 42 CML (31CP)
- Prior Rx: imatinib 100%, dasatinib 88%, nilotinib 65%; 97% failed 2 TKIs and 81% failed 3 TKIs
- 18 with T315I mutations
- CHR 85%, CG major 48%, CGCR 33%
- T315I: CG major 71%, CGCR 57%
- DLT pancreatitis at 60mg/D

Homoharringtonine

Cephalotaxus fortunei Hook
Chinese Plum Yew

CEPHALOTAXINE (natural)

SIDE CHAIN MOIETY (natural or synthetic)
## Omacetaxine for CML with T315I Response to Therapy

Data independently adjudicated by Data Monitoring Committee

<table>
<thead>
<tr>
<th>Response</th>
<th>CP N=40</th>
<th>AP N=16</th>
<th>BP N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHR</td>
<td>34 (85)</td>
<td>8 (50)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>HI</td>
<td>NA</td>
<td>2 (13)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>RCP</td>
<td>NA</td>
<td>1 (6)</td>
<td>1 (10)</td>
</tr>
<tr>
<td><strong>Cytogenetic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCyR</td>
<td>6 (15)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CCyR</td>
<td>4 (10)</td>
<td>1 (6)</td>
<td>-</td>
</tr>
<tr>
<td>PCyR</td>
<td>2 (5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Minimal</td>
<td>5 (13)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Omacetaxine for CML with T315I
Overall Survival

Survival Time in Months

N=40
Median: NA

N=16
Median: 18.75

N=10
Median: 1.81

Chronic Phase
Accelerated Phase
Blast Phase
CML in 2010

• Imatinib, nilotinib, dasatinib are standard frontline Rx (except p190 CML)
• Dose optimization and adequate monitoring
• Sub-optimal response
  — ↑ dose imatinib (400mg → 800mg)
  — New TKI
• Failure
  — Dasatinib, nilotinib, bosutinib
  — Allogeneic SCT
• T315I: AP24534, DCC2036, omacetaxine
Leukemia Questions?

• Dial Pager 713-404-3387

• Email: hkantarj@mdanderson.org

• Hagop Kantarjian, M.D.