Should nilotinib replace imatinib as first line treatment of chronic myeloid leukemia in chronic phase (CML-CP)?


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Learning objectives:

- Outline the epidemiology, pathophysiology, standard treatment, and monitoring parameters for CML
- Understand the limitations of current treatment options
- Assess clinical trials supporting the use of imatinib and nilotinib as first-line treatment for in CML-CP
- Formulate evidence-based conclusions
Epidemiology

- CML accounts for approximately 15% of all leukemias
- The annual incidence is about 5000 new cases
- Risk increases with age
  - Median age at diagnosis is 55 years
- Affect both genders equally
- Only identifiable risk factor for CML is exposure to high-dose radiation

Myeloproliferative disease resulting from a specific genetic mutation

Pathophysiology

- Characterized by the presence of the Philadelphia (Ph+) chromosome and BCR-ABL transcript in leukemic cells
  - 90% of CML are Ph+
- A translocation between chromosome 9 and 22, t(9:22) (q34q11) → fusion of abelson (ABL) gene on chromosome 9 and the break-point cluster (BCR) gene on chromosome 22

- The fusion product BCR-ABL encodes for the BCR-ABL protein

- BCR-ABL protein has constitutively activated tyrosine kinase activity
  - Uncontrolled myeloproliferation
  - Decreased apoptosis
  - Altered cellular adhesion
  - Defective DNA repair

![Diagram of CML Mechanism](image)

**Figure 2. Mechanism of CML.** Savage GD, et al. N Engl J Med. 2002;346:685

- Clinical presentation²,⁴

  - Signs and symptoms
    - LUQ abdominal pain
    - Weight loss
    - Fatigue
- **Laboratory**
  - Leukocytosis, thrombocytosis, anemia
  - Increased granulocytes
  - Increased uric acid and lactase dehydrogenase (LDH)
  - Decreased alkaline phosphatase

- **Physical exam**
  - Splenomegaly

- **Diagnosis**
  - Bone marrow
    - Hypercellular
    - Myeloid to erythroid ratio at least 10 to 1
    - Normal is 3 to 1
  - Cytogenetics
    - Gold standard for diagnosis
    - t(9,22)
    - Ph+
  - Reverse transcriptase polymerase chain reaction (RT-PCR)
    - BCR-ABL transcripts

- **Prognosis**
  - Triphasic
    - Chronic → accelerated → blast

<table>
<thead>
<tr>
<th>Table 1. M.D. Anderson Cancer Center CML criteria&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
</tr>
<tr>
<td><strong>Chronic (CP)</strong></td>
</tr>
<tr>
<td><strong>Accelerated (AP)</strong></td>
</tr>
<tr>
<td><strong>Blast (BP)</strong></td>
</tr>
</tbody>
</table>

Abbreviations: CML-chronic myeloid leukemia; CP-chronic phase; AP-accelerated phase; BP-blast phase

- More than 90% of newly diagnosed patients are in chronic phase
- Progression from chronic to blast phase increases with time
  - 5-10% in the first 2 years
  - 20-25% after two years
Risk stratification
- Calculated based on age, platelet count, peripheral blast, and spleen size
- Hasford score places fewer people in the high-risk category vs. Sokal score

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Low</td>
<td>50-60</td>
<td>102</td>
</tr>
<tr>
<td>Intermediate</td>
<td>36-40</td>
<td>80-95</td>
</tr>
<tr>
<td>High</td>
<td>24-30</td>
<td>45-60</td>
</tr>
</tbody>
</table>

- No current risk stratification system derived from TKI therapy

Monitoring Parameters

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>CHR</td>
</tr>
<tr>
<td></td>
<td>Plt &lt;450x10^9/L</td>
</tr>
<tr>
<td></td>
<td>WBC &lt;10x10^9/L</td>
</tr>
<tr>
<td></td>
<td>No immature granulocytes</td>
</tr>
<tr>
<td></td>
<td>Basophils &lt;5%</td>
</tr>
<tr>
<td></td>
<td>Non palpable spleen</td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>CCR</td>
</tr>
<tr>
<td></td>
<td>No Ph+ metaphases</td>
</tr>
<tr>
<td></td>
<td>1-35%</td>
</tr>
<tr>
<td></td>
<td>36-65%</td>
</tr>
<tr>
<td></td>
<td>66-95%</td>
</tr>
<tr>
<td></td>
<td>&gt;95%</td>
</tr>
<tr>
<td></td>
<td>PCR</td>
</tr>
<tr>
<td></td>
<td>mCR</td>
</tr>
<tr>
<td></td>
<td>minCR</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Molecular</td>
<td>CMR</td>
</tr>
<tr>
<td></td>
<td>Undetectable BCR-ABL mRNA transcripts by real time quantitative and/or nested PCR in 2 consecutive samples</td>
</tr>
<tr>
<td></td>
<td>MMR</td>
</tr>
<tr>
<td></td>
<td>BCR-ABL to ABL ratio less than or equal to 0.1%</td>
</tr>
</tbody>
</table>

Abbreviations: CHR-complete hematologic response; CCR-complete cytogenetic response; PCR-partial cytogenetic response; mCR-minor cytogenetic response; minCR-minimal cytogenetic response; CMR-complete molecular response; MMR-major molecular response

Evolution of treatment

- Busulfan
  - Effective in lowering white blood count (WBC)
  - No effect on disease progression
  - Significant toxicity

- Hydroxyurea
  - Better tolerated than busulfan
  - Effective in lowering WBC and reducing splenomegaly
  - No effect on disease progression

- Allogeneic stem cell transplant
  - Only curative option
  - 3-5 year survival rate of 40-80%
  - Limited by transplant related mortality (5-50%) and lack of suitable donor
- **Interferon alpha (TNFα)**
  - Naturally occurring glycoprotein found to be effective in CML in 1980
  - High rate of hematologic response (40-80%)
  - Minimal complete cytogenetic response (5-25%)
  - Median survival: 60-90 months
  - Poor safety profile

- **Tyrosine kinase inhibitors (see appendix 1)**\(^2,3,9,11-13\)
  - **Mechanism of action**
    - Blocks the binding of ATP to the BCR-ABL tyrosine kinase and inhibit the tyrosine kinase activity of BCR-ABL mediated signaling pathways
    - Induced inactivation of downstream pathways results in reduction of excessive myeloid cell proliferation
    - Imatinib and nilotinib binds to the inactive conformation of BCR-ABL tyrosine kinase

![Figure 3. Mechanism of tyrosine kinase inhibitor. Adapted from An X, et al. Leukemia Research 2010;34:1255-68](image)

- **First generation: imatinib**
  - FDA approved in 2003 for first-line treatment
  - Currently the standard first-line treatment

- **Second-generation: nilotinib**
  - More potent than imatinib
  - FDA approved in 2007 for second-line treatment
  - On June 2010, FDA approved for first-line
International Randomized Study of Interferon and STI571 (IRIS)\textsuperscript{14}

- **Objective**
  - To compare the efficacy of imatinib versus interferon alfa and low-dose cytarabine in newly diagnosed CML-CP

- **Design**
  - Prospective, multicenter, open-label, phase 3, randomized, controlled

- **Methods**
  - **Inclusion**
    - Adults with newly diagnosed Ph+ CML in chronic phase
    - Previously untreated (except hydroxyurea, anagrelide, or both)
    - Eastern Cooperative Oncology Group (ECOG) <3
    - Adequate organ function
  - **Exclusion**
    - Breast-feeding or pregnant
    - Uncontrolled serious medical conditions
    - Undergone major surgery within the preceding four weeks
    - Seropositive for HIV
    - History of another cancer within the previous five years (except basal-cell carcinoma or cervical carcinoma in situ)
  - **Treatment**
    - Stratified according to Sokal and Hasford score
    - Arm 1: imatinib 400 mg PO daily
    - Arm 2: interferon alfa and low-dose cytarabine (I+C)
      - Gradual dose escalation of interferon alfa to a target of 5 mU/m\textsuperscript{2} as tolerated
      - Once maximum dose of interferon alfa was achieved, cytarabine 20 mg/m\textsuperscript{2}/d SC x 10 days every month
    - Dose modification allowed if no CHR within 3 months or minor CR at 12 months
      - Double imatinib dose (400 mg BID) or increase cytarabine to 40 mg/day x 15 days each month
  - **Crossovers**
    - No or loss of response, increase WBC, or treatment intolerance
  - **End points**
    - **Primary**
      - Progression-free survival (PFS)
        -Death from any cause during treatment
        -Development of AP/BP
        -Loss of complete hematologic response (CHR)
        -Loss of major cytogenetic response (MCR)
        -Doubling of WBC
    - **Secondary**
      - Rate of CHR
      - Rate of MCR
      - Safety and tolerability
  - **Statistics**
    - Intent-to-treat analysis of primary endpoint
    - Rates of hematologic and cytogenetic response were estimated according to Kaplan-Meier method
    - Treatment effect was evaluated with the log-rank test
All patients who received at least one dose of study drug were included in the safety analysis.

- Results
  - N = 1106
  - Imatinib (n=533)
  - I+C (n=533)
  - Similar characteristics at baseline
  - Mean follow-up: 19 months
  - Progression-free survival
    - At 12 months: 96.6% in imatinib vs. 79.9% in I+C (P<0.001)
    - At 18 months: 92.1% vs. 73.5% (no P value)

![Figure 4. Kaplan-Meier estimate of progression-free survival. Adapted from O'Brien S, et al. Eng J Med 2003;348:994-1004](image)

- Responses
  - Statistically significant difference in CHR and MCR between imatinib and I+C (P<0.0001)

<table>
<thead>
<tr>
<th>Table 4. Rates of best observed hematologic and cytogenetic responses^14</th>
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<tbody>
<tr>
<td><strong>Response</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Percent (95% CI)</strong></td>
</tr>
<tr>
<td><strong>CHR</strong></td>
</tr>
<tr>
<td><strong>MCR</strong></td>
</tr>
<tr>
<td><strong>CCR</strong></td>
</tr>
<tr>
<td><strong>PCR</strong></td>
</tr>
</tbody>
</table>

Abbreviations: I+C-interferon alfa and cytarabine; CHR-complete hematologic response; MCR-major cytogenetic response; CCR-complete cytogenetic response; PCR-partial cytogenetic response.
• No difference in estimated overall survival at 18 months
  • 97.2% in imatinib vs. 95.1% in I+C (P = 0.16)

• Adverse events
  • Most common in imatinib group (30%-50%)
    ♦ Superficial edema
    ♦ Elevated liver enzymes
    ♦ Nausea, diarrhea
    ♦ Muscle cramps, musculoskeletal pain
    ♦ Rash, fatigue, HA
  • Most common in I+C (30-80%)
    ♦ Elevated liver enzymes
    ♦ Musculoskeletal and joint pain
    ♦ Nausea, diarrhea, constipation
    ♦ Pyrexia, insomnia, depression, rigors
  • Grade 3 or 4

<table>
<thead>
<tr>
<th>Table 5. Rate of most common grade 3 or 4 adverse effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Effect</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

➢ Strengths
  ▪ Adequately powered, randomized study
  ▪ Patients were stratified using appropriate criteria
  ▪ Imatinib was compared to standard therapy at the time that the study was conducted

➢ Weaknesses
  ▪ High crossover rate prevented true assessment of overall survival between the two arms
  ▪ Although the study duration was adequate to show short-term benefit, it was too short to show long-term benefit

❖ Molecular response of IRIS
  ➢ At least 3-log reduction of BCR-ABL transcript among those who achieved CCR at 12 months
    • 39% imatinib vs. 2% I+C, P < 0.001

➢ Progression free survival

<table>
<thead>
<tr>
<th>Table 6. Correlation between response and PFS</th>
</tr>
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<tbody>
<tr>
<td>Response at 12 months</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>CCR and MMR</td>
</tr>
<tr>
<td>CCR and &lt;MMR</td>
</tr>
<tr>
<td>&lt;CCR, no MR</td>
</tr>
</tbody>
</table>

Abbreviations: PFS—progression free survival; CCR—complete cytogenetic response; MMR-major molecular response; MR—molecular response
Eight-year follow up of IRIS\textsuperscript{16}

- 55% (n=304) remained on imatinib treatment
- Estimated event-free survival (EFS) was 81%
- Freedom from progression to AP/BC was 92%
  - None of the patient who achieved MMR at 12 months progressed to AP/BC
- Estimated OS was 85%
  - 93% when based on CML-related deaths and those prior to stem cell transplant only
- Patients with partial CR at 6 months and 12 months were more likely to achieve a stable CCR than have an event
  - At 6 months: 63% stable CCR vs. 17% estimated event rate
  - At 12 months: 57% stable CCR vs. 20% estimated event rate
  - No P-value reported
- 86% achieved MMR
- No new unreported adverse effect

Suboptimal or failure to imatinib (see appendix 2)\textsuperscript{5,17,19,18}

- Imatinib intolerance
- Poor compliance
- Imatinib resistance\textsuperscript{17}
  - Incidence is about 2-4% annually
  - Rate decline after two years of continuous treatment

<table>
<thead>
<tr>
<th>Table 7. Annual rate of imatinib resistance</th>
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<tr>
<td><strong>Year</strong></td>
</tr>
<tr>
<td><strong>Rate (%)</strong></td>
</tr>
</tbody>
</table>

- Mechanisms of imatinib resistance (figure 5)\textsuperscript{19}
  - Drug efflux
  - Plasma-protein binding
  - BCR-ABL domain mutations
    - Several mutants have been identified
    - Some are sensitive to second-generation TKIs
    - T315I mutants are resistant to all approved TKIs
  - Activation of downstream pathways (eg. SCR family)
  - BCR-ABL gene amplification
Figure 5. Mechanisms of resistance to tyrosine kinase inhibitors. Adapted from Krause SD, Van Etten AR. N Engl J Med. 2005;353:172-87

- Treatment strategies
  - High-dose imatinib as first line
    - Overcoming drug efflux and plasma protein binding
    - The randomized phase 3 Tyrosine Kinase Inhibitor Optimization and Selectivity study (TOPS)\textsuperscript{20}
      - 400 mg vs. 800 mg of imatinib in newly diagnosed CML-CP
        - CCR at 12 months: 66% vs. 70% (P=0.002)
        - MMR at 12 months: 40% vs. 46% (NS)
        - Higher rate of neutropenia, thrombocytopenia, rash, diarrhea, myalgia, edema, and dypsnea in the 800-mg imatinib group
    - Baccarani et al\textsuperscript{21}
      - 400 mg vs. 800 mg imatinib in newly diagnosed CML-CP
      - CCR and MMR at 12 months: no difference
    - Limitations of using high-dose imatinib as first line
      - Inconsistent efficacy
      - Higher rate of adverse event
  - Nilotinib\textsuperscript{22}
    - 30 times more potent than imatinib
    - Active against most imatinib-resistant mutants
    - Cellular transport independent of human organic cation transporter 1 (hOCT1)
Nilotinib

- Nilotinib as second line\textsuperscript{4,22,23}

| Table 8. Results of trials evaluating nilotinib as second-line therapy |
|-------------------|-------------------|
|                    | Kantarjian et al\textsuperscript{24} | Le Coutre et al\textsuperscript{25} |
| No. of patient     | 321              | 137              |
| Follow-up duration (months) | 19              | 11              |
| CHR (%)            | 91               | 31               |
| MCR (%)            | 59               | 32               |
| CCR (%)            | 41               | 20               |

Abbreviations: CHR-complete hematologic response; MCR-major cytogenetic response; CCR-complete cytogenetic response

- Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients (ENESTnd) study\textsuperscript{24}

  ➢ **Objective**
    - To compare the efficacy and safety of nilotinib versus imatinib in patients with newly diagnosed Ph+ CML-CP

  ➢ **Design**
    - Phase 3, randomized, open-label, multicenter

  ➢ **Methods**
    - **Inclusion**
      - Adults with newly diagnosed Ph+ CML-CP
      - No prior treatment with a TKI or any medical treatment for CML for more than 2 weeks
      - Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
      - Adequate organ function
    - **Exclusion**
      - Impaired cardiac function
      - Currently taking warfarin, CYP3A4 inducers or inhibitors, or any medication with the potential to prolong QT interval
    - **Treatment**
      - Stratified according to Sokal risk score
      - Arm 1: Nilotinib 300 mg PO BID
      - Arm 2: Nilotinib 400 mg PO BID
      - Arm 3: Imatinib 400 mg PO once daily
      - Imatinib dose escalation to 400 mg BID was permitted if suboptimal response or treatment failure
      - Dose escalation of nilotinib and crossover were not permitted
    - **End points**
      - **Primary**
        - Rate of MMR at 12 months
      - **Secondary**
        - Rate of CCR by 12 months
      - **Others**
        - Progression to AP or BP
        - Adverse events
    - **Statistics**
      - Intention-to-treat analysis of primary end point
      - A 2-sided Cochran-Mantel-Haenszel test was used at a 5% level to test statistical significance of response rates
Time-to-event comparisons were estimated using Kaplan-Meier curves and compared using the log-rank test.

Safety analysis included all patients who received at least 1 dose of study drug.

Results

- N = 846
  - Nilotinib 300 (n = 282) vs. nilotinib 400 (n = 281) vs. imatinib (n = 283)
  - No difference in baseline characteristics or Sokal risk score

- Duration
  - 14 months for all treatment groups

- Treatment is ongoing; pending 5-years follow-up

- MMR

![Major molecular response (%)](image)


- Median time to first MMR
  - Nilotinib 300: 8.6 months
  - Nilotinib 400: 11 months
  - Imatinib: median not yet achieved
  - No P value reported

- CCR at 12 months (Nilotinib 300 vs. nilotinib 400 vs. imatinib)
  - 80% vs. 78% vs. 65% (P < 0.001 for both comparisons)

- Progression to AP/BP at 12 months (Nilotinib 300 vs. nilotinib 400 vs. imatinib)
  - Nilotinib 300 vs. imatinib: <1% (n = 2) vs. 4% (n = 11), P = 0.01
  - Nilotinib 400 vs. imatinib: <1% (n = 1) vs. 4% (n = 11), P = 0.004

- No patient who had a MMR progressed to AP/BP at 12 months

- Adverse events
  - Most common in nilotinib (30-70%)
    - Rash, pruritis
    - Elevated total bilirubin, liver enzymes
    - Hyperglycemia
Most common in imatinib (30-45%)
  - Nausea
  - Increased alkaline phosphatase
  - Decreased phosphate

- Grade 3 or 4

| Table 9. Rate of most common grade 3 or 4 adverse effect (%) |
|------------------|----------------|----------------|----------------|
| Adverse Effect   | Nilotinib 300  | Nilotinib 400  | Imatinib       |
| Neutropenia      | 12             | 10             | 30             |
| Thrombocytopenia | 10             | 12             | 9              |
| Anemia           | 3              | 3              | 5              |
| Increased total bilirubin | 4 | 8 | <1 |
| Increased ALT   | 4              | 9              | 2              |

- Strengths
  - Adequately powered
  - Patients were stratified using appropriate criteria
  - Compared to current standard therapy

- Weaknesses
  - Longer follow-up needed to confirm response durability (pending results)
  - No report of compliance
  - Although MMR was shown to predict PFS for imatinib, there is no data validating this surrogate endpoint for nilotinib.

Summary

- IRIS established imatinib as standard first-line therapy
- Eight year follow-up data of IRIS confirmed the durable efficacy and safety of imatinib
- Nilotinib is active against most imatinib-resistant mutations
- ENEStnd showed improved response rates and shorter time to response for nilotinib vs. imatinib
- Correlation between early response and durability of response was based on imatinib data
- Nilotinib is more potent than imatinib

Discussion

- Standard time to response based on imatinib might not be applicable to nilotinib
- Remaining questions
  - What are the long-term benefits of achieving an early response with nilotinib?
  - Could earlier exposure to nilotinib result in new mutations that are resistant to all TKIs?
  - What is the overall long-term clinical impact of using nilotinib as first-line therapy?
- Benefit of response vs. risk of resistance and unknown long-term effect

Conclusions

- Imatinib remains a reasonable, effective, and safe therapeutic option for newly diagnosed CML-CP
- Long-term follow-up of the ENEStnd study is needed to confirm the benefit of using nilotinib as first-line therapy in CML-CP
- Until longer follow up data is available, nilotinib should not replace imatinib as first-line treatment of CML-CP
# Appendix A

## Table 11. TKIs approved for first-line therapy of CML-Cp\textsuperscript{11-13}

<table>
<thead>
<tr>
<th></th>
<th>Imatinib (Gleevec)</th>
<th>Nilotinib (Tasigna)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Binds to inactiv\textsubscript{e} conformation of BCR-ABL</td>
<td>Binds to the inactive conformation of the BCR-ABL protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30x more potent than imatinib</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>400 mg daily</td>
<td>300 mg BID</td>
</tr>
<tr>
<td><strong>Dose adjustments</strong></td>
<td>Hepatic: 25% decrease in severe impairment</td>
<td>Hepatic: 25%-33% initial dose reduction for mild to moderate impairment, 50% dose reduction for severe impairment</td>
</tr>
<tr>
<td></td>
<td>Renal: Initial 50% decrease in moderate to severe impairment; may titrate up as tolerated</td>
<td>Renal: none</td>
</tr>
<tr>
<td></td>
<td>Other: 50% decrease if use with a strong CYP450 inducer</td>
<td>Other: adjustments indicated for QT prolongation, neutropenia, thrombocytopenia according to abnormal values</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Orally with food</td>
<td>Orally on an empty stomach</td>
</tr>
<tr>
<td><strong>Common adverse effects</strong></td>
<td>Edema, n/v/d/dyspepsia (improved when taken with food), muscle cramps, musculoskeletal pain, rash, fatigue</td>
<td>Rash, pruritus, HA, n/v/c/d, fatigue, myalgia, dyspepsia, nasopharyngitis, arthralgia, pyrexia, upper urinary tract infection, cough, myelosuppression</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP450 (mostly CYP3A4)</td>
<td>CYP450</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Biliary</td>
<td>Biliary</td>
</tr>
<tr>
<td><strong>Drug interaction</strong></td>
<td>CYP450 inducers and inhibitors may alter level</td>
<td>Strong CYP450 inducers may alter level</td>
</tr>
<tr>
<td></td>
<td>Increase APAP level</td>
<td>The drug is an inhibitor of CYP3A4, 2C8, 2C9, 2D6.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>It is also an inducer of CYP2B6, 2C8, and 2C9</td>
</tr>
<tr>
<td><strong>Contraindication</strong></td>
<td>None</td>
<td>Hypokalemia, hypomagnesemia, long QT syndrome</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Scored tablets: 100 mg and 400 mg</td>
<td>Hard capsules: 150 mg and 200 mg</td>
</tr>
</tbody>
</table>

**Abbreviations:** TKIs-tyrosine kinase inhibitors; MOA-mechanism of action; CML-CP-chronic myeloid leukemia in chronic phase; BID-twice daily; CYP450–cytochrome P450; d/n/v-diarrhea/nausea/vomiting; HA-headache; c-constipation; APAP-acetaminophen
### Appendix B

| Table 11. European LeukemiaNet response evaluation criteria to imatinib
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Optimal</td>
<td>Suboptimal response</td>
<td>Failure</td>
</tr>
<tr>
<td><strong>At 3 months</strong></td>
<td>CHR + mCR</td>
<td>No CR</td>
</tr>
<tr>
<td><strong>At 6 months</strong></td>
<td>PCR</td>
<td>&lt;PCR</td>
</tr>
<tr>
<td><strong>At 12 months</strong></td>
<td>CCR</td>
<td>PCR</td>
</tr>
<tr>
<td><strong>At 18 months</strong></td>
<td>MMR</td>
<td>&lt;MMR</td>
</tr>
</tbody>
</table>

Any time during treatment:
- Stable or improving MMR
- Loss of MMR or obtain mutations
- Loss of CHR, loss of CCR, or obtain mutations

Abbreviations: CHR-complete hematologic response; mCR-minor cytogenetic response; CR-cytogenetic response; PCR-partial cytogenetic response; CCR-complete cytogenetic response; MMR-major molecular response

### Appendix C

| Table 12. Risk score equations
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<td><strong>Sokal risk score equation</strong></td>
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<td><strong>Hasford risk score equation</strong></td>
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### References

16. Deininger, Michael, O’Brien, et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. ASH Annual Meeting Abstracts. 2009;114:1126
18. Stein B, Smith BD. Treatment options for patients with chronic myeloid leukemia who are resistant to or unable to tolerate imatinib. Clin Ther 2010;32:804-820