Gleevec®
(imatinib mesylate)

Advancing the Treatment of Ph+
Chronic Myeloid Leukemia (CML)
# CML: a Progressive and Fatal Disease

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accelerated phase</td>
<td>Blast crisis</td>
</tr>
<tr>
<td>Median duration 5–6 years</td>
<td>Median duration 6–9 months</td>
<td>Median survival 3–6 months</td>
</tr>
</tbody>
</table>
CML: Linked to a Single Molecular Abnormality

The Philadelphia (Ph) Chromosome: t(9;22) Translocation
CML: Its Cause and Management

- The Ph chromosome generates the Bcr-Abl tyrosine kinase—the molecular cause of CML
  - Constitutive activation leads to malignant transformation

- Eliminating the Ph chromosome—a primary goal of therapy
  - Complete cytogenetic response (0% Ph+ cells)
  - Major cytogenetic response (≤35% Ph+ cells)
  - Patients who achieved a complete/major cytogenetic response with SCT or IFN-α had prolonged survival vs patients without such a response
  - Longer follow-up required to determine survival benefit of Gleevec

Diagram:
- Cytogenetic Response → Delayed Disease Progression → Survival Advantage?
Gleevec® Targets the Cause of CML

- Gleevec—a specific inhibitor of a small family of tyrosine kinases, including Bcr-Abl, Kit, and PDGF receptor
Gleevec®: Pharmacokinetics

- Rapidly and completely absorbed after oral administration.
- Terminal half-life ($t_{1/2}$) of Gleevec $\approx 18$ h and of active metabolite $\approx 40$ h, allowing convenient once-daily oral dosing.
- 81% of Gleevec eliminated within 7 days.
- Metabolized in the liver primarily by the cytochrome P$_{450}$ enzyme CYP3A4.
  - In vitro competitive inhibitor of CYP3A4, CYP2C9, and CYP2D6.
- Potential drug interactions between Gleevec and other substrates, inhibitors, or inducers of these enzymes.
### Phase I Study: Gleevec® Achieves Hematologic and Cytogenetic Responses

<table>
<thead>
<tr>
<th></th>
<th>Chronic Phase IFN-α Failure 300–1000mg/day (n=54)</th>
<th>Blast Crisis, Myeloid 300–1000mg/day (n=38)</th>
<th>Blast Crisis, Lymphoid 300–1000mg/day (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic response</strong></td>
<td>100%</td>
<td>55%</td>
<td>70%</td>
</tr>
<tr>
<td>Complete</td>
<td>98%</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Cytogenetic response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>31%</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>Complete</td>
<td>13%</td>
<td>8%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- Typically 4 weeks to achieve CHR, 2 to 10 months to achieve MCR
- A maximal tolerated dose (MTD) was not reached (up to 1000mg/day)


## Phase II Results: Highest Response Rates in Chronic Phase

<table>
<thead>
<tr>
<th></th>
<th>Study 0110 Chronic Phase IFN-α Failure* (N=454)</th>
<th>Study 0109 Accelerated Phase* (N=181)</th>
<th>Study 0109 Blast Crisis (N=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>93%</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>No evidence of leukemia</td>
<td>–</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>Return to chronic phase</td>
<td>–</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Major cytogenetic response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>53%</td>
<td>19%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Chronic phase: 400mg/day; advanced phases: 400mg/day or 600mg/day. Dose escalation permitted in all trials.*

**Prevevec® (imatinib mesylate) Prescribing Information:**

For important safety information, please see slide 3 or full Prescribing Information.
Higher Dose: Longer Time to Disease Progression

Study 0109 (accelerated phase)

% Without Progression

Months Since Start of Treatment

600mg (n=119)

400mg (n=62)

P<0.002


Some adverse events appear to be dose related.
IRIS Study: Reevaluating First-Line CML Therapy

- Gleevec® versus IFN-α + ara-C (Study 106)
- Rationale for first-line use of Gleevec
  - High response rate in patients failing IFN-α
  - Higher response rates in earlier phases
- Phase III, multinational, randomized, open-label
- Inclusion criteria: newly diagnosed chronic phase CML patients
- Primary objective—determine time to progression, defined as:
  - Increasing WBC count
  - Loss of CHR or MCR
  - Accelerated phase or blast crisis
  - Death
- Secondary objectives—determine rate and duration of CHR and MCR; overall survival; safety; molecular response; quality of life (QoL) using FACT-BRM
IRIS: The Largest Phase III CML Study to Date

1106 patients enrolled from June 2000 to January 2001

Gleevec® (n=553)
- Loss of MCR or CHR
- Increasing WBC count
- Intolerance of treatment
- Failure to achieve MCR at 12 (vs 24) mos*
- Failure to achieve CHR at 12 (vs 24) mos*
- Request to discontinue IFN-α*

IFN-α + ara-C (n=553)

S = screening.
R = randomization.
Longer Time to Progression With Gleevec®

Patients Free of Any Disease Progression*

- Estimated rate at 12 months
  - Gleevec: 97%†
  - IFN-α + ara-C: 80%

Patients Free of Progression to Advanced Disease*

- Estimated rate at 12 months
  - Gleevec: 98%†
  - IFN-α + ara-C: 93%

*BRIS study; n=553 in each arm.
†p<0.0001.
Higher Cytogenetic Response Rates With Gleevec®

Major Cytogenetic Response†

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleevec</td>
<td>76%</td>
</tr>
<tr>
<td>IFN-α + ara-C</td>
<td>12%</td>
</tr>
</tbody>
</table>

Complete Cytogenetic Response‡

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleevec</td>
<td>54%</td>
</tr>
<tr>
<td>IFN-α + ara-C</td>
<td>3%</td>
</tr>
</tbody>
</table>

†E1AIS Study; n=553 in each arm.
‡≥85% Ph+ cells.
§≥95% Ph+ cells.

For important safety information, please see Section 3 or full Prescribing Information.

$\text{P}<0.001$. Confirmed responses shown.

Unconfirmed MCR—Gleevec: 83%; IFN-α + ara-C: 8%
Unconfirmed CCR—Gleevec: 68%; IFN-α + ara-C: 2%
Early Responses in More Patients With Gleevec®

Major Cytogenetic Response

Complete Cytogenetic Response

Months Since Randomization

% Responding

Gleevec (n=553)
IFN-α + ara-C (n=553)

For important safety information, please see slide 3 or full Prescribing Information.
## More Patients Remain on Gleevec® Therapy

<table>
<thead>
<tr>
<th></th>
<th>Gleevec</th>
<th>IFN-α + ara-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Crossovers</strong></td>
<td>1% (n=7)</td>
<td>39% (n=218)</td>
</tr>
<tr>
<td>Intolerance</td>
<td>&lt;1%</td>
<td>23%</td>
</tr>
<tr>
<td>No CHR at 6 months</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>Increasing WBC count</td>
<td>&lt;1%</td>
<td>5%</td>
</tr>
<tr>
<td>Loss of CHR</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Loss of MCR</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>All Discontinuations</strong></td>
<td>9% (n=51)</td>
<td>31% (n=170)</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>2%</td>
<td>13%</td>
</tr>
<tr>
<td>Adverse events</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Progression to accelerated phase or blast crisis</td>
<td>1.5%</td>
<td>5%</td>
</tr>
<tr>
<td>All other causes</td>
<td>3.5%</td>
<td>7%</td>
</tr>
<tr>
<td>Remained on originally assigned treatment</td>
<td>90% (n=495)</td>
<td>30% (n=165)</td>
</tr>
<tr>
<td>Event</td>
<td>All Grades (%)</td>
<td>Grades 3/4 (%)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>Gleevec n=551 †</td>
<td>IFN-α + ara-C n=533 †</td>
</tr>
<tr>
<td>Superficial edema</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>43</td>
<td>61</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>34</td>
<td>41</td>
</tr>
<tr>
<td>Rash</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31</td>
<td>65</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30</td>
<td>41</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>Joint pain</td>
<td>27</td>
<td>38</td>
</tr>
</tbody>
</table>

*RIS study; most common adverse events, listed by incidence with Gleevec (≥25%, regardless of causality). Data collected for all patients who received at least 1 dose of study drug.
# Fewer Hematologic Adverse Events With Gleevec®

<table>
<thead>
<tr>
<th></th>
<th>Gleevec (%)</th>
<th>IFN-α + ara-C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=551)†</td>
<td>(n=533)†</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

* Patients who received at least 1 dose of study drug.
Gleevec®—CML Indications

Gleevec is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML). Follow-up is limited. Gleevec is also indicated for treatment of patients with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph+ CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival, in patients with CML in blast crisis, accelerated phase, or chronic phase after failure of interferon alpha therapy.
Gleevec®—Important Considerations

- Use of Gleevec is contraindicated in patients with hypersensitivity to imatinib or to any other component of Gleevec.
- Women of childbearing potential should be advised to avoid becoming pregnant.
- Gleevec is often associated with edema and occasionally serious fluid retention*; GI irritation (and should be taken with food and a large glass of water to minimize this problem); anemia, neutropenia, thrombocytopenia, or occasionally severe hepatotoxicity or hemorrhage.
- Gleevec is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Please see full Prescribing Information for potential drug interactions.

*Patients should be weighed and monitored regularly for signs and symptoms of edema, which can be serious or life threatening.
Gleevec®: Evolving First-Line CML Therapy

- Gleevec surpasses IFN-α + ara-C by the following parameters measured in the IRIS study:
  - Progression-free survival
  - Complete cytogenetic response
  - Major cytogenetic response
  - Complete hematologic response

- Mild to moderate safety and tolerability profile

Additional important safety information, including serious and severe adverse events, please see slide 3 or full Prescribing Information.
Inhibition of Cellular Proliferation by Gleevec

http://www.biocarta.com/pathfiles/h_gleevecepathway.asp
CDK Regulation of Cell Division

http://www.biocarta.com/genes/
IL7 Regulatory Pathway

http://www.biocarta.com/pathfiles/h_il7Pathway.asp/
NCCN* CML Guidelines for Monitoring Response to Gleevec®

Month evaluation

Gleevec initiated

Hematologic response

Continue Gleevec
Monitor cytogenetics every 3 to 6 months

No hematologic response

Increase dose of Gleevec or switch to IFN-α ± ara-C, or perform SCT if feasible

Month evaluation

Complete cytogenetic response

Continue Gleevec

Partial cytogenetic response or no cytogenetic response

Increase dose of Gleevec or continue same dose or switch to IFN-α ± ara-C, or perform SCT if feasible, or join clinical trial

*National Comprehensive Cancer Network
www.nccn.org/physician_gls/index.html
Optimal Dosing for Optimal Results

- Recommended starting doses of Gleevec®
  - Chronic phase: 400mg once daily
  - Advanced phases: 600mg once daily
- Monitor responses every 3–6 months
- Consider dose escalation (400mg to 600mg in chronic phase, 600mg to 800mg in advanced phases) in absence of severe adverse reactions or severe hematologic abnormalities for any of the following:
  - Failure to achieve a CHR after at least 3 months
  - Failure to achieve a cytogenetic response after 6–12 months
  - Loss of a previously achieved hematologic or cytogenetic response
  - Disease progression (at any time)
- Dose escalation when appropriate may overcome resistance
Gleevec® Has Advanced the Treatment of Ph+ CML

- Therapy specifically designed to target the molecular cause of CML (Bcr-Abl)
- High rates of cytogenetic and hematologic response in all phases of disease
- Significant delay in time to disease progression for patients in chronic phase
- Mild to moderate side-effect profile
- Convenient, once-daily, oral dosing*
- Evolving first-line therapy for CML

*300mg should be administered as 400mg twice a day.