Report from the FDA

Approval Summary: Imatinib Mesylate Capsules for Treatment of Adult Patients with Newly Diagnosed Philadelphia Chromosome-positive Chronic Myelogenous Leukemia in Chronic Phase

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Abstract

Purpose: The purpose is to describe the Food and Drug Administration (FDA) review and approval of imatinib (Gleevec; Novartis Pharmaceuticals, East Hanover, NJ) for treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia (CML) in chronic phase.

Experimental Design: The FDA reviewed data in electronic format from a randomized controlled clinical trial of 1106 adult patients with newly diagnosed Philadelphia chromosome-positive CML in chronic phase, comparing imatinib with the combination of IFN-α and cytarabine.

Results: Imatinib showed clinically and statistically significantly better results for time-to-progression to accelerated phase or blast crisis, progression-free survival, complete hematological response rate, and cytogenetic response rate. With a median follow-up of 14 months, a maximum follow-up of 19.5 months, and an expected median survival of 5–6 years on the IFN-α/cytarabine control arm, few of the expected progressions to accelerated or blast phase or deaths have occurred. Imatinib was also better tolerated. Edema, nausea, rigors, neutropenia, and headache were more frequent in women. Only 57% of the IFN-α target dose was administered, and only 68% of patients received any cytarabine. However, this does not appear to adequately explain the superiority of imatinib observed in this trial. Results of a population pharmacokinetic study in a subgroup of 371 patients and a separate rifampin-imatinib drug-drug interaction study in healthy volunteers are presented.

Conclusions: On December 20, 2002, imatinib was granted accelerated approval under subpart H, rather than regular approval. Follow-up is short compared with the natural history of chronic phase CML or more mature results with established therapies such as IFN-α or transplantation. If imatinib should stop working after 1.5–2 years, the results could be importantly different from the present analysis. As a Phase IV postmarketing commitment, the applicant has agreed to provide follow-up reports on this imatinib study annually for the next 6 years.

Introduction

CML2 is a clonal myeloproliferative disorder characterized by progressive granulocytosis, marrow hypercellularity, and splenomegaly. CML occurs with an incidence of ~1–2 cases/100,000 and accounts for ~15% of newly diagnosed cases of adult leukemia. The median age at diagnosis is 45–55 years. The disease course is characteristically triphasic: a chronic phase is followed by transformation to an accelerated phase and then to a blast phase. The chronic phase is relatively stable and responds to therapy but eventually evolves into an intermediate, accelerated phase, where increasing hydroxyurea doses are needed to control disease, followed by a blast phase, resembling acute leukemia. The blast phase phenotype is lymphoblastic in about one-third of patients and myeloblastic in the remaining two-thirds. The median duration of the chronic phase is 3–5 years, the accelerated phase 1–1.5 years, and the blast phase 3–6 months (1, 2).

The molecular biology of CML has been well described. The hallmark of CML is the Ph chromosome found in 90–95% of patients (3). This cytogenetic abnormality consists of an abnormally short chromosome 22, resulting from a reciprocal translocation of chromosomes 9 and 22. The Ph chromosome links the BCR of chromosome 22 with the ABL of chromosome 9. The product of the BCR-ABL gene, the BCR-ABL protein, is a protein tyrosine kinase with an important role in cell growth regulation (2, 4). Insertion of the BCR-ABL gene into murine stem cells induces a leukemia-like disease (5).

Imatinib (Gleevec; Novartis Pharmaceuticals, East Hanover, NJ) is a p.o. administered protein tyrosine kinase inhibitor of the BCR-ABL protein-tyrosine kinase (4, 6). The drug blocks proliferation and induces apoptosis of BCR-ABL-expressing CML cell lines. Similar effects were observed using fresh leukemic cells from Ph+ CML patients (4, 7). In animal models, the drug displays potent antitumor activity against BCR-ABL-expressing cells at tolerated doses.

Regulatory History. Imatinib was initially granted accelerated approval under subpart H on May 10, 2001, for treatment of Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of IFN-α therapy. Approval was based on results of Phase II single arm studies as shown in Table

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2 The abbreviations used are: CML, chronic myelogenous leukemia; Ph, Philadelphia chromosome; CHR, complete hematological response; MCyR, major cytogenetic response; PFS, progression-free survival; CCyR, complete cytogenetic response; ITT, intent to treat.
Patients have no prior treatment for CML with the exception of hydroxyurea. Patients with identified sibling donors who may be eligible for allogeneic transplant are discouraged from entering the study.

**Treatment.** Imatinib is administered p.o. daily at a dose of 400 mg. In patients not achieving a CHR at 3 months or a MCyR at 12 months who are tolerating the drug well, the dose may be escalated stepwise to 400 mg twice daily. For grade 2 nonhematological toxicity (National Cancer Institute Common Toxicity Criteria), imatinib is withheld until toxicity resolves. After resolution of grade 2 toxicity, the drug is resumed at 400 mg daily. After resolution of grade 3 or 4 toxicity, the drug is resumed at 300 mg daily.

On the control treatment arm, IFN-α is suggested to start at a dose of $3 \times 10^6$ IU s.c. three times a week and gradually increased over a 4-week period to $5 \times 10^6$ IU/m$^2$ daily as tolerated.

Once the target dose or the maximum-tolerated dose of IFN-α is reached, cytarabine is started at $20 \times 10^9$/liter, platelets $\geq 100 \times 10^9$/liter, and in patients with low hemoglobin and with thrombocytopenia. The concomitant use of chronic systemic corticosteroid therapy for $\geq 2$ weeks is not permitted.

Because of the possible risk of either reduced activity or enhanced toxicity of the concomitant medication and/or imatinib, drugs known to be metabolized by the same cytochrome

### Table 1: Bases for prior imatinib approvals for chronic myelogenous leukemia

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Chronic phase, IFN-α failure (n = 532)</th>
<th>Accelerated phase (n = 235)</th>
<th>Blast crisis (n = 260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR[f]</td>
<td>88%</td>
<td>63%</td>
<td>26%</td>
</tr>
<tr>
<td>NEL[d]</td>
<td>88%</td>
<td>28%</td>
<td>4%</td>
</tr>
<tr>
<td>RTC[e]</td>
<td>NA</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Major cytogenetic response[g]</td>
<td>49%</td>
<td>21%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Complete (confirmed)[h]</td>
<td>30% (16%)</td>
<td>14% (4%)</td>
<td>5% (1%)</td>
</tr>
</tbody>
</table>

[f] Hematological responses must be of $\geq 4$ weeks duration.
[d] CHR, complete response; NEL, no evidence of leukemia; RTC, return to chronic phase.
[e] CHR for patients in accelerated phase or blast crisis: absolute neutrophil count $\geq 1.5 \times 10^9$/liter, platelets $\geq 100 \times 10^9$/liter, no blood blasts, bone marrow blasts $<5\%$ and no extramedullary disease. CHR for patients in chronic phase: WBC $<10 \times 10^9$/liter, platelets $<450 \times 10^9$/liter, myelocytes + metamyelocytes $<5\%$ in blood, no blasts or promyelocytes in blood, basophils $<20\%$, no extramedullary involvement.
[g] NEL for patients in accelerated phase or blast crisis: same criteria as for CHR but absolute neutrophil count $\geq 1 \times 10^9$/liter and platelets $\geq 20 \times 10^9$/liter.
[h] RTC (blast crisis & accelerated phase): $<15\%$ blasts in blood and marrow, $<30\%$ blasts + promyelocytes in blood and marrow, $<20\%$ basophils in blood, no extramedullary disease other than spleen or liver.
[i] Cytogenetic response criteria: a major response combines both complete and partial responses. Complete (0% Ph+ metaphases). Partial (1–35% Ph+ metaphases).
[j] Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed $\geq 4$ weeks after the initial study.

1. Hematological and cytogenetic responses were the approval basis. Follow-up was relatively short. As a condition of approval, the applicant, Novartis Pharmaceuticals, committed to provide additional follow-up data on safety and efficacy from these Phase II studies. In addition, the applicant committed to conduct a randomized, controlled trial in patients with newly diagnosed Ph+ CML in chronic phase (8).

In response to a Food and Drug Administration request for pediatric studies, the applicant has conducted Phase I studies in children with relapsed or refractory leukemia and is conducting a Phase II study in children with newly diagnosed or relapsed CML in cooperation with the Children’s Oncology Group under the sponsorship of the National Cancer Institute.

In addition, imatinib was granted accelerated approval under subpart H on February 1, 2002, for treatment of Kit (CD117)-positive unresectable and/or metastatic gastrointestinal stromal tumors. The approval basis was tumor response (9).

The following randomized, controlled trial was conducted by Novartis Pharmaceuticals to gain marketing approval for imatinib for treatment of adult newly diagnosed patients with Ph+ CML in chronic phase.

### Patients and Methods

#### Study Design.

Patients are equally randomized to treatment with either imatinib or the combination of IFN-α and cytarabine. Patients are allowed to cross over to the other treatment arm if they do not have a CHR at 6 months (eliminated as a reason for crossover in protocol amendment no. 2), a MCyR at 12 months, lose a CHR, or lose a MCyR. With approval of the Independent Data Monitoring Board, patients are also allowed to cross over with IFN-α intolerance or with a doubling of the WBC at least 1 month apart with at least the second WBC $> 20 \times 10^9$/liter.

A population pharmacokinetic study in 371 patients is performed as part of this protocol. A sparse sampling method (three blood samples/patient on days 1 and 29) is used.

### Patient Selection.

Patients must be adults with Ph+ CML in chronic phase within 6 months of initial diagnosis.
P-450 isoenzymes as imatinib should be used with caution. Special care is required for the concomitant use of paracetamol (acetaminophen, Tylenol) with imatinib. The use of leukopheresis and anagrelide is permitted during the first treatment month and the first three treatment months, respectively. Patients with WBC ≥20.0 × 10^9/liter should receive allopurinol (300 mg) administered by single oral daily dose beginning preferably 48 h before study drug administration. If the WBC count stabilizes, allopurinol may be discontinued at the investigator’s discretion.

**Efficacy Endpoints.** PFS is the primary efficacy end point. The criteria for progression are progression to accelerated phase or blast crisis, increasing WBC defined as a doubling of the WBC at least 1 month apart with at least the second WBC ≥20 × 10^9/liter, loss of CHR, loss of MCyR, or death from any cause.

Secondary efficacy endpoints are CHR, CCyR, MCyR, and time-to-accelerated phase or blast crisis. CHR, CCyR, and MCyR are defined in the subtext of Table 8. Accelerated phase is defined as blasts in the blood or bone marrow > 15 and < 30% or percentage of blasts plus promyelocytes in the peripheral blood or bone marrow > 30% or peripheral blood basophils > 20% or thrombocytopenia < 100 × 10^9/liter unrelated to therapy. Blast crisis is defined as blasts in the blood or bone marrow > 30% or appearance of extramedullary involvement (e.g., chloromas), except for liver and spleen.

**Statistical Methods.** Sample size estimates used an 80% power to detect a hazard ratio of 0.75 for the imatinib arm relative to the IFN-α + cytarabine arm by two-tailed log-rank analysis. This corresponds to an increase in the 5-year PFS rate from 50% on the IFN-α + cytarabine arm to ~60% on the imatinib arm. A median follow-up of 5.25 years and an accrual time of 0.5 years with a uniform patient entry are assumed. The total observation period is expected to be 5.5 years. Under these conditions, the total observation period is expected to be 5.5 years. Under these conditions, the total observation period is expected to be 5.5 years. Under these conditions, the total observation period is expected to be 5.5 years.
shown in Table 2. The treatment groups are well balanced.

between June 16, 2000 and January 30, 2001, a total of 1106 patients were enrolled and randomized, to the target dose for imatinib and IFN-α/H9251 compared with 259 days for IFN-α. Mean dose intensity relative to the target dose for imatinib and IFN-α is 97 and 58%, respectively.

assumptions, ~822 patients should be randomized to obtain the required 385 events. The required 385 events are expected to have occurred after 5.5 years. However, the analysis will be conducted at the time point when the required number of events is reached. To account for a yearly 10% dropout rate, a total of 1032 patients will be enrolled.

Kaplan-Meier estimates will be provided for PFS, time-to-accelerated phase, or blast crisis and survival. The primary analysis of time-to-event end points is ITT. Patients who crossover to the other treatment without an event will not be censored at the time of crossover. Patients who are still receiving treatment without showing an event are censored at the time of last examination. The two-sided log-rank test at the 5% significance level will be used for comparison of treatment groups.

Hematologic and cytogentic response rates on first-line treatment will be calculated. Patients who crossover without a response will be considered nonresponders and will be censored at crossover. Treatment groups will be compared using the two-sided Fisher’s exact test.

Results

Administrative. Between June 16, 2000 and January 30, 2001, a total of 1106 patients were enrolled and randomized, 553 in each arm. These patients were randomized at 177 centers in 16 countries. This report presents the results of an interim analysis using data up to 12 months after last patient was randomized into the study.

Patient Characteristics. Patient characteristics are shown in Table 2. The treatment groups are well balanced.

Drug Exposure. Tables 3–5 describe drug exposure during the study. The mean duration of imatinib dosing is 411 days compared with 259 days for IFN-α. Mean dose intensity relative to the target dose for imatinib and IFN-α is 97 and 58%, respectively.

Clinical Pharmacology. The results of the population pharmacokinetic study in 371 adult patients with newly diagnosed Ph+ CML in chronic phase, using sparse sampling, were similar to the earlier results in the refractory patient population, using dense sampling. Values of the pharmacokinetic parameters included: apparent oral clearance 10.0 liter/h/80 kg; apparent volume of distribution 244.2 liter/80 kg; and half-life 17.1 h.

A rifampin-imatinib drug-drug interaction study was performed in 14 healthy volunteers. The purpose of this study was to determine the effect of a potent cytochrome P450 3A4 inducer on the pharmacokinetics of imatinib, which is metabolized primarily by this enzyme system. Rifampin increased the apparent oral clearance of imatinib 3.8-fold and reduced area under the curve by 70%. This interaction may produce subtherapeutic imatinib concentrations. It is therefore suggested that patients receiving cotreatment with a potent inducer of the cytochrome P450 3A4 system, e.g., phenytoin, phenobarbital, or carbamazepine, initiate treatment with an imatinib dose 50% higher than the usual recommended dose in association with close clinical monitoring.

Patient Disposition. Patient disposition is shown in Table 6. At the time of data cutoff, 90% of patients randomized to imatinib were still on imatinib, whereas only 30% of patients randomized to IFN-α/cytarabine were still receiving IFN-α/cytarabine.

Nine percent of patients initially randomized to imatinib discontinued the study compared with 31% of patients initially randomized to IFN-α/cytarabine. The most common reason for discontinuation on the IFN-α/cytarabine arm was withdrawal of consent (13%).

Table 7 shows the reasons for crossover. Thirty-nine percent of IFN-α/cytarabine patients crossed over to the imatinib arm, whereas only 1% of imatinib patients crossed over to the IFN-α/cytarabine arm. Twenty-three percent of IFN-α/cytarabine patients crossed over to imatinib because of intolerance to treatment.

A total of 47% of patients initially randomized to the IFN-α/cytarabine treatment either crossed over to imatinib because of intolerance to treatment (23%) or discontinued treatment for reasons other than lack of efficacy (24%).

Hematological and Cytogenetic Response Rates. CHR, MCyR, and CCyR rates are shown in Table 8. Imatinib is superior to the IFN-α/cytarabine regimen in all response categories.

PFS. PFS is markedly superior on the imatinib treatment as shown in Fig. 1. Patients are not censored at crossover, and events after crossover are attributed to the initial randomized treatment arm (ITT analysis). There are 24 and 103 patients with progression on the imatinib and IFN-α/cytarabine treatment arms, respectively (Table 9). The comparison of PFS favors imatinib (two-sided log-rank test, P < 0.0001). Median PFS is not reached on either treatment arm.

Time-to-Accelerated Phase or Blast Crisis. All patients diagnosed with blast crisis were previously diagnosed with

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Median duration</th>
<th>Mean duration</th>
<th>Maximum duration</th>
<th>Minimum duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>421</td>
<td>411</td>
<td>563</td>
<td>5</td>
</tr>
<tr>
<td>IFN-α</td>
<td>235</td>
<td>259</td>
<td>554</td>
<td>1</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>4</td>
<td>5.3</td>
<td>22</td>
<td>1</td>
</tr>
</tbody>
</table>

* Number of cytarabine cycles.

a Only 374 of 553 patients randomized to the IFN-α/cytarabine group received cytarabine.

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Median dose</th>
<th>Mean dose</th>
<th>Min mean daily dose</th>
<th>Max mean daily dose</th>
<th>Min mean daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (mg)</td>
<td>400</td>
<td>386</td>
<td>717</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>IFN-α (1 × 10^6 IU/m²)</td>
<td>2.6</td>
<td>2.7</td>
<td>6.0</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Cytarabine (mg/m²)</td>
<td>19</td>
<td>17.7</td>
<td>27.3</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th></th>
<th>Median RDI</th>
<th>Mean RDI</th>
<th>Max Mean RDI</th>
<th>Min Mean RDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>1</td>
<td>0.97</td>
<td>1.79</td>
<td>0.28</td>
</tr>
<tr>
<td>IFN-α</td>
<td>0.57</td>
<td>0.58</td>
<td>1.3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

a RDI, relative dose intensity.
accelerated phase. Thus, in this study, time-to-accelerated phase or blast crisis is the same as time to accelerated phase. Patients are not censored at crossover and events after crossover are attributed to the initial randomized treatment arm (ITT analysis). Ten and 36 patients progress to accelerated phase or blast crisis on the imatinib and IFN-α/cytarabine arms, respectively (Table 10). Fig. 2 shows the comparison of time-to-accelerated phase or blast crisis favoring imatinib (two-sided log-rank test, \(P < 0.0001\)). Median time to accelerated phase or blast crisis is not reached on either treatment arm.

**Survival.** There were 11 deaths in patients randomized to imatinib (1 after crossover to IFN-α/cytarabine), and 20 deaths in patients randomized to IFN-α/cytarabine (4 after crossover to imatinib and 5 after documented extension treatment with imatinib).

The median follow-up is 14 months with a maximum follow-up of 19.5 months. Comparison of overall survival with censoring of survival at bone marrow transplantation in patients who had transplantation fails to show a statistically significant difference between treatment arms (two-sided log-rank test, \(P = 0.112\) and two-sided Wilcoxon test, \(P = 0.202\)).

**Safety.** Imatinib has substantially less severe adverse effects than the combination of IFN-α and cytarabine. The most common imatinib adverse effect is edema seen in 54% of patients. However, only 0.6% of patients have National Cancer Institute Common Toxicity Criteria grade 3 or 4 edema. The other most common adverse effects (per patient analyses) are nausea (43%), muscle cramps (33%), musculoskeletal pain (34%), rash (32%), fatigue (31%), diarrhea (30%), headache (29%), arthralgia (27%), abdominal pain (23%), and myalgia (21%). The \(\geq\)grade 3 imatinib adverse effects seen in \(\geq\)1% of patients include neutropenia (14%), thrombocytopenia (7%), anemia (3%), elevated aspartate aminotransferase (3%), elevated alanine aminotransferase (4%), and arthralgia (2%).

**Gender and Age Effects on Safety.** The following imatinib adverse effects appear to be more frequent in women: periorbital edema; peripheral edema; face edema; rigors; nausea; neutropenia; and headache. There are no adverse effects that are more frequent in men.

The explanation for the increased incidence of imatinib adverse effects in women is unknown. One might think it is on the basis of size because the imatinib dose is not adjusted for size, and women, as a group, are smaller than men. However, exploratory analyses based on body weight does not show that small women have a higher incidence of adverse effects than large women. Likewise, small men do not have a higher incidence of adverse effects than large men. In addition, analyses of pharmacokinetic

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**Table 6 Patient disposition**

<table>
<thead>
<tr>
<th>Disposition/Reason</th>
<th>Imatinib (n = 553)</th>
<th>IFN + cytarabine (n = 553)</th>
<th>Second-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing at time of cut-off</td>
<td>495 (89.5%)</td>
<td>165 (29.8%)</td>
<td></td>
</tr>
<tr>
<td>Crossed over to other treatment arm</td>
<td>7 (1.3%)</td>
<td>218 (39.4%)</td>
<td></td>
</tr>
<tr>
<td>Discontinued treatment</td>
<td>51 (9.2%)</td>
<td>170 (30.7%)</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>11 (2.0%)</td>
<td>31 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>Unsatisfactory therapeutic effect</td>
<td>9 (1.6%)</td>
<td>29 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>No longer required study drug</td>
<td>5 (0.9%)</td>
<td>7 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>(bone marrow transplant)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol violation</td>
<td>10 (1.8%)</td>
<td>15 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Subject withdrew consent</td>
<td>10 (1.8%)</td>
<td>74 (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2 (0.4%)</td>
<td>6 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Administrative problems</td>
<td>0</td>
<td>6 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (0.7%)</td>
<td>6 (1.1%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 7 Reasons for crossover**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Imatinib (n = 553)</th>
<th>IFN-α + cytarabine (n = 553)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients who crossed over</td>
<td>7 (1.3%)</td>
<td>218 (39.4%)</td>
</tr>
<tr>
<td>Reason other than progression</td>
<td>4 (0.7%)</td>
<td>126 (22.8%)</td>
</tr>
<tr>
<td>Intolerance of treatment</td>
<td>4 (0.7%)</td>
<td>126 (22.8%)</td>
</tr>
<tr>
<td>No CHR at 6 months</td>
<td>0 (0.0%)</td>
<td>41 (7.4%)</td>
</tr>
<tr>
<td>No MCyR at 12 months</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Progression</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Increase in WBC</td>
<td>2 (0.4%)</td>
<td>25 (4.5%)</td>
</tr>
<tr>
<td>Loss of CHR</td>
<td>0 (0.0%)</td>
<td>20 (3.6%)</td>
</tr>
<tr>
<td>Loss of MCyR</td>
<td>1 (0.2%)</td>
<td>4 (0.7%)</td>
</tr>
</tbody>
</table>

**Table 8 Response in newly diagnosed CML (first-line)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Imatinib (n = 553)</th>
<th>IFN-α + cytarabine (n = 553)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHR</td>
<td>522 (94.4%)</td>
<td>302 (54.8%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(92.1%, 96.2%)</td>
<td>(50.4%, 58.8%)</td>
</tr>
<tr>
<td>M CyR</td>
<td>419 (75.8%)</td>
<td>67 (12.1%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(72.0%, 79.3%)</td>
<td>(9.5%, 15.1%)</td>
</tr>
<tr>
<td>M CyR</td>
<td>297 (53.7%)</td>
<td>15 (2.7%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(49.5%, 57.9%)</td>
<td>(1.5%, 4.4%)</td>
</tr>
</tbody>
</table>

*Approved by Study Monitoring Committee.
*Only before amendment 2 or in case the patient did not reconsent.
*Changed to 24 months at amendment 2.

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Discussion

The only curative treatment for CML is allogeneic stem cell transplantation. However, only 20–25% of patients are candidates because of advanced age or lack of a suitable donor. CML in chronic phase has been treated using busulfan and, more recently, hydroxyurea. Several studies published in the 1990s showed that treatment with IFN-α resulted in longer survival than busulfan or hydroxyurea (10–14). The study by Guilhot et al. (15, 16) indicated that the addition of cytarabine to IFN-α further prolonged survival. However, the study by Baccarani et al. (17) failed to confirm that the addition of cytarabine to IFN-α prolongs survival.

Thus IFN-α alone or in combination with cytarabine appears to be a reasonable standard for comparison with a new treatment for CML such as imatinib.

CML is a chronic illness with a median survival with available nontransplant treatment of 5–6 years. Thus survival should be the primary end point in studies of newly diagnosed CML in chronic phase. The surrogacy for survival of end points such as CHR, MCyR, and CCyR is uncertain.

Table 11 shows the results of randomized, controlled trials using various IFN-α regimens. Both the Guilhot et al. (15, 16) and Baccarani et al. (17) studies show a statistically significant increase in the cytogenetic response rate with addition of cytarabine to IFN-α, whereas only the Guilhot et al. (15, 16) study shows a statistically significant increase in survival. Therefore, the surrogacy of cytogenetic response rate for survival is questionable when the combination of IFN-α and cytarabine is used. In the remainder of the randomized controlled trials in Table 11, a modest correlation between cytogenetic response rate and survival appears to exist.

CHR appears to be an even less reasonably likely surrogate for survival than cytogenetic response rate. As shown in Table 11, the CHR rates and survival actually go in opposite directions in the Hehlmann et al. (10) and Onishi et al. (12) studies. In the Benlux (13) study, a large difference in CHR rate between the two treatment arms results in similar survival.

PFS as defined in the imatinib study has not been used in reporting the results of most CML studies. Loss of CHR, loss of MCyR, or increase in WBC are criteria for progression in the imatinib study. It is not clear that these are reliable surrogates for survival.
Time-to-progression to accelerated phase or blast crisis is not routinely used in reporting results of CML studies. However, progression to accelerated phase or blast crisis indicates a sufficiently short remaining life that it appears to be a reasonably likely surrogate for survival. Time-to-blast crisis may be an even better surrogate for survival than time-to-accelerated phase because the criteria in most studies are more clearly delineated, and the time to death is shorter. In the imatinib study, all patients who progressed to blast crisis were previously diagnosed with accelerated phase. So time-to-accelerated phase or blast crisis in the imatinib study is really time-to-accelerated phase.

Another issue in interpreting the results of the imatinib study is the 24% of patients initially randomized to the IFN-Hydeara-cytarabine treatment arm. The overall mean dose intensity of IFN-Hydeara achieved was 58% of the target dose, compared with 97% of the target dose for patients on the imatinib treatment arm. A comparison of the imatinib study with previous studies of the combination of IFN-Hydeara and cytarabine shows that in the Guilhot et al. (15, 16) and Baccarani et al. (17) studies, the mean IFN-Hydeara dose was 57 ± 70% of the target dose (5 million IU/m^2), respectively. The percentage of patients receiving any cytarabine was 68, 91, and 95% on the imatinib, Guilhot et al. (15, 16) and Baccarani et al. (17) studies, respectively.

Thus, other studies using the IFN-Hydeara-cytarabine regimen have also not achieved the target dose of IFN-Hydeara but come close to achieving the target dose of cytarabine. As shown in Table 11, the results in these studies do not closely correlate with the success in achieving the target dose of IFN-Hydeara or cytarabine. Thus, in the imatinib study, failure to achieve the target doses with the IFN-Hydeara-cytarabine regimen does not appear to adequately explain the large difference in efficacy between the imatinib and IFN-Hydeara-cytarabine treatment arms.

Another issue in interpreting the results of the imatinib study is the 24% of patients initially randomized to the IFN-Hydeara-cytarabine regimen...
treatment who discontinued treatment for reasons other than lack of efficacy. The 24% discontinuation rate for reasons other than lack of efficacy is high but is similar to other published studies using the IFN-α/cytarabine treatment. By comparison in the Guilhot et al. study (15, 16) and in the Baccarani et al. study (17), 30 and 21% of patients discontinued IFN-α/cytarabine treatment for reasons other than lack of efficacy, respectively.

The high crossover rate (39%) from IFN-α/cytarabine to imatinib may make demonstrating increased survival with imatinib treatment difficult. Using the ITT analysis of survival, any statistically significant survival advantage should be valid. However, ultimately any failure to achieve a statistically significant survival advantage may occur from lack of better efficacy or from the large number of crossovers.

**Regulatory Basis for Approval.** Survival is the efficacy endpoint of primary interest in this chronic disease. IFN-α and allogeneic transplantation are well-established therapies that prolong survival. There is no statistically significant survival difference in the imatinib study at present. However, there are few deaths in either treatment group at the present median follow-up of 14 months. Median survival on the control arm is expected to be 5–6 years.

The imatinib longer median time-to-accelerated phase or blast crisis is a reasonably likely surrogate for longer survival and, furthermore, is considered clinical benefit per se. The results with imatinib are encouraging, but a very small proportion of the expected events has occurred, and the duration of follow-up is relatively short for this chronic disease. If imatinib should stop working after 1.5–2.0 years, the present results could change importantly. Thus, accelerated approval under subpart H, rather than regular approval, was granted on December 20, 2002.

This approval is based primarily on longer time-to-accelerated phase or blast crisis with imatinib treatment and is supported by better results with imatinib for CHR, MCyR, CCyR, and PFS. The approved indication is “for the treatment of newly diagnosed adult patients with Ph chromosome-positive chronic myeloid leukemia in chronic phase. Follow-up is limited.”

**Phase IV Postmarketing Commitments.** As a condition of accelerated approval under subpart H, the applicant committed to provide complete follow-up safety and efficacy information on this imatinib study annually for 3 additional years and survival data and serious adverse event data annually for another 3 years. The first interval report is expected January 2004 with subsequent reports annually until January 2009.

The applicant also committed to conduct and submit a final study report on a prospective study in patients receiving both imatinib and a potent cytochrome P450 3A4 inducer such as phenytoin, phenobarbital, or carbamazepine. The purpose of this study is to determine the imatinib dose necessary to produce area under the curves in patients on enzyme inducers similar to area under the curves achieved in adult patients receiving the recommended imatinib dose (400 mg/day). This study is not a condition for accelerated approval under subpart H. The final study report is expected in December 2004.

**References**

Approval Summary: Imatinib Mesylate Capsules for Treatment of Adult Patients with Newly Diagnosed Philadelphia Chromosome-positive Chronic Myelogenous Leukemia in Chronic Phase

John R. Johnson, Peter Bross, Martin Cohen, et al.


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