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EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

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ABSTRACT

Background BCR-ABL is a constitutively activated tyrosine kinase that causes chronic myeloid leukemia (CML). Since tyrosine kinase activity is essential to the transforming function of BCR-ABL, an inhibitor of the kinase could be an effective treatment for CML.

Methods We conducted a phase 1, dose-escalating trial of STI571 (formerly known as CGP 57148B), a specific inhibitor of the BCR-ABL tyrosine kinase. STI571 was administered orally to 83 patients with CML in the chronic phase in whom treatment with interferon alfa had failed. Patients were successively assigned to 1 of 14 doses ranging from 25 to 1000 mg per day.

Results Adverse effects of STI571 were minimal; the most common were nausea, myalgias, edema, and diarrhea. A maximal tolerated dose was not identified. Complete hematologic responses were observed in 53 of 54 patients treated with daily doses of 300 mg or more and typically occurred in the first four weeks of therapy. Of the 54 patients treated with doses of 300 mg or more, cytogenetic responses occurred in 29, including 17 (31 percent of the 54 patients who received this dose) with major responses (0 to 35 percent of cells in metaphase positive for the Philadelphia chromosome); 7 of these patients had complete cytogenetic remissions.

Conclusions STI571 is well tolerated and has significant antileukemic activity in patients with CML in whom treatment with interferon alfa had failed. Our results provide evidence of the essential role of BCR-ABL tyrosine kinase activity in CML and demonstrate the potential for the development of anticancer drugs based on the specific molecular abnormality present in a human cancer. (N Engl J Med 2001;344:1031-7.)

CHRONIC myeloid leukemia (CML) is a clonal disorder in which cells of the myeloid lineage undergo massive clonal expansion. The disease progresses through three distinct phases — chronic phase, accelerated phase, and blast crisis — during which the leukemic clone progressively loses its ability to differentiate.[1,2] Current therapies include allogeneic bone marrow transplantation and drug regimens including interferon alfa.[3,4] Interferon alfa prolongs overall survival but has considerable adverse effects. Allogeneic bone marrow transplantation, the only curative treatment for CML, is associated with substantial morbidity and mortality and is limited to patients for whom a suitable donor is available.

The characteristic genetic abnormality of CML, the Philadelphia (Ph) chromosome,[5] results from a reciprocal translocation between the long arms of chromosomes 9 and 22.[6] The molecular consequence of this translocation is the generation of the fusion protein BCR-ABL, a constitutively activated tyrosine kinase, which is present in virtually all patients with CML. In vitro studies and studies in animal models have established that BCR-ABL alone is sufficient to cause CML, and mutational analysis has established that the tyrosine kinase activity of the protein is required for its oncogenic activity.[7-10] For these reasons, an inhibitor of the BCR-ABL tyrosine kinase should be an effective and selective treatment for CML.

STI571 (4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phen-

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yl]benzamide methanesulfonate; Glivec, Novartis, Basel, Switzerland) was synthesized after a compound was identified by in vitro screening for tyrosine kinase inhibitors and its activity was optimized for specific kinases. STI571 functions through competitive inhibition at the ATP-binding site of the enzyme, which leads to the inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction. It shows a high degree of specificity for BCR-ABL, the receptor for platelet-derived growth factor, and c-kit tyrosine kinases.[11] STI571 causes arrest of growth or apoptosis in hematopoietic cells that express BCR-ABL but does not affect normal cells.[12-14] On the basis of its antileukemic activity in preclinical models, we conducted a phase 1 trial of STI571 in patients with CML in whom treatment with interferon alfa had failed.

METHODS

Characteristics of the Patients

Patients with CML in the chronic phase (defined by the presence of less than 15 percent blasts or basophils in the peripheral blood or bone marrow) were eligible if they were 18 years of age or older, if they tested positive for the Ph chromosome, and if treatment with interferon alfa had failed. A failure of treatment with interferon alfa was defined as the lack of a complete hematologic response despite three months of treatment with a regimen containing interferon alfa (hematologic resistance), the lack of a cytogenetic response despite one year of treatment with a regimen containing interferon alfa (cytogenetic resistance), or a hematologic or cytogenetic relapse. Patients with severe intolerance to interferon alfa were included after safety data had been obtained for the first seven cohorts of patients treated with STI571. The minimal interval between the discontinuation of prior therapies and the initiation of treatment with STI571 was one week for hydroxyurea, two weeks for interferon alfa and cytarabine, and six weeks for busulfan. Patients with a platelet count of less than 100,000 per cubic millimeter were excluded; adequate renal, hepatic, and cardiac function and performance status were required. Written informed consent was obtained from all patients before they enrolled in the study.

Study Design

The primary end point of this phase 1, dose-escalation trial was the safety and tolerability of STI571; antileukemic activity was a secondary end point. Patients were successively assigned to 1 of 14 dose cohorts, which ranged from 25 to 1000 mg per day. Doses of STI571 were administered orally once daily, except for 800 and 1000 mg, which were administered twice daily as doses of 400 and 500 mg, respectively. Patients received continuous daily therapy with STI571 unless unacceptable adverse effects or disease progression occurred. There was no intrapatient dose escalation. Dose escalation among cohorts was allowed if after 28 days of therapy, none of three or one of six patients had grade 3 (severe) or grade 4 (life-threatening) adverse nonhematologic effects. No other cytoreductive agents were allowed during the study. Complete blood counts were obtained twice a week for the first four weeks, once a week for the next four weeks, and then once every two weeks. Assessments of bone marrow, including cytogenetic analyses, were performed after 8 weeks of therapy and then once every 12 weeks.

Assessment of Toxicity and Response

Safety assessments included the evaluation of adverse events, hematologic assessment, biochemical testing, urinalysis, and physical examination. Toxicity was graded in accordance with the Common Toxicity Criteria of the National Cancer Institute.[15]

A hematologic response was defined as a 50 percent reduction in the white-cell count from base line, maintained for at least two weeks. A complete hematologic response was defined as a reduction in the white-cell count to less than 10,000 per cubic millimeter and in the platelet count to less than 450,000 per cubic millimeter, maintained for at least four weeks.

Cytogenetic responses were determined by the percentage of cells in metaphase that were positive for the Ph chromosome in the bone marrow. Cytogenetic responses, based on analysis of 20 cells in metaphase, were categorized as complete (no cells positive for the Ph chromosome), partial (1 to 35 percent of cells positive for the Ph chromosome), minor (36 to 65 percent of cells positive for the Ph chromosome), and absent (over 65 percent of cells positive for the Ph chromosome). Major responses were defined as complete or partial responses.

Pharmacokinetics

Samples for pharmacokinetic analysis were collected on day 1 and day 28 of treatment, and plasma STI571 concentrations were determined with a liquid chromatographic and mass spectrophotometric assay. The concentration–time curves of STI571 in plasma were evaluated by a noncompartmental analysis (with the use of WinNonlin Pro, version 2.0, Pharsight, Mountain View, Calif.). The variables analyzed were the time to the maximal concentration, the maximal concentration, the terminal half-life, and the area under the concentration–time curve (AUC) from time zero to infinity.

Assessment of BCR-ABL Tyrosine Kinase Inhibition

BCR-ABL kinase activity was determined from samples of peripheral blood obtained before the first dose of STI571 and two hours after the second dose of STI571. Samples were collected in tubes treated with heparin, and white cells were prepared and lysed as described.[16] Cell lysates were separated by electrophoresis on 12.5 percent sodium dodecyl sulfate–polyacrylamide gels, followed by electrophoretic transfer to nylon membranes.[16] The extent of tyrosine phosphorylation of CRK-oncogene–like protein (CRKL) in BCR-ABL–positive neutrophils[17-19] was assessed by gel electrophoresis and immunoblotting with anti-CRKL antiserum.[20]

RESULTS

Enrollment of Patients

From June 1998 to May 2000, 83 patients in whom treatment with interferon alfa had failed, or who could not tolerate the drug, were enrolled at three participating study centers. The characteristics of the patients are summarized in Table 1. Of the 83 patients, 37 had hematologic resistance or relapse, 33 had cytogenetic resistance or relapse, and 13 could not tolerate interferon alfa. The median duration of disease was 3.8 years (range, 0.8 to 14), and the median duration of therapy with interferon alfa was 8.5 months (range, 1 week to 8.5 years). Nineteen patients had had findings suggestive of accelerated disease (5 to 15 percent blasts or basophils in the bone marrow).

The median duration of treatment with STI571 was 310 days (range, 17 to 607). Half of the patients assigned to receive daily doses of 25, 50, or 85 mg of STI571 were removed from the study within two months because of elevated white-cell or platelet counts requiring therapy prohibited by the protocol. The study is ongoing and the results presented here represent an interim analysis of the data.

Pharmacokinetics

STI571 was rapidly absorbed after oral administration, and a mean maximal concentration of 2.3 μg

TABLE 1. CHARACTERISTICS OF THE 83 PATIENTS.

CHARACTERISTIC	VALUE
Sex — no. (%)	
Male	55 (66)
Female	28 (34)
History of disease — no. (%)	
Hematologically resistant or relapsed CML	37 (45)
Cytogenetically resistant or relapsed CML	33 (40)
Intolerance to treatment with interferon	13 (16)
Age — yr	
Median	55
Range	19–76
Duration of disease — yr	
Median	3.8
Range	0.8–14
White-cell count at base line — cells/mm^3	
Median	27,800
Range	9,400–199,000
Platelet count at base line — cells/mm^3	
Median	430,000
Range	102,000–1,814,000

per milliliter (4.6 μM) was reached at steady state by once-daily administration of 400 mg of STI571. The half-life of the drug in the circulation ranged from 13 to 16 hours, and the levels of the drug increased by a factor of 2 or 3 at steady state with once-daily dosing. The mean plasma trough concentration was 0.72 μg per milliliter (1.46 μM) 24 hours after the administration of 400 mg of STI571 at steady state. This amount exceeded the concentration required for the inhibition of cellular phosphorylation by BCR-ABL (concentration required for 50 percent inhibition, 0.25 μM),[12] and this concentration caused the death of cell lines positive for BCR-ABL in vitro.[12-14] The increase in the mean plasma STI571 AUC values was proportional to the administered dose.

Safety Profile

STI571 was generally well tolerated, and a maximal tolerated dose was not identified. The frequency of adverse effects attributable to STI571 is summarized in Table 2. The most common adverse effects included nausea (in 43 percent of patients), myalgias (41 percent), edema (39 percent), and diarrhea (25 percent). Most adverse effects, even at the highest doses, were grade 1 (mild) or grade 2 (moderate). Most patients had a reduction in the hemoglobin level of 1 to 2 g per deciliter; the hemoglobin level typically increased to base-line values or higher with continued therapy. Two patients taking the 600-mg dose, one patient taking the 800-mg dose, and one patient taking the 1000-mg dose had grade 3 anemia. Grade 3 thrombocytopenia and neutropenia occurred in 16 percent and 14 percent of the patients, respectively, receiving doses of 200 mg or more. Elevations of liver-enzyme levels of grade 2 or higher were reported in seven patients; in some of these patients, the abnormalities were reversed during treatment with STI571, whereas in others, persistent elevations required the temporary interruption of therapy or a reduction in the dose.

TABLE 2. DRUG-RELATED ADVERSE EVENTS ACCORDING TO THE DAILY DOSE OF STI571.*

ADVERSE EVENT	25–140 mg (N=14)		200–300 mg (N=23)		350–500 mg (N=18)		600–1000 mg (N=28)		TOTAL (N=83)
	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADE 1 OR 2	GRADE 3 OR 4	GRADES 1–4
	% of patients								no. (%)
Nausea	21	0	30	0	50	0	59	0	36 (43)
Myalgias	21	0	52	0	33	6	28	14	34 (41)
Edema	21	0	22	0	33	0	55	7	32 (39)
Diarrhea	14	0	4	0	33	0	38	3	21 (25)
Fatigue	14	0	22	0	11	0	24	3	17 (20)
Rash	7	0	17	0	11	0	28	3	16 (19)
Dyspepsia	14	0	13	0	28	0	17	0	15 (18)
Vomiting	0	0	13	0	11	0	34	0	15 (18)
Thrombocytopenia	0	0	4	0	11	6	7	24	13 (16)
Neutropenia	0	0	9	4	6	6	0	24	12 (14)
Arthralgias	0	0	4	0	6	0	28	3	11 (13)

*The adverse events listed here were considered to be related to STI571 and were reported in more than 10 percent of patients. A grade of 1 indicates a mild adverse effect, a grade of 2 a moderate effect, a grade of 3 a severe effect, and a grade of 4 a life-threatening effect.

Only two patients receiving doses of STI571 of 300 mg or more discontinued therapy prematurely. One patient with a history of coronary artery disease discontinued therapy because of the recurrence of angina, and a second patient discontinued therapy because of a persistent and progressive rash. There were no deaths during the study.

Hematologic Responses

Hematologic responses occurred in all patients who were treated with 140 mg or more of STI571 per day (Table 3). Of the patients treated with daily doses of 300 mg or more, 53 of 54 had complete hematologic responses and 1 discontinued therapy prematurely (on day 17) because of the recurrence of angina. Hematologic responses typically occurred within two weeks after the initiation of therapy with STI571, as illustrated in Figure 1. In all but one patient treated with 300 mg or more per day, a complete hematologic response was evident within four weeks after the initiation of treatment. Complete hematologic responses have been maintained in 51 of 53 patients with a median follow-up of 265 days (range, 17 to 468). One patient relapsed with chronic-phase disease, whereas CML progressed to the blast phase in a second patient.

TABLE 3. HEMATOLOGIC RESPONSES.

DOSE (MG/DAY)	ALL PATIENTS	PATIENTS WITH RESPONSES	PATIENTS WITH COMPLETE RESPONSES
	no.	no. (%)	
25 or 50	6	2 (33)	0
85	4	2 (50)	1 (25)
140	3	3 (100)	1 (33)
200 or 250	16	16 (100)	9 (56)
300–1000	54	54 (100)	53 (98)
Total	83	77 (93)	64 (77)

Cytogenetic Responses

One patient each in the groups receiving daily doses of 200 mg and 250 mg had a cytogenetic response. As shown in Table 4, 29 of the 54 patients treated with doses of 300 mg or more per day (54 percent) had major or minor cytogenetic responses. Of the 54 patients, 17 (31 percent of the group receiving 300 mg or more per day) had major responses (35 percent or less of cells in metaphase positive for the Ph chromosome); 7 of these were complete cytogenetic remissions (13 percent).

Figure 2 shows data on the 17 patients who had a major cytogenetic response. Cytogenetic responses occurred as early as 2 months and as late as 10 months after the initiation of treatment with STI571. The median time to the best cytogenetic response (the lowest percentage of cells in metaphase that were positive for the Ph chromosome) was 148 days (range, 48 to 331). Two of the seven patients who had a complete cytogenetic response tested negative for BCR-ABL by fluorescence in situ hybridization, and one patient tested negative for BCR-ABL messenger RNA (mRNA) by the polymerase chain reaction.

Inhibition of BCR-ABL–Induced Tyrosine Phosphorylation

Blood samples from treated patients were tested to determine whether BCR-ABL tyrosine kinase activity was inhibited. A major substrate of the enzyme is CRKL, which is the most heavily tyrosine-phos-

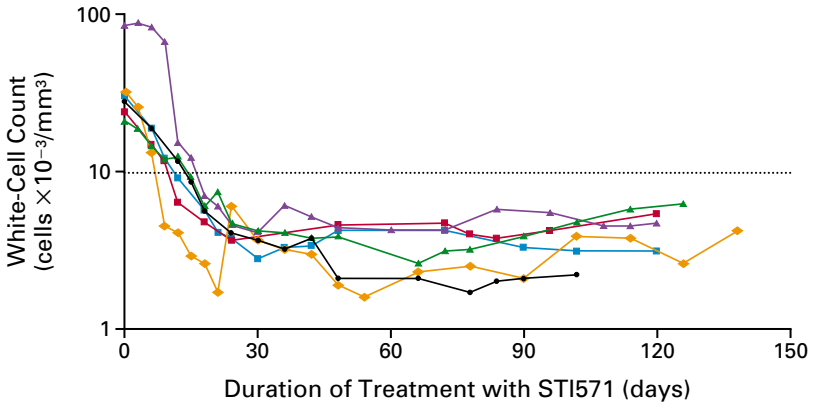

Figure 1. Hematologic Responses in Six Patients Receiving 500 mg of STI571 per day.
Each line represents the white-cell counts for an individual patient. The dotted line indicates the upper limit of a normal white-cell count.

TABLE 4. CYTOGENETIC RESPONSES.

DOSE (mg/DAY)	ALL PATIENTS	PATIENTS WITH COMPLETE OR MAJOR RESPONSES	PATIENTS WITH MINOR RESPONSES
	no.	no. (%)	
300–350	13	5 (38)	2 (15)
400	6	3 (50)	2 (33)
500	6	1 (17)	1 (17)
600	8	4 (50)	4 (50)
750	6	2 (33)	0 (0)
800	8	1 (12)	2 (25)
1000	7	1 (14)	1 (14)
Total	54	17 (31)	12 (22)

phorylated protein in neutrophils from patients with CML.[17-20] CRKL that is phosphorylated by BCR-ABL migrates more slowly on electrophoresis than the unphosphorylated form.[21] Low doses (25 to 50 mg) of STI571 caused no alteration in the mobility of CRKL. An increase in the levels of the rapidly migrating unphosphorylated form and a concomitant decrease in the levels of the slowly migrating phosphorylated form were seen in patients receiving the 85-mg dose of STI571; these changes were more prominent in patients receiving a daily dose of 140 mg and appeared to reach a plateau in patients receiving a daily dose of 250 to 750 mg (Fig. 3).

DISCUSSION

The presence of the BCR-ABL fusion protein in virtually all patients with CML and its required tyrosine kinase activity make CML ideal for testing a specific inhibitor of this enzyme. In our phase 1 study, STI571, an oral, specific inhibitor of the BCR-ABL tyrosine kinase, was well tolerated and had substantial activity against CML. These results were obtained in patients with late-stage disease, in all of whom standard therapy with interferon alfa had failed.

The rate of complete hematologic responses increased as the daily dose increased from 85 mg to 250 mg and reached 98 percent in patients treated with 300 mg or more of STI571. Complete hematologic responses typically occurred within four weeks after the initiation of therapy. The exception was a patient in the 350-mg group in whom the plasma half-life of STI571 was short (seven hours) and the AUC was similar to that for patients in the 85-mg group. STI571 is metabolized primarily by the CYP3A4 enzyme, and the patient in the 350-mg group was being treated with phenytoin, a known inducer of CYP3A4. When treatment with phenytoin was discontinued and the dose of STI571 was increased to 500 mg, the patient had a complete hematologic response associated with trough levels of STI571 similar to those observed

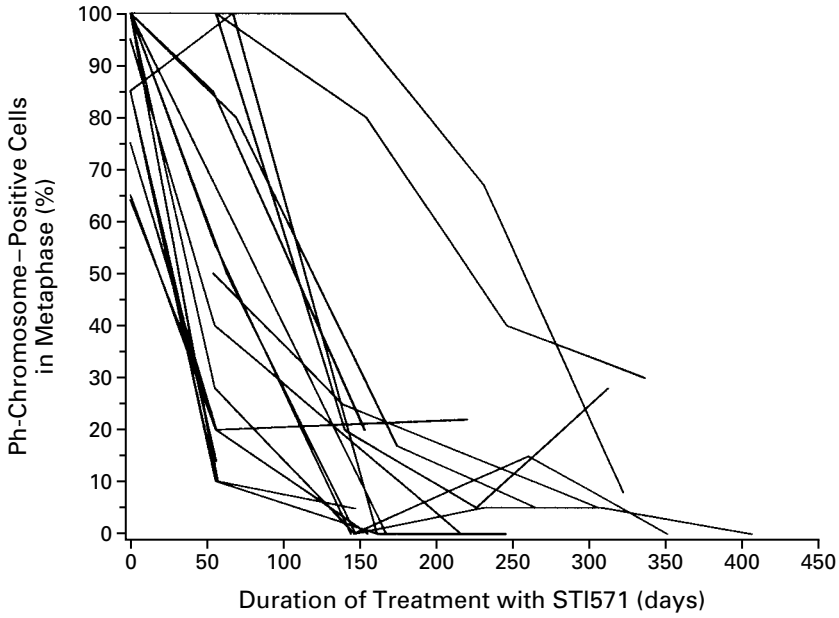

Figure 2. Patients with a Major Cytogenetic Response.

The percentage of cells in metaphase positive for the Ph chromosome (in bone marrow) and the number of days that the patients received STI571 are shown. Each line represents the cytogenetic response for an individual patient.

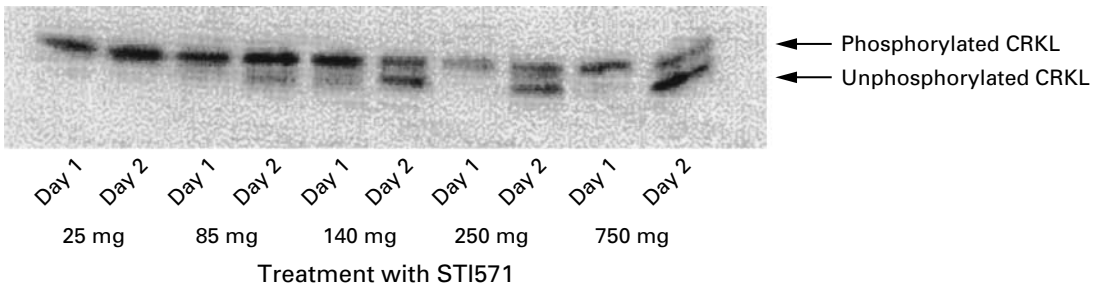

Figure 3. Immunoblot Assays Demonstrating the Degree of Phosphorylation of the BCR-ABL Substrate CRKL in Individual Patients in the Groups Receiving Daily Doses of 25, 85, 140, 250, and 750 mg of STI571.

in other patients in the 500-mg group. This observation suggests that drugs that induce CYP3A4 could lead to low and ineffective levels of STI571, whereas drugs that interfere with the activity of the CYP3A4 enzyme could decrease the metabolism of STI571, leading to increased levels of STI571 and thereby causing toxic effects.

During treatment with STI571, blood counts gradually returned to normal during the first month, suggesting that the drug does not rapidly induce apoptosis, as would be expected with standard chemotherapy. Blood counts were maintained within normal limits regardless of whether a cytogenetic response was observed. This suggests that inhibition of the BCR-ABL tyrosine kinase restores normal regulatory behavior to the leukemic clone. Cytogenetic responses might follow if, over time, the leukemic clone was displaced either by normal hematopoietic progenitors that had regained a proliferative advantage or by differentiation of the leukemic stem cell, which leads to its elimination.

Of the 54 patients treated with at least 300 mg of STI571 per day, 29 (54 percent) had cytogenetic responses, including 7 with complete cytogenetic remissions. As compared with the cytogenetic responses during therapy with interferon alfa, those during treatment with STI571 occurred relatively rapidly. In one patient, BCR-ABL mRNA could not be detected by polymerase chain reaction.

The most frequent adverse effects that seemed to be related to treatment with STI571 were nausea, edema, myalgias, and diarrhea; overall, most were mild. In seven patients, there were elevations of liver-enzyme levels of grade 2 or higher, as was also seen in our study of patients with acute leukemia, reported elsewhere in this issue of the *Journal*.[22] Myelosuppression, which occurred in up to a quarter of the patients, was not dose limiting and was managed by temporary interruption of treatment or dose reduction. Myelosuppression may be either a consequence of a pharmacologic effect of STI571 through inhibition of c-kit or a reflection of compromised underlying normal hematopoiesis in patients with leukemia.

We did not identify a maximal tolerated dose for STI571, but other end points could be used to choose a dose for future trials. One is the pharmacokinetic profile of STI571. Levels of the drug that killed CML cells in vitro correlated well with clinical response and serum drug levels in the 400-mg group. The dose–response curve clearly demonstrates a relation between dose and hematologic response. Also, there is substantial in vivo inhibition of the enzymatic activity of BCR-ABL at the 400-mg dose, as demonstrated by decreased phosphorylation of CRKL, a substrate of BCR-ABL. For these reasons, we recommend a daily dose of at least 400 mg for future studies.

These results show that the BCR-ABL tyrosine kinase is critical to the development of CML and demonstrate the potential for the development of anticancer drugs based on the specific molecular abnormality in a human cancer.

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