PERGAMON

European Journal of Cancer Vol. 38 Suppl. 5 (2002) S77–S82

European Journal of Cancer

www.ejconline.com

Imatinib: the first 3 years

Renaud Capdeville [a,*], Sandra Silberman [b] and Sasa Dimitrijevic [a]

[a] *International Clinical Research Oncology, Novartis Pharma AG, CH-4056 Basel, Switzerland*
[b] *Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936, USA*

Abstract

Imatinib (Glivec®, formerly STI571, Novartis Pharma AG, Basel, Switzerland) potently inhibits several protein tyrosine kinases, including Bcr-Abl, Kit, and the platelet-derived growth factor receptor. Phase I and II studies demonstrated that orally administered imatinib is highly effective and well tolerated in all phases of chronic myeloid leukemia (CML) at doses ranging from 400 to 600 mg. Importantly, preliminary evidence suggests that patients with advanced CML achieving hematologic or major cytogenetic responses to imatinib may have longer survival than those without such responses, whereas chronic phase patients who respond to treatment may have longer times to disease progression. Ongoing and planned studies are focused on optimizing CML treatment with imatinib, evaluating imatinib-based combination therapy, defining additional therapeutic targets and exploring the use of imatinib in children. In particular, results from several combination phase I studies are expected shortly, including an evaluation of combination imatinib–interferon-α therapy and imatinib–cytarabine in chronic phase CML, and a phase I study of single-agent imatinib in children with Philadelphia chromosome-positive leukemia is ongoing. A large phase III trial comparing imatinib with standard inferferon alfa plus cytarabine in first-line CML treatment is also ongoing.

Keywords: Chronic myeloid leukemia; Imatinib mesylate; Proto-oncogene protein c-Kit; Receptor protein-tyrosine kinase; Enzyme inhibitor; Antineoplastic agent; Anterferon a; Muscle-tissue neoplasm

1. Introduction

Imatinib (Glivec®, formerly STI571, Novartis Pharma AG, Basel, Switzerland) inhibits the activity of the tyrosine kinase Bcr-Abl, a constitutively activated fusion product of the Philadelphia chromosome that appears to be responsible for chronic myeloid leukemia (CML) [1]. This genetic abnormality arises from the reciprocal translocation of the long arms of chromosomes 9 and 22 [2]. Imatinib competitively inhibits the ATP binding of the enzyme, thereby blocking the phosphorylation of protein substrates involved in signal transduction and consequent CML cell growth. In animal models, the expression of Bcr-Abl is sufficient for causing CML, and the protein tyrosine kinase activity is mandatory in this malignant process [3,4]. Accordingly, the clinical activity of imatinib was initially evaluated in CML patients.

CML was an ideal target for the initial clinical development of imatinib, not only because of the strong understanding of the basic biology of the disease but also because of the relatively easy methods of measuring drug activity. Hematologic responses to imatinib treatment were determined by reductions in peripheral leukocyte counts, and cytogenetic responses were measured by the percentage of bone marrow metaphase cells containing the Philadelphia chromosome [5]. The experience with imatinib in preclinical models as well as the early promising results in the clinic suggests that the development of future targeted agents should put more emphasis in the early integration of disease-specific phase I studies, in which there is a strong understanding of the biology and an easy method of determining clinical activity. Such

* Corresponding author. Tel.: +41 (61) 3244181; Fax: +41 (61) 3242034.
E-mail address: renaud.capdeville@pharma.novartis.com

0959-8049/02/$ – see front matter

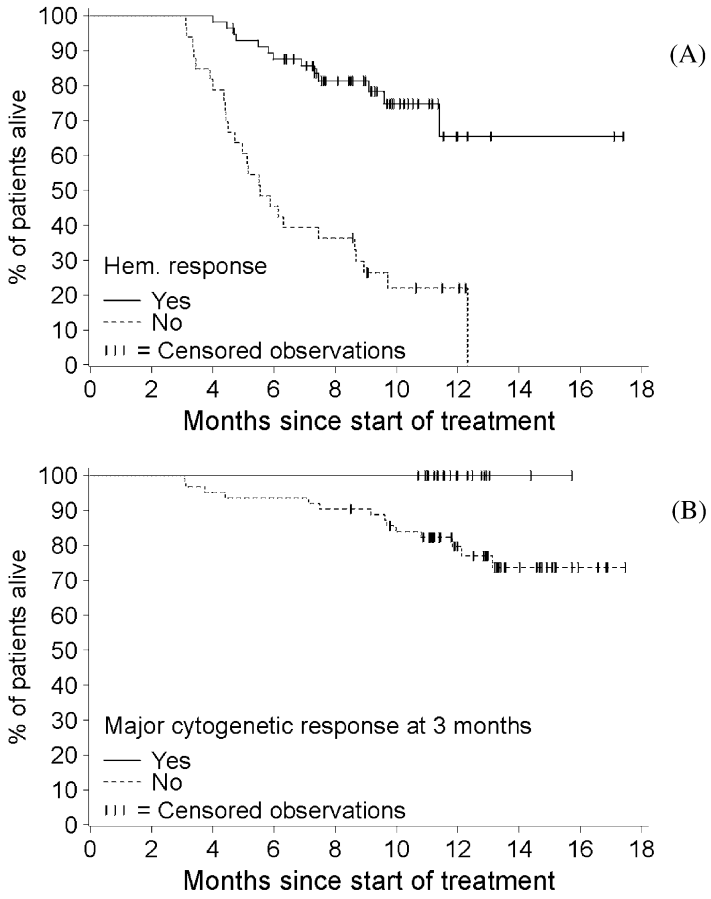

Fig. 1. Fig. 1 (A) Survival of patients with myeloid blast crisis according to hematologic response (HR) to imatinib therapy at 3 months ($p < 0.001$) and (B) of patients with accelerated phase CML according to major cytogenetic response at 3 months ($p = 0.0339$).

studies may greatly enhance the amount of information that can be generated from phase I trials, including not only safety and pharmacokinetic data but also data on pharmacodynamic activity and potential clinical efficacy. Consequently, disease-specific phase I studies are expected to provide much greater insight into the dose-response and dose-activity relationships, which is critical in determining a range of potentially active doses to be recommended for subsequent studies. This paper will provide an overview of clinical studies that are ongoing or expected to start shortly in CML as well as in other malignancies (Fig. 1).

2. Phase I study in chronic phase CML

In the first phase I study, patients with chronic phase CML who had failed previous interferon-α therapy were treated at doses ranging from 25 to 1000 mg daily. No maximum tolerated dose was formally identified despite a trend for a higher frequency of grade 3-4 adverse events and hematologic toxicity at doses of 750 mg or higher [5]. A clear dose-response relationship was evident and, at doses of 300 mg or higher, 98% of the patients achieved a complete hematologic response. Furthermore, a cytogenetic response was seen in 54% of patients treated at a dose of 300 mg or higher, including 31% major responses (complete and partial responses). Subsequently, this dose-response relationship was further described with modeling analyses using the leukocyte count at day 28 as pharmacodynamic endpoint [6].

Pharmacokinetic analysis showed that daily oral doses of 250 mg and higher produced trough serum imatinib levels greater than the drug concentration needed to inhibit Bcr-Abl kinase activity by 50% in vitro (IC_{50}). Accordingly, the serum drug levels achieved in the phase I study were compatible with the desired therapeutic level. Importantly, imatinib showed linear pharmacokinetics over the dose range of the phase I study in terms of the area under the serum concentration vs. time curve (AUC) as well as the maximal serum drug concentration (C_{max}).

Later, analysis of blood samples from patients treated with imatinib showed that Bcr-Abl kinase was inhibited. As the dose of imatinib increased, phosphorylation of CRKL, a major substrate of the kinase, was progressively inhibited, and reappearance of unphosphorylated CRKL increased correspondingly [5].

From this study, doses of 400 to 600 mg daily were recommended for subsequent trials in CML and other ma-

lignancies on the basis of the hematological and cytogenetic responses, the trough serum levels above the IC_{50} of the kinase, and the effective inhibition of the downstream target of the kinase.

3. Phase II studies in CML

Three large phase II studies have been conducted in CML patients, with record accrual seen in each (Table 1). The first study enrolled 260 patients with myeloid blast crisis [9]; the second study enrolled 235 patients with accelerated phase CML [8]; the third study enrolled 532 patients with chronic phase CML, following failure of prior interferon-α therapy [7]. Patients with a myeloid blast crisis were treated for a median of 121 days, whereas those in the other 2 trials were treated for a median of nearly 1 year. As expected on the basis of the underlying prognosis of each form of CML, a higher proportion of patients with blast crisis (67%) and accelerated phase disease (34%), as compared with chronic phase CML (9%), discontinued the study due to progressive disease or death. Discontinuations due to drug-related adverse events were limited, ranging from 2.1% of those with chronic phase CML to 5% of those with blast crisis.

Hematologic and cytogenetic response rates declined in relationship to the severity of CML. Hematologic responses were achieved by 95% of chronic phase CML patients, 69% of those with accelerated phase disease, and 31% of those with blast crisis (Table 1). Major cytogenetic responses (MCR) were achieved by 60%, 24%, and 16% of patients in these groups, respectively, underscoring the need to treat CML patients as early as possible. Interestingly, these rates of MCR are superior to those obtained with any other drug therapy, including first-line therapy with interferon-α, where response rates ranging from 9% to 37% have been reported [10].

Table 1
Phase II studies of imatinib in CML

	Chronic phase [7]	Accelerated phase [8]	Blast crisis [9]
Patients, *n*	532	235	260
Months of treatment, median (range)	18 (<1–20)	11 (<1–17)	4 (<1–23)
Discontinuations, %	13	43	85
Progressive disease	8	31	58
Death	1	3	9
Adverse events [a]	2.4	6	9
Transplantation	0	2	5
Other	2	<1	3
Response rates, %			
Hematologic	95	69	31
Cytogenetic	60	24	16

[a] Discontinuations due to drug-related adverse events were 2.1%, 2.5% and 5% in the three studies, respectively.

In the two studies of advanced disease, the first third of patients were treated with 400 mg of imatinib daily, but when more safety data became available from the phase I study, the remaining two thirds were treated with 600 mg daily. In both studies, there was clear evidence of higher hematologic and major cytogenetic response rates with the higher dose. Notably, responses to imatinib appeared to have a significant impact on patient survival using landmark analysis. Patients in myeloid blast crisis who achieved hematologic responses at 3 months had significantly longer survival than those without such responses ($P < 0.001$). Similarly, patients in the accelerated phase of CML with major cytogenetic responses had significantly longer survival as compared with patients without this response ($P = 0.011$). Finally, in patients with chronic phase CML, 97% of patients with major cytogenetic responses at 3 months did not progress to accelerated phase or blast crisis at 1 year as compared to 88% of those without cytogenetic responses ($P = 0.005$).

The phase II studies demonstrate that imatinib is effective at all stages of CML and shows a favorable safety profile. However, several rare but potentially serious adverse events were seen (edema and fluid retention syndrome, hepatotoxicity), and therefore caution is warranted on the part of the treating physician. Myelosuppression occurs more commonly in accelerated phase and blast crisis than in chronic phase CML, suggesting that it might be related to an increasingly compromised normal bone marrow reserve as the disease evolves towards more advanced stages in its natural history.

4. The next steps

Several steps need to be taken in order to expand on the high efficacy seen in CML patients who were previously treated with interferon-α.

4.1. Optimizing CML therapy with imatinib

The first step will be to determine how to optimize CML treatment. Accordingly, the role of imatinib in front-line treatment of CML is being evaluated in the International Randomized Trial of Interferon vs. STI571 (IRIS), which was initiated in June 2000. A total of 1106 newly diagnosed CML patients were randomly assigned to receive single-agent imatinib 400 mg daily or standard combination treatment with interferon-α and cytarabine [11]. The primary endpoint of the study is time-to-progression, where progression is defined as progression to accelerated phase or blast crisis, rapidly increasing leukocyte count despite appropriate patient management, or loss of either hematologic or cytogenetic response. If disease progression occurred or patients were unable to tolerate treatment, patients were allowed to cross over to the other treatment arm.

Another aspect of optimizing treatment is to gain a greater understanding of the mechanisms involved in drug resistance. In vitro data indicate that resistance to imatinib can arise from amplification of the Bcr-Abl gene; emergence of new Abl mutations; overexpression of the multidrug resistance-associated P-glycoprotein (Pgp); and binding of drug in serum to α_1 acid glycoprotein [12–14]. In clinical samples, drug resistance has been associated with either Bcr-Abl gene amplification or de novo mutations on Bcr-Abl [15–18].

4.2. Combining imatinib with other agents

The second step is to explore imatinib-based combination therapy. A large number of in vitro studies have been conducted in which the antiproliferative effect of imatinib has been evaluated in combination with various chemotherapeutic agents, mostly on leukemic cells using isobologram methodology [19–23]. Synergistic interactions have been reported with a number of drugs, including carboplatin, daunorubicin, cytarabine, etoposide, gemcitabine, mafosfamide, mitoxantrone, vincristine and interferon-α. In most other cases, additive effects were reported, but antagonistic effects have also been seen in some experiments when imatinib was combined with hydroxyurea, methotrexate or topotecan.

The feasibility of combining imatinib with other agents is being explored in patients with chronic phase CML. A phase II study evaluating imatinib in combination with low-dose cytarabine is currently being analyzed [24]. Several studies are testing the feasibility of combining imatinib with interferon-α or pegylated interferon-α. Preliminary results from a large phase II study being conducted in the United Kingdom are expected by the end of 2001 [25]. Studies are also ongoing in which more complex combinations are being tested, including combination therapy with imatinib, interferon-α and low-dose cytarabine and sequential therapy with high-dose cytarabine followed by imatinib. The results of these trials will be essential in designing future randomized phase III trials in newly diagnosed CML to determine the relative efficacy of imatinib as a single agent as compared with imatinib in combination therapy with either interferon-α or cytarabine.

Other studies are exploring the use of imatinib-based combination therapy in patients with advanced disease. For example, studies of patients with myeloid blast crisis are evaluating imatinib in combination with high-dose cytarabine; daunorubicin and cytarabine; and mitoxantrone, etoposide and cytarabine. Finally, the role of imatinib in bone marrow transplantation protocols is being evaluated to determine whether it is feasible to administer the drug before or after transplant in order to decrease the rate of relapse posttransplant.

4.3. Identifying new potential indications for imatinib

The most challenging next step is the search for new therapeutic indications for imatinib. In addition to inhibiting Bcr-Abl, imatinib potently inhibits several other important kinases, including the stem cell factor receptor Kit and the platelet-derived growth factor (PDGF) receptor [26]. Accordingly, the roles of these imatinib-sensitive kinases in malignant transformation as well as in tumors with multiple signaling pathways must be defined, and their clinical significance in terms of prognosis and response to treatment must be determined. Once disease targets are identified, several important questions must be addressed: for which patients will imatinib be of benefit?; how will drug efficacy be determined both biochemically and clinically?; and what is the optimal way to administer imatinib (i.e., single-agent, combination, sequential, adjuvant, continuous or intermittent)?.

The search for new indications has been integrated into the concept of a “target incubator”, which includes conducting disease-specific phase I/II trials that include appropriate pharmacodynamic measurements and correlative scientific assessments, molecularly targeted clinical trials, continuing preclinical research, and the development of suitable diagnostic assays. It will be important to capitalize on continuing preclinical research in which new animal models are being identified and various imatinib-based combinations are being evaluated. The development of methodologies to detect these imatinib-sensitive kinases in clinical specimens will be critical to gain a better understanding of these targets in various malignancies.

Potential indications based on Kit, the receptor encoded by the c-Kit proto-oncogene, as the molecular target include gastrointestinal stromal cell tumors (GISTs), small-cell lung cancer (SCLC), neuroblastoma and Kit-positive hematologic malignancies (Table 2). Small-cell lung cancer has a poor prognosis, with a median survival of approximately 9 months [27]. The coexpression of stem cell factor and Kit is involved in a functional autocrine loop in this disease, and imatinib has been shown to inhibit Kit signaling and SCLC cell growth [28,29]. Clinical investigations are ongoing in patients with Kit-positive SCLC to determine the feasibility and potential clinical activity of imatinib as a single agent or in combination with standard chemotherapy. An essential part of these protocols is clearly a very careful assessment by a central pathology review of the expression patterns of Kit. In addition, the value of functional imaging using F-18-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans will be evaluated.

Potential indications based on the PDGF receptor as the imatinib-sensitive target include chronic myelomonocytic leukemia (CMML), gliomas and prostate cancer (Table 2). In prostate cancer, ongoing clinical research includes one trial of imatinib in patients with hormone refractory prostate cancer, a neoadjuvant study designed to

Table 2
Potential therapeutic indications for imatinib based on c-Kit and the PDGF receptor as the molecular target

c-Kit-expressing tumors	PDGF receptor-expressing tumors
• Gastrointestinal stromal cell tumors	• Chronic myelomonocytic leukemia
• Small cell lung cancer	• Gliomas
• Neuroblastoma	• Prostate cancer
• Kit-positive acute myeloid leukemia	• Other solid tumors (e.g., breast, ovarian, colon)
• Kit-positive non-Hodgkin's lymphoma	• Bone metastasis

assess the effect of imatinib therapy on pharmacodynamic markers measured on tumor tissue at the time of prostatectomy, and studies of the feasibility of combining imatinib with chemotherapy. In glioma patients, where the PDGF receptor has been shown to play a role as a growth factor signal based on an autocrine loop, imatinib is being tested in single-agent and combined-modality regimens.

The approach to identify potential indications for imatinib by selecting patients on the basis of their molecular profile rather than their histological profile is being tested in an open-label, multicenter, pilot study. This study was designed to evaluate single-agent imatinib in patients with life-threatening malignant diseases known to be associated with one or more imatinib-sensitive kinases. Eligible patients had tumors with no other treatment alternatives, and either Kit expression on more than 50% of their neoplastic cells or PDGF receptor and/or Abl expression with additional proof of functional significance on the basis of published literature or in vitro data. The study is still ongoing and as of September 2001, a total of 48 patients with a wide range of malignancies have been enrolled. Interestingly, one patient described as having CMML with a t(5;12) translocation achieved a complete hematologic and cytogenetic response. A second patient with a myeloproliferative disorder with eosinophilia and skin involvement and a genetic rearrangement involving the PDGF receptor also responded to imatinib therapy [30]. These two successes based on primary identification of the molecular target support the premise of this clinical design approach.

4.4. Using imatinib in children

The pediatric development program for imatinib includes a number of studies that are ongoing or are expected to start shortly. A phase I study of Philadelphia chromosome-positive leukemias has closed accrual and results are expected to be available by the end of 2001. In a preliminary communication, four (29%) of 14 patients at the first three dose levels of 260 to 440 mg/m^2 experienced grade 4 hematological toxicity, but the maximum tolerated dose had not yet been reached [31]. This study will provide important information that is necessary for dosing recommendations in children.

Following this initial study, phase II trials are ongoing in North America and Europe in children with CML and acute lymphocytic leukemia (ALL), and exploratory multitargeted protocols similar to the study described above, but for patients with selected solid tumors, are also in the planning phase.

5. Conclusion

The development of imatinib may have established a new standard for the development of targeted cancer therapy. This agent has only been in clinical development for 3 years, but already it has set a record in the speed of approval by health authorities. The Food and Drug Administration approved imatinib after a 2.5-month review process, which is unprecedented in the field of oncology. Despite the short development time, approximately 10 000 patients with CML and more than 1000 patients with solid tumors have been treated in clinical trials. Large phase III trials in CML and GIST are already ongoing, with patient accrual already completed in several of them. This exceptional clinical research effort will rapidly generate invaluable knowledge that will be critical for the optimization of the use of this agent in these diseases. The potential of this drug in other cancers believed to involve either Kit or PDGF-R signaling pathways will be better characterized when the ongoing exploratory clinical studies are completed.

References

[1] Deininger MW, Goldman JM, Lydon N, Melo JV. The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL-positive cells. *Blood* 1997; **90**: 3691–3698.
[2] Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 1973; **243**: 290–293.
[3] Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. *Science* 1990; **247**: 824–830.
[4] Lugo TG, Pendergast AM, Muller AJ, Witte ON. Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. *Science* 1990; **247**: 1079–1082.
[5] Druker BJ, Talpaz M, Resta DJ, *et al*. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; **344**: 1031–1037.
[6] Peng B, Hayes M, Racine-Poon A, *et al*. Clinical investigation of the pharmacokinetic and pharmacodynamic relationship for Glivec (STI571): a novel inhibitor of signal transduction [abstract]. *Proc Am Soc Clin Oncol*, 2001; **20**: 280A.
[7] Kantarjian H, Sawyers C, Hochhaus A, *et al*. Gleevec (imatinib mesylate) induced hematologic and cytogenetic responses confirmed and expanded in patients with chronic myeloid leukemia (CML): a phase II study update. *Blood* 2001; **98**: 845a, abstract #3508.
[8] Talpaz M, Silver R, Druker B, *et al*. Glivec (imatinib mesylate) induces durable hematologic and cytogenetic responses in patients

with accelerated phase chronic myeloid leukemia: results of a phase II study. *Blood* 2002, in press.

[9] Sawyers C, Hochhaus A, Feldman E, *et al*. Glivec (imatinib mesylate) induces hematologic and cytogenetic responses in patients with chronic myeloid leukemia in myeloid blast crisis: results of a phase II study. *Blood* 2002, in press.

[10] Silver T, Woolf SF, Hehlmann R, *et al*. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. *Blood* 1999; **94**: 1517–1536.

[11] Guilhot F, Chastang C, Michallet M, *et al*. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. *N Engl J Med* 1997; **337**: 223–229.

[12] Mahon FX, Deininger MW, Schultheis B, *et al*. Selection and characterization of BCR-ABL positive cell lines with differential sensitivity to the tyrosine kinase inhibitor STI571: diverse mechanisms of resistance. *Blood* 2000; **96**: 1070–1079.

[13] Weisberg E, Griffin JD. Mechanism of resistance to the ABL tyrosine kinase inhibitor STI571 in BCR/ABL-transformed hematopoietic cell lines. *Blood* 2000; **95**: 3498–3505.

[14] Gambacorti-Passerini C, Barni R, le Coutre P, *et al*. Role of alpha$_1$ acid glycoprotein in the in vivo resistance of human BCR-ABL(+) leukemic cells to the abl inhibitor STI571. *J Natl Cancer Inst* 2000; **92**: 1641–1650.

[15] Gorre ME, Mohammed M, Elwood K, *et al*. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science* 2001; **293**: 876–880.

[16] Gorre M, Shah N, Ellwood K, *et al*. Roots of clinical resistance to STI-571 cancer therapy. *Science*, 2001; **293**: 2164–2165 (letter).

[17] Barthe C, Cony-Makhoul P, Melo JV, *et al*. Roots of clinical resistance to STI-571 cancer therapy. *Science*, 2001; **293**: 2163 (letter).

[18] Hochhaus A, Kreil S, Corbin A, *et al*. Roots of clinical resistance to STI-571 cancer therapy. *Science*, 2001; **293**: 2164 (letter).

[19] Kano Y, Akutsa M, Tsunoda S, *et al*. In vitro cytotoxic effects of a tyrosine kinase inhibitor STI571 in combination with commonly used antileukemic agents. *Blood* 2001; **97**: 1999–2007.

[20] Topaly J, Zeller WJ, Fruehauf S. Synergistic activity of the new ABL-specific tyrosine kinase inhibitor STI571 and chemotherapeutic drugs on BCR-ABL positive chronic myelogenous leukemia cells. *Leukemia* 2001; **15**: 342–347.

[21] Thiesing JT, Ohno-Jones S, Kolibaba KS, Druker BJ. Efficacy of STI571, an abl tyrosine kinase inhibitor, in conjunction with other antileukemic agents against bcr-abl-positive cells. *Blood* 2000; **96**: 3195–3199.

[22] Uemura N, Griffin JD. The ABL kinase inhibitor STI571 does not affect survival of hematopoietic cells after ionizing radiation. *Blood* 2000; **96**: 3294–3295.

[23] Fang G, Kim CN, Perkins CL, *et al*. CGP57148B (STI-571) induces differentiation and apoptosis and sensitizes Bcr-Abl-positive human leukemia cells to apoptosis due to antileukemic drugs. *Blood* 2000; **96**: 2246–2253.

[24] Druker BJ, Kantarjian H, Talpaz M, *et al*. A phase I study of Gleevec (imatinib mesylate) administered concomitantly with cytosine arabinoside (Ara-C) in patients with philadephia positive chronic myeloid leukemia (CML). *Blood* 2001; **98**: 845a, abstract #3511.

[25] O'Brien S, Vallance SE, Craddock C, *et al*. PEGIntron and STI571 combination evaluation study (PISCES) in chronic phase chronic myeloid leukemia. *Blood* 2001; **98**: 846a, abstract #3512.

[26] Buchdunger E, Cioffi CL, Law N, *et al*. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther* 2000; **295**: 139–145.

[27] Chute JP, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol* 1999; **17**: 1794–1801.

[28] Krystal GW, Honsawek S, Litz J, Buchdunger E. The selective tyrosine kinase inhibitor STI571 inhibits small cell lung cancer growth. *Clin Cancer Res* 2000; **6**: 3319–3326.

[29] Wang WL, Healy ME, Sattler M, *et al*. Growth inhibition and modulation of kinase pathways of small cell lung cancer cell lines by the novel tyrosine kinase inhibitor STI 571. *Oncogene* 2000; **19**: 3521–3528.

[30] Apperley JF, Schultehis B, Chase A, *et al*. Chronic myeloproliferative diseases involving rearrangements of the platelet derived growth factor receptor -beta (PDGFR-β]) within t(5;12): complete cytogenetic remissions on STI571. American Society of Hematology 43rd annual meeting, Orlando, FL, December 2001.

[31] Champagne MA, Hershon L, Rosamilia M, Capdeville R, Bernstein ML. STI571 in the treatment of pediatric Philadelphia (Ph+) chromosome-positive leukemia: a Children's Oncology Group phase I study (P-9973) [abstract]. *Proc Am Soc Clin Oncol* 2001; **20**: 1466A.