

## Phase II Study of Imatinib in Patients with Small Cell Lung Cancer

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### ABSTRACT

**Purpose:** The purpose of our study was to assess the objective response to imatinib administered to patients with small cell lung cancer (SCLC).

**Experimental Design:** Eligible patients were those with SCLC who either had chemotherapy-naïve extensive-stage or had SCLC in a sensitive relapse. Patients enrolled on the trial were treated with 600 mg of imatinib daily. The response was assessed using Southwest Oncology Group (SWOG) criteria after 3 and 6 weeks. Tumor specimens were examined by immunohistochemistry for the KIT receptor.

**Results:** Nineteen patients with SCLC entered on the study, including 16 men and 3 women. Nine patients had previously untreated extensive-stage disease and 10 patients had sensitive relapse. A central pathology review confirmed SCLC in only 14 of the 19 patients. There were no objective responses; however, one patient with sensitive-relapse disease had prolonged stabilization of disease (>3 months) while on imatinib therapy. The median time to progression was 0.8 months (range, 0.6–1.3 months) and 1.2 months (range, 0.2–4.1 months) in the previously untreated and sensitive-relapse groups, respectively. Tumor tissue samples from 4 (21%) of the 19 patients had the KIT receptor (CD117).

**Conclusions:** There was no observed antitumor activity in this limited Phase II trial of patients with SCLC, of which only a few tumors showed expression of the imatinib target. The results of this trial are, thus, inconclusive about the antitumor activity of imatinib against SCLC with the tar-

geted KIT receptor (CD117). Further testing of imatinib in patients with SCLC will focus on demonstration of KIT expression in the setting of confirmed SCLC histology.

### INTRODUCTION

SCLC<sup>7</sup> represents 20% of all lung cancers and can rarely be cured with currently available therapy. Chemotherapy has improved survival during the past 20 years but the 5-year survival for patients with extensive-stage SCLC is still only 2% (1, 2). Therefore, additional effective anticancer therapies are needed for these patients.

Autocrine and paracrine growth mechanisms can stimulate the growth of SCLC. For example, bombesin-like peptides (gastrin-releasing peptide and neuromedin B) are produced and secreted by SCLC cells, bind to one of three bombesin receptors, and stimulate their own growth (3–8). An antibody (2A11) that binds to these bombesin-like peptides has shown antitumor activity in a single patient with sensitive-relapse SCLC (9, 10).

The identification of more of these rationally targeted agents, particularly molecules that inhibit specific cellular mechanisms responsible for tumor growth and survival including those associated with TK receptors, may provide an opportunity to interrupt the growth stimulation and survival pathways described for SCLC. Imatinib, (Glivec, formerly STI571; Novartis AG, Zurich, Switzerland), is an orally bioavailable small molecule that selectively inhibits several protein TKs. These include the chimeric Bcr-Abl fusion protein found in chronic myeloid leukemia, the PDGFR- $\alpha$  and PDGFR- $\beta$ , and the *c-KIT* proto-oncogene-encoded TK receptor. Imatinib (400 or 600 mg/day) is approved for the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia in which the clinical efficacy is a result of the inhibition of the dysregulated Abl kinase activity associated with the chimeric Bcr-Abl fusion protein (11, 12). Imatinib is also approved for the treatment of patients with GISTs, a rare GI tumor of mesenchymal origin, in most cases expressing a mutant and/or activated KIT receptor (13, 14). Recently, imatinib has demonstrated clinical efficacy in certain myeloproliferative disorders and dermatofibrosarcoma protuberans, both diseases shown to have dysregulated cell signaling associated with PDGFR- $\beta$  TK activity (15, 16).

The *in vitro* IC<sub>50</sub> for inhibition of the Bcr-Abl, KIT, and PDGFR target kinases is in the submicromolar range (17, 18). The dose of 600 mg/day was selected as a daily dose because imatinib had shown antitumor activity in GIST using a daily dose of 400 and 600 mg/day, and increasing hematological and other toxicities were encountered at daily doses of 800 and 1000 mg (11–14, 19).

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<sup>7</sup> The abbreviations used are: SCLC, small cell lung cancer; TK, tyrosine kinase; PDGFR, platelet-derived growth factor receptor; GIST, gastrointestinal stromal tumor; SCF, stem cell factor; TTP, time to progression; <sup>18</sup>FDG-PET, 18-fluorodeoxyglucose positron emission tomography.

Previous reports have shown that ~70% of SCLC cells express the KIT receptor and/or its ligand SCF (20–23). In addition, an autocrine and paracrine loop involving SCF and the KIT receptor has been described in SCLC by *in vitro* studies (23–25). Stimulation via the KIT/SCF pathway leads to chemotaxis, cell proliferation, and is thought to be involved in the pathogenesis and rapid tumor growth of SCLC in patients (23–26). The autocrine production and subsequent elevation of the ligand SCF in the plasma may lead to increased stimulation of the KIT receptor and more rapid growth of the SCLC; therefore, plasma SCF was assessed in the patients participating in this trial. Additional studies have shown that imatinib inhibits the growth of SCLC cells *in vitro* via inactivation of the TK activity associated with the KIT receptor (23, 25). Therefore, a study was designed to assess the anticancer activity of imatinib in patients with SCLC.

Patients with previously untreated extensive-stage SCLC were included because prior studies have shown higher single-agent activity with investigational agents in these previously untreated patients compared with patients with relapsed disease after initial chemotherapy (27, 28). To assure the safety and to provide effective care for patients with untreated extensive-stage SCLC, we used a “windowed” Phase II study design, with frequent evaluations to allow appropriate and immediate intervention with combination chemotherapy (29–31). This windowed approach has generally been considered an ethical, safe, and effective method for the initial assessment of the potential efficacy of new agents, and particularly useful for those considered to be cytostatic.

Previously treated patients with progressive SCLC were also eligible for this study. Patients with SCLC treated with chemotherapy whose tumors grow during treatment rarely respond to subsequent treatment. Therefore, it is difficult to identify new effective agents in these patients with progressive SCLC (27, 28). A subpopulation of these patients in which the regrowth of cancer after an initial response has been maintained (sensitive relapse) has been described in both retrospective and prospective studies (32, 33). The response rates to topotecan or combination chemotherapy for patients with relapsed SCLC who are off therapy for more than 2 months are ~20%, and the median survival is ~6 months from the start of second-line treatment (32). These outcomes suggest that it is both reasonable and important to assess the antitumor activity of novel agents in this group of patients based on TTP. This becomes an important measurement in solid tumors because pharmacotherapeutic agents like imatinib may exert cytostatic effects, and conventional clinical end points (objective tumor response rates; Ref. 34) may be less meaningful as compared with traditional (cytotoxic) therapeutic agents (35). This cohort was also monitored frequently to allow timely therapeutic intervention by salvage chemotherapy or other investigational agents after the development of progressive disease.

## PATIENTS AND METHODS

**Eligibility.** Patients were eligible if they had been histologically or cytologically diagnosed with SCLC with at least one measurable site of disease (34). For patients with sensitive-relapsed SCLC, both limited- or extensive-stage disease were allowed if they had received a single chemotherapy regimen or a combined modality (chemotherapy plus chest radiotherapy) regimen and responded and maintained the response for at least

60 days, as defined previously (32). Patients with extensive-stage SCLC who had not received chemotherapy were also eligible. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; adequate cardiac, hepatic, renal, and bone marrow function; and a life expectancy of 6 months or more. The exclusionary criteria included medical conditions requiring urgent intervention; superior vena cava syndrome, lobar obstruction, spinal cord compression, liver metastases involving more than one-third of the liver, or hyponatremia (<130 mmol/liter). Patients who had received prior radiation therapy to  $\geq 25\%$  of the bone marrow within 4 weeks prior to study were not eligible (32). Patients were also excluded if they had other severe and/or uncontrolled medical disease (*i.e.*, uncontrolled diabetes, congestive heart failure, myocardial infarction within 6 months of study, chronic renal disease, or active uncontrolled infection) that could compromise participation in the study or symptomatic brain/central nervous system metastases requiring intervention or management. The Human Investigations Committees at the participating institutions approved the study. All of the subjects signed a written informed consent.

**Study Design.** All of the patients were treated by 600 mg daily dose of imatinib for up to 12 months.

**Arm 1: Previously Untreated Patients.** Patients with previously untreated extensive-stage SCLC were assessed for response after 6 weeks of therapy using the Southwest Oncology Group criteria (34). Patients achieving either a complete or a partial response continued with treatment. Those with progressive or stable disease at the assessment performed at 6 weeks, or progressive disease at any time in the study, were discontinued from the study and were offered treatment with standard chemotherapy (*e.g.*, etoposide and cisplatin). The choice of chemotherapy to be administered was left to the discretion of the investigator.

**Arm 2: Patients in Sensitive Relapse.** Patients in sensitive relapse also underwent scheduled tumor assessments after 6 weeks. They continued on therapy with imatinib if they had a complete response or partial response but were also allowed to continue if they had stable disease, which was freedom from progression for at least 90 days (3 months) after treatment with imatinib. Patients with disease progression were discontinued from the study and were offered treatment with standard chemotherapy or other investigational agents at the discretion of the treating physician.

**Immunohistochemical Analysis.** Histology slides were sent to the Pathology Department of the Brigham and Women’s Hospital. The slides underwent a central review (C. F. and J. H.) and were pathologically classified using the WHO classification of lung and pleural tumors (36). Immunohistochemical staining for KIT (CD117) was performed using a 1:250 dilution of the rabbit polyclonal antibody A4502 (DAKO, Carpinteria, CA) with the EnVision detection system, and tumors were scored as focally positive, positive, or strongly positive as described previously (37).

**Determination of Serum SCF Levels.** Quantitation of SCF in serum from SCLC patients (pretreatment) and healthy volunteers was performed using the Quantikine human SCF ELISA kit from R&D Systems (R&D Systems, Inc., Minneapolis, MN) according to the manufacturer’s instructions. Normal sera were used as control. Sera containing known amounts of

SCF were used for calibration and quantitative analyses. Samples were tested in duplicate.

**Toxicity Evaluation.** Toxicity was recorded using the National Cancer Institute/NIH clinical toxicity criteria (CTC) every 3 weeks.<sup>8</sup> Dose modifications were made for toxicity as published previously (13).

**Pharmacological Analyses.** Five patients on each arm underwent full pharmacokinetic profiling with plasma samples collected before the administration of imatinib and then at 1, 2, 3, 8, 24, 48, and 72 h after the first dose. All other patients underwent a sparse pharmacokinetic sampling regimen with plasma samples taken at 1–3 h and at 6–9 h after the initial administration of imatinib and before the administration of the next dose of imatinib. Plasma imatinib concentrations were determined by high-performance liquid chromatography-mass spectrometry (HPLC-MS) as described previously (38).

**Sample Size Estimation and Statistical Analyses.** An initial analysis of imatinib efficacy in newly diagnosed patients was performed after 9 patients (stage 1) were treated and evaluated for response. Documentation of at least one response (complete or partial) after 6 weeks of treatment was required before enrolling an additional 53 patients into this cohort. An initial evaluation of efficacy in sensitive-relapse patients was performed after 10 patients (stage 1) were treated and evaluated for responses. Documentation of at least one response (complete or partial response after 6 weeks of treatment, or stable disease maintained for >90 days) was required before enrolling 54 more patients into this cohort. Responding patients continued treatment with imatinib until the next evaluation, which was 3 months after starting the study drug. Patients who maintained their response and were clinically stable could continue therapy for 1 year while on study until disease progression if they were tolerating treatment with imatinib. The patients' response rates are reported as the fraction (%) of patients that responded over the total number treated. The TTP and survival were computed using Kaplan-Meier curves (39).

Early stopping rules in the trial were used to be able to analyze the response rate, TTP data, and survival. The previously untreated patients in arm 1 needed to have a minimal response rate of 20% with a response rate of interest 35%. The  $\alpha$  error rate to accept a drug with 20% response rate was 10% and the  $\beta$  error rate to reject a drug with at least 35% response rate was 10%. The sensitive-relapse patients in arm 2 needed to have a minimal response rate of 25% and the response rate of interest was 40%. The  $\alpha$  error rate to accept a drug with a 25% response rate was 10% and the  $\beta$  error rate to reject a drug with at least 40% response rate was 10%. The early stopping rules were used so that information could be analyzed and a decision made about continuing this trial or performing another trial for patients with SCLC who had documented KIT receptor in their tumor.

## RESULTS

**Patients.** Nineteen patients with a diagnosis of SCLC that was made at individual institutions were entered on the

Table 1 Patients characteristics

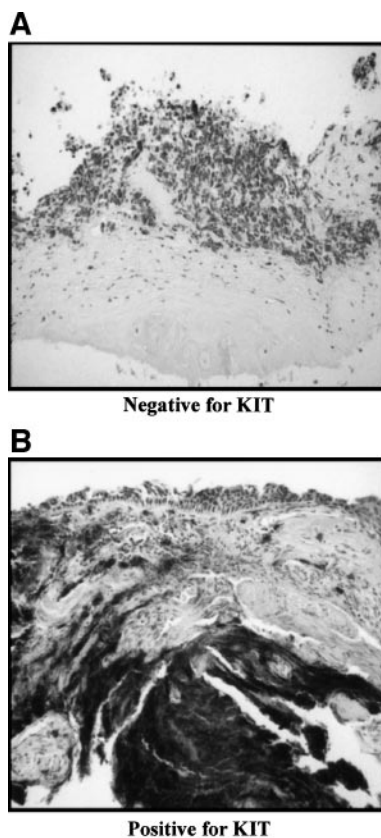
Characteristic	No. of patients (untreated/treated) <sup>a</sup>		Percentage
	n = 19	(9/10)	
Gender			
Male	16	(8/8)	84%
Female	3	(1/2)	16%
Age, years			
Median	59	(68/58)	
Range	39–76	(48–76 /39–74)	
Performance status			
0	8	(5/3)	42%
1	8	(1/7)	42%
2	3	(3/0)	16%
Treatment status			
Untreated extensive stage	9		47%
Previously treated	10		53%
Limited	6		
Extensive stage	4		

<sup>a</sup> Untreated, newly diagnosed extensive-stage SCLC; treated, sensitive relapse as described in the "Patients and Methods" section.

study between November 2000 and May 2001 (Table 1). Study data reported here were collected through October 2002. Seventeen patients have died. A majority (84%) of patients were men, the median age was 59, and 16 had an Eastern Cooperative Oncology Group performance status of 0 or 1 (Table 1). Nine patients had previously untreated extensive-stage SCLC. Ten patients had sensitive relapse. Six of the 10 patients with sensitive-relapse disease were initially treated with chemotherapy and chest radiotherapy for limited-stage disease. Five of the six had been treated with etoposide in combination with other chemotherapeutic agents as follows: cisplatin (two patients); ifosfamide and carboplatin (one patient); doxorubicin and cyclophosphamide (one patient); and doxorubicin, cyclophosphamide, and cisplatin (one patient). The sixth patient had been treated with doxorubicin, cyclophosphamide, and vincristine before entry into the trial. Of the four patients with extensive-stage SCLC, three were treated with the combination of etoposide and cisplatin, including one who also treated with chest and cranial irradiation. The fourth patient was treated with doxorubicin, cyclophosphamide, and vincristine before entry into the trial. The median length of time between the initial diagnosis and relapse (for the sensitive-relapse patients) was 7 months (range, 3–12 months).

Pathology slides were sent to reference pathologists (C. F. and J. H.) for immunohistochemical studies. An unplanned review of the histopathology of all 19 patients confirmed the WHO classification of SCLC in 14 of the patients. Ten were categorized as small cell carcinoma, 2 as combined small cell and large cell neuroendocrine carcinoma, 1 a small cell carcinoma (mixed small/intermediate cell type), and 1 as a small cell carcinoma, intermediate cell type. The remaining five were categorized as non-SCLC: two as non-SCLC, two as large cell neuroendocrine carcinoma, and one as a poorly differentiated unclassified carcinoma. Three of those categorized as non-SCLC were from patients with previously untreated extensive-stage disease and two were from patients with previously treated disease. Four of the 19 tumors were positive for CD117 (Fig. 1),

<sup>8</sup> Internet address: <http://ctep.cancer.gov/reporting.ctc.html>.



**Fig. 1** Immunohistochemical staining of SCLC. **A**, the SCLC biopsy specimen was stained for CD117 (KIT). The tumor is negative for CD117. **B**, the SCLC biopsy specimen was stained for CD117 (KIT). The tumor is strongly positive for CD117.

all of them from the 14 (29%) with the confirmed diagnosis of SCLC, 2 in each disease cohort.

**SCF Values.** Analysis of SCF was performed in 16 patients on the study from whom serum was available and from 14 healthy volunteer subjects, although not matched for age, gender, or smoking status. The mean value of SCF was higher in the serum of the patients with SCLC (mean  $\pm$  SD, 791  $\pm$  207 pg/ml) than in normal subjects (mean  $\pm$  SD, 517  $\pm$  307;  $P = 0.001$  by a two-tailed test). The mean SCF values from seven patients with previously untreated extensive-stage patients (806  $\pm$  220) was similar to that of five patients with sensitive relapse initially diagnosed with limited-stage SCLC (772  $\pm$  184) and the four patients with sensitive relapse initially diagnosed with extensive-stage SCLC (790  $\pm$  269). There was no obvious relationship between initial serum SCF levels and the outcome of the patients with SCLC.

**Treatment.** Patients were treated for a median of 1.2 months (range, 0.1–4.1 months) with a 600-mg daily dose of imatinib. The nine patients with previously untreated extensive-stage disease were treated for a median of 0.8 months (range, 0.4 to 1.3 months). The patients with sensitive-relapsed disease were treated for a median of 1.4 months (range, 0.1–4.1 months). Seventeen of the 19 discontinued participating in the study because of progressive SCLC. One patient stopped ima-

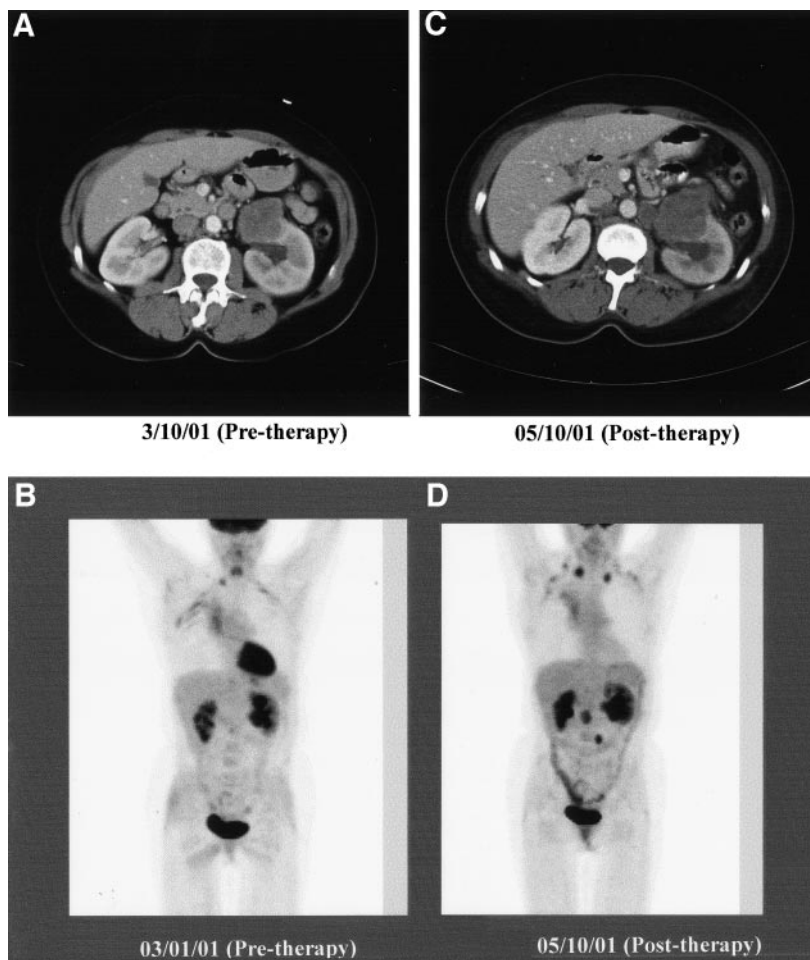
tinib because of grade 3 nausea and vomiting, the only grade-3 toxicity encountered in the trial. One patient was discontinued after 3 days of treatment because of the presence of brain metastases not initially recorded, making the patient ineligible for the trial.

**Pharmacokinetics.** Patients achieved a mean maximal concentration of 3.7  $\mu$ g/ml (7.4  $\mu$ M) after administration of a single dose of 600 mg. The mean half-life of the drug in the plasma for these patients was 17 h, and a mean area under plasma-concentration time curve (AUC<sub>0–24</sub>) of 48.8  $\mu$ g·h/ml was achieved on day 1. These pharmacokinetic parameters are consistent with that observed for patients with GIST, suggesting that pharmacokinetic behavior for patients with solid tumors is likely to be similar (13). The mean maximal concentration of imatinib is well above the concentrations needed to observe antitumor efficacy *in vitro* against SCLC cell lines (23, 25).

**Efficacy and Outcomes.** There were no objective responses; although one patient (SCLC, CD117-negative, sensitive-relapsed disease) had stabilization of disease for 4.1 months, fulfilling the criteria for a response. Four of the 19 patients underwent functional imaging using <sup>18</sup>F-FDG-PET; all four had sensitive-relapse disease. Three of the four patients had scans before and after therapy, which corroborated the progression of the disease determined by other radiographic assessments (Fig. 2). The median TTP was 0.8 months (range, 0.6–1.3 months) and 1.2 months (range, 0.2–4.1 months) for the previously untreated and sensitive-relapse groups, respectively (Fig. 3A). The TTP for the four patients with CD117-positive SCLC was 1.2 months, whereas the TTP was 1.0 month in the 15 patients whose tumors were CD117 negative. The two patients with previously untreated KIT-positive SCLC had progression of their cancer within 1.2 months compared with a median of 0.8-month TTP for the seven patients whose tumors were negative for CD117 expression. The two patients with previously treated CD117-positive SCLC progressed at 1.2 and 2.2 months compared with a median of 1.2 months for the eight patients whose cancers were negative for CD117 expression.

Eight of the nine patients with previously untreated SCLC were subsequently treated with combination chemotherapy after progression of their cancer on imatinib therapy. One patient was treated with 18 days of imatinib and died in the setting of pulmonary complications (infection, effusion) 2 days after stopping therapy without any additional antitumor therapy being administered. The other eight patients with previously untreated extensive-stage SCLC were treated with a median of four cycles of combination chemotherapy (range, 1–6 cycles). Three patients were treated with a second combination (2 patients) or single drug (1 patient). Three patients underwent palliative radiation. Overall, the best responses to subsequent chemotherapy in patients with previously untreated SCLC were one patient with a complete response, three with a partial response, two with stable disease, and two with progressive disease. The overall response rate in this cohort was 50%.

Five patients with sensitive-relapse SCLC were treated with combination chemotherapy after failure of imatinib therapy. Three were treated with combination chemotherapy (1, 2, and 6 cycles) and two were treated with a single agent. One of the three patients treated with combination chemotherapy had a partial response, whereas the other four had progressive disease.



**Fig. 2** Sequential computerized tomography (CT) and  $^{18}\text{F}$ FDG PET scans of the same patient treated with imatinib for 6 weeks. **A**, images from an abdominal CT scan of the patient after relapsing with SCLC depicting a renal mass that was cytologically documented to have SCLC. **B**, the  $^{18}\text{F}$ FDG- PET scan taken at the same time shows uptake in the renal mass as well as the mediastinum. **C**, the abdominal CT scan of the same patient showing enlargement of the renal mass 6 weeks later. **D**, the  $^{18}\text{F}$ FDG-PET scan taken 6 weeks after starting imatinib shows increased uptake in the renal mass and new areas of uptake in the mediastinum.

One patient was treated with a total of three subsequent regimens, but disease continued to progress.

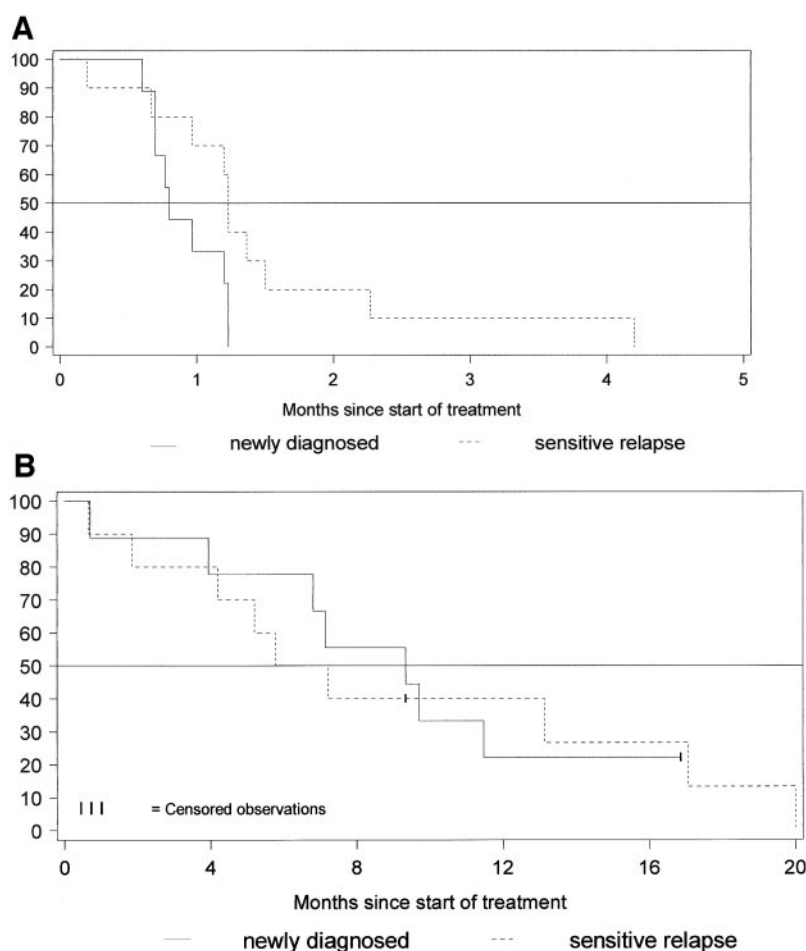
The survival of the previously untreated extensive-stage patients and sensitive-relapse patients was similar to the survival in historically similar, unselected patient cohorts (Fig. 3B; Refs 1, 2, and 32). The median survival for the nine previously untreated patients was 9.3 months (range, 1–17 months) and the median survival from the time of treatment with imatinib for the 10 sensitive-relapse patients was 6.5 months (range, 1 to  $\geq 20$  months). The two patients with untreated extensive stage, CD117-positive SCLC survived 10 and 17+ months (alive at the time of analysis) compared with a median of 7.1 months for the patients whose tumors were negative for CD117. The two patients with previously treated, CD117-positive SCLC survived 13 and 20 months (both dead at time of analysis) compared with 5.5 months for the patients whose tumors were negative for CD117.

## DISCUSSION

No objective evidence for antitumor activity was shown in this Phase II trial of imatinib for patients with either sensitive-relapse or untreated extensive-stage SCLC. This trial was based on the hypothesis that imatinib activity in SCLC would be based on

inhibition of the KIT receptor. It was also based on the premise that a majority of tumors express the imatinib-sensitive target as detected by CD117 immunohistochemistry, and it was undertaken without defining the presence or absence of the KIT receptor before patient entry. Previously published research had identified that  $\sim 70\%$  of SCLC cell lines and tumor samples had evidence of KIT receptor mRNA expression by Northern blot and RNase protection assay (20, 22, 40). There was less information about detection of the KIT receptor by Western blot and immunohistochemical analyses. Approximately 50% of the cell lines and tumor samples had detectable KIT receptor and there has been conflicting information on the same cell lines (22, 23, 41). For example, the KIT protein was detected by Western blot analyses by Wang *et al.* (23) and Plummer *et al.* (40) in NCI-H69, whereas Rygaard (22) did not detect KIT in the same cell line. Therefore, it is obvious that fewer patients with SCLC had evidence of CD117 (KIT receptor) expression than expected based on the existing literature. A systematic characterization using immunohistochemistry of SCLC specimens similar to what was been done in sarcomas had not been performed at the time the trial was initiated (37). Although our reference pathologists have extensive experience in characterizing GISTs, this was their first study of SCLC. Two immunohistochemical studies of SCLC have been reported after completion of the study,

**Fig. 3** Kaplan-Meier estimates of TTP and survival. **A**, Kaplan-Meier estimate of TTP of patients with previously untreated extensive-stage SCLC and sensitive-relapse SCLC from the time of initiating treatment with Imatinib. **B**, Kaplan-Meier estimate of survival from the time of initiating treatment with Imatinib for patients with previously untreated extensive-stage SCLC and sensitive-relapse SCLC.



reporting a total of 54 (40%) of 132 SCLC specimens with detectable CD117 (KIT receptor) by immunohistochemistry (42, 43). These studies might have led us to test for CD117 expression as a requirement for entry onto the study in testing the original hypothesis.

A second potential reason for the lack of significant clinical activity is that 5 (26%) of the 19 patients did not have SCLC confirmed on the central pathology review. None of these cases had detectable CD117 expression. Pulmonary pathologists have typically been able to agree among themselves in about 90% of cases when distinguishing SCLC from non-SCLC (44). This speaks both to the importance of rigorous central pathology review in studies of targeted therapies and to the potential use of supportive analyses of specific disease markers to better define populations who might benefit from imatinib or other rationally targeted agents. The initial entry criteria included a diagnosis of SCLC made by the pathologists at their own institutions and did not require a central pathology review. The pathology specimens were sent to Brigham and Women's Hospital for immunohistochemical analyses of the KIT receptor, and the histology was reviewed as part of this process. Thus, the patients met the entry criteria but were subsequently identified by an unplanned histology review by our reference pathologists as having non-SCLC. Therefore, they were not replaced in the study.

Two other patients were not eligible for response assessment. One patient stopped treatment because brain metastases were discovered 3 days after starting treatment and one patient could not tolerate imatinib because of nausea and vomiting. Therefore, the 5 patients whose unplanned central pathology identified non-SCLC and the two patients whose treatment was discontinued because of toxicity or identification of a metastatic site that excluded them from the trial leaves only 12 patients with SCLC evaluable for their response to imatinib. This includes 5 patients with previously untreated extensive-stage disease and 7 patients with previously treated SCLC who were evaluable for response, fewer than the number called for in the design of the trial. The interim analysis of the ongoing trial after 19 patients were enrolled was performed by the investigators and corporate sponsor, Novartis. A joint decision was made to discontinue the trial rather than replace those who were not eligible for assessment of response. This was done because of the rapid tumor progression in the patients with previously untreated SCLC, few tumor specimens with detectable KIT receptor, and the central pathology review assessment that some of the pathology specimens that gave an original diagnosis of SCLC were non-SCLCs.

This trial does provide important experience and information about using agents with unproven antitumor activity in patients

with untreated SCLC. There were 9 patients with extensive-stage SCLC who met the entry criteria. The criteria were generated to identify patients who were at minimal risk for excessive morbidity and mortality undergoing novel treatments. Eight of the nine prospectively identified patients in whom disease progressed after treatment with imatinib were then successfully treated with chemotherapy. This corroborates a previously reported study of 94 patients with extensive-stage SCLC that showed no statistically significant difference in outcome between patients who were treated with an inactive experimental agent (menagaril) followed by combination chemotherapy and patients initially treated with combination chemotherapy. The previously untreated patients with extensive-stage SCLC selected for our trial were excluded if they had hyponatremia, superior vena cava syndrome, or lobar obstruction so that eight of these nine patients were able to be treated with combination chemotherapy after progression of their SCLC. Further work will be needed to continue to define untreated populations of patients with SCLC who are candidates for initial treatment with investigational agents.

This trial also raises important considerations for trial design using targeted agents. Imatinib has shown dramatic effects in treatment of diseases in which the target (Abl kinase) is activated by chromosomal translocation (*e.g.*, BCR-ABL in chronic myeloid leukemia and chromosomal translocation of PDGFR- $\beta$  in myeloproliferative disorders) or activating genomic mutations (*c-KIT*) as seen in GIST (11, 12, 14, 15). The efficacy of imatinib when the targeted receptors are present but not activated or of unknown activation status is less well defined. Therefore, because this trial included only four KIT receptor-positive SCLC patients, definitive conclusions about the potential role and clinical impact of imatinib have yet to be made.

The experience from this trial has led us to recommend some designs and methods to use in future trials of imatinib and other targeted agents. Future testing of single-agent imatinib should focus on patients with the sensitive-relapse SCLC. Most of the patients were able to be treated with imatinib for the planned 6 weeks before they developed evidence of disease progression, whereas the previously untreated patients were not. We also propose that the entry criteria for future studies include a central pathology review to confirm the diagnosis of SCLC and the presence of the KIT receptor. The pathology specimens will be needed to be evaluated for the presence of the KIT receptor so that confirmation of the SCLC by an experienced reference pulmonary pathologist can be readily accomplished. The KIT receptor was detected by immunohistochemistry in only 4 of the 19 (21%) enrolled patients in this trial and 4 of the 14 (29%) of the patients in whom central pathology review confirmed SCLC. Therefore, future clinical testing of imatinib in patients with SCLC should focus on the subgroup with the proposed target for the agents in SCLC, the KIT receptor.

Further research has taken place to provide guidance on the techniques to identify the presence of the KIT receptor. Assuming that finding *c-kit*-activating mutations in SCLC are unlikely and that, instead, possible mechanisms of KIT might include autocrine/paracrine pathways, immunostaining for KIT remains the best (and most practical) method for screening at the current time. On the basis of our experience (45) and recent studies comparing antibodies and methodologies (46, 47), it appears that the DAKO A4502 antibody without antigen retrieval has

the greatest specificity and the least background staining for immunohistochemical detection of KIT, and we would recommend this technique until additional information becomes available to support other methods.

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