Phase I dose-escalation and pharmacokinetic study of dasatinib (BMS-354825), a Src and multi-kinase inhibitor, in patients with advanced solid tumors

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Running Head: Phase I study of dasatinib

Keywords:

Dasatinib; clinical trial, phase I; pharmacokinetics; tyrosine kinases; SRC

Previous presentations and preliminary abstract publications:

Evans TRJ**,** Morgan JA, van den Abbeele AD, et al. Phase I dose-escalation study of the SRC and multi-kinase inhibitor BMS-354825 in patients (pts) with GIST and other solid tumors. J Clin Oncol 2005; 23 (16S): 200s, 3034 (poster presented at ASCO, 2005).

Luo FR, Luo FR, Barrett Y, et al. Dasatinib (BMS-354825) pharmacokinetics correlate with pSRC pharmacodynamics in phase I studies of patients with cancer (CA180002, CA180003). J Clin Oncol 2006;24(18S):132s, 3046.

Morgan JA, Demetri G, Wang D, et al. A phase I study of dasatinib, a SRC and multi-kinase inhibitor, in patients (pts) with GIST and other solid tumors. Eur J Cancer Supplements 2006; 4(12):118, abs 383. Poster presented at 18th EORTC-NCI-AACR International Conference on "Molecular Targets and Cancer Therapeutics" (7-10 November 2006, Prague).

Statement of Translational Relevance (max 150 words)

Dysregulated pathways of kinase signaling, including those involving c-KIT and SRC family kinases (SFKs), play an important role in tumorigenesis. Dasatinib is an oral, small-molecule multi-kinase inhibitor of several SFKs as well as c-KIT, PDGFR, BCR-ABL, and ephrin receptor kinases. Although the benefits of dasatinib in patients with hematologic malignancies have been demonstrated previously, its activity in patients with solid tumors has yet to be established. This work is relevant to current and future anticancer drug therapy because our results show that dasatinib, a multikinase inhibitor with activity against SFKs, is acceptably well tolerated in patients with solid tumors with encouraging preliminary evidence of efficacy in patients with advanced refractory disease. Importantly the results of our study form the basis of dasatinib dosing for further clinical development in solid tumor oncology.

ABSTRACT

Purpose: To determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and recommended phase II dose of dasatinib in metastatic solid tumors refractory to standard therapies or for which no effective standard therapy exists.

Experimental Design : In this phase I, open-label, dose-escalation study, patients received dasatinib 35-160 mg twice daily (BID) in 28-day cycles, either every 12 hours for five consecutive days followed by two non-treatment days every week (5D2), or as continuous, twice-daily (CDD) dosing.

Results: Sixty-seven patients were treated (5D2: n=33, CDD: n=34). The MTDs were 120 mg BID 5D2 and 70 mg BID CDD. DLTs with 160 mg 5D2 were recurrent grade 2 rash, grade 3 lethargy, and one patient with both grade 3 prolonged bleeding time and grade 3 hypocalcemia; DLTs with 120 mg BID CDD were grade 3 nausea, grade 3 fatigue, and one patient with both grade 3 rash and grade 2 proteinuria. The most frequent treatment-related toxicities across all doses were nausea, fatigue, lethargy, anorexia, proteinuria, and diarrhea, with infrequent hematologic toxicities. Pharmacokinetic data indicated rapid absorption, dose proportionality, and lack of drug accumulation. Although no objective tumor responses were seen, durable stable disease was observed in 16% of patients.

Conclusion: Dasatinib was well tolerated in this population, with a safety profile similar to that observed previously in leukemia patients though with much less hematologic toxicity. Limited, though encouraging, preliminary evidence of clinical activity was observed. Doses of 120 mg BID (5D2) or 70 mg BID (CDD) are recommended for further studies in patients with solid tumors.

INTRODUCTION

Dysregulated cell signaling through multiple kinases is associated with oncogenesis in many tumors. SRC-family kinases (SFKs), including SRC, YES, and FYN, are non-receptor tyrosine kinases with a critical role in cellular proliferation. Together with YES and FYN, SRC has an ubiquitous distribution with particularly high levels in platelets, neurons, osteoclasts and at epithelial cell-cell junctions (1,2). Expression of the remaining SFKs is restricted primarily to hematopoietic cells. SFKs are basic components of the cell signaling machinery and are involved in pathways regulating growth, survival, motility and adhesion (3). SFKs also promote several aspects of tumor progression and metastasis (4) and have a role in osteoclast function (5–7). SRC expression and/or activity are upregulated in a variety of human tumors (8–16). Additionally, more than 90% of gastrointestinal stromal tumors (GISTs) harbor activating mutations in either *KIT* or platelet-derived growth factor receptor-alpha (*PDGFRA*) (17).

Dasatinib is a kinase inhibitor with potent activity against several kinases, including SFKs, KIT, PDGFRA, EPHA2 and BCR-ABL *in vitro* (18,19). Dasatinib inhibits cellular Src autophosphorylation and cellular proliferation in a number of cancer cell lines *in vitro*, and has demonstrated *in vivo* anti-tumor efficacy in mice against a range of human tumor xenografts (19–21). *In-vitro* studies have demonstrated that dasatinib potently inhibits both wild-type and mutated KIT (22). Dasatinib has proven clinical efficacy in patients with chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) (23–26).

Consequently, we have performed a Phase I study with dasatinib in patients with advanced solid tumors that were refractory to standard therapies or for whom no effective standard

therapy existed. The primary objective of this study was to establish the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and recommended phase II dose of dasatinib. Secondary objectives included evaluation of the safety, tolerability, and plasma pharmacokinetics of dasatinib, and assessing any preliminary evidence of anti-tumor efficacy.

PATIENTS AND METHODS

Patients and Eligibility Criteria

This was a non-randomized, open-label, Phase I, dose-escalation study conducted in accordance with the International Conference on Harmonization Good Clinical Practice (ICH GCP) with the ethical principles of the current Declaration of Helsinki and approved by the Research Ethics Committee at each of the participating institutions. All patients provided written, informed consent prior to performing any study-related procedures.

All patients entered into this study had a verified advanced solid malignancy, refractory to conventional therapy or for which there was no effective therapy. Eligible patients were aged e 18 years with an Eastern Cooperative Oncology Group (ECOG) performance status 0-1. They should not have received chemotherapy, immunotherapy, or radiotherapy within 4 weeks of entering the study (6 weeks for nitrosoureas, mitomycin C, and liposomal doxorubicin) and at least 2 weeks must have elapsed since exposure to other kinase inhibitors. Eligibility criteria also included adequate hematologic, hepatic, and renal function, serum potassium and magnesium within the institution's normal range, corrected serum calcium above the institution's lower limit of normal, and either a bleeding time which was less than the institution's upper limit of normal or a platelet aggregometry test within normal limits.

Patients were excluded if they had received prior radiotherapy to e25% of the bone marrow-containing skeleton, or if they had uncontrolled or significant cardiovascular disease, known brain metastasis, prolonged QT syndrome or QT_c >450 msec, history of a significant bleeding disorder, vasculitis, or a significant bleeding episode from the GI tract in the preceding 6 months. Patients who were pregnant or breastfeeding, or who were of childbearing potential but unwilling or unable to use adequate contraception were also excluded. Prohibited medications included those known to increase the risk of Torsades de Pointes, irreversible inhibitors of platelet function and anticoagulants.

Treatment Administration

Pre-treatment evaluation included a complete history and clinical examination, vital signs, assessment of performance status, full blood count, biochemical profile, coagulation screen, bleeding time or platelet aggregometry, fasting cholesterol, triglycerides, and glucose, $CD4^+$ T-cell count, creatine kinase (CK), CK-MB, troponin I and T, thyroid-stimulating hormone (TSH), urinalysis, chest x-ray, and pregnancy test. Electrocardiograms (EKGs) were performed in triplicate 1-3 days prior to study treatment. Relevant radiologic studies to evaluate sites of disease were performed within 3 weeks prior to dosing on day 1.

Dasatinib was administered orally on an empty stomach in 28-day treatment cycles either every 12 hours for 5 consecutive days followed by two non-treatment days every week (5D2 schedule), or continuously, twice-daily (CDD schedule). No concomitant anti-cancer therapy was permitted. Hematopoietic growth factors and erythropoietin were permitted, but not within the first 28 days of drug administration during which time DLTs were assessed.

The dasatinib starting dose (35 mg BID) was based on prior clinical experience from studies in hematologic malignancies (27) and was escalated in subsequent dose cohorts until the MTD was determined. Once the MTD was reached on the 5D2 schedule, subsequent patients were enrolled on the CDD schedule, with a starting dose two levels below the 5D2 MTD. Dose escalation on the CDD schedule continued until the CDD MTD was reached. Once the MTD had been defined, an additional cohort of up to 15-20 patients was recruited.

Study treatment continued until progressive disease (PD), death, pregnancy, withdrawal of consent, or unacceptable toxicity. Patients initially treated on the 5D2 schedule had the option of crossing over to the CDD schedule at the investigator's discretion. All patients were followed for a minimum of 30 days after the last dose of study therapy, or until recovery from any treatment-related toxicity.

Evaluation of Toxicity

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) Version 3.0. Physical examinations and assessment of ECOG performance status were performed weekly. Laboratory assessments, similar to those performed pre-treatment, were also performed at regular intervals. EKGs were performed in triplicate 10 minutes pre-administration and 1, 2, 3, 4, 6, 8, and 10 hours post-administration on day 1, once between days 3-5, and once between days 24-26, of cycle 1. Toxicity assessments of subjects who remained on study with no dose reductions or interruptions $\geq$3 months were subsequently performed every 4 weeks.

DLT was defined as grade 4 neutropenia for $\geq$5 consecutive days; febrile neutropenia [defined as absolute neutrophil count (ANC) $<1000/mm^3$ with temperature $\geq$38.5ºC];

thrombocytopenia (d25,000 cells/mm^3 or bleeding requiring platelet transfusion); QT_c interval of e500 msec; grade 3-4 nausea, vomiting, or diarrhea despite maximal prophylaxis and intervention; any other grade e3 non-hematologic event except alopecia or fatigue (unless the fatigue were recurrent); drug-related toxicity that delayed scheduled re-treatment for >14 days; and any grade of toxicity requiring dose reduction or discontinuation of study drug within the DLT assessment period. Description of DLTs, dose-escalation decisions, and determination of the MTD were based on toxicities occurring within the first 4 weeks of drug administration. Cumulative toxicities were recorded at all dose cohorts.

At least three patients were enrolled at each dose cohort. If a DLT occurred, the cohort was expanded up to a maximum of six patients. The MTD was defined as the dose level below which >1 out of 3 or e2 of 6 patients experienced a DLT. Intrapatient dose escalation was permitted if the maximum toxicity during prior cycles of therapy was grade 2 or less and if d1 DLT was observed in cycle 1 in 3-6 patients who had completed 4 weeks of study drug at the next higher dose level.

Dose Delays and Modifications

Dose delays and modifications were performed on the basis of toxicity. Re-treatment after dose interruption could be delayed for up to 14 days to allow recovery from any toxicity. Dose reductions were to the previous dose level or by 25%, whichever was larger. Following dose interruption for non-hematologic toxicities, dosing was recommenced when toxicities had resolved to grade 1 or baseline levels. Dosing was interrupted for any grade 2 non-hematologic toxicity (except alopecia or fatigue) thought to be related to the study drug, with dose reduction after recovery from the second occurrence. Dosing was interrupted, with subsequent reduction on recovery, following the first occurrence of grade 2 neuropathy and

grade 3 nausea, vomiting, or diarrhea, despite adequate/maximal intervention and/or prophylaxis. For QTc prolongation e500 msec but <530 msec by both the Bazett and Fridericia methods which resolved without any associated clinically significant arrhythmia, study drug was recommenced with a dose reduction after a minimum of 2 days interruption of dosing. Dosing was also interrupted following grade 3/4 neutropenia or thrombocytopenia, with dose reductions implemented depending on time to recovery and severity. Patients who had their dose of dasatinib reduced due to toxicity did not have subsequent dose increases. Patients who developed recurrent toxicity despite dose reduction could remain on study after a second dose reduction at the discretion of the investigators. However, study drug was discontinued after the first occurrence of grade 4 non-hematologic toxicity, ≥ grade 3 neuropathy, or QTc prolongation e530 msec.

Disease Evaluation and Objective Response Assessment

Tumor size was evaluated by computed tomography (CT) or magnetic resonance imaging (MRI), chest X-ray, and by physical examination in patients before starting study therapy. Assessments were repeated after every two cycles of treatment, after every 12 weeks for patients who had been on study treatment for 24 weeks and at the end of treatment. Responses to treatment were defined using the modified World Health Organization criteria (28), and all analyses performed on an intention-to-treat basis.

Pharmacokinetics

Blood samples for pharmacokinetic analysis were collected predose, 30 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 hours post dose on the morning of day 1, once on days 3-5, and once on days 24-26 during Cycle 1. Samples were assayed for dasatinib and BMS-606181, the N-oxide metabolite of dasatinib, concentrations by Bristol-Myers Squibb and Cedra Corporation

(Texas, United States) using a cross-validated liquid chromatography tandem mass spectrometry method. Pharmacokinetic parameters were derived from plasma concentration–time data by a non-compartmental method, using Kinetica™ Basic Version 4.4.1 in the eToolbox (version 2.6.1; Thermo Electron Corporation, Pennsylvania, United States). These included the maximal plasma concentration (C_{max}) and time of C_{max} (t_{max}) (obtained from experimental observations), the apparent plasma elimination half-life ($t_{1/2}$) (calculated as ln2/Lz, where Lz was the absolute value of the slope of the terminal log-phase), the apparent oral clearance (CLo), the apparent volume of distribution in the terminal phase (Vz/F), and the area under the curve (AUC) within the dosing interval (12 hours) [AUC_{TAU}]. AUC_{TAU} were calculated using the mixed log-linear trapezoidal algorithm in Kinetica™. Dose-proportionality was assessed by performing linear regression analyses on log_{AUC} versus log_{dose} for day 8 and day 26 with combined data from 5D2 and CDD schedules.

Pharmacodynamic Studies

The amount of phosphorylated SRC (pSRC) in peripheral blood cells was determined as a surrogate biomarker of kinase activity by ELISA as previously described (29). Additionally, FDG-PET imaging analyses were performed in a subset of 35 patients at baseline prior to treatment and periodically while receiving dasatinib. Metabolic response was assessed based on criteria established by the European Organization for Research and Treatment of Cancer (EORTC) (30). A quantitative analysis of the PET imaging as a pharmacodynamic readout for this study is beyond the scope of this report and will be presented in a separate manuscript.

RESULTS

Patient characteristics

Sixty-seven patients were enrolled (5D2, n=33; CDD, n=34). All 67 patients were included in the analysis of toxicity, with 48 patients evaluable for response. Patient baseline characteristics are summarized in Table 1; a large percentage of the trial consisted of patients with advanced GIST resistant to other kinase inhibitors. Two patients (3%), both in the CDD group, were alive with stable disease lasting >90 days at study closure and continuing to receive dasatinib. The median time from cancer diagnosis to study start was 43.1 months. Prior cancer treatment included surgery (n=67), systemic therapy/chemotherapy (n=63), radiotherapy (n=19), hormonal/immunotherapy/biological therapy (n=4), or other investigational agents (n=8). Most patients had received more than one prior systemic therapy regimen including nine (13%) patients who had received two regimens, 13 (19%) three regimens, 19 (28%) four regimens and 11 (16%) five or more regimens.

Patients received dasatinib in nine dose cohorts: 35, 50, 70, 90, 120 and 160 mg BID (5D2) and 70, 90, and 120 mg BID (CDD), with a subsequent expanded dose cohort enrolled at an intermediate dose level (100 mg BID, CDD) (Table 2). Duration of therapy was greater for patients on the 5D2 schedule compared with those on the CDD schedule for all dose cohorts. In contrast, dose intensity was greater for patients on the CDD schedule.

Toxicity

DLTs were observed in six of 26 evaluable patients with the 5D2 schedule, and in 11 of 27 evaluable patients with the CDD schedule. On the 5D2 schedule, one of seven evaluable patients enrolled at 35 mg BID reported a DLT of grade 3 dehydration and anorexia, one of six patients enrolled at 90 mg BID reported grade 3 dehydration and hyponatremia, and one of

nine patients enrolled at 120 mg BID reported grade 3 tumor lysis syndrome. None of the patients enrolled at 50 or 70 mg BID had a DLT. Of four evaluable patients enrolled at 160 mg BID, three reported DLTs: grade 2 rash that interrupted, grade 3 lethargy, and one patient with both grade 3 prolonged bleeding time and grade 3 hypocalcemia.

On the CDD schedule, none of the three patients enrolled at 70 mg BID reported DLTs. At the 90 mg BID dose level, DLTs were observed in two of seven patients (grade 3 proteinuria and grade 2 rash in 1 patient, and grade 1 cognitive impairment with grade 2 somnolence, altered taste, slurred speech and unsteady gait). During the dose-escalation part of the study, it had been unclear if the grade 1 cognitive impairment with grade 2 somnolence was related to the study drug and this patient was therefore replaced and the subsequent dose-escalation proceeded as per protocol. However, based on the observed toxicities at 100 and 120 mg BID (CDD), it was concluded retrospectively that this event had been drug-related and was dose limiting. The first four patients at the intermediate (100 mg BID) dose level reported no DLTs. However, when this cohort was further expanded, six of the 13 patients reported DLTs, including one patient who developed grade 2 myocardial toxicity and EKG T-wave inversion, and grade 4 elevation of cardiac troponin. The myocardial toxicity and elevated cardiac troponin resolved following appropriate treatment. Other DLTs in this cohort included grade 3 dyspnea, grade 3 constipation, grade 2 proteinuria, grade 4 fatigue and grade 3 lethargy. At the 120 mg BID dose level, three of four patients reported DLTs, which were grade 3 nausea, grade 3 fatigue, and one patient with both grade 3 rash and grade 2 proteinuria. Consequently, the MTDs (and recommended doses) were defined as 120 mg BID on the 5D2 schedule (DLT in 1/6 patients) and 70 mg BID on the CDD schedule (no DLTs).

Cumulative Toxicity

Cumulative toxicity (worse grade per patient, all cycles) is summarized in Tables 3 and 4. Hematologic toxicity was reported in four patients. Two patients on the 5D2 schedule who had grade 1-2 anemia at baseline developed grade 3 anemia while on study drug (50 mg BID, 70 mg BID). On the CDD schedule, one patient had grade 4 neutropenia (120 mg BID) and another grade 3 anemia (100 mg BID).

On the 5D2 schedule, the most common treatment-related non-hematologic toxicities were nausea (64%), and fatigue (42%) (Table 3). One patient on the 5D2 schedule (50 mg BID) experienced moderate QTc prolongation and EKG ST segment changes (grade 2). On the CDD schedule, the most common treatment-related non-hematologic toxicities were nausea (53%), and anorexia (50%) (Table 4). Pleural effusion considered by the study investigator to be related to dasatinib treatment was observed in three patients on the CDD schedule. All were grade 1-2 and occurred at the 70 mg (n=2) or 90 mg (n=1) BID dose level. The majority of non-hematologic events were grade 1-2. However, three grade 4 events were observed (suicidal depression [35 mg BID, 5D2], fatigue [100 mg BID, CDD], and elevated cardiac troponin [100 mg BID, CDD]). The occurrence of non-hematologic toxicities did not appear to be dose related with either the 5D2 or CDD schedules.

Thirteen patients discontinued treatment due to drug-related toxicity: three patients on the 5D2 schedule (suicidal ideation withdepression; vomiting; and prolonged bleeding time) and ten patients on the CDD schedule (nausea, headache, vomiting, gait disturbance, cognitive disorder, dysarthria, dysgeusia, somnolence, fatigue, proteinuria, cardiotoxicity, constipation, EKG T-wave inversion, increased troponin, and anorexia).

Ten patients died during the study or within 30 days of their last dose of dasatinib, and eight died more than 30 days after their last dose of dasatinib. All of these deaths were due to disease progression; one patient died from vomiting and gastrointestinal bleeding which was considered to be most likely due to disease progression, although a possible contribution from the study drug could not be excluded.

Dose Interruptions and Dose Modifications

Dose reductions were necessary for 19% of patients and were more frequent in the CDD group (n=9, 27%) than in the 5D2 group (n=4, 12%). The most common reason for first dose reduction was hematologic (3%; 5D2, n=1; CDD, n=1) or non-hematologic (8%; 5D2, n=3; CDD, n=2) toxicity. Hematologic toxicities requiring first dose reduction were thrombocytopenia in the 5D2 group (160 mg BID) and anemia in the CDD group (100 mg BID). Non-hematologic toxicities reported by the investigators requiring first dose reduction in the 5D2 group were elevated serum glutamic pyruvic transaminase (SGPT) levels (35 mg BID) and rash and grade 3 hypocalcemia (160 mg BID). Non-hematologic toxicities in the CDD group were grade 2 rash (n=1; 90 mg BID), and fatigue (n=1; 100 mg BID).

Dose interruptions for toxicity were necessary for 28 patients (42%), and were more frequent in the CDD group (n=17) compared with the 5D2 group (n=11). Dose interruptions were most commonly the result of non-hematologic (31%; 5D2, n=6, CDD, n=15) rather than hematologic (3%; 5D2, n=1, CDD, n=1) toxicity. Non-hematologic toxicities reported by the investigators requiring first dose interruption in the 5D2 group included rectal bleeding/pain (70 mg BID), and grade 3 hypocalcemia (160 mg BID). Non-hematologic toxicities reported by the investigators requiring first dose interruption in the CDD group included patient

undergoing laser therapy (70 mg BID), dyspnea, shortness of breath, proteinuria and, fatigue (100 mg BID) and rash (120 mg BID).

The median time to first dose reduction/interruption due to toxicity was 12 days [5D2 = 10 (2-208) days; CDD = 12 (2–56) days]. The median length of dose interruptions due to toxicity was 7 days [5D2 = 8 (3-12) days; CDD = 5.5 (3-19) days].

Antitumor Activity

There were no observed objective tumor responses. Eleven patients [including GIST (three patients), colon, melanoma, biliary tract, epithelial sarcoma, small bowel carcinoma, myoepithelioma, thigh sarcoma, and renal cell cancer; 16%] had RECIST-defined stable disease as their best response including seven of 33 (21%) of patients on the 5D2 schedule and four of 34 (12%) on the CDD schedule. The median duration of stable disease in these patients was 3.6 months (range 1.7-23.6).

Similar findings were observed when comparing the metabolic response on ^{18}FDG-PET imaging of individual lesions and the overall metabolic response of patients. Only four patients (12.9%) demonstrated an early metabolic partial response (PR) during the first week of treatment with dasatinib. However, by the end of Cycle 1 the proportion of patients with metabolic PR was nearly twice as large (23.8%). A similar proportion of patients with metabolic PR was observed at the end of Cycle 2 (25%).

There was high variability in the pSrc assay using peripheral blood cells and, although pSrc inhibition was observed, a dose-response trend could not be determined (data not shown).

Pharmacokinetic Analyses

The plasma concentration–time curves at steady-state (Day 26) are shown in Figure 1. Dasatinib was detectable in plasma 30 minutes after oral administration and reached C_{max} at median T_{max} values of 0.5-3.1 hours. The AUC_{TAU} increased approximately proportionally with dose, the slope (90% CI) being 1.08 (90% CI: 0.63, 1.54) on Day 8 and 1.07 (90% CI: 0.63, 1.51) on Day 26. The C_{max} and AUC_{TAU} values on Days 8 and 26 were similar, suggesting no clinically relevant accumulation on repeated dosing. Across the range of 35-160 mg BID, the mean $t_{1/2}$ of dasatinib was consistent on Days 8 and 26. Although consistent across the dose groups, there was considerable variability in both CLo and Vz/F.

BMS-606181 was rapidly formed in subjects with metastatic tumors and is considered a minor metabolite of dasatinib. The metabolite-to-parent ratio unadjusted for molecular weight difference (which was less than 10%) ranged from less than 1% to 13%.

DISCUSSION

Dasatinib potently inhibits several kinases, including KIT, PDGFRA, EPHA2, and BCR-ABL in addition to SFKs *in vitro*. Specific somatic mutations in the *KIT* gene resulting in kinase activation are implicated in the pathogenesis of GIST (31), and KIT dysregulation is also implicated in the pathobiology of a number of other tumor types including small cell lung carcinoma and certain melanomas. Similarly, dysregulation of expression and activation of the PDGF ligand and receptor systems is implicated in many forms of solid tumors including glioblastoma and prostate cancer (32). Furthermore, EPHA2 may promote angiogenesis (33), enhance tumor cell motility, invasion and metastasis (34, 35), and is over-expressed in melanoma and in several solid tumors.

In this study, the recommended doses of dasatinib for phase II development appeared to be schedule-dependent: 120 mg BID for the 5D2 schedule, and 70 mg BID for the CDD schedule. A dose of 70 mg BID on a continuous administration schedule is currently approved for second-line treatment of patients with accelerated-phase CML (CML-AP), myeloid or lymphoid blast-phase CML (CML-BP), or Ph+ALL, and is well tolerated in these patients (23, 24, 26).

The DLTs in this study were recurrent grade 2 rash requiring dose modification, grade 3 lethargy, grade 3 prolonged bleeding time and grade 3 hypocalcemia with the 5D2 schedule, and grade 3 nausea, grade 3 fatigue, and 1 patient with both grade 3 rash and grade 2 proteinuria with the CDD schedule. The most frequent cumulative toxicities in this present study were non-hematologic including diarrhea, nausea, fatigue, and lethargy. Other toxicities included anorexia, although this may have been secondary to nausea or other gastrointestinal toxicities in several cases, proteinuria and dyspnea. These toxicities were manageable with

dose interruption and reduction. However, hematologic toxicity was uncommon in this study with only one episode of grade 4 neutropenia, and no evidence of thrombocytopenia although prolonged bleeding time was observed as a DLT in one patient. In contrast, in the Phase I study of dasatinib in patients with CML or Ph+ALL intolerant or resistant to imatinib (27), grade 3 or 4 neutropenia occurred in 45% of patients with chronic-phase disease (CML-CP) and in 89% of patients with CML-AP, CML-BP, or Ph+ALL, although 55% of the latter group had grade 3 or 4 myelosuppression at study entry. Similarly, grade 3 or 4 thrombocytopenia occurred in 35% of patients with CML-CP and in 80% of patients with CML-AP, -BP, or Ph+ALL (27). However, the contrasting hematologic toxicities observed between this study and that reported by Talpaz and colleagues is most likely due to either the result of the action of dasatinib against Ph+ leukemia cells or due to the disease-related compromised bone marrow function in the patients in the latter study. Dose interruptions and dose reductions (42% and 19% of patients respectively) were also less common in this study, and mostly due to non-hematologic toxicities.

The role of SRC-dependent signaling on lymphovascular permeability is of great interest, and pleural effusion has been reported previously with dasatinib (27). In leukemic patients, pleural effusion is adequately managed by dose interruption/reduction and appropriate medical intervention (36). Moreover, findings from a trial comparing 70 mg BID dosing with 100 mg once-daily (QD) dosing in patients with CML-CP showed that the QD schedule improved tolerability, including reducing the occurrence of pleural effusion, while maintaining efficacy (37). In the present study, pleural effusion was infrequent with only two patients developing pleural effusion and both were grade 1/2. It appears that pleural effusions are observed less frequently with dasatinib in patients with solid tumors than in patients with hematologic

malignancies [35%; grade 3 or 4 in 17%] (38), although the reasons for this observation are unclear.

Preliminary evidence suggests that dasatinib is not directly cardiotoxic *per se*, unlike other kinase inhibitors such as imatinib, sunitinib, and nilotinib, which have more profound *in vitro* effects on cardiac tissue (39). Although QT prolongation has been reported with dasatinib (27), extensive serial electrocardiographic monitoring demonstrated only one case of QTc prolongation (grade 2) in this study. The increase was moderate (e455 msec and d490 msec by the Bazett method) and resolved with a temporary dose reduction. Nevertheless, screening for patients at risk of QT prolongation is recommended before starting dasatinib therapy. Dose-limiting cardiac toxicity was observed in one patient in this study (grade 2 myocardial toxicity and EKG T-wave inversion, and grade 4 elevated cardiac troponin) which was reversible. Asymptomatic grade 1 or 2 hypocalcemia was noted in about 60% of the patients treated with dasatinib for hematologic malignancies (27). We observed one episode of grade 3 hypocalcemia in this current study (dose limiting at 160 mg BID 5D2 schedule). This is most likely due to the key role of Src in osteoclast formation, activation, and survival (reviewed in Boyce et al (40)), raising the intriguing notion that dasatinib might justifiably be studied for the management of metastatic bone disease.

Although studies suggest an immunosuppressant effect for dasatinib (41), there have been no indications of an increased susceptibility to infection following dasatinib in patients with CML. In this study hematologic toxicity was rare. Lymphopenia (grade 2) was reported for one patient (120 mg BID, 5D2) and was resolved by dose interruption.

The pharmacokinetic data suggest that there is no long-term drug accumulation. Although the small number of evaluable patients used for this analysis resulted in substantial variance, the data suggest rapid absorption and dose proportionality. *In vitro* studies of the activity of dasatinib metabolites, including BMS-606181, against SRC and BCR-ABL suggest that dasatinib metabolites do not contribute significantly toward *in vivo* activity (42). Further pharmacokinetic modeling will be required to determine whether the levels of drug achieved in this study are sufficient to inhibit specific kinases.

No objective responses were observed in this study. However, this study was performed in patients with advanced, treatment-refractory solid tumors, in whom objective responses might not be observed despite an optimal biological effect on the proposed drug targets. The observation of stable disease in 16% of patients is encouraging, particularly as disease stabilization appeared durable, lasting for over 90 days in several patients, including stable disease for approximately 2 years in a patient with refractory metastatic melanoma. In addition, stable disease was observed in three of the 19 patients with GIST, lasting for more than three months in one of these patients. Two of these three patients with GIST had also received prior treatment with imatinib. These preliminary observations suggest dasatinib may have differential activity in patients with GIST compared to other available kinase inhibitors, similar to the distinctive clinical activity of dasatinib observed in CML patients (25). Gain-of-function mutations of KIT are a critical oncogenic contributing factor to the malignant phenotype of most GISTs (43). *In vitro* data with dasatinib show that it potently inhibits both wild-type and mutated KIT, including inhibiting imatinib-resistant KIT activation loop mutants (22). It is unclear why more patients on the 5D2 schedule had stable disease than patients on the CDD schedule.

PET scan changes and biomarkers may act as additional indicators of a pharmacodynamic and meaningful biological response with dasatinib. A metabolic PR was observed in 23.8% of a subset of 35 patients at the end of cycle 1 and in 25% at the end of cycle 2. These results will be discussed more fully in a separate communication. The preliminary effects of dasatinib on levels of the biomarker pSRC were reported by Luo et al using data from the study reported here and from a phase I study in patients with CML (29). The results showed that with BID dosing, pSrc inhibition was dose dependent across the dosing range (25-160 mg BID). Inhibition also directly correlated with dasatinib plasma concentration, with maximal inhibition achieved at approximately 2.5 hours (29). Upon database closure and data analysis of the study reported herein, there was a higher variability of the assay than previously found, and although pSrc inhibition was observed, a dose-response trend could not be determined.

In conclusion, this is the first clinical study of an inhibitor of SFKs in patients with solid tumors. Dasatinib was well tolerated and hematologic toxicities were infrequent. Doses of 120 mg BID on the 5D2 schedule or 70 mg BID on a continuous administration schedule are recommended for future studies. Encouraging preliminary evidence of efficacy was observed, and further studies are required in patients with solid tumors.

ACKNOWLEDGEMENTS

Funding for this trial was provided in part by Bristol-Myers Squibb, with additional support to GDD from The Virginia and Daniel K. Ludwig Trust for Cancer Research, the Pan-Mass Challenge of Paul's Posse and Leslie's Links, and the Russo Family GIST Research Fund. Editorial and writing support was provided by Gardiner-Caldwell US and funded by Bristol-Myers Squibb. The authors are grateful to all the staff at the study centers for their support of this trial.

REFERENCES

1. Calautti E, Cabodi S, Stein PL, Hatzfeld M, Kedersha N, Paolo DG. Tyrosine phosphorylation and src family kinases control keratinocyte cell-cell adhesion. J Cell Biol 1998;141:1449–65.

2. Tsukita S, Oishi K, Akiyama T, Yamanashi Y, Yamamoto T, Tsukita S. Specific proto-oncogenic tyrosine kinases of src family are enriched in cell-to-cell adherens junctions where the level of tyrosine phosphorylation is elevated. J Cell Biol 1991;113:867–79.

3. Thomas SM, Brugge JS. Cellular functions regulated by Src family kinases. Annu Rev Cell Dev Biol 1997;13:513–609.

4. Warmuth M, Damoiseaux R, Liu Y, Fabbro D, Gray N. SRC family kinases: potential targets for the treatment of human cancer and leukemia. Curr Pharm Des 2003;9:2043–59.

5. Boyce BF, Yoneda T, Lowe C, Soriano P, Mundy GR. Requirement of pp60c-src expression for osteoclasts to form ruffled borders and resorb bone in mice. J Clin Invest 1992;90:1622–27.

6. Sanjay A, Houghton A, Neff L et al. Cbl associates with Pyk2 and Src to regulate Src kinase activity, alpha(v)beta(3) integrin-mediated signaling, cell adhesion, and osteoclast motility. J Cell Biol 2001;152:181–95.

7. Soriano P, Montgomery C, Geske R, Bradley A. Targeted disruption of the c-src proto-oncogene leads to osteopetrosis in mice. Cell 1991;64:693–702.

8. Bolen JB, Veillette A, Schwartz AM, DeSeau V, Rosen N. Activation of pp60c-src protein kinase activity in human colon carcinoma. Proc Natl Acad Sci USA 1987;84:2251–55.

9. Cartwright CA, Meisler AI, Eckhart W. Activation of the pp60c-src protein kinase is an early event in colonic carcinogenesis. Proc Natl Acad Sci U S A 1990;87:558–62.

10. Kumble S, Omary MB, Cartwright CA, Triadafilopoulos G. Src activation in malignant and premalignant epithelia of Barrett's esophagus. Gastroenterology 1997;112:348–56.

11. Lutz MP, Esser IB, Flossmann-Kast BB et al. Overexpression and activation of the tyrosine kinase Src in human pancreatic carcinoma. Biochem Biophys Res Commun 1998;243:503–8.

12. Ottenhoff-Kalff AE, Rijksen G, van Beurden EA, Hennipman A, Michels AA, Staal GE. Characterization of protein tyrosine kinases from human breast cancer: involvement of the c-src oncogene product. Cancer Res 1992;52:4773–78.

13. Summy JM, Gallick GE. Src family kinases in tumor progression and metastasis. Cancer Metastasis Rev 2003;22:337–58.

14. Takekura N, Yasui W, Yoshida K et al. pp60c-src protein kinase activity in human gastric carcinomas. Int J Cancer 1990;45:847–51.

15. Talamonti MS, Roh MS, Curley SA, Gallick GE. Increase in activity and level of pp60c-src in progressive stages of human colorectal cancer. J Clin Invest 1993;91:53–60.

16. Verbeek BS, Vroom TM, Driaansen-Slot SS et al. c-Src protein expression is increased in human breast cancer. An immunohistochemical and biochemical analysis. J Pathol 1996;180:383–88.

17. Liegl B, Hornick JL, Lazar AJ. Contemporary pathology of gastrointestinal stromal tumors. Hematol Oncol Clin North Am 2009;23:49–viii. (need page number here)

18. Lee FY, Lombardo L, Borzilleri R et al. BMS-354825 - A potent dual SRC/ABL kinase inhibitor possessing curative efficacy against imatinib sensitive and resistant human CML models in vivo [abstract 3987]. Proc Amer Assoc Cancer Res 2004;45 Suppl:92

19. Lombardo LJ, Lee FY, Chen P et al. Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide

(BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. J Med Chem 2004;47:6658–61.

20. Lesslie DP, Parikh NU, Shah J et al. Combined activity of dasatinib (BMS-354825) and oxaliplatin in an orthotopic model of metastatic colorectal carcinoma [abstract 4745]. Proc Amer Assoc Cancer Res 2006;47.

21. Trevino JG, Summy JM, Lesslie DP et al. Inhibition of Src expression and activity inhibits tumor progression and metastasis of human pancreatic adenocarcinoma cells in an orthotopic nude mouse model. Am J Pathol 2006;168:962–72.

22. Schittenhelm MM, Shiraga S, Schroeder A et al. Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, juxtamembrane, and activation loop mutant KIT isoforms associated with human malignancies. Cancer Res 2006;66:473–81.

23. Cortes J, Rousselot P, Kim DW et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. Blood 2007;109:3207–13.

24. Guilhot F, Apperley J, Kim DW et al. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. Blood 2007;109:4143–50.

25. Hochhaus A, Kantarjian HM, Baccarani M et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Blood 2007;109:2303–9.

26. Ottmann O, Dombret H, Martinelli G et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a Phase II study. Blood 2007;110:2309–15.

27. Talpaz M, Shah NP, Kantarjian H et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med 2006;354:2531–41.

28. WHO. World Health Organization Handbook for Reporting Results for Cancer Treatment. Geneva, Switzerland. WHO 1979.

29. Luo FR, Barrett Y, Ji P et al. Dasatinib (BMS-354825) pharmacokinetics correlate with pSRC pharmacodynamics in phase I studies of patients with cancer (CA180002, CA180003) [abstract 3046]. J Clin Oncol 2006;24 (June 20 Suppl)

30. Young H, Baum R, Cremerius U et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 1999;35:1773–82.

31. Demetri GD. Targeting c-kit mutations in solid tumors: scientific rationale and novel therapeutic options. Semin Oncol 2001;28:19–26.

32. Ostman A, Heldin CH. Involvement of platelet-derived growth factor in disease: development of specific antagonists. Adv Cancer Res 2001;80:1–38.

33. Pandey A, Shao H, Marks RM, Polverini PJ, Dixit VM. Role of B61, the ligand for the Eck receptor tyrosine kinase, in TNF-alpha-induced angiogenesis. Science 1995;268:567–69.

34. Andres AC, Reid HH, Zurcher G, Blaschke RJ, Albrecht D, Ziemiecki A. Expression of two novel eph-related receptor protein tyrosine kinases in mammary gland development and carcinogenesis. Oncogene 1994;9:1461–67.

35. Miao H, Burnett E, Kinch M, Simon E, Wang B. Activation of EphA2 kinase suppresses integrin function and causes focal-adhesion-kinase dephosphorylation. Nat Cell Biol 2000;2:62–69.

36. Bergeron A, Rea D, Levy V et al. Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: a case series. Am J Respir Crit Care Med 2007;176:814–18.

37. Shah NP, Kantarjian HM, Kim DW et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 2008;26:3204–12.

38. Quintas-Cardama A, Kantarjian H, O'Brien S et al. Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. J Clin Oncol 2007;25:3908–14.

39. Freebern WJ, Fang HS, Slade MD et al. In Vitro Cardiotoxicity Potential Comparative Assessments of Chronic Myelogenous Leukemia Tyrosine Kinase Inhibitor Therapies: Dasatinib, Imatinib and Nilotinib [abstract 4582]. Blood 2007;110.

40. Boyce BF, Xing L, Yao Z et al. SRC inhibitors in metastatic bone disease. Clin Cancer Res 2006;12:6291s–95s.

41. Weichsel R, Dix C, Wooldridge L et al. Profound inhibition of antigen-specific T-cell effector functions by dasatinib. Clin Cancer Res 2008;14:2484–91.

42. Christopher LJ, Cui D, Wu C et al. Metabolism and disposition of dasatinib after oral administration to humans. Drug Metab Dispos 2008;36:1357–64.

43. Ali S, Ali S. Role of c-kit/SCF in cause and treatment of gastrointestinal stromal tumors (GIST). Gene 2007;401:38–45.

TABLES AND FIGURES

Table 1. Baseline demographic and clinical characteristics

	Dasatinib schedule		
	5D2 (n = 33)	CDD (n = 34)	Total (N = 67)
Median age, years (range)	56 (32-81)	59 (31-82)	57 (31-82)
Gender			
Male	20 (60.6%)	18 (52.9%)	38 (56.7%)
Female	13 (39.4%)	16 (47.1%)	29 (43.3%)
Baseline ECOG score			
0	18 (54.5%)	14 (41.2%)	32 (47.8%)
1	15 (45.5%)	20 (58.8%)	35 (52.2%)
Tumor type			
GIST	17 (51.5%)	2 (5.9%)	19 (28.4%)
Colon	2 (6.1%)	6 (17.6%)	8 (11.9%)
Sarcoma	4 (12.1%)	4 (11.8%)	8 (11.9%)
Melanoma	3 (9.1%)	2 (5.9%)	5 (7.5%)
Rectum	2 (6.1%)	3 (8.8%)	5 (7.5%)
Gastric	1 (3.0%)	3 (8.8%)	4 (6.0%)
Mesothelioma	0	3 (8.8%)	3 (4.5%)
MPN sheath tumor	1 (3.0%)	1 (2.9%)	2 (3.0%)
Ovary	0	1 (2.9%)	1 (1.5%)
Other*	3 (9.1%)	9 (26.5%)	12 (17.9%)

*Other tumors reported by study investigators were desmoid tumor, biliary tract, small bowel (5D2); adenoid cystic carcinoma, myoepithelioma, chordoma, squamous cell carcinoma of left pinna, meningioma, chromophobe renal cell carcinoma, medullary thyroid, endometrial and breast (CDD).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumor; MPN, malignant peripheral nerve sheath tumor.

Table 2. Overview of dasatinib treatment

Dasatinib cohort (n)	Treatment duration Median (range), months	Treatment duration excluding interruptions Median (range), months	Total dose Median (range), mg	Net dose intensity, mg/day*
5D2 schedule				
35 mg (n = 7)	0.9 (0.1-7.4)	0.9 (0.1-7.2)	1400 (210.0-14190)	54 (40-70)
50 mg (n = 3)	4.0 (1.1-5.0)	3.7 (1.1-5.0)	7850 (2450-14110)	75 (71-93)
70 mg (n = 4)	2.8 (1.1-4.1)	2.8 (1.1-3.8)	8750 (3430-11480)	103 (99-104)
90 mg (n = 6)	2.1 (0.7-3.6)	1.9 (0.7-3.6)	7560 (3330-14400)	132 (126-180)
120 mg (n = 9)	1.1 (0.2-4.4)	0.9 (0.2-4.4)	4800 (1080-23160)	182 (157-216)
160 mg (n = 4)	4.0 (1.3-23.8)	3.7 (0.8-21.6)	20875 (3970-84720)	152 (129-225)
CDD schedule				
70 mg (n = 5)	1.0 (0.1-9.6)	0.8 (0.1-9.6)	3500 (170-40950)	140 (85-140)
90 mg (n = 7)	1.7 (0.6-18.3)	1.6 (0.3-16.9)	8550 (1710-90630)	177 (149-182)
100 mg (n = 17)	1.2 (0.1-12.9)	0.8 (0.1-12.5)	4700 (400-75800)	197 (157-216)
120 mg (n = 5)	0.3 (0.2-1.8)	0.2 (0.2-1.8)	1440 (1080-21720)	236 (197-240)

*Net dose intensity = cumulative total dose divided by treatment duration (excluding interruption) per patient

Table 3. Treatment-related non-hematologic toxicities occurring in ≥10% of patients on the 5D2 dosing schedule (Gr = Grade)

	35 mg (n=7)		50 mg (n=3)		70 mg (n=4)		90 mg (n=6)		120 mg (n=9)		160 mg (n=4)		Overall (N=33)	
Event, n (%)	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**
Nausea	4 (57)	0 (0)	1 (33)	0 (0)	3 (75)	0 (0)	1 (17)	0 (0)	7 (78)	1 (11)	4 (100)	0 (0)	20 (61)	1 (3)
Fatigue	3 (43)	0 (0)	2 (66)	0 (0)	3 (75)	0 (0)	3 (50)	0 (0)	2 (22)	0 (0)	1 (25)	0 (0)	14 (42)	0 (0)
Diarrhea	3 (43)	1 (14)	1 (33)	0 (0)	1 (25)	0 (0)	1 (17)	0 (0)	4 (44)	0 (0)	3 (75)	0 (0)	13 (39)	1 (3)
Vomiting	2 (29)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (44)	1 (11)	2 (50)	0 (0)	9 (27)	1 (3)
Anorexia	1 (14)	1 (14)	1 (33)	0 (0)	2 (50)	0 (0)	1 (17)	0 (0)	1 (11)	0 (0)	2 (50)	1 (25)	8 (24)	2 (6)
Lethargy	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	2 (33)	0 (0)	2 (22)	0 (0)	2 (50)	1 (25)	7 (21)	1 (3)
Headache	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	2 (22)	0 (0)	1 (25)	0 (0)	5 (15)	0 (0)
Pyrexia	1 (14)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (25)	0 (0)	4 (12)	0 (0)
Chills	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	3 (75)	0 (0)	4 (12)	0 (0)
Proteinuria	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	2 (50)	1 (25)	3 (9)	1 (3)

Table 4. Treatment-related non-hematologic toxicities occurring in e 10% of patients on the CDD dosing schedule (Gr = Grade)

	70 mg (n=5)		90 mg (n=7)		100 mg (n=17)		120 mg (n=5)		Overall (N=34)	
Event, n (%)	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**	**Gr 1-2**	**Gr 3-4**
Nausea	4 (80)	0 (0)	4 (57)	0 (0)	7 (41)	0 (0)	2 (40)	1 (20)	17 (50)	1 (3)
Anorexia	2 (40)	0 (0)	4 (57)	0 (0)	9 (53)	0 (0)	2 (40)	0 (0)	17 (50)	0 (0)
Fatigue	1 (20)	0 (0)	2 (29)	0 (0)	8 (47)	1 (6)	2 (40)	1 (20)	13 (38)	2 (6)
Diarrhea	1 (20)	0 (0)	3 (43)	0 (0)	6 (35)	0 (0)	1 (20)	0 (0)	11 (32)	0 (0)
Lethargy	2 (40)	0 (0)	3 (43)	0 (0)	2 (12)	1 (6)	0 (0)	0 (0)	7 (21)	1 (3)
Vomiting	1 (20)	0 (0)	3 (43)	0 (0)	3 (18)	0 (0)	0 (0)	0 (0)	7 (21)	0 (0)
Headache	2 (40)	0 (0)	0 (0)	0 (0)	3 (18)	0 (0)	1 (20)	0 (0)	6 (18)	0 (0)
Proteinuria	0 (0)	0 (0)	0 (0)	1 (14)	4 (24)	0 (0)	1 (20)	0 (0)	5 (15)	1 (3)
Rash	0 (0)	0 (0)	2 (29)	0 (0)	3 (18)	0 (0)	0 (0)	1 (20)	5 (15)	1 (3)
Pruritus	0 (0)	0 (0)	1 (14)	0 (0)	2 (12)	0 (0)	1 (20)	0 (0)	4 (12)	0 (0)
Anemia	0 (0)	0 (0)	1 (14)	0 (0)	2 (12)	0 (0)	1 (20)	0 (0)	4 (12)	0 (0)
Dyspnea	0 (0)	0 (0)	1 (14)	0 (0)	2 (12)	1 (6)	0 (0)	0 (0)	3 (9)	1 (3)

Table 5. Summary of pharmacokinetic parameters

Dasatinib schedule (BID dose)	Day	n	C_{max} (ng/mL) Geometric mean (CV %)	AUC (ng•h/mL) Geometric mean (CV %)	T_{max} (hour) Median (minimum, maximum)	$T_{1/2}$ (hour) Mean (SD)	Clo (L/h) Mean (SD)	Vz/F (L) Mean (SD)
5D2 (35 mg)	8	6	25 (99)	85 (73)	1.5 (0.5, 4.0)	3.0 (1.1)	642 (651)	3083 (3866)
	26	4	19 (84)	84 (30)	1.4 (0.5, 1.6)	3.0 (0.9)	433 (146)	1842 (602)
5D2 (50 mg)	8	3	38 (45)	140 (22)	1.0 (0.5, 3.0)	3.8 (0.6)	402 (74)	2144 (205)
	26	3	43 (100)	158 (4)	0.5 (0.5, 2.0)	4.4 (2.2)	317 (13)	2034 (1052)
5D2 (70 mg)	8	3	46 (91)	165 (78)	0.5 (0.5, 2.0)	4.9 (1.5)	1188 (1716)	9464 (14175)
	26	4	25 (80)	161(8)	2.0 (1.0, 6.0)	4.3 (1.6)	488 (37)	3649 (94)
CDD (70 mg)	8	3	78 (90)	245 (57)	1.0 (0.5, 6.0)	4.0 (0.8)	327 (210)	2039 (1715)
	26	3	50 (86)	325 (19)[a]	3.1 (1.1, 6.1)	2.5 (1.0)[a]	217 (42)[a]	739 (162)[a]
5D2 (90 mg)	8	5	89 (44)	251 (37)	1.0 (0.5, 4.0)	3.2 (0.7)	438 (311)	1922 (1204)
	26	5	83 (58)	492 (33)[b]	3.0 (1.0, 8.0)	2.3 (0.7)[b]	191 (64)[b]	600 (82)[b]
CDD (90 mg)	8	6	52 (84)	204 (68)	1.6 (0.0, 3.1)	4.1 (1.3)	545 (364)	3516 (2894)
	26	5	72 (59)	274 (45)	1.5 (0.5, 5.0)	3.1 (1.2)	409 (360)	2176 (2727)
CDD (100 mg)	8	12	56 (118)	218 (102)	1.5 (0.5, 3.6)	4.3 (1.7)	667 (538)	4224 (3549)
	26	7	52 (96)	207 (79)	2.0 (0.5, 5.0)	3.20 (1.7)	697 (793)	2740 (2541)
5D2 (120 mg)	8	5	77 (73)	298 (66)	1.0 (0.5, 2.0)	3.2 (0.8)	511 (326)	2223 (1079)
	26	7	98 (82)	396(74)	1.0 (0.5, 2.0)	3.3 (1.5)	368 (234)	1679 (1145)
CDD (120 mg)	8	5	131 (48)	526 (49)	0.5 (0.0, 2.0)	3.4 (0.7)	270 (195)	1401 (1336)
	26	1	60 (n/a)	207 (n/a)	1.5 (1.5, 1.5)	2.2 (n/a)	590 (n/a)	1877 (n/a)
5D2 (160 mg)	8	2	203 (53)	436 (56)	0.8 (0.5, 1.0)	2.7 (0.6)	411 (224)	1523 (549)
	26	1	178 (n/a)	502 (n/a)	1.5 (1.5, 1.5)	2.6 (n/a)	319 (n/a)	1195 (n/a)

Abbreviations: C_{max}, maximum plasma concentration; AUC, area under the plasma concentration-time curve; CV, coefficient of variation; T_{max}, time to reach C_{max}; $T_{1/2}$, apparent plasma elimination half-life; n/a, not available.

[a]n=2; [b]n=4.

Figure 1. Mean plasma concentration time profiles of dasatinib at steady state (Day 26): A) 5D2 (5 days on treatment/2 days off treatment) schedule B) CDD (continuous twice-daily) schedule. BID = twice-daily dosing