Cancer Therapy: Clinical

Clinical Cancer Research

Dasatinib as a Single Agent in Triple-Negative Breast Cancer: Results of an Open-Label Phase 2 Study

Richard S. Finn[1], Carmelo Bengala[2], Nuhad Ibrahim[3], Henri Roché[4], Joseph Sparano[5], Lewis C. Strauss[6], Justin Fairchild[6], Oumar Sy[6], and Lori J. Goldstein[7]

Abstract

Purpose: Dasatinib is a potent, oral SRC-family kinase inhibitor with preclinical antiproliferative, antimetastatic, and antiosteoclastic activity suggesting dasatinib sensitivity in triple-negative, or basal-like, breast cancer cell lines. This phase 2 trial assessed efficacy and safety of single-agent dasatinib in patients with advanced triple-negative breast cancer (TNBC).

Experimental Design: Female patients with measurable, locally advanced or metastatic TNBC initially received dasatinib 100 mg twice daily (BID); to improve tolerability, the protocol was amended and subsequent patients received 70 mg BID. Primary endpoint was Response Evaluation Criteria in Solid Tumors–defined objective response rate (ORR); secondary endpoints included progression-free survival (PFS), disease control rate (DCR), safety, and limited pharmacokinetics.

Results: Of the 44 treated patients, 43 were response evaluable. ORR was 4.7%: two patients had confirmed partial responses lasting 14 and 58 weeks, respectively. Of 11 patients with stable disease, two continued for more than 16 weeks, thus protocol-defined DCR was 9.3%. Median PFS was 8.3 weeks (95% CI: 7.3–15.3). Five patients discontinued before first tumor assessment. No grade 4 adverse events (AE) were reported; grade 3 AEs occurring in more than 5% of patients were fatigue (9.1%), diarrhea, pleural effusion, and dyspnea (all 6.8%). Laboratory abnormalities were uncommon. Dasatinib at 100 mg BID was not well tolerated; rates of treatment interruption, dose reduction, and serious AEs were lower with dasatinib 70 mg BID.

Conclusions: Single-agent dasatinib has limited activity in unselected patients with TNBC. Dasatinib 70 mg BID was better tolerated than 100 mg BID. Future studies will investigate dasatinib in other breast cancer settings, including chemotherapy combinations. *Clin Cancer Res; 17(21); 6905–13. ©2011 AACR.*

Introduction

Breast cancer is the most commonly diagnosed female cancer in the United States with approximately 207,000 new cases per year (3). Targeted therapies, including antiestrogens, aromatase inhibitors, and trastuzumab, have been effective against cancers expressing relevant target molecules, that is, estrogen receptor (ER), progesterone receptor (PgR), or HER2 (4, 5).

Triple-negative breast cancer (TNBC) is particularly challenging because tumors lack validated molecular targets. Molecular profiling has identified TNBC as a heterogeneous group including the basal-like breast cancer subtype (6, 7). Generally, TNBC is highly proliferative (8), has a poor outcome (7), is more likely to recur (9), and progresses rapidly (10). Treatment with cytotoxic drugs for TNBC is common, although durable disease control is rare (11). Therefore, identification of molecular targets for TNBC therapy is critical.

Authors' Affiliations: [1]Department of Medicine, Division of Hematology, Oncology, Geffen School of Medicine, UCLA Medical Center, Los Angeles, California; [2]Department of Oncology and Hematology, University of Modena and Reggio Emilia, Modena, Italy; and [3]Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; [4]Department of Medical Oncology, Institut Claudius Regaud, Toulouse, France; [5]Montefiore-Einstein Cancer Center, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York; [6]Bristol-Myers Squibb Inc., Wallingford, Connecticut; [7]Breast Evaluation Center, Fox Chase Cancer Center, Philadelphia, Pennsylvania

Note: This manuscript contains original material. A portion of the work described herein was presented in an abstract at the 31st San Antonio Breast Cancer Symposium, December, 2008 (1).

Submitted in parallel with the primary manuscript by E. Mayer and colleagues titled "A phase 2 trial of dasatinib in patients with advanced HER2-positive and/or hormone receptor-positive breast cancer" (2).

Corresponding Author: Richard S. Finn, Department of Medicine, Division of Hematology, Oncology, Geffen School of Medicine at UCLA, 10833 Le Conte Ave., 11-934 Factor Bldg, Los Angeles, CA 90095. Phone: 310-206-3180; Fax: 310-586-6830; E-mail: rfinn@mednet.ucla.edu

doi: 10.1158/1078-0432.CCR-11-0288

Translational Relevance

The potential of SRC-family kinases as drivers of oncogenesis is highlighted by their diverse roles in cellular proliferation, invasion, angiogenesis, and survival, making them an attractive therapeutic target in oncology. This article reports the first phase 2 data from a prospective clinical study to evaluate a targeted SRC inhibitor in patients with "triple-negative" breast cancer (TNBC) as a unique disease entity. These data show that dasatinib has limited single-agent activity in unselected patients with locally advanced or metastatic TNBC, a group with poor prognosis and limited treatment options. Although patients were not selected for specific biomarkers other than the lack of estrogen receptor, progesterone receptor, and HER2 ("triple negative"), these data built on the growing data that TNBC is not a homogeneous disease and that further identification of biomarkers may identify subpopulations of patients with TNBC who will benefit from SRC inhibition.

SRC is a ubiquitously expressed intracellular tyrosine kinase that regulates protein–protein interactions and signaling pathways involved in adhesion, migration, invasion, protection against apoptosis, and vascular endothelial growth factor expression (12, 13). Abnormal activation or amplification of SRC and SRC-family kinases (SFK) has been detected in various tumors, including breast cancer (12–14), and has been shown to play a role in proliferation, migration, and invasion of breast cancer cell lines (15, 16). SRC also regulates osteoclast function in healthy bone and bone metastases (17, 18). SRC therefore represents a rational molecular target for breast cancer treatment, including TNBC.

Dasatinib, a potent oral inhibitor of SFKs, is approved for treating patients with Philadelphia chromosome-positive leukemias (19). Preclinical studies showed growth inhibition of breast cancer cells with a basal-like phenotype by single-agent dasatinib more frequently than other phenotypes, also identifying specific markers of response (15, 20). Preclinical TNBC models also showed synergistic or additive dasatinib activity with chemotherapy (21), suggesting that dasatinib may provide clinical benefit in TNBC.

We report results from CA180059, a prospective, open label, phase 2 trial of twice-daily (BID) dasatinib in patients with locally advanced or metastatic TNBC that had progressed after prior chemotherapy for advanced disease.

Materials and Methods

Patients

Eligible patients were female with an Eastern Cooperative Oncology Group performance status of 0 to 1, and had measurable recurrent or progressive locally advanced or metastatic TNBC that had progressed after anthracycline and/or taxane therapy (maximum of 2 prior chemotherapy regimens for advanced disease). Tumor receptor status was determined using immunohistochemistry (IHC) analysis from a previous biopsy showing ER/PgR negativity (<10% of cells with positive staining) and HER2-normal staining (IHC 0–1+ or negative by chromogenic/fluorescent *in situ* hybridization). At the time of study initiation, the definition of ER/PgR positivity was driven by response to hormone therapy and thus the cutoff was less than 10% ER/PgR by IHC. The current American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) guidelines are more stringent and may better define this group of patients (22). Women of childbearing potential were required to have adequate contraception during study. Patients were excluded if they were pregnant or breast feeding, had symptomatic central nervous system metastases, or bone metastases only, had any antineoplastic therapy within 14 days prior to starting dasatinib, had reduced hematologic, hepatic, or renal function, pleural effusion or any concurrent medical condition potentially increasing toxicity risk. Eligible patients had adequate liver function [grade 0–1 aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin], serum Ca^{2+} of lower limit of normal or more, grade 0 to 1 serum K^{+}, Mg^{2+}, and phosphate, grade 0 to 2 creatinine, and grade 0 to 1 hemoglobin, neutrophil count, platelet count, prothrombin time, and partial thromboplastin time. Patients were excluded if they had any concurrent medical condition which may have increased toxicity risk, including pleural or pericardial effusion, clinically significant coagulation or platelet function disorder, infection requiring intravenous antibiotics, requirement for prohibited concomitant therapy, ongoing or recent ($\leq$3 months) significant gastrointestinal bleeding, or clinically significant cardiovascular disease.

Trials were conducted in accordance with the Declaration of Helsinki and approved by responsible Institutional Review Boards or Ethics Committees of participating centers. All patients gave written informed consent.

Study design

The primary objective of this open label phase 2 study was to estimate objective response rate (ORR). Secondary objectives were to estimate response duration, disease control rate (DCR) at week 17, overall progression-free survival (PFS), safety and tolerability, and pharmacokinetics. A Gehan 2-stage design, involving 29 and 16 response evaluable patients in the first and second stages, respectively, was used. If no response was observed in the first stage, the study would have been closed to accrual with the conclusion that an ORR of 10% or more was unlikely (95% CI). Initially, dasatinib was administered as 100 mg BID, which was decreased to 70 mg BID by protocol amendment after the first 23 patients.

Dose modifications

Dasatinib dose was interrupted, reduced, or treatment suspended in the event of drug-related grade 3 to 4 toxicity

or recurrent unacceptable or unmanageable drug-related grade 2 toxicity. Dasatinib was reduced to either 50 mg BID, or 100 mg once daily (QD) based on individual tolerability. Patients were discontinued on recurrence of unacceptable toxicity with 50 mg BID dosing, confirmed progressive disease (PD), or excessive toxicity despite dose reduction. Dose reescalation or reinitiation was permitted at investigator discretion once toxicity had decreased to grade 0 to 1.

Patient assessments

Patients were evaluated at least every 2 weeks ± 4 days for the first 8 weeks (weeks 3, 5, 7, and 9), every 4 weeks for 2 visits (after 3 and 4 months on treatment), and every 8 weeks ± 1 week until the end of treatment. Tumor responses were classified according to Response Evaluation Criteria in Solid Tumor (RECIST) guidelines (23) defined as: complete response (CR) = disappearance of all target and nontarget lesions confirmed after 4 weeks or more; partial response (PR) = 30% or more decrease from baseline in the sum of largest diameters (SLD) of target lesions confirmed after 4 weeks or more; PD = appearance of new lesions, 20% or more increase in the SLD of target lesions, or unequivocal progression of nontarget lesions; and stable disease = insufficient change to qualify as PR or PD without unequivocal progression of nontarget lesions after 6 weeks or more on-study. Patients with equivocal evidence of PD remained on-study at investigator's discretion. ORR was defined as the proportion of response evaluable patients with CR or PR as best response. DCR was defined as the proportion of response evaluable patients with CR or PR as best response or with stable disease for 16 weeks or more. The response evaluable population included nonresponding patients who discontinued therapy for toxicity, even if no on-study assessment was carried out. Duration of response was measured from the first date that CR or PR criteria were met until PD. PFS, assessed in all treated patients, was defined as time from first dose until PD. Patients who died without documented PD were considered to have progressed at date of death; those who neither progressed nor died were censored at last tumor evaluation. Kaplan–Meier analysis was used to calculate median values and 95% CI for response duration and PFS.

Adverse events (AE) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, with causal relationship assigned by investigators.

Pharmacokinetics

Because pharmacokinetic information for dasatinib 70 mg BID is already available, pharmacokinetic assessment was optional (24, 25). Blood samples were collected at 0, 1, 3, 6, and 12 hours at week 3 and week 7 or week 9. Mean plasma dasatinib concentrations and SDs were assayed by tandem liquid chromatography mass spectrometry.

Results

Patient characteristics

Forty-four of 55 enrolled patients were treated. Of the 11 patients who were not treated, 10 were found to be ineligible and one withdrew consent prior to treatment. Of the 44 treated patients, 43 were response evaluable (1 patient was withdrawn without progression for grade 1 pneumonia unrelated to treatment). Four response evaluable patients discontinued treatment before on-study tumor assessment because of study drug-related toxicity. Patient demographics are reported in Table 1. Documentation of confirmed PR (cPR) in the 16th and 25th treated patients satisfied protocol-defined criteria for continued accrual. All patients discontinued treatment because of disease progression ($n = 26$, 59%), study drug toxicity ($n = 8$, 18%), or other reasons ($n = 10$, 23%; Table 1).

Treatment

Initially, 23 patients received dasatinib at 100 mg BID; following protocol amendment, 21 patients received 70 mg BID. In the 100 mg BID group, median daily dose was 146 mg/d (range 87–200), and 39% of patients received 85% or more of their planned dose. In the 70 mg BID group, median daily dose was 135 mg/d (range 87–140) and 86% of patients received 85% or more of their planned dose. Median therapy duration in both groups was 1.61 months excluding interruptions, and median durations were 1.35 and 1.61 months in the 100 and 70 mg BID groups, respectively. Only 3 patients continued dasatinib beyond week 17.

A higher percentage of patients received dose interruptions in the 100 mg BID group ($n = 19$; 83%) than in the 70 mg BID group ($n = 11$; 52%), and 2 or more interruptions were required by 43% ($n = 10$) and 19% ($n = 4$), respectively. In the 100 mg BID group, 18 first dose interruptions were due to nonhematologic toxicity; those occurring in more than 2 patients were pleural effusion ($n = 3$) and diarrhea ($n = 4$). In the 70 mg BID group, all first dose interruptions ($n = 11$) were due to nonhematologic toxicity, those occurring in more than 1 patient were chest-wall pain ($n = 2$) and vomiting ($n = 2$).

Dose reduction was carried out in 14 patients receiving 100 mg BID (61%), but only 5 patients receiving 70 mg BID (24%); 2 or more dose reductions were carried out in 30% and 5%, respectively. In the 100 mg BID group, 9 first dose reductions were related to nonhematologic toxicity; those occurring in more than 1 patient were cough ($n = 2$) and asthenia ($n = 2$). In the 70 mg BID group, 2 first dose reductions were related to nonhematologic toxicity (diarrhea, pleural effusion, and headache). Median times to toxicity related first dose reduction or interruption were 18 and 14 days in the 100 and 70 mg BID groups, respectively.

Efficacy

Of 43 response evaluable patients, 2 cPRs were observed (response durations of 14 and 58 weeks), resulting in an

Table 1. Patient demographics and disposition

	Assigned starting dose		
	100 mg BID	**70 mg BID**	**Overall**
Mean age, y	56.4	51.5	54.0
Range	39–71	29–67	29–71
Age, *n* (%)			
Less than 50 y	4 (17.4)	9 (42.9)	13 (29.5)
50 y or more	19 (82.6)	12 (57.1)	31 (70.5)
Gender, *n* (%)			
Female	23 (100.0)	21 (100.0)	44 (100.0)
Race, *n* (%)			
White	20 (87.0)	19 (90.5)	39 (88.6)
Black/African American	2 (8.7)	1 (4.8)	3 (6.8)
Asian	0 (0)	1 (4.8)	1 (2.3)
Other	1 (4.3)	0 (0)	1 (2.3)
Patients treated, *n*	23	21	44
Response evaluable patients, *n*	23	20	43
Patients available for safety analysis, *n*	23	21	44
Median time from cancer diagnosis, months (range)	30.3 (7.2–89.7)	26.0 (6.5–161.7)	29.5 (6.5–161.7)
Number of prior regimens in the advanced setting, *n* (%)			
0	8 (34.8)	5 (23.8)	13 (29.5)
1	14 (60.9)	13 (61.9)	27 (61.4)
2	1 (4.3)	3 (14.3)	4 (9.1)
Discontinuations, *n*	23	21	44
Disease progression, *n* (%)	13 (56.6)	13 (61.9)	26 (59.1)
Study drug toxicity, *n* (%)	3 (13.0)	5 (23.8)	8 (11.4)
Patient request, *n* (%)	5 (21.7)	0 (0)	5 (11.4)
Other, *n* (%)	2 (8.7)	0 (0)	2 (4.5)
Nonstudy AE, *n* (%)	0 (0)	1 (4.8)	1 (2.3)
Lost to follow up, *n* (%)	0 (0)	1 (4.8)	1 (2.3)
Patient withdrew consent, *n* (%)	0 (0)	1 (4.8)	1 (2.3)

ORR of 4.7% (2 of 43; 95% CI: 0.57–15.81). Additional details of the 2 patients who had PRs are as follows. Patient 19 had prior adjuvant chemotherapy, prior hormonal therapy for a previous contralateral ER^+ tumor, and recurrent TNBC that was considered to have metastasized. She started dasatinib at 100 mg BID, reduced to 70 mg BID in week 5 due to grade 3 diarrhea, and reduced to 50 mg BID in week 24 due to grade 2 neutropenia. Normalization of tumor markers was reported as indicated by serum markers, resolution of bone pain, and regression of clinically palpable and radiographically measurable lymph nodes. However, bone scans were persistently positive, therefore the response was considered PR, first recorded in week 8 and lasting for 58 weeks. Patient 30 had prior treatment with chemotherapy and hormonal therapy, including gemcitabine plus capecitabine in the advanced setting, and recurrent disease in multiple lymph nodes. She started dasatinib at 100 mg BID, reduced to 70 mg BID in week 8, and to 50 mg BID in week 13 due to asthenia, then withdrew from the trial at week 17. Complete regression of a clinically measured lymph node and PR of a radiographically measured lymph node (>50% reduction in SLD) were recorded. PR was first recorded in week 8 and disease progression at week 22.

DCR was 4 of 43 (9.3%; 95% CI: 2.59–22.14), including 2 patients who had stable disease lasting 16 weeks or more (25 and 33 weeks). Twelve patients had stable disease as best response (Table 2). Tumor size decreased from baseline in 11 patients (Fig. 1A); the 2 patients who had a cPR had the greatest decreases in tumor size of −86% and −100% (the latter did not qualify as CR because of residual nontarget lesions). Median PFS for treated patients ($n = 44$) was 8.3 weeks (95% CI: 7.3–15.3). Proportions of treated patients with PFS at weeks 9, 17, and 25 were 0.37, 0.22, and 0.09, respectively (Fig. 1B).

Safety

Of 23 patients who received dasatinib 100 mg BID, 5 (22%) experienced a drug-related serious AE (SAE), 12 (52%) had a grade 3 drug-related AE, 19 (83%) required at least 1 dose interruption, and 14 (61%) had their dose reduced. Following protocol amendment to reduce the starting dose to 70 mg BID, dasatinib was reasonably well

Table 2. Tumor responses in evaluable patients

	Assigned starting dose		
	100 mg BID ($n = 23$)	**70 mg BID ($n = 20$)**	**Total ($n = 43$)**
Best overall response, *n* (%)			
PR	2 (8.7)	0	2 (4.7)
Stable disease	7 (30.4)	5 (25)	12 (27.9)
PD	10 (43.5)	12 (60)	22 (51.2)
Discontinuation due to drug toxicity, *n* (%)	4 (17.4)	3 (15)	7 (16.3)
ORR, *n* (%)	2 (8.7)	0	2 (4.7)
95% CI	1.07, 28.04		0.57, 15.81
DCR, *n* (%)	3 (13.0)	1 (5)	4 (9.3)
95% CI	2.78, 33.59	0.13, 24.87	2.59, 22.14

tolerated (Table 3) with only 5 patients (24%) requiring dose reduction.

The most common drug-related AEs (>25% incidence) were fatigue, nausea, dyspnea, diarrhea, pleural effusion, rash, vomiting, anorexia, cough, and headache. No grade 4 or 5 drug-related events were reported. Seven deaths due to disease progression were reported; the study did not require follow-up for survival. Fourteen patients (32%) reported SAEs of any grade, regardless of relationship to drug (11 in the 100 mg BID group and 3 in the 70 mg BID group). Drug-related SAEs of any grade were seen in 6 patients (14%), of which one occurred in the 70 mg BID group and 5 occurred in the 100 mg BID group, with only pericardial and pleural effusion occurring in more than 1 patient (Table 4).

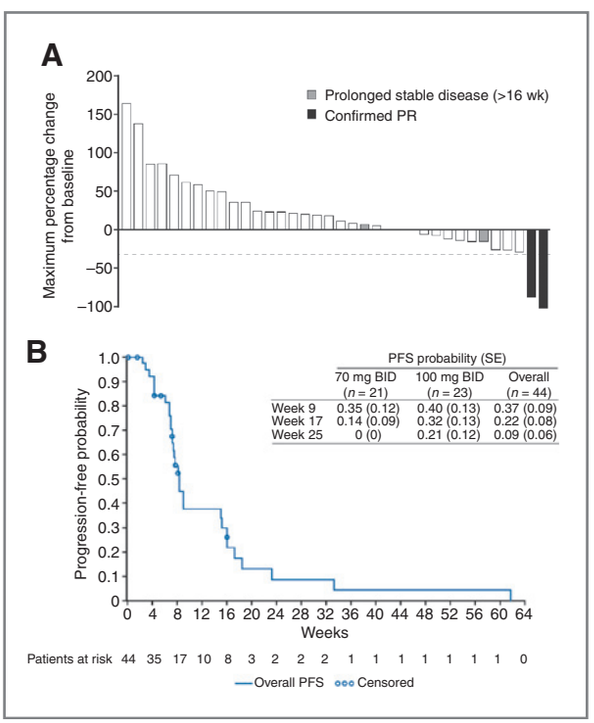

Figure 1. Efficacy of single-agent dasatinib in patients with TNBC. A, maximum change in tumor size in individual treated patients. B, PFS in all treated patients.

On-study grade 3 to 4 laboratory abnormalities were uncommon. Except for grade 3 neutropenia in 3 patients, all hematologic abnormalities were grade 1 to 2. In the 70 mg BID group, 1 patient had on-study worsening of ALT and AST from grade 0 to 3. In the 100 mg BID group, 1 patient had on-study worsening in hypokalemia from baseline grade 0 to 4. Hypophosphatemia was seen in both groups (70 mg BID: grade 3, $n = 2$; 100 mg BID: grade 4, $n = 1$).

Of 10 patients who discontinued for AEs, 4 were in the 100 mg BID group and 6 were in the 70 mg BID group. Of 8 patients who discontinued for drug-related AEs (18%), 3 were in the 100 mg BID group (fatigue, headache, and myopericarditis) and 5 were in the 70 mg BID group (nausea, heartburn, and rash; nausea, fatigue, chest wall pain, insomnia, and anxiety; dyspnea; pleural effusion, and pneumonia; elevated ALT/AST).

Pharmacokinetics

Samples for pharmacokinetic analysis were collected from 22 patients (Table 5). Plasma concentrations of dasatinib predose and after 1, 3, and 6 hours in patients with TNBC were within the range of values obtained using the same dose regimens in patients with solid tumors (25) or leukemia (24).

Discussion

Preclinical data suggest that dasatinib may be effective in treating TNBC by inhibiting proliferation, migration, and invasion of metastatic breast cancer. This article reports one of the first phase 2 studies of an SRC inhibitor in breast cancer and development of a targeted therapy in patients with TNBC, an entity whose definition is still being refined. This study uses a definition of TNBC that is not as stringent as the current ASCO-CAP guidelines would dictate.

Single-agent dasatinib showed limited efficacy in patients with TNBC. Overall, 2 of 43 patients (5%) achieved a RECIST PR, both occurring in lymph nodes and lasting

Table 3. On-study drug-related AEs occurring in at least 10% of patients treated with dasatinib 70 or 100 mg BID

AE	Number of patients ($n = 44$)				
	100 mg BID ($n = 23$)		70 mg BID ($n = 21$)		Total (%)
	All grades, *n* (%)	Grade 3, *n* (%)	All grades, *n* (%)	Grade 3, *n* (%)	
Fatigue	10 (43.5)	2 (8.7)	14 (66.7)	2 (9.5)	24 (54.5)
Nausea	10 (43.5)	1 (4.3)	14 (66.7)	0	24 (54.5)
Diarrhea	12 (52.2)	2 (8.7)	7 (33.3)	1 (4.8)	19 (43.2)
Dyspnea	11 (47.8)	0	6 (28.6)	3 (14.3)	17 (38.6)
Pleural effusion	9 (39.1)	2 (8.7)	7 (33.3)	1 (4.8)	16 (36.4)
Rash	11 (47.8)	0	5 (23.8)	0	16 (36.4)
Vomiting	7 (30.4)	1 (4.3)	6 (28.6)	1 (4.8)	13 (29.5)
Anorexia	9 (39.1)	1 (4.3)	3 (14.3)	0	12 (27.3)
Cough	7 (30.4)	0	5 (23.8)	0	12 (27.3)
Headache	8 (34.8)	0	4 (19.0)	1 (4.8)	12 (27.3)
Abdominal pain	7 (30.4)	2 (8.7)	2 (9.5)	0	9 (20.5)
Flushing	3 (13.0)	0	6 (28.6)	0	9 (20.5)
Arthralgia	4 (17.4)	0	3 (14.3)	0	7 (15.9)
Asthenia	5 (21.7)	0	1 (4.8)	0	6 (13.6)
Constipation	4 (17.4)	1 (4.3)	1 (4.8)	0	6 (13.6)
Musculoskeletal pain	3 (13.0)	1 (4.3)	3 (14.3)	0	6 (13.6)
Myalgia	1 (4.3)	0	5 (23.8)	0	6 (13.6)
Neuropathy	3 (13.0)	0	1 (4.8)	0	4 (9.1)
Pain	3 (13.0)	0	1 (4.8)	0	4 (9.1)
Weight loss	3 (13.0)	0	1 (4.8)	0	4 (9.1)
Abdominal distension	0	0	3 (14.3)	0	3 (6.8)
Erythema	3 (13.0)	0	0	0	3 (6.8)

NOTE: No grade 4 or 5 AEs occurred.

for 14 and 58 weeks. In addition, 11 of 43 patients (26%) experienced stable disease, including 2 lasting for 25 and 33 weeks, and tumor size decreased from baseline in 11 of 36 evaluable patients (31%). Median PFS was 8.3 weeks and only 3 patients continued dasatinib beyond the week 17 assessment. Despite low response rates, a subpopulation of patients with TNBC may exist, whose tumors have increased sensitivity to SRC inhibition and could potentially achieve

Table 4. On-study drug-related SAEs

Drug-related SAE	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Total, *n* (%)
Pleural effusion	0	1 (2.3)	1 (2.3)	2 (4.5)
Pneumonitis	0	0	1 (2.3)	1 (2.3)
Respiratory failure	0	0	1 (2.3)	1 (2.3)
Pericardial effusion	1 (2.3)	0	1 (2.3)	2 (4.5)
Myopericarditis	0	1 (2.3)	0	1 (2.3)
Abdominal pain	0	0	1 (2.3)	1 (2.3)
Constipation	0	0	1 (2.3)	1 (2.3)
Vomiting	0	0	1 (2.3)	1 (2.3)
Generalized edema	0	0	1 (2.3)	1 (2.3)
Periorbital edema	0	1 (2.3)	0	1 (2.3)
Hypotension	0	0	1 (2.3)	1 (2.3)

NOTE: Overall, 6 of 44 patients (14%) had drug-related SAEs of any grade, either during the study or within 30 days following the final dose of study medication, including 1 patient who received dasatinib 70 mg twice daily (BID; who experienced pneumonitis) and 5 patients who had received dasatinib 100 mg BID. No grade 4 or 5 SAEs occurred.

Table 5. Pharmacokinetics for dasatinib 70 mg BID and 100 mg BID at weeks 3 and 7

		Week 3			Week 7		
Dose	**Time (h)**	**Patients (*n*)**	**Mean plasma concentration (ng/mL)**	**SD**	**Patients (*n*)**	**Mean plasma concentration (ng/mL)**	**SD**
100 mg BID	0	10	9.02	3.79	2	8.87	0.49
	1	10	103.35	80.94	2	120.92	23.16
	3	10	50.98	35.23	3	37.04	2.26
	6	10	19.02	8.43	2	15.75	0.14
	12	7	9.11	3.39	1	8.39	NC
70 mg BID	0	10	7.14	4.41	6	4.89	2.16
	1	10	66.41	47.53	6	84.36	62.01
	3	10	35.47	21.51	6	44.80	12.40
	6	10	14.28	8.78	6	14.25	4.69
	12	6	15.43	17.60	5	18.87	30.11

Abbreviation: NC, not calculated.

improved responses to dasatinib. It is increasingly apparent that TNBC is not a single disease but a heterogeneous group of tumors. Interpretation of this study is limited by an absence of biomarker data which could be used to determine which tumors are truly SRC dependent, and further biomarker development is required. To address the importance of identifying appropriate predictive markers, biomarker data from this study are being aggregated with data from other dasatinib studies.

SRC biology is complex and optimal use of SRC inhibitors in breast cancer remains to be determined. A recent study found that subcellular SRC localization and the site of SRC phosphorylation were associated with different breast cancer survival outcomes. Tumors with high cytoplasmic SRC levels or membrane-associated tyrosine-419 phosphorylated SRC were associated with decreased survival, whereas those with activated nuclear and cytoplasmic tyrosine-215 phosphorylated SRC had a significantly improved survival benefit (26). Preclinical evidence suggests that, as a result of complex crosstalk between SRC-regulated signaling pathways, SRC inhibition may result in a paradoxical increase in proliferative signaling in breast cancer cells (27). A 200-gene signature for breast cancer epithelial-mesenchymal transition has been identified, including the SFK member LYN, which is associated with shorter overall survival and the basal (triple negative) subtype. LYN inhibition by dasatinib inhibited TNBC cell invasion *in vitro* without inhibiting proliferation (16). Future studies will correlate treatment responses to dasatinib with investigational biomarkers in patients with breast cancer.

The limited efficacy observed in this trial is similar to those of other single-agent tyrosine kinase inhibitors in unselected patients with advanced breast cancer. For example, in two phase 2 studies of patients with metastatic breast cancer previously exposed to anthracyclines or taxanes treated with sorafenib, no patient had a PR or CR (28), and only 3 of 20 (15%) patients with TNBC treated with sunitinib had a PR (29). These results suggest that better patient selection strategies are required.

The dosing regimen for this study was based on a phase 1 study in which patients with solid tumors received dasatinib at a putative maximum-tolerated dose of 120 mg BID (25). However, almost all patients who received this dose in this study required treatment interruption. Therefore, the starting dose was reduced first to 100 mg BID, then to 70 mg BID, equal to the first dose reduction level for patients who could not tolerate 100 mg BID. Although this study was not designed to compare dosing groups, data suggest that dasatinib 70 mg BID had improved tolerability relative to dasatinib 100 mg BID, including numerically lower rates of treatment interruption, dose reduction, and grade 3 AEs. No grade 4 or 5 AEs were recorded in either dosing group. Importantly, AEs observed were in line with previous clinical experience with dasatinib and no unexpected AEs were reported. Median dasatinib dose intensities were similar in the 100 mg BID and 70 mg BID groups (146 and 135 mg/d, respectively). Overall median duration of study therapy was unexpectedly short (1.61 months), possibly because of discontinuation for toxicity.

To further evaluate the potential of dasatinib in breast cancer, several phase 2 trials are ongoing. These include biomarker-driven studies in TNBC (NCT00780676, NCT00546104, and NCT00817531) and studies evaluating dasatinib combined with chemotherapy in the metastatic setting (NCT00924352 and NCT00820170). For hormone receptor–positive breast cancer, dasatinib combined with endocrine therapy is being evaluated in patients who have received either no prior hormonal therapy in the metastatic setting (NCT00903006 and NCT00696072) or who have progressed following prior aromatase inhibitor therapy (NCT00767520 and NCT00754325). On the basis of data indicating that dasatinib inhibits osteoclast activity (30, 31), dasatinib effects on bone metastases will also be evaluated. Building on dose optimization trials in leukemia showing

significantly improved tolerability and equivalent efficacy (32), dasatinib 100 mg QD is being administered in recently initiated studies. Future data will therefore provide a broader evaluation of the therapeutic potential of dasatinib-mediated SRC inhibition in patients with breast cancer.

Disclosure of Potential Conflicts of Interest

R.S. Finn has received research grants from Bristol-Myers Squibb and Novartis, received honoraria from Genentech, and acted as a consultant or advisor for Bristol-Myers Squibb. C. Bengala, N. Ibrahim, and H. Roché have no conflicts of interest to disclose. J. Sparano has received honoraria from Bristol-Myers Squibb. L.J. Goldstein has acted as a consultant or advisor for Bristol-Myers Squibb. L.C. Strauss, J. Fairchild, and O. Sy are employees of and hold stock interests in Bristol-Myers Squibb.

Acknowledgments

We thank the patients and their families who participated in this trial and acknowledge the efforts of study staff at the investigational sites. Professional medical writing assistance was provided by StemScientific, funded by Bristol-Myers Squibb.

Grant Support

This study was sponsored by Bristol-Myers Squibb Oncology, Princeton, NJ. R.S. Finn is a recipient of an NIH-LRP Award.

This study was designed by employees of Bristol-Myers Squibb and R.S. Finn. Patient data were collected at participating institutes, analyzed using the sponsor's data management systems, and interpreted by the sponsor's statistical team in collaboration with the authors. Study data were available to all authors. An initial outline of the article was developed following discussions with the first and last authors by an independent company with funding provided by Bristol-Myers Squibb. All authors contributed to writing and reviewing of the manuscript and agreed with the decision to submit for publication.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received February 1, 2011; revised May 18, 2011; accepted June 16, 2011; published OnlineFirst October 25, 2011.

References

1. Finn RS, Bengala C, Ibrahim N, Strauss LC, Fairchild J, Sy O, et al. Phase 2 trial of dasatinib in triple-negative breast cancer: results of study CA180059. Cancer Res 2008;69 (Suppl): 242s [abstract #3118].
2. Mayer EL, Baurain J-F, Sparano J, Strauss L, Campone M, Fumoleau P, et al. A phase 2 trial of dasatinib in patients with advanced HER2-positive and/or hormone receptor-positive breast cancer. Clin Cancer Res 2011;17.
3. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
4. Howell A. The endocrine prevention of breast cancer. Best Pract Res Clin Endocrinol Metab 2008;22:615–23.
5. Nielsen DL, Andersson M, Kamby C. HER2-targeted therapy in breast cancer. Monoclonal antibodies and tyrosine kinase inhibitors. Cancer Treat Rev 2009;35:121–36.
6. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000; 406:747–52.
7. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100: 8418–23.
8. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869–74.
9. Kaplan HG, Malmgren JA, Atwood M. T1N0 triple negative breast cancer: risk of recurrence and adjuvant chemotherapy. Breast J 2009;15:454–60.
10. Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer 2009;9:29–33.
11. Arslan C, Dizdar O, Altundag K. Pharmacotherapy of triple-negative breast cancer. Expert Opin Pharmacother 2009;10:2081–93.
12. Yeatman TJ. A renaissance for SRC. Nat Rev Cancer 2004;4:470–80.
13. Finn RS. Targeting Src in breast cancer. Ann Oncol 2008;19:1379–86.
14. Dehm SM, Bonham K. SRC gene expression in human cancer: the role of transcriptional activation. Biochem Cell Biol 2004;82: 263–74.
15. Finn RS, Dering J, Ginther C, Wilson CA, Glaspy P, Tchekmedyian N, et al. Dasatinib, an orally active small molecule inhibitor of both the src and abl kinases, selectively inhibits growth of basal-type/"triple-negative" breast cancer cell lines growing in vitro. Breast Cancer Res Treat 2007;105:319–26.
16. Choi YL, Bocanegra M, Kwon MJ, Shin YK, Nam SJ, Yang JH, et al. LYN Is a mediator of epithelial-mesenchymal transition and a target of dasatinib in breast cancer. Cancer Res 2010;70:2296–306.
17. Araujo J, Logothetis C. Targeting Src signaling in metastatic bone disease. Int J Cancer 2008;124:1–6.
18. Myoui A, Nishimura R, Williams PJ, Hiraga T, Tamura D, Michigami T, et al. C-SRC tyrosine kinase activity is associated with tumor colonization in bone and lung in an animal model of human breast cancer metastasis. Cancer Res 2003;63:5028–33.
19. Brave M, Goodman V, Kaminskas E, Farrell A, Timmer W, Pope S, et al. Sprycel for chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. Clin Cancer Res 2008;14:352–9.
20. Huang F, Reeves K, Han X, Fairchild C, Platero S, Wong TW, et al. Identification of candidate molecular markers predicting sensitivity in solid tumors to dasatinib: rationale for patient selection. Cancer Res 2007;67:2226–38.
21. Pichot CS, Hartig SM, Xia L, Arvanitis C, Monisvais D, Lee FY, et al. Dasatinib synergizes with doxorubicin to block growth, migration, and invasion of breast cancer cells. Br J Cancer 2009;101:38–47.
22. Hammond ME, Hayes DF, Wolff AC, Mangu PB, Temin S. American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Oncol Pract 2010;6:195–7.
23. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
24. Dai G, Pfister M, Blackwood-Chirchir A, Roy A. Importance of characterizing determinants of variability in exposure: application to dasatinib in subjects with chronic myeloid leukemia. J Clin Pharmacol 2008;48:1254–69.
25. Demetri GD, Lo Russo P, MacPherson IR, Wang D, Morgan JA, Brunton VG, et al. Phase I dose-escalation and pharmacokinetic study of dasatinib (BMS-354825), a Src and multi-kinase inhibitor, in patients with advanced solid tumors. Clin Cancer Res 2009;15: 6232–40.
26. Elsberger B, Tan BA, Mitchell TJ, Brown SB, Mallon EA, Tovey SM, et al. Is expression or activation of Src kinase associated with cancer-specific survival in ER-, PR- and HER2-negative breast cancer patients?Am J Pathol 2009;175:1389–97.
27. Fleming JM, Desury G, Polanco TA, Cohick WS. Insulin growth factor-I and epidermal growth factor receptors recruit distinct upstream

signaling molecules to enhance AKT activation in mammary epithelial cells. Endocrinology 2006;147:6027–35.

28. Moreno-Aspitia A, Morton RF, Hillman DW, Lingle WL, Rowland KM, Wiesenfeld M, et al. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. J Clin Oncol 2009;27:11–5.
29. Burstein HJ, Elias AD, Rugo HS, Cobleigh MA, Wolff AC, Eisenberg PD, et al. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2008;26:1810–6.
30. Vandyke K, Dewar AL, Farrugia AN, Fitter S, Bik To L, Hughes TP, et al. Therapeutic concentrations of dasatinib inhibit in vitro osteoclastogenesis. Leukemia 2009;23:994–7.
31. Yu EY, Wilding G, Posadas E, Gross M, Culine S, Massard C, et al. Phase II study of dasatinib in patients with metastatic castration-resistant prostate cancer. Clin Cancer Res 2009; 15:7421–8.
32. Shah NP, Kantarjian HM, Kim DW, Réa D, Dorlhiac-Llacer PE, Milone JH, 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.