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A Phase 2 Trial of Dasatinib in Patients with Advanced HER2-Positive and/or Hormone Receptor–Positive Breast Cancer

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Abstract

Purpose: SRC-family kinases (SFK) are involved in numerous oncogenic signaling pathways. A phase 2 trial of dasatinib, a potent oral tyrosine kinase inhibitor of SFKs, was carried out in patients with human epidermal growth factor receptor 2–positive (HER2+) and/or hormone receptor–positive (HR+) advanced breast cancer.

Experimental Design: Patients with measurable tumors and progression after chemotherapy and HER2 and/or HR-targeted agents in adjuvant or metastatic settings (maximum of two prior metastatic setting regimens) received twice daily dasatinib. Primary endpoint was Response Evaluation Criteria in Solid Tumors–defined response rate. Secondary endpoints included toxicity and limited pharmacokinetics.

Results: Seventy patients (55 years median age) were treated, 83% of HER2+ patients had received prior HER2-directed therapy, and 61% of HR+ patients had received prior endocrine therapy in the advanced setting. Dasatinib starting dose was reduced from 100 to 70 mg twice daily to limit toxicity. Median therapy duration was 1.8 months in both dose groups and most discontinuations were due to progression. Of 69 evaluable patients, three had confirmed partial responses and six had stable disease for 16 weeks or more (disease control rate = 13.0%); all nine of these tumors were HR+ (two were also HER2+). The most common drug-related toxicities were gastrointestinal complaints, headache, asthenia, and pleural effusion. Grade 3–4 toxicity occurred in 37% of patients and was comparable between doses; drug-related serious adverse events were less frequent with 70 mg twice daily than 100 mg twice daily.

Conclusion: Limited single-agent activity was observed with dasatinib in patients with advanced HR+ breast cancer. *Clin Cancer Res; 17(21); 6897–904. ©2011 AACR.*

Introduction

SRC, a nonreceptor tyrosine kinase, plays a well-described and central role in cellular signaling pathways controlling growth and survival (2). Multiple tumor types exhibit increased SRC activity or overexpression, including breast cancer, in which it is associated with increased metastatic potential in xenografts (3–5). SRC–induced vascular endothelial growth factor expression *in vivo* also supports a tumor angiogenesis role (6).

Multiple studies have identified roles for SRC and other SRC-family kinases (SFK) in oncogenic activities of breast cancer subtypes, indicating that SRC is a potential therapeutic target. SRC and SFK overexpression in breast tumor tissue is associated with recurrence, metastasis, and shorter survival (7–10). In hormone receptor–positive (HR+) breast cancer cell lines, SRC activity increases in response to estrogen stimulation, suggesting that SRC may facilitate estrogen receptor (ER)-activated proliferative signaling (11). In addition, constitutive activation of SRC-dependent signaling pathways can lead to estrogen-independent growth (12). SRC may also facilitate heterodimerization and activation of human epidermal growth factor receptor-2 (HER2; refs. 12, 13), and increased SRC activity has been observed in HER2-positive (HER2+) cell lines (14). Finally, targeted SRC inhibition in a mouse model of metastatic breast cancer (MBC) resulted in fewer metastases and increased survival (15).

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Submitted in parallel with the primary manuscript by R.S. Finn and colleagues titled "Dasatinib as a single agent in triple-negative breast cancer: results of an open-label phase 2 study" (1).

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Translational Relevance

SRC-family kinases (SFK) are involved in a range of oncogenic signaling pathways, offering a novel molecular target for anticancer agents. Our article reports the first phase 2 clinical data for dasatinib, a potent oral tyrosine kinase inhibitor of SFKs, in patients with human epidermal growth factor receptor 2-positive and/or hormone receptor-positive advanced breast cancer. These data show that in patients with advanced or metastatic breast cancer, dasatinib exhibits acceptable tolerability and some activity, which is deserving of further investigation and discussion.

Dasatinib (Bristol-Myers Squibb) is an oral tyrosine kinase inhibitor that potently inhibits SRC and SFKs. Dasatinib also has activity against KIT, platelet-derived growth factor receptor, and BCR-ABL (16). Dasatinib is approved for treatment of imatinib-resistant and imatinib-intolerant chronic myeloid leukemia and Philadelphia chromosome–positive acute lymphoblastic leukemia (17). A phase 1 solid tumor study has shown that dasatinib monotherapy is safe and well tolerated (18).

Based on preclinical data supporting a central role for SRC in tumor biology, particularly in breast cancer, 2 phase 2 monotherapy studies of dasatinib in breast cancer were initiated in different breast cancer subtypes. In patients with triple-negative breast cancer (TNBC), dasatinib had good tolerability and modest activity (1). This article describes a parallel phase 2 study evaluating efficacy and safety of dasatinib monotherapy in patients with HER2+ and/or HR+ advanced breast cancer.

Materials and Methods

Patients

Eligible patients were female, aged 18 years or more, with measurable locally advanced or MBC (assessed within 28 days before initiating treatment) that was HER2+ and/or ER or progesterone receptor (PgR) positive, whose disease had progressed after anthracycline and taxane treatment. Per protocol eligibility requirements, all patients had an Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and were required to have received prior chemotherapy with an anthracycline and/or a taxane in either adjuvant or metastatic settings (maximum of 2 prior chemotherapy regimens in the metastatic settings); all patients with ER/PgR-positive disease received prior endocrine therapy, and all patients with HER2+ disease received prior HER2-directed therapy in the early stage and/or advanced settings. Trials were conducted in accordance with the Declaration of Helsinki and were approved by the responsible Institutional Review Board or Ethics Committee of all participating centers and all patients gave written informed consent.

Key exclusion criteria included the following: symptomatic central nervous system metastases; reduced hematologic, hepatic, or renal function; any antineoplastic therapy within 14 days before starting dasatinib therapy; presence of pleural effusion at baseline; or any concurrent medical condition increasing the potential risk for toxicity. Eligible patients had adequate liver function (grade 0/1 aspartate aminotransferase, alanine aminotransferase, and total bilirubin), serum Ca^{2+} greater than or equal to lower limit of normal, grade 0/1 serum K^{+}, Mg^{2+}, and phosphate, grade 0–2 creatinine, and grade 0/1 hemoglobin, neutrophil count, platelet count, and prothrombin time partial thromboplastin time. Patients were excluded if they had any concurrent medical condition which may increase toxicity risk, including the following: 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, clinically significant cardiovascular disease, or antineoplastic therapy (including radiotherapy, or bisphosphonates) within 14 days before commencing study drug (21 days for trastuzumab).

Study design

CA180-088 was an open-label, phase 2, two-stage trial. Patients received oral dasatinib at a starting dose of 100 mg twice daily; due to emergent toxicity, the dose was subsequently reduced by protocol amendment to 70 mg twice daily. Treatment was continued until disease progression (or unacceptable toxicity). Patients were classified according to biological subtype as HER2+ with any HR status (group A) or HER2-normal and HR+ (group B). A Gehan 2-stage design was used (19). In the first stage, 29 response-evaluable patients were accrued in groups A and B, with the assumption that if no responses were observed, the study would be closed to accrual with the conclusion that the true response rate was unlikely (95% confidence) to reach 10% or higher. Otherwise, if there was at least one response, 16 additional response-evaluable patients would be accrued into the responding subgroup(s) in the second stage.

The primary objective was to estimate objective response rate (ORR) by Response Evaluation Criteria In Solid Tumors (RECIST), defined as the proportion of response-evaluable patients with confirmed complete response (CR) or partial response (PR) recorded as best response during study. Secondary endpoints included, disease control rate (DCR), defined as the proportion of response-evaluable patients with a best response of CR, PR, or stable disease (SD) lasting 16 weeks or more; progression-free survival (PFS) at weeks 9, 17, and 25, defined as time from first dosing date to recorded date of disease progression or death; safety and tolerability of dasatinib; and pharmacokinetics (PK). For ORR, DCR and PFS, 95% exact confidence intervals (CI) were calculated. Duration of response was defined as the time between achieving CR or PR criteria until the first date that progressive disease (PD) was observed. Patients who

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died without reported PD were considered to have PD on the date of death. Patients who neither progressed nor died were censored at the last tumor evaluation.

Dasatinib doses were discontinued or reduced to either 50 mg twice daily, or 100 mg once daily based on individual tolerability. In the event of drug-related grade 3–4 toxicity or recurrent drug-related grade 2 toxicity that was insufficiently controlled by outpatient therapy or was considered unacceptable by the physician or patient, dasatinib dose was reduced or treatment was suspended. Dose reescalation after reduction or reinitiation was permitted at investigator discretion, once toxicity had decreased to grade 0–1. Patients were discontinued from study treatment if toxicity had not resolved to grade 0–1 within 21 days.

Patient assessments

ER, PgR, and HER2 status of tumors was determined at each participating institution. ER and PgR positivity was defined as greater than 10% of cells positive by immunohistochemistry (IHC). At the time of study initiation, the definition of ER/PgR positivity was driven by response to hormone therapy and thus the cut-off for ER/PgR negativity of less than 10% ER/PgR by IHC. The current ASCO-CAP guidelines are more stringent and may better define patients with ER/PgR-positive disease (20). HER2 positivity was assessed by either fluorescence or chromogenic in situ hybridization (FISH+ or CISH+) to determine *HER2* amplification, or by IHC (3+ staining intensity). Central testing was not done; samples were assessed per report only.

Patients were considered to have measurable disease if they had at least 1 lesion that was accurately measured in at least 1 dimension with a longest diameter of 20 mm or more using conventional techniques or 10 mm or more with spiral computed tomography scan or magnetic resonance imaging. The same method(s) were used for baseline and follow-up evaluations.

Study assessments were done every 2 weeks for the first 2 months, every 4 weeks for 2 visits (after 3 and 4 months on treatment), and every 8 weeks thereafter. All treated patients who received at least 1 dose of dasatinib were assessed for toxicity (according to Common Terminology Criteria for Adverse Events version 3.0), PK, and tumor response. Per protocol, patients were classified as response-evaluable if they had at least 1 measurable lesion at baseline and at least 1 on-study tumor assessment. Patients without tumor response assessment because of rapid progression or study drug toxicity were included in the response-evaluable subject dataset as nonresponders. Primary analysis was done after all treated patients had been observed for 24 weeks or more or had discontinued treatment. Clinical and radiographic efficacy assessments were done prior to study treatment and at least every 8 weeks during treatment.

Blood samples for PK assessment were collected predose and at 1, 3, and 6 hours after dosing at the week 3 visit (day 15 ± 4 days). Sampling was repeated at week 7 or 9. A trough sample was obtained immediately prior to any dose and approximately 12 hours after last dose, as convenient. Because pharmacokinetic information for dasatinib 70 mg twice daily is already available, pharmacokinetic assessment was optional (18, 21).

Archival tumor samples from participants in multiple dasatinib trials are being collected for planned biomarker analyses, data will be aggregated to provide statistical power.

Results

Patient characteristics

Ninety-two patients with locally advanced or MBC were enrolled at 20 institutions between December 2006 and May 2008. Of these, 70 were treated: 24 in group A (HER2+ tumors) and 46 in group B (HER2-normal, HR+ tumors). The 22 patients who were not treated were found to be ineligible. Documentation of PR in the second treated patients in group A and group B satisfied protocol-defined criteria for continued accrual. Because of slower accrual, group A was electively closed when group B reached full accrual.

Baseline characteristics and prior breast cancer therapies are summarized in Table 1. Most patients in both groups (92% in group A and 89% in group B) had received prior advanced setting chemotherapy. In group A (HER2+ tumors), 83% of patients had received prior HER2-directed therapy in the advanced setting (79% had received trastuzumab, 33% had received lapatinib); in group B (HR+ tumors), 61% had received prior advanced setting hormonal therapy (33% had received fulvestrant and 33% had received letrozole); prior hormonal therapy had also been received by 33% of group A. In both groups, patients may have received more than 1 prior targeted therapy.

Exposure

Twenty-three patients initially received a starting dose of dasatinib 100 mg twice daily (median duration 1.81 months, median daily dose 176 mg). Only 52% of patients had a relative dose intensity of at least 85% of their planned dose and 43% required a dose reduction. Subsequently, 47 patients received a protocol-specified amended starting dose of 70 mg twice daily (median duration 1.84 months, median daily dose 136 mg), which was well tolerated in a phase 1 study in patients with advanced solid tumors (18). Of these patients, 72% received a relative dose intensity of at least 85% of their planned dose and 23% required dose reduction. The most common reason for dose reduction was study drug toxicity (Table 2).

Safety

Most treatment-related adverse events (AE) were mild to moderate in severity (Table 3). The most frequent AEs of any grade were fatigue/asthenia, gastrointestinal symptoms, headache, pleural effusion, and rash. The most frequent grade 3/4 AEs with 100 mg twice daily were diarrhea (9%) and pleural effusion (9%) and with 70 mg twice daily were fatigue/asthenia (15%) and dyspnea

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Table 1. Baseline characteristics and prior therapies

	All patients	HER2+, any ER status	HER2-normal, ER+ and/or PgR+
Treated, *n*	70	24	46
Age, median (range)	55 (32–70)	54 (32–68)	56 (33–70)
ECOG score, %			
0	62	67	59
1	38	33	41
Tumor subtype, %			
HER2+	34	100	0
ER+	84	58	98
PgR+	56	33	67
Time since initial diagnosis			
Median, mo	67	51	76
Less than 24 mo, %	9	17	4
24–48 months, %	17	21	15
Greater than 48 mo, %	64	58	67
Unknown, %	10	4	14
Prior therapies in advanced disease setting			
Chemotherapy, %			
0		8	11
1		38	41
2		46	44
Greater than 2		8	4
Hormonal therapy (letrozole and/or fulvestrant), %			
0		67	39
1		21	30
2		13	22
Greater than 2		0	9
HER2-directed therapy (trastuzumab and/or lapatinib), %			
0		17	—
1		42	
2		38	
Greater than 2		4	

NOTE: Percentage values have been rounded to the nearest whole number.

(6%). Overall fatigue/asthenia incidences were the same for both dosing groups (57%). Treatment-related serious AEs were reported in 26% of patients treated with 100 mg twice daily and 15% treated with 70 mg twice daily. Except for hypophosphatemia (100 mg twice daily: 9%; 70 mg twice daily: 2%), grade 3/4 laboratory abnormalities were uncommon. The study was not designed to compare differences in incidence of AEs between dosing groups.

Primary efficacy measure (ORR)

Of 70 treated patients, 69 were response-evaluable (1 patient was considered unevaluable for response and removed from the study within the first week after identification of preexisting brain metastases that required radiotherapy). ORR for the response-evaluable population was 4.3% (3/69; 95% CI: 0.9–12.2; Table 4). Best responses (change from baseline) in individual target tumors are presented in Fig. 1A. Three patients (1 in group A and 2 in group B) had a confirmed PR lasting 18, 23+, and 31 weeks; their on-study durations were 42, 47, and 39 weeks, respectively. Patient 02 (group B; HER2-normal, ER+, PgR+) had received prior chemotherapy and hormonal therapy and had recurrent liver, bone, and lung disease. Dasatinib was initiated at 100 mg twice daily then reduced to 70 mg twice daily in week 5 due to grade 3 diarrhea and reduced again to 50 mg twice daily in week 12 following grade 2 dyspnea and cough. After gradual regression, PR was recorded at week 23, lasting for 18 weeks until progression at week 42. Patient 09 (group A; HER2+, ER+, and PgR+) had received prior chemotherapy, hormonal therapy, and trastuzumab and had recurrent disease in mediastinal nodes. Dasatinib was initiated at 100 mg twice daily then reduced to 70 mg twice daily at week 8 for grade 2 fever. PR was recorded at week 8 and lasted 31 weeks until progression at week 39. Patient 85 (group B; HER2-normal, ER−, PgR+) had received prior

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Table 2. Exposure and dose adjustments

	100 mg BID ($n = 23$)	70 mg BID ($n = 47$)
Dasatinib treatment duration		
Median, mo	1.8	1.8
Greater than 3 mo, %	26.1	17.0
Median daily dose, mg (interquartile range)	175.7 (125.6–197.6)	136.1 (116.7–138.8)
Dose intensity (% of planned), %		
Less than 60	13.0	4.3
60 to less than 85	34.8	23.4
Greater than or equal to 85	52.2	72.3
Dose interruption, %	60.9	55.3
Dose reduction, %	43.5	23.4
Discontinued therapy, %	100	100
Disease progression	83	79
Study drug toxicity	4	15
Other	13	6

Abbreviation: BID, twice daily.

chemotherapy and had recurrent disease in multiple lymph nodes. Dasatinib was intiated at 70 mg twice daily and several dose interruptions were required for toxicity. After gradual regression, PR was recorded at week 32 (23+ weeks duration) until withdrawal for toxicity.

A sensitivity analysis was designed and done retrospectively to identify patients who had had a clinical or radiographic efficacy assessment after at least 21 days on study. In this subpopulation ($n = 54$), the ORR was 5.6% (3/54).

Other outcome measures

DCR in the response-evaluable population was 13.0% (9/69; 95% CI: 6.1–23.3). Six of the 9 patients (1 in group A and 5 in group B) had SD lasting at least 16 weeks. DCR by tumor subtype was 8.3% (2/24; 95% CI: 1.0–27.0) in patients with HER2+ tumors and 15.6% (7/45; 95% CI: 6.5–29.5) in patients with HR+ (HER2-normal) tumors. Notably, the 2 patients from group A who had a clinical benefit (PR or prolonged SD) had ER+ tumors. A retrospective sensitivity analysis found that DCR among 54 patients

Table 3. Treatment-related AEs occurring in at least 10% of patients in dasatinib 70 or 100 mg twice daily dosing groups

	Patients, %			
	100 mg BID ($n = 23$)		70 mg BID ($n = 47$)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Fatigue/asthenia	57	4	57	15
Diarrhea	43	9	47	2
Headache	39	0	34	2
Nausea	35	4	34	2
Abdominal pain	22	0	32	4
Pleural effusion	39	9	26	0
Rash	35	0	23	0
Dyspnea	39	0	21	6
Vomiting	35	4	19	0
Anorexia	22	0	17	0
Cough	9	0	13	2
Pyrexia	17	0	9	0
Arthralgia	13	4	4	0

Abbreviation: BID, twice daily.

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Table 4. Tumor response

	All patients	HER2+, any ER status	HER2-normal, HR+
Patients, *n*			
Response evaluable	69	24	45
Responses, *n*			
Confirmed PR	3	1[a]	2
SD	13	4	9
SD greater than or equal to 16 weeks	6	1[a]	5
PD	40	15	25
Responses rates, %			
ORR (95% CI)	4.3 (0.9–12.2)	4.4 (0.5–15.2)	4.4 (0.9–12.2)
DCR (95% CI)	13.0 (6.1–23.3)	8.3 (1.0–27.0)	15.6 (6.5–29.5)

NOTE: DCR (CR+PR+SD for at least 16 weeks).
[a]Two patients of 12 with HER2+ and ER+ tumors.

who had had a clinical or radiographic efficacy assessment done after at least 21 days on study was 16.7% (9/54). DCRs in this group of patients classified by tumor subtype were 10.0% (2/20) in patients with HER2+ tumors and 20.6% (7/34) in patients with HR+ (HER2-normal) tumors.

PFS

Sixty-one of 70 treated patients progressed or died during the study (Fig. 1B). Median PFS was 8.1 weeks (95% CI: 7.7–8.3). In the HER2+ subgroup, PFS rate was 32% at 9 weeks, 14% at 17 weeks, and 5% at 23 weeks, and median PFS was 8.1 weeks (95% CI:7.1–9.3). Similarly, in the HR+ (HER2-normal) subgroup, PFS rate was 33% at 9 weeks, 20% at 17 weeks, and 10% at 23 weeks, and median PFS was 8.1 weeks (95% CI: 7.7–8.7).

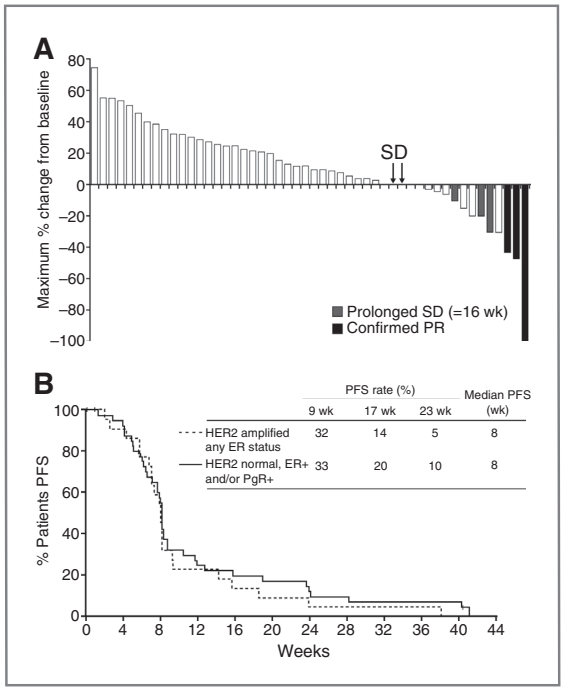

Figure 1. Dasatinib monotherapy efficacy in patients with HER2+ or ER- and/or PgR+ breast cancer. A, best response in patients (% change in sum of target lesion diameters). B, PFS in treated patients.

PK

Thirty-one patients were available for PK analysis (Table 5), 17 of whom received the initial dasatinib dose of 100 mg twice daily and 14 of whom received 70 mg twice daily. Dasatinib plasma concentrations were within ranges observed in patients with other solid tumors or leukemia who received the same doses (Table 5).

Discussion

In this single-arm phase 2 study in patients with advanced HER2+ and/or HR+ breast cancer, dasatinib monotherapy was generally well tolerated, with a more favorable toxicity profile and greater dose intensity delivered for dasatinib 70 mg twice daily compared with 100 mg twice daily. Plasma concentrations for both dose levels were within the expected therapeutic range without accumulation. Observed toxicities were consistent with prior phase 1 experience, generally consisting of fatigue, diarrhea, headache, and nausea. Hematologic toxicity was noted during dasatinib treatment of CML (17) but was not observed at a high frequency in patients with breast cancer. Pleural effusion, also observed in previous trials of dasatinib treatment, occurred with moderate frequency and was manageable with steroid treatment, diuresis, and dose reduction.

Limited activity was observed, with an ORR of 4% in each tumor subset cohort, and DCRs of 8% and 16% in the HER2+ and HR+ subsets, respectively, suggesting greater drug sensitivity in HR+ tumors. All patients with disease control (i.e., PR or prolonged SD) were either in group B or had tumors that were both HER2+ and ER+.

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Table 5. Pharmacokinetic analysis: dasatinib plasma concentrations at week 3

	Dasatinib concentration, ng/mL	
	100 mg BID ($n = 17$)	70 mg BID ($n = 14$)
1 h (mean ± SD)	107.1 (64.5)	77.2 (61.9)
3 h (mean ± SD)	58.0 (37.4)	30.2 (18.4)
Trough (range)	1.1–18.5	2.3–11.6

Abbreviations: BID, twice daily; SD, standard deviation.

There are several possible explanations for the limited activity observed in this study, particularly lack of enrichment of the patient population for biologic subtypes likely to respond. Use of advanced molecular methods may better identify tumor subsets potentially sensitive to targeted therapy. Preclinical studies, published after initiation of the current clinical study, suggest that basal-like TNBC may have preferential sensitivity to SRC inhibition (22, 23). Dasatinib efficacy in TNBC was assessed in a parallel clinical trial to this study (1). Genomic examination of breast cancer cell lines suggests that molecular identifiers, including 3-gene (*moesin*, *caveolin*, and *YAP-1*; ref. 22) or 6-gene signatures (23), may better identify cell types with a greater likelihood of response to dasatinib. Future analyses of human cancers using contemporary genomic techniques to evaluate entire signaling pathways may allow identification of patients with increased probability of responding to targeted therapies (24). Recently, more complete pharmacogenomic approaches have indicated that the SRC expression "signature" is independent of breast tumor HR or HER2-positivity (25), suggesting that current biological indicators for breast cancer may not be helpful for selecting patient subgroups for future clinical trials of SRC inhibitors.

When evaluating activity of novel biological agents, it has been widely acknowledged that signal transduction inhibitors are unlikely to produce the types of objective radiological responses observed with chemotherapy, instead acting to stabilize disease (a cytostatic rather than cytocidal effect). Therefore findings from this study do not reject a role for SRC inhibition in breast cancer therapy, instead suggesting that a more thoughtful and rational strategy may be needed to reveal a role for SRC inhibitors. One setting of interest is treatment of patients with endocrine-resistant breast cancer. Multiple *in vitro* observations have shown increased SRC expression and activity in ER+ cell lines exposed to estrogen (26) and in those with tamoxifen resistance (27). Recent preclinical studies have shown a role for activated SRC in ER degradation, suggesting a potential mechanism in development of endocrine resistance (28). Preclinical studies combining SRC inhibitors with antiestrogens have shown synergistic antitumor activity (26, 29, 30). Trials of dasatinib combined with endocrine therapy in patients with HR+ MBC are underway using a better-tolerated once daily schedule of dasatinib.

Another approach to better demonstrate the potential role of SRC inhibition may be in combination with other targeted inhibitors. Multiple studies have highlighted the central role of SRC in regulating cellular signaling through interactions with upstream and downstream factors, such as epidermal growth factor receptor (EGFR), HER2, and mitogen-activated protein kinase (2, 31, 32). Given the extensive knowledge about SRC-dependent cellular signaling, partnering a SRC inhibitor with another agent targeting a receptor or a step in signal transduction may provide a rational and synergistic approach for inhibiting tumor growth. Preliminary data on combinations of SRC inhibitors and EGFR inhibitors in tamoxifen-resistant cell lines have been encouraging (27) and clinical investigation is warranted.

In summary, this phase 2 study showed that treatment of HR+ and/or HER2+ breast cancer with the potent SRC inhibitor dasatinib as monotherapy resulted in very modest activity, possibly greater in HR+ tumors. Tolerability seemed to improve with use of a 70 mg twice daily dosing schedule. Future studies of SRC inhibitors in breast cancer should utilize novel genomic techniques to enrich appropriate patient populations following identification of verifiable specific biomarkers and explore combination treatment with endocrine therapy and/or novel biological agents.

Disclosure of Potential Conflicts of Interest

E.L. Mayer has acted as a consultant or advisor for Bristol-Myers Squibb and Sanofi-Aventis. J-F. Baurain, A. Awada, and H. Rugo have no conflicts of interest to disclose. J. Sparano has received honoraria from Bristol-Myers Squibb. P. Fumoleau has acted as a consultant or advisor for Sanofi-Aventis, Roche, Johnson and Johnson, and GlaxoSmithKline. M. Campone has acted as a consultant or advisor for Novartis and has received research grants from Novartis and Abbott. A. Llombart-Cussac has acted as a consultant or advisor for Bristol-Myers Squibb. L. Strauss and O. Sy are employees of and hold stock interests in Bristol-Myers Squibb.

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