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Dasatinib plus Capecitabine for Advanced Breast Cancer: Safety and Efficacy in Phase I Study CA180004

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Abstract

Purpose: Dasatinib is an Src family kinase inhibitor with modest activity in advanced breast cancer. We aimed to assess toxicity and maximum tolerated dose (MTD) for dasatinib plus capecitabine, estimate efficacy, and explore effects on angiogenesis.

Experimental Design: Dose levels (DL) were dasatinib 50 mg twice daily (DL1), 70 mg twice daily (DL2 and DL3), or 100 mg daily (DL3a); plus capecitabine on days 1 to 14 of a 21-day cycle, at 825 mg/m^2 twice daily (DL1 and DL2) or 1,000 mg/m^2 twice daily [DL3 and DL3a (MTD)]. DL3a was expanded to evaluate safety/efficacy. Plasma samples were collected for biomarker analysis.

Results: Thirty-one and 21 patients were treated in the escalation and expansion phases. Sixty percent of tumors were hormone receptor–positive. Most common adverse events (AE) were any grade nausea (58%), hand–foot syndrome (44%), diarrhea (33%), fatigue (33%), vomiting (31%), and asthenia (31%). Most common grade 3/4 AEs were hand–foot syndrome (12%), diarrhea (8%), fatigue (8%), pleural effusion (8%), and vomiting (6%). The MTD was defined at DL3a (capecitabine 1,000 mg/m^2 twice daily and dasatinib 100 mg daily). Of 25 response-evaluable patients treated at DL3a, confirmed partial response was noted in 24% and stable disease in an additional 32%; median progression-free survival was 14.4 weeks. Significant decreases in plasma VEGF-A and increases in VEGFR-2 and collagen-IV were observed.

Conclusions: Dasatinib 100 mg once daily plus capecitabine 1,000 mg/m^2 twice daily were tolerable and were associated with clinical benefit in 56% of response-evaluable patients. Biomarker changes were consistent with an antiangiogenic effect. *Clin Cancer Res; 19(7); 1884–93. ©2013 AACR.*

Introduction

Breast cancer is the most common cancer in women, accounting for more than 1 million cancers diagnosed worldwide each year, an estimated 227,000 newly diagnosed cancers in the United States in 2012, and 14.5% of all female cancer-related deaths (1). Although death rates from breast cancer have decreased, advanced breast cancer (ABC) is typically incurable and has a median survival of 21.7 months (2). Treatments including chemotherapy, hormonal agents, or HER-2–targeted therapies are clearly effective, but even if an initial response is obtained, long-term disease control is rare (3). Targeted therapies such as anti-estrogens, aromatase inhibitors, and Her2/neu-specific agents have efficacy in breast cancers expressing the relevant target molecules (4, 5). Options available for disease progression following anthracycline and/or taxane chemotherapy and indicated targeted therapies include the oral 5-fluorouracil prodrug capecitabine (3).

The Src family kinases (SFK) are involved in key signaling pathways relevant to breast cancer (6, 7). Elevated expression or activity of Src kinase in breast cancer has been associated with metastasis to bone (8, 9) with tumor cell invasiveness (10) and with poorer clinical outcomes (11). Src activity has been shown to mediate signaling by growth factor receptors including EGF receptor (EGFR; ref. 12) and Her2/neu (13) and via the estrogen receptor (ER; refs. 14, 15) and contribute to endocrine therapy resistance (16, 17) as well as resistance to Her2 inhibition (18). Src kinase activity also plays a role in VEGF-induced angiogenesis and

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Translational Relevance

Src family kinases (SFK) play a major role in the pathogenesis of malignancy, including proliferation, invasion, angiogenesis, and survival. On the basis of promising preclinical data, we investigated the combination of the potent oral SFK inhibitor dasatinib with capecitabine to identify maximum-tolerated and recommended phase II doses and estimate combined treatment efficacy in advanced breast cancer and to explore the potential antiangiogenic activity of dasatinib. We show that the combination of dasatinib with capecitabine is well tolerated and provides preliminary evidence of efficacy. We show significant inhibition of VEGF production and corresponding increase in shed VEGFR and collagen type IV. These findings may facilitate better understanding of mechanisms of actions of SFK inhibitors and allow for further exploration of rational combinations in breast cancer and other malignancies.

vascular permeability (19), VEGF production (20), and downstream VEGF signaling (21).

Dasatinib, a potent orally available SFK inhibitor (22), is being studied in various solid tumors (23). Preclinical data suggest that dasatinib has therapeutic potential in breast cancer, including inhibition of "triple-negative" breast cancer cell lines *in vitro* (24, 25), inhibition of breast cancer bone metastasis in *in vivo* models (9, 26), and by other mechanisms (27, 28).

Dasatinib as a single-agent, however, provided only limited clinical benefit in patients with ABC. In phase II trials, the disease control rate [confirmed partial response (PR) or stable disease (SD) for $\geq$16 weeks] in "triple-negative" tumors was 9.3% (29), and in Her2- or hormone receptor–positive (HR+), ABC was 13% (30).

The combination of dasatinib and 5-fluorouracil was shown *in vitro* to produce synergistic cytotoxicity in some breast cancer cell lines (see Supplementary Fig. S1A and S1B). Oral capecitabine has shown clinical efficacy, both as monotherapy and in combination with lapatinib. The potential combination of dasatinib with a widely used oral agent provides an attractive alternative approach in ABC.

Here, we report results from a phase I study (CA180004) assessing treatment with dasatinib combined with capecitabine in women with ABC. Circulating levels of VEGF-A, VEGFR-2, and collagen type IV (COL-IV) were assessed, as surrogate markers of dasatinib effects on the vasculature, in the present study and in 2 previous single-agent studies (29–31).

Patients and Methods

Patient selection

Women aged 18 years or more with a prior histologic diagnosis of invasive metastatic breast cancer who had received prior taxane and/or anthracycline therapy (either in the adjuvant or metastatic setting) were eligible. Performance status of 0–1 (Eastern Cooperative Oncology Group scale) was required. Patients were required to have a paraffin-embedded tumor sample available for analysis and presence of unresectable metastatic and/or locally advanced breast cancer. For the expansion cohort, measurable tumor [using Response Evaluation Criteria in Solid Tumors (RECIST)] was also required. Local (chest wall) relapse, if unresectable, was considered eligible for enrollment in this trial.

Patients were permitted to have received up to 2 prior chemotherapy-containing regimens in the advanced setting (no limit on hormonal therapies). No prior capecitabine or Src inhibitor therapy was allowed, no antitumor therapy was allowed within 21 days before study entry (7 days for hormonal therapy), and no prior intravenous bisphosphonates were allowed within 7 days before study entry. Patients with symptomatic central nervous system metastases were excluded as were those with significant cardiovascular disease (left ventricular ejection fraction of <40%, congestive heart failure deemed as New York Heart Association Class III or IV), recent myocardial infarction (within 6 months), major conduction abnormality (unless pacemaker is in place), grade $\geq$ 1 pleural or pericardial effusion, creatinine $\geq$ upper limit of normal, grade $\geq$ 1 hepatic abnormalities (grade 2 permitted if due to liver metastasis), grade $\geq$ 2 hematologic abnormalities, calcium < lower limit of normal, and grade $\geq$ 2 other electrolyte abnormalities. Patients on therapeutic doses of coumadin or strong inhibitors of CYP3A4 were excluded. Women of childbearing potential were eligible provided that adequate contraception was used during study.

Study design

This was an open-label phase I study, and women with recurrent or progressive ABC received combination oral treatment with dasatinib plus capecitabine. Patient cohorts were treated with alternately escalated doses of dasatinib and capecitabine in 4 defined dose levels (DL; Table 1). Capecitabine was administered twice daily on days 1 to 14 of 21-day cycles. Dasatinib was administered continuously using a twice daily schedule in DL1–3. The initial design called for defining the maximum tolerated dose (MTD) based on toxicities observed during the first cycle. However, on the basis of the consensus of the investigators who observed difficulties with delivering the planned cycles beyond the first treatment cycle in 3 of 15 patients treated at DL3a, a new dose level 3a, using dasatinib 100 mg once-daily together with capecitabine 1,000 mg/m^2, was defined by amendment during the study, Once-a-day administration of dasatinib had been shown to be better tolerated than twice daily dosing in other studies (32, 33). The feasibility of the combination was then tested in the escalation phase, and this dosing was chosen for treating the expansion cohort. In cohort 3a, the study team elected to enroll an additional 3 subjects (total of 9) to assure tolerability conservatively by assessing the first 6 patients [1 with dose-limiting toxicity (DLT)] beyond just one cycle, before proceeding to expansion phase. No additional toxicities

Table 1. Doses of dasatinib and capecitabine administered, by DL, and DLTs observed

DL	Dasatinib, mg BID	Dasatinib, mg QD	Capecitabine, mg/m^2 BID	Treated (*n*)	Evaluable for DLT (*n*)	DLT (event)
1	50	—	825	7	6	1 (grade 3 headache)
2	70	—	825	9	7	1 (grade 3 pneumonia)
3	70	—	1000	6	6	1 (grade 3 diarrhea)
3a	—	100	1000	9	9	1 (grade 3 pneumonia)
3a[a]		100	1000	21	21	1 (grade 4 neutropenia and diarrhea, grade 3 mucositis and emesis)[b]

Abbreviations: BID, twice daily; QD, daily.

[a]Expansion phase.

[b]Considered by investigator to represent severe capecitabine-related toxicity consistent with dihydropyrimidine dehydrogenase deficiency.

were noted in those nonevaluable, and (as in any trial) all treated subjects were included in analyses of on-study adverse events.

Subsequently, an expanded cohort using DL3a was enrolled to confirm feasibility and DLT frequencies and to derive a preliminary efficacy estimate. Patients remained on treatment until disease progression, unacceptable toxicity, or withdrawal of consent occurred. No maximum treatment duration was specified.

Statistics

The primary objective of this study was to identify major toxicities and determine an MTD and recommended phase II doses for the combination of dasatinib and capecitabine in treatment of ABC. The secondary objective was to estimate the efficacy of combined treatment using objective response [complete response (CR) or PR as best response] and response duration, disease control (objective response or SD $\geq$ 24 weeks) and progression-free survival (PFS). An exploratory objective was plasma biomarker analysis for effects of dasatinib on biomarkers of angiogenesis.

A standard 3 + 3 escalation design was used to identify an MTD for the combination, based on cycle 1 toxicities. Escalation was permitted if 0 to 1 DLT was observed in 6 DLT-evaluable subjects.

Subjects were considered evaluable for DLT only if they had received $\geq$21 days of study treatment or had interruptions due to a drug-related toxicity; subjects who discontinued for other reasons (e.g., disease progression or noncompliance) were not DLT-evaluable and were replaced. Up to 6 DLT-evaluable subjects were planned to be treated at each dose level, and up to 25 patients were planned to be treated in the expansion phase. If a DLT rate of 20% (5/25) was observed, then there is 79% confidence that the true DLT rate will not exceed 30%.

Assessments and study definitions

The MTD was defined as the highest DL at which no more than one of the first 6 DLT-evaluable patients experienced a DLT. DLTs were defined as any adverse event occurring during the first cycle (21 days of treatment) that was considered at least possibly related to dasatinib and/or capecitabine and was either clinically evident and grade $\geq$3; clinically evident and grade 2 requiring interruption lasting a total of $\geq$7 days (not necessarily consecutive); grade $\geq$ 3 nonhematologic laboratory abnormality; grade 4 hematologic adverse event lasting $\geq$7 days, or any toxicity requiring dose reduction or discontinuation. Patients who received $\geq$21 days of protocol therapy during the first treatment cycle or who stopped treatment due to toxicities (but not if due to noncompliance or early progression) were considered DLT-evaluable.

Patients were considered response-evaluable if there was at least one measurable lesion at baseline and at least one on-study tumor assessment (including clinical progression) or if study treatment was stopped because of drug-related toxicity. Patients with no measurable disease or who stopped treatment before tumor assessment for reasons unrelated to disease or to study drug (e.g., withdraw consent) were not considered response-evaluable.

Measurable disease was required for the expansion cohort only, but tumor response, defined by RECIST 1.0 criteria, was assessed for all patients with measurable disease. Tumors were evaluated at baseline, every 6 weeks ($\pm$1 week) for the first 24 weeks, and every 9 weeks thereafter. Objective response rate (ORR) was defined as the proportion of patients with measurable disease whose best response was either a CR or PR. Disease control rate (DCR) was defined as the proportion of patients whose best on-study response was either a CR or PR or SD lasting $\geq$24 weeks.

PFS was defined as the number of weeks from the first dosing to PD. Patients who died without evaluation were considered to have progressed on the date of death. Patients who continued to receive treatment or discontinued without progression were censored at the date of last assessment. Kaplan–Meier limit estimates with 95% confidence intervals (CI) were to be provided. If an objective response rate of 30% were observed in a total of 30 response-evaluable patients, including those treated at the MTD during escalation, the corresponding 95% CI would be (14%–46%).

The study was not designed or powered to compare data between subsets, hence *P* values are not provided. A *post hoc* exploratory analysis focusing on patients with hormone receptor–positive (the subset with the largest sample size) was conducted.

Dose modifications and supportive guidelines

Study therapy was interrupted for clinically evident grade $\geq$3 treatment-related adverse events and at investigator's discretion for grade 2 adverse event, grade 2–3 toxicity, or grade $\geq$ 4 treatment-related laboratory abnormalities. Dose de-escalations from the phase II dose (3a) of dasatinib 100 mg/d included 70 and 50 mg/d. Dose de-escalations from capecitabine 1,000 mg/m^2 were 825 and 660 mg/m^2. Because of the difficulty of attributing toxicities to one or the other agent, dose modification of one or both drugs was at the discretion of investigators (in consultation with the study monitor) based on the specific toxicity observed. Dosing could be re-escalated at the investigator's discretion if the toxicity resolved with medical management or considered unlikely to be related to study drug.

Maintenance of calcium levels in the normal range (per institutional values) was recommended, but the methods of calcium and vitamin D supplementation were at the investigators' discretion.

Circulating biomarkers

Plasma samples were obtained at baseline (or day 1 predose), at weeks 3 and 6 (after cycles 1 and 2) and if possible at week 24. In single-agent studies (29, 30), plasma samples were collected at weeks 2 and 4 of dasatinib therapy. Blood was collected in EDTA K2 tubes and centrifuged immediately; plasma was stored at −80°C and transported on dry ice.

Quantitative Sandwich Enzyme Immunoassay was conducted using a Human VEGF Immunoassay (R&D Systems, Inc. Cat. DVE00) for VEGF-A, a Human Soluble VEGF R2 Immunoassay (R&D Systems Quantikine; Cat DVR200) for VEGFR-2, and a Collagen IV EIA (Biotrin; Cat: BIO82) for Collagen Type IV. Analyses were conducted on a Molecular Devices SpectraMax instrument. Quantitative results were visualized using Array Studio; a nonparametric method was used to compute CIs about the median (34) for non-normally distributed biomarker values.

Regulatory considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by Institutional Review Boards or Ethics Committees of participating centers. All patients gave signed informed consent. The registered study number was CA180004 (ClinicalTrials.gov: NCT00452673).

This study was designed by employees of Bristol-Myers Squibb with input from the first and last authors. Patient data were collected at participating institutions, analyzed using the sponsor's data management systems, and interpreted by the sponsor's statistical team and the authors.

Results

Patient characteristics

Of 57 patients enrolled, 52 received study treatment; 31 in the escalation phase (9 at the MTD) and 21 in the expansion phase. Five patients did not receive treatment due to not meeting eligibility criteria, for example, low performance status or baseline pleural effusion. Key baseline characteristics are shown in Table 2. Median age was 52 years. Tumor subtypes were HER2-amplified in 6 patients (12%), HR+ in 31 patients (60%, of which 3 were also HER2-amplified), and "triple-negative" in 16 patients (31%). Most patients (79%) had measurable disease, predominantly in lymph nodes, liver, or lung; 1 of 6 patients with locally advanced (chest wall) disease had no other disease site. Seven patients (13%) had bone-only disease. A total of 30 response-evaluable patients (9 in escalation + 21 in expansion phase) were treated at the MTD.

DLTs

Safety data were recorded for all treated patients. In 4 cohorts of patients treated in the escalation phase, 4 DLTs were reported, one in each cohort, consisting of headache, pneumonia (2 with associated pain and pleural effusion), and diarrhea (Table 1). In cohort 1, there was 1 non–DLT-evaluable subject due to early progression. In cohort 2, there were 2 non–DLT-evaluable patients [1 with early progressive disease (PD) and 1 due to noncompliance with early withdrawal]. Overenrollment to 7 DLT-evaluable subjects of 9 accrued on DL2 was due to team decision to reconsider a subject as DLT-evaluable who had previously been reported to be inevaluable by her treating physician. In cohort 3, all 6 enrolled were DLT-evaluable.

No protocol-defined MTD (assessed during cycle 1) was identified. However, 6 of 15 patients treated with

Table 2. Baseline tumor and patient characteristics

Treated patients, *N*	52
Tumor subtype, *n* (%)	
HER2-amplified	6 (11.5)
ER+ and/or PgR+	31 (59.6)
ER−, PgR−, HER2 normal (triple-negative)	16 (30.8)
Median age (range), y	52 (35–77)
Median time since diagnosis (range), mo	34 (8.6–271.1)
Prior chemotherapy regimens in advanced setting, *n* (%)	
0	19 (37)
1	18 (35)
2	15 (29)
Performance score (ECOG), *n* (%)	
0	(44)
1	(56)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PgR, progesterone receptor.

dasatinib at 70 mg twice daily (DL2 + DL3) subsequently discontinued because of toxicity or noncompliance as a result of adverse events (most commonly pleural effusion, diarrhea, and fatigue) during the second (3 patients) or subsequent cycles. On the basis of these observations, the protocol was amended, and a DL3a (dasatinib 100 mg daily) was implemented. One DLT occurred in the first 6 patients, but the study team elected to assess 3 more patients (total of 9) in the escalation phase at DL3a to allow assessment of the first 6 patients beyond one cycle. Tolerability was much better in this DL, in which patients received a median of 6 cycles of treatment; therefore, DL3a was selected for the expansion phase. One DLT of severe capecitabine intolerance (neutropenia and diarrhea grade 4, mucositis, and emesis grade 3), consistent with dihydropyrimidine dehydrogenase deficiency, was recorded among 21 patients in the expansion phase.

Treatment-related adverse events

Frequencies of adverse events related to either or both drugs for all 52 treated patients at any time on study are shown in Table 3. During treatment, 50 patients (96%) had a drug-related adverse event at any time. The most frequent adverse events (any grade occurring in >20%) were nausea (58%), hand–foot syndrome (44%), diarrhea (33%), fatigue (33%), vomiting (31%), asthenia (31%), decreased appetite (27%), and pleural effusion (25%). Twenty-six patients (50%) had grade 3/4 drug-related adverse events; the most frequent (>5%) were hand–foot syndrome (12%), diarrhea (8%), fatigue (8%), pleural effusion (8%), and vomiting (6%). Drug-related serious adverse events occurred in 13 patients (25%), of which pleural effusion ($n = 4$), dyspnea ($n = 3$), chest pain ($n = 3$), diarrhea ($n = 3$), and vomiting ($n = 2$) occurred in >1 patient. Four patients were reported to have died during follow-up >30 days after study drug discontinuation; deaths were attributed to disease (note: follow-up was not required in this trial after resolution of adverse effects). Pleural effusion was reported in 15 subjects and was considered by the investigator to be treatment related (i.e., at least possibly related) for 13 subjects. Of the 13 patients with drug-related effusion, there were 3 with grade 3 and 1 with grade 4. Pleural effusion required hospitalization (SAE) in 4 of 13 subjects. In 3 subjects, it was associated with discontinuation and in 5 with interruption of study drug.

Dose reduction and treatment discontinuation due to adverse events were common in DL1–3. However, in DL3a, dasatinib dose reduction and discontinuation for toxicity were uncommon (Table 4). A total of 8 patients (15%) discontinued study treatment due to adverse

Table 3. Treatment-related adverse events occurring at any time during therapy in at least 10% of patients for all treated patients and for patients treated at DL3a

	Patients, *n* (%)			
	All treated patients ($n = 52$)		DL3a ($n = 30$)	
AE	Any grade	Grade 3/4	Any grade	Grade 3/4
Any event	50 (96)	26 (50)		
Nausea	30 (58)	0 (0)	19 (63)	0 (0)
Hand–foot syndrome	23 (44)	6 (12)	18 (60)	3 (10)
Diarrhea	17 (33)	4 (7.7)	10 (33)	1 (3.3)
Fatigue	17 (33)	4 (7.7)	8 (27)	1 (3.3)
Vomiting	16 (31)	3 (5.8)	12 (40)	2 (6.7)
Asthenia	16 (31)	1 (1.9)	9 (30)	0 (0)
Decreased appetite	14 (27)	0 (0)	6 (20)	0 (0)
Pleural effusion[a]	13 (25)	4 (7.7)	10 (33)	3 (10)
Rash	10 (19)	1 (1.9)	5 (17)	2 (6.7)
Dyspnea	10 (19)	2 (3.8)	9 (30)	1 (3.3)
Headache	10 (19)	1 (1.9)	7 (23)	1 (3.3)
Mucosal inflammation	7 (14)	2 (3.8)	4 (13)	2 (6.7)
Pain	7 (14)	1 (1.9)	5 (17)	1 (3.3)
Dysgeusia	7 (14)	0 (0)	5 (17)	0 (0)
Hypokalemia	7 (14)	2 (3.8)	3 (10)	0 (0)
Pyrexia	6 (12)	0 (0)	7 (23)	0 (0)
Cough	6 (12)	0 (0)	7 (23)	0 (0)

[a]Pleural effusion was reported in 15 subjects (site of disease progression in 2 of 15 cases) and was considered by the investigator to be treatment related (i.e., at least possibly related) for 13 subjects (25%, listed above). Of the 13 patients with drug-related effusion, there were 3 with grade 3 and 1 with grade 4. Pleural effusion required hospitalization (SAE) in 4 of 13 subjects. In 3 subjects, it was associated with discontinuation and in 5 with interruption of study drug.

Table 4. Dose reductions, discontinuations, and treatment duration

	Patients, *n* (%)			
DL	Dasatinib dose reduced	Capecitabine dose reduced	Discontinued for toxicity	Median treatment duration (interquartile range), mo
1 ($n = 7$)	2 (28.6)	3 (42.9)	1 (14.3)	3.65 (0.46–16.33)
2 ($n = 9$)	3 (33.3)	3 (33.3)	3 (33.3)	1.38 (0.69–1.51)
3 ($n = 6$)	2 (33.3)	2 (33.3)	3 (50.0)	1.18 (1.15–7.33)
3a ($n = 30$)	3 (10)	13 (43.3)	1 (3.3)	3.24 (2.07–7.36)

NOTE: Patients may appear in more than one column.

events, including 1 of 7 (14%) in DL1, 3 of 9 (33%) in DL2, 3 of 6 (50%) in DL3, and 1 of 30 (3%) in DL3a. Adverse event leading to discontinuation were pleural effusion ($n = 5$), gastrointestinal toxicity ($n = 4$), fatigue or asthenia ($n = 3$), or other adverse events ($n = 3$).

Laboratory abnormalities were uncommon. Grade 3/4 abnormalities were hypophosphatemia ($n = 4$), hypocalcaemia ($n = 2$), alanine aminotransferase elevation ($n = 2$, both grade 3), neutropenia ($n = 4$), and anemia ($n = 4$, all grade 3). Hypocalcaemia was anticipated (due to osteoclast inhibition) and was managed with oral calcium supplementation.

Treatment at the selected dose level

DL3a, that is, dasatinib 100 mg daily continuously and capecitabine 1,000 mg/m^2 twice daily on days 1 to 14, was selected for the expansion phase. Of 30 patients treated at DL3a, 9 and 21 were treated in the escalation and expansion phases, respectively. The most frequent adverse events (occurring in >20% of the 30 patients treated at DL3a) were nausea (63%), hand–foot syndrome (60%), diarrhea (33%), fatigue (27%), vomiting (40%), asthenia (30%), decreased appetite (20%), dyspnea (30%), headache (23%), pyrexia (23%), cough (23%), and pleural effusion (33%).

Median treatment duration for the DL3a cohort was 3.24 months (range, 1–30+ months); 9 patients (30%) remained on treatment for >6 months. At the time of analysis, 2 patients were still receiving treatment at 30+ and 36+ months on study and 28 patients had discontinued treatment: 25 for progression, 1 for DLT, 1 for an unrelated adverse event, and 1 for withdrawal of consent after 1 month due to unrelated adverse events and pleural effusion.

In DL3a, dasatinib dosing was interrupted at some time in 18 patients (60%, after a median of 29 days) but was reduced in only 3 patients (10%). However, capecitabine dosing was interrupted in 23 patients (77%) and reduced in 13 patients (43%) at a median of 34 days, similar to observation in the DL1–3 cohorts.

Efficacy

Efficacy was assessed as a secondary endpoint, and subset analyses were conducted as exploratory analyses; no efficacy comparisons between subsets were conducted.

Median PFS was 13.3 weeks (95% CI, 11.6–19.1) in all treated patients, 14.4 weeks (95% CI, 11.7–22.0) in the DL3a cohort and 23.1 weeks (95% CI, 17.1–43.1) in patients with HR+ tumors (see Supplementary Fig. S2A–S2C) and 7.7 weeks (95% CI, 5.7–11.6; not shown) in patients with HR-negative tumors. At the time of submission, 3 patients, all with HR+ tumors, remain on study treatment at 40+, 50+, and 56+ months.

Best tumor response and response durations for treated patients with measurable disease are shown in Table 5. A confirmed PR occurred in 9 of 40 patients (22%), including in 6/25 (24%) from DL3a. In an unplanned analysis, PR was found to be 8 of 23 (35%) in patients with HR+ tumors but 1 of 17 (6%) with HR− tumors. Median response duration was 33 weeks in all treated patients, 24 weeks in the DL3a cohort, and 41 weeks in patients with HR+ disease. DCR was 52% in all evaluable patients, 56% in DL3a, 78% in patients with HR+ tumors, and 18% in patients with HR− tumors.

Plasma biomarkers

Plasma levels of VEGF-A, VEGFR-2, and collagen type IV (COL-IV) were measured at baseline (sample available from

Table 5. Best response to dasatinib plus capecitabine in patients with measurable disease

	Overall	DL3a	ER/PgR-positive
Evaluable, *n*	40	25	23
CR, *n* (%)	0 (0)	0 (0)	0
cPR, *n* (%)	9 (22)	6 (24)	8 (35)
ORR (CR + cPR), *n* (%)	9 (22)	6 (24)	8 (35)
Median response duration, wk	33.14	23.72	40.92
SD, *n* (%)	20 (50)	14 (56)	13 (57)
SD $\geq$ 6 mo, *n* (%)	12 (30)	8 (32)	10 (44)
DCR (CR + cPR + SD $\geq$ 6 mo), *n* (%)	21 (52)	14 (56)	18 (78)
PD, *n* (%)	10 (25)	4 (16)	1 (4.3)
Not evaluable, *n* (%)	1 (2.5)	1 (4.0)	1 (4.3)

$N = 47$ patients) and after 3 weeks ($n = 40$) and 6 weeks ($n = 31$) of study therapy. Levels of VEGFR-2 and COL-IV obtained in 2 previous single-agent studies of dasatinib in breast cancer (29, 30) were also available, as previously reported (31).

Compared with baseline values, levels of VEGF-A decreased significantly, by a median of −49.5% (95% CI around median, −78.6 to −20.3) after 3 weeks and remained significantly decreased by a median of −34.9% (95% CI, −63.8 to −6.0) after 6 weeks of study treatment (Fig. 1A and Supplementary Materials). Conversely, significant and sustained increases in VEGFR2 and COL-IV levels were observed, with VEGFR2 and COL-IV increased by a median of 22.2% (95% CI, 17.5–27.0) and 22.9% (95% CI, 18.0–27.8), respectively, after 3 weeks and remained increased by a median of 24.7% (16.0–33.4) and 23.5% (16.4–30.5), respectively (Fig. 1B and C and Supplementary Materials) after 6 weeks. In single-agent studies, median increases of VEGFR2 and COL-IV respectively, were 23.5% and 32.7% after 2 weeks and 28.9% and 38.4% after 4 weeks (ref. 31; Supplementary Table S3A–S3C, Supplementary Fig. S3A–S3G).

Discussion

The results of this phase I extended cohort study show that dasatinib can be combined with capecitabine. Because of toxicities observed in second or subsequent cycles with the combination of capecitabine and dasatinib at a dose of 70 mg twice daily, the protocol was amended to evaluate dasatinib 100 mg daily, which had shown improved tolerability relative to twice daily dosing in other disease settings (32, 33). This dose was well-tolerated and used for the expansion cohort. The recommended phase II dose for this combination in patients with ABC is dasatinib 100 mg daily continuously plus capecitabine 1,000 mg/m^2 twice daily on days 1 to 14 of a 21-day cycle, with dose modification as required. The frequency and severity of adverse events were as expected; common severe toxicities were hand–foot syndrome (palmar–plantar erythrodysesthesia), fatigue, vomiting, and diarrhea. Capecitabine dose was reduced in 43% of patients treated at the MTD, in line with the reported 41% rate of dose reduction following single-agent administration of this agent (35). Pleural effusion was reported in 15 subjects and was considered by the investigator to be treatment related (i.e., at least possibly-related and likely caused by dasatinib) for 13 subjects (an incidence of 25%). Pleural effusion required short hospitalization (SAE) in 4 of 13 subjects. In general, this well-described toxicity was manageable by holding therapy and/or with administration of short-course low-dose steroids and/or diuretics, prescribed at the discretion of the investigators. No new toxicities were observed with combined treatment.

Preliminary evidence of efficacy was observed; however, this study was not powered to assess the additional contribution of dasatinib to efficacy. DCR was 53% for all evaluable patients and median PFS was 13 weeks, which was similar to the median PFS reported for capecitabine monotherapy in other studies (36, 37). However, in *post hoc* subset analysis of patients with HR+ tumors, DCR was 78% and median PFS was 23.1 weeks; the suggestion of enhanced activity against HR+ tumors and bone metastases may be related to the role of Src kinase in HR signaling (14–17) and inhibition by dasatinib on osteoclasts and on tumor resident in bone (9, 26).

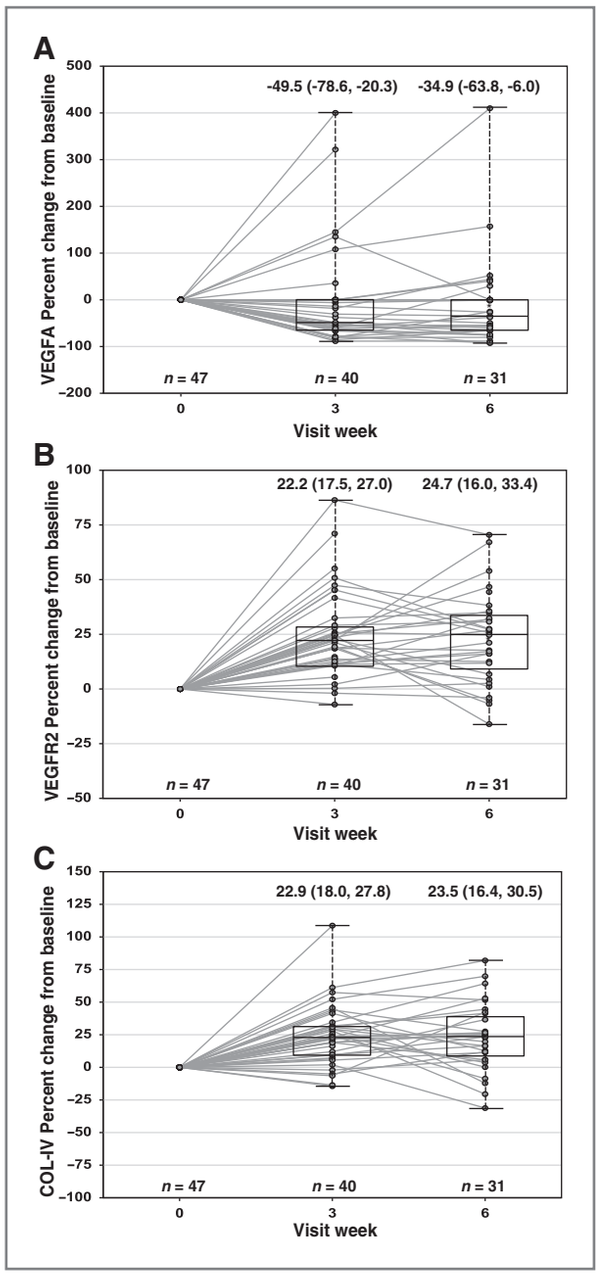

Figure 1. Interval percentage change from baseline value for each biomarker is shown by patient over time. Medians, 25th, and 75th percentiles are indicated by the box, the number of samples at each time point is given below, and median with corresponding 95% CI is given above each set of values. A, VEGF-A; B, VEGFR-2; C, COL-IV. See Supplementary Materials for additional data.

Dasatinib has been studied in ABC in combination with paclitaxel (38) or with ixabepilone (39) and in combination with hormonal therapies for ER+ disease, including fulvestrant (40), exemestane (41), and letrozole (in progress, NCT00696072). Studies of breast cancer molecular markers may identify patient subgroups that may benefit from dasatinib (42), permitting selection of appropriate patients for this targeted therapy. As biomarkers predictive of dasatinib response have not been clearly identified in ABC to date, tissues obtained in this study are reserved for future analysis.

VEGF is a principal regulator of angiogenesis and is required for tumor growth and viability; circulating biomarkers for response to anti-VEGF therapies have been explored (43). Production of VEGF is thought to be mediated by Src kinase (44, 45, reviewed in 46), possibly via STAT signaling (47). A reciprocal relationship between VEGF and shed VEGFR-2 has been shown in multiple clinical trials: VEGF clearance by bevacizumab was reported to increase soluble VEGFR-2 (48). Conversely, oral VEGFR-2 inhibitors reduce circulating levels of the receptor, accompanied by increased VEGF production (49, 50, reviewed in ref. 51) as a compensatory response.

Therefore, to investigate a potential role of dasatinib on angiogenesis, we assessed plasma levels of VEGF-A, VEGFR-2, and COL-IV as surrogate biomarkers. We found consistent and significant decreases in circulating VEGF-A (presumably via inhibition of Src kinase) and marked increases in VEGFR-2 and COL-IV after several weeks of dasatinib treatment. Although occurring via a different mechanism, these effects are the same as reported with bevacizumab (48); indeed, studies of the combination of dasatinib with bevacizumab (e.g., NCT00892177, NCT01015222, and NCT01445509) are in progress. Importantly, the reciprocal relationship between VEGF levels and shed VEGFR-2 reported in multiple studies of VEGFR inhibitors is maintained. Further studies of dasatinib effects on the vasculature are warranted and the combination of dasatinib with a VEGFR inhibitor may be of interest.

Overall, the safety and efficacy data obtained in this study could support further study of dasatinib in combination with capecitabine standard treatment in patients with advanced breast cancer.

Disclosure of Potential Conflicts of Interest

A. Rybicki owns stock in Bristol Myers Squibb. J. Cortes has honoraria from speakers bureau of Roche and is a consultant/advisory board member of Roche. The other authors disclosed no potential conflicts of interest.

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