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Phase II study of single-agent bosutinib, a Src/Abl tyrosine kinase inhibitor, in patients with locally advanced or metastatic breast cancer pretreated with chemotherapy

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Background: This phase II study evaluated single-agent bosutinib in pretreated patients with locally advanced or metastatic breast cancer.

Patients and methods: Patients received oral bosutinib 400 mg/day. The primary end point was the progression-free survival (PFS) rate at 16 weeks. Secondary end points included objective response rate, clinical benefit rate, 2-year overall survival rate, safety, and changes in levels of bone resorption/formation biomarkers.

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Results: Seventy-three patients were enrolled and treated. Median time from diagnosis of metastatic disease to initiation of bosutinib treatment was 24.5 months. For the intent-to-treat population, the PFS rate at 16 weeks was 39.6%. Unexpectedly, all responding patients (n = 4) were hormone receptor positive. The clinical benefit rate was 27.4%. The 2-year overall survival rate was 26.4%. The main toxic effects were diarrhea (66%), nausea (55%), and vomiting (47%). Grade 3–4 laboratory aminotransferase elevations occurred in 14 (19%) patients. Myelosuppression was minimal. No consistent changes in the levels of bone resorption/formation biomarkers were seen.
Conclusions: Bosutinib showed promising efficacy in prolonging time to progression in chemotherapy-pretreated patients with locally advanced or metastatic breast cancer. Bosutinib was generally well tolerated, with a safety profile different from that of the Src/Abl tyrosine kinase inhibitor dasatinib in a similar patient population.
Key words: Abl, bosutinib, breast neoplasms, Src, tyrosine kinase inhibitors

introduction

Despite recent progress in the management of early breast cancer, nearly half of women with breast cancer develop metastatic disease [1]. The median survival of patients with metastatic breast cancer has improved over the last decade to 36 months, but 10-year survival rates remain low, at only 5%–10% [2]. Treatment is therefore aimed at symptom palliation, improving quality of life, inhibiting disease progression, and improving survival. Due to a recent shift in treatment protocols, aggressive cytotoxic drugs like anthracyclines and taxanes are being used earlier in the course of the disease [3]. After patients have failed treatment with these agents, it is a challenge to identify active agents for this patient population.

Besides standard cytotoxic treatments, targeted therapies have now been developed to treat metastatic disease. The overexpression of human epidermal growth factor receptor 2 (HER2) is a well-recognized prognostic factor of tumor aggressiveness and poor survival. However, HER2 is also a therapeutic target for trastuzumab, a recombinant humanized antibody that binds to the receptor's extracellular domain. Treatment of patients with HER2-positive metastatic breast cancer with trastuzumab led to a 44% decrease in the risk of death compared with HER2-negative patients [4]. Resistance occurs, however, and the current challenge is to bypass such resistance by targeting alternative tumor growth pathways.

Tyrosine kinases are therapeutic targets for small-molecule inhibitors. Bosutinib (SKI-606) is a substituted 4-anilino-3-quinoline carbonitrile and a selective dual inhibitor of Src and Abl tyrosine kinases [5–7]. Src kinase is a key component of pathways mediated by growth factor receptors [8] and is involved in the function of osteoclasts [9, 10]. Elevations of Src kinase activity have been reported in a wide variety of tumor types [8]. In human breast cancer, elevated Src kinase activity has been found in 70% of the samples examined [11]. In preclinical studies, bosutinib inhibited the proliferation, migration, and invasion of cells of a highly invasive breast cancer cell line and also tumor growth and metastasis of these cells in a xenograft mouse model [7].

Based on the effects of bosutinib in human breast cancer cells in preclinical studies, a phase I study in patients with advanced solid tumors was conducted to identify a maximum tolerated dose. Bosutinib was generally well tolerated, and stable disease (SD) was observed in patients with various primary tumor types [12]. Thus, we conducted a phase II study of bosutinib in pretreated patients with locally advanced or metastatic breast cancer to further evaluate efficacy and safety. In addition, because Src kinase plays a key role in osteoclast function and osteoclasts are primarily involved in osteolytic metastatic bone disease [13–15], a common aspect of breast cancer, we monitored bone resorption and formation biomarkers.

patients and methods

study population

Patients of at least 18 years of age with a pathological diagnosis of breast cancer and current stage IIIB, IIIC, or IV disease, not curable with available therapies, were eligible. Patients had to have disease progression after one to three prior chemotherapy regimens for locally advanced or metastatic disease and at least one measurable lesion as defined by modified RECIST (version 1.0) [16]. Other eligibility criteria included a Karnofsky performance status of at least 70% that had not declined within 4 weeks before the first dose of bosutinib; a life expectancy of at least 16 weeks; serum calcium levels ≤3.1 mmol/l; adequate hematologic, renal, cardiac, and hepatic functions; and ability to swallow whole capsules. Patients were not eligible if bisphosphonates, which inhibit bone resorption, had been used within 8 weeks before the first dose of bosutinib; if they had received prior therapy with a Src kinase inhibitor; or if they had extensive visceral disease, symptomatic or clinically active central nervous system metastases, or skin or bone as the only site of disease.

Written informed consent was obtained before enrollment. The protocol was reviewed and approved by the Ethics Committees/Institutional Review Boards of the participating institutions and the study was conducted according to the Declaration of Helsinki and European Good Clinical Practice requirements.

treatment

Bosutinib (Pfizer Inc, New York, NY) 500 mg was identified as the maximum tolerated dose in a phase I dose escalation study in patients with solid tumors, but 400 mg was the recommended dose because a number of patients who were treated with 500 mg had grade 2 gastrointestinal toxic effects [12]. Bosutinib was given orally as a single dose of 400 mg/day. Patients remained on treatment for as long as treatment was tolerated or until there was evidence of disease progression.

Bosutinib treatment was withheld if grade 2 or 3 (National Cancer Institute—Common Terminology Criteria for Adverse Events, version 3.0) diarrhea occurred and lasted for >2 days despite optimal medical therapy or was associated with fever or dehydration, or if a grade 3 or 4 nonhematologic adverse event occurred, or if a grade 4 hematologic event occurred. Upon recovery to grade 1 or the baseline condition within

3 weeks, bosutinib treatment was restarted at a reduced dose of 300 mg/day. Patients who failed to recover to grade 1 or the baseline condition after 3 weeks discontinued bosutinib treatment. More than one dose reduction was not permitted unless discussed with the sponsor.

efficacy assessment

Screened patients underwent contrast-enhanced computed tomography scans or magnetic resonance imaging at baseline and at study weeks 4, 8, and 16 and then every 8 weeks thereafter until disease progression. A patient was considered assessable if she met all eligibility criteria, had completed at least 14 days of treatment with bosutinib, and had a screening scan and at least one follow-up scan after starting treatment. Patients whose disease clinically progressed or who died early and for whom a postbaseline assessment was not possible were considered assessable for efficacy.

safety assessment

Patients receiving at least one dose of bosutinib were assessable for safety. Safety was assessed by physical examination, laboratory tests, electrocardiogram measurements, and adverse events reports. Safety follow-up continued until resolution of any drug-related toxicity. Patients with documented disease progression discontinued bosutinib treatment.

bone turnover assessment

The bone resorption biomarkers, crosslinked N-telopeptide of type I collagen and crosslinked C-telopeptide of type I collagen (CTX), and the bone formation biomarkers bone-specific alkaline phosphatase (BSAP), osteocalcin, and procollagen type 1 aminoterminal propeptide (P1NP) were analyzed. Serum and urine samples were collected at baseline; weeks 4, 12, and 24; and then every 8 weeks thereafter to measure biomarker levels. Measurements were carried out independently by a central laboratory (Quest Diagnostics, West Hills, CA).

statistical analysis

This was an open-label, two-stage, phase II trial. The primary efficacy end point was the progression-free survival (PFS) rate at 16 weeks. The null hypothesis was that the PFS rate at 16 weeks was not >20%. The alternative hypothesis was that the rate was not <40%. A type I error rate of 0.05 and a type II error rate of 0.15 gave a sample size of 51 assessable patients, using an optimal Simon two-stage design [17]. To obtain 51 assessable patients, assuming a nonevaluable rate of 15%, ~60 patients were to be accrued. The primary analysis of the PFS rate at 16 weeks was to be based on the intent-to-treat (ITT) population, the total number of enrolled and treated patients.

Secondary end points included the objective response rate [ORR, the percentage of patients with confirmed complete response (CR) plus confirmed partial response (PR)], the clinical benefit rate (the percentage of patients with confirmed CR and PR and SD lasting longer than 24 weeks), the 2-year overall survival rate, the safety profile, and pharmacodynamic analysis of bosutinib activity on bone. Prespecified subgroup analyses were carried out based on hormone receptor (HR) and HER2 tumor status. This status was determined from medical histories or, if unknown, attempts were made to obtain tumor samples for identification of status by a central laboratory.

PFS was defined as the time from first day of treatment until the first documented date of progression or death due to any cause. Overall survival was defined as the time from first day of treatment until death due to any cause. Patients who were alive at the time of last contact were censored. PFS and the 2-year overall survival rate were computed according to the Kaplan–Meier method.

results

characteristics of patients and treatment

From June 2006 to January 2007, 73 patients from 15 centers in 8 countries were enrolled and treated with at least one dose of bosutinib (Figure 1). The baseline characteristics of patients are summarized in Table 1. At baseline, 72 patients had metastatic disease and 1 patient had stage IIIC disease. Seventy-eight percent of patients had received one to three prior regimens (chemotherapy, immunotherapy, and/or hormonal therapy) for their locally advanced or metastatic disease; all patients had received at least one chemotherapy regimen and 51% had received at least one hormonal therapy regimen. The median time from first diagnosis of locally advanced or metastatic disease to first dose of bosutinib was 24.5 months (range, 2.7 months–17.6 years).

Sixty-six (91%) patients received at least 14 days of bosutinib treatment; among them, two (3%) received bosutinib beyond 12 months. The median dose received was 400 mg per day (range, 308–400 mg). The median duration of treatment was 9.9 weeks (range, 3 days–77 weeks).

efficacy

For the ITT population, the PFS rate at 16 weeks was 39.6% (95% confidence interval [CI] 28.1%–50.8%) and the median PFS was 9.9 weeks (95% CI 6.7–16.7 weeks; Figure 2A). For patients with HR-positive disease ($n = 49$), the PFS rate at 16 weeks was 43.1% (95% CI 28.8%–56.5%); for those with HER2-positive disease ($n = 12$), the rate was 41.7% (95% CI 15.2%–66.5%); and for those with triple-negative disease (negative for estrogen and progesterone receptors and HER2; $n = 13$), the rate was 25.0% (95% CI 6.0%–50.5%). Similar results were obtained for the evaluable population (Figure 2B).

The best overall responses and clinical benefit rates for the ITT and evaluable populations are summarized in Table 2. In the ITT population, no patients achieved a CR and four patients achieved a confirmed PR for an ORR of 5.5%. All the confirmed PRs were in the subset of patients with HR-positive disease (HR positive/HER2 negative, $n = 3$; HR positive/HER2 unclassified, $n = 1$) for an ORR of 8.2%. Twenty-four patients had SD, and 16 of these had duration of >24 weeks for a clinical benefit rate of 27.4%. Twelve of the 16 patients with SD beyond

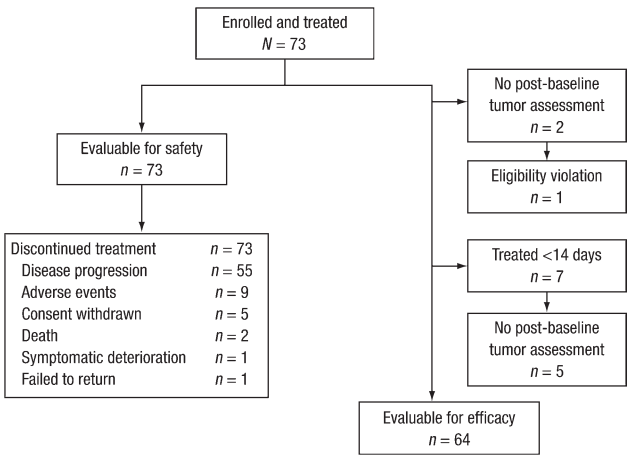

Figure 1. Study flowchart.

Table 1. Baseline characteristics of patients

Characteristic	Number of patients ($N = 73$)	Percent
Median age (range), years	54 (33–71)	
Karnofsky performance status (%)		
>70	65	89
≥60 and ≤70	8	11
Breast cancer stage at screening		
IIIC	1	1
IV	72	99
Number of metastatic sites		
1	40	55
2	23	32
≥3	10	14
Primary sites of disease[a]		
Liver	31	42
Lymph nodes	18	25
Lung	13	18
Breast	7	10
Brain	1	1
Skin	1	1
Other	2	3
HR status and HER2 status		
HR+, HER2+	7	10
HR+, HER2−	32	44
HR+, HER2 unclassified	10	14
HR−, HER2+	5	7
HR−, HER2−	13	18
HR unclassified, HER2−	1	1
HR unclassified, HER2 unclassified	5	7
Prior adjuvant/neoadjuvant therapy	50	68
Number of prior chemotherapy, immunotherapy, and hormonal regimens for locally advanced or metastatic disease		
1–3	57	78
>3	16	22
At least one chemotherapy regimen	73	100
At least one hormonal therapy regimen	37	51
Median time from first diagnosis of locally advanced or metastatic disease to first bosutinib dose (range)	24.5 months (2.7 months–17.6 years)	

[a]Most frequent location per patient or location with longest diameter (if number of locations is the same).

HR, hormone receptor (estrogen and/or progesterone receptor); HER2, human epidermal growth factor receptor 2.

24 weeks had HR-positive disease for a clinical benefit rate of 32.7% in that subgroup. For patients with HER2-positive disease ($n = 12$), the clinical benefit rate was 25.0%. The median duration of response for the four patients with a confirmed PR was 37.1 weeks (range, 16.1–61.6 weeks).

The maximum percent reduction in target tumor sizes, based on HR and HER2 status, is presented in Figure 3. Of 59 patients assessable for efficacy who had target lesions assessed at baseline and at least one follow-up, 46% ($n = 27$) had a decrease in target

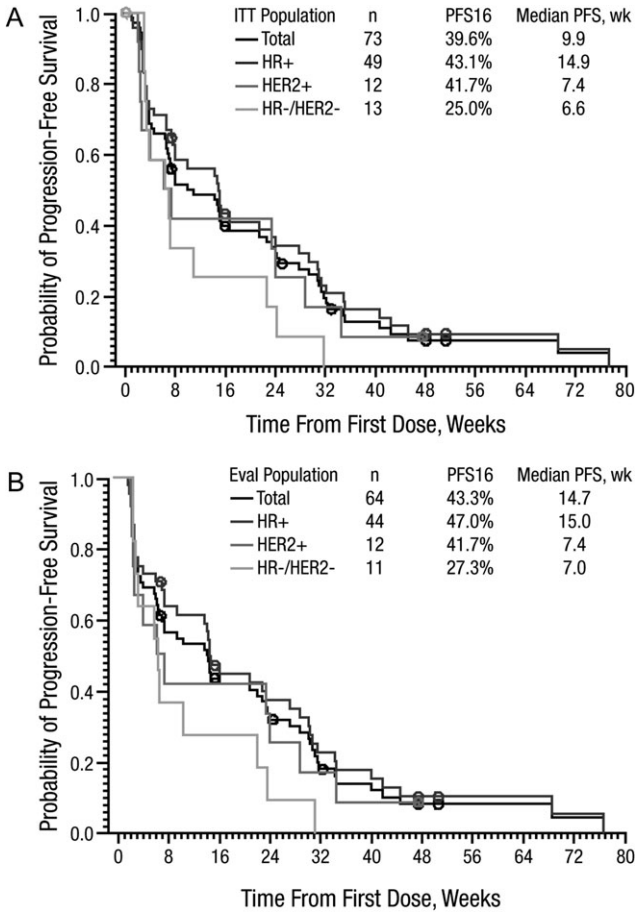

Figure 2. Kaplan–Meier estimates of progression-free survival (PFS) of (A) the ITT population and (B) the evaluable population. PFS for the HR-positive and HER2-positive subgroups is not mutually exclusive. ITT, intent-to-treat; PFS, progression-free survival; HR, hormone receptor (estrogen and/or progesterone receptor); HER2, human epidermal growth factor receptor 2; PFS16, progression-free survival rate at 16 weeks; Eval, evaluable.

tumor size. In subgroups of patients, 57% ($n = 4/7$) with HR-positive/HER2-positive disease, 48% ($n = 13/27$) with HR-positive/HER2-negative disease, 0% ($n = 0/3$) with HR-negative/HER2-positive disease, and 30% ($n = 3/10$) with triple-negative disease had maximum decreases in target tumor size.

At the time of final analysis, March 2009, 47 (64%) patients had died, 46 from disease progression and 1 from suicide believed to be unrelated to bosutinib. The 2-year overall survival rate for the ITT population was 26.4% (95% CI 14.7% to 39.7%) and for the evaluable population was 29.3% (95% CI 16.3% to 43.6%).

safety

Seventy-one (97%) of the 73 treated patients experienced treatment-emergent adverse events (TEAEs), any grade, during bosutinib treatment. The most common TEAEs were diarrhea (66% patients), nausea (55%), and vomiting (47%, Table 3). Of those patients who had diarrhea, most had grade 1 events as the maximum toxicity (grade 1, 65% patients; grade 2, 27%; grade 3,

Table 2. Best overall response and clinical benefit rates

Response	Total	HR+[a]	HER2+[a]	HR+/HER2−	HR−/HER2−	Unclassified[b]
Intent-to-treat population						
Number of patients	73	49	12	32	13	6
PR, *n* (%)	4 (5.5)	4 (8.2)	0	3 (9.4)	0	0
SD[c], *n* (%)	24 (32.9)	17 (34.7)	5 (41.7)	7 (21.9)	3 (23.1)	3 (50.0)
SD ≤24 weeks[d]	8 (11.0)	5 (10.2)	2 (16.7)	2 (6.3)	2 (15.4)	0
SD >24 weeks[d]	16 (21.9)	12 (24.5)	3 (25.0)	5 (15.6)	1 (7.7)	3 (50.0)
Clinical benefit rate, % (95% CI)	27.4 (17.6%–39.1%)	32.7 (19.9%–47.5%)	25.0 (5.5%–57.2%)	25.0 (11.5%–43.4%)	7.7 (0.2%–36.0%)	50.0 (11.8%–88.2%)
PD, *n* (%)	36 (49.3)	22 (44.9)	6 (50.0)	17 (53.1)	9 (69.2)	2 (33.3)
Unknown, *n* (%)	18 (24.7)	12 (24.5)	2 (16.7)	9 (28.1)	2 (15.4)	2 (33.3)
Evaluable population						
Number of patients	64	44	12	29	11	4
PR, *n* (%)	4 (6.3)	4 (9.1)	0	3 (10.3)	0	0
SD[c], *n* (%)	24 (37.5)	17 (38.6)	5 (41.7)	7 (24.1)	3 (27.3)	3 (75.0)
SD ≤24 weeks[d]	8 (12.5)	5 (11.4)	2 (16.7)	2 (6.9)	2 (18.2)	0
SD >24 weeks[d]	16 (25.0)	12 (27.3)	3 (25.0)	5 (17.2)	1 (9.1)	3 (75.0)
Clinical benefit rate, % (95% CI)	31.3 (20.2%–44.1%)	36.4 (22.4%–52.2%)	25.0 (5.5%–57.2%)	27.6 (12.7%–47.2%)	9.1 (0.2%–41.3%)	75.0 (19.4%–99.4%)
PD, *n* (%)	33 (51.6)	21 (47.7)	6 (50.0)	17 (58.6)	8 (72.7)	1 (25.0)
Unknown, *n* (%)	5 (7.8)	3 (6.8)	2 (16.7)	3 (10.3)	0	0

[a]The subgroups are not mutually exclusive.
[b]Both HR and HER2 status were unknown.
[c]The criteria for SD must have been met at least once at a minimum of 8 weeks (window of −2 days) after start of treatment.
[d]SD at 24 weeks is defined from the start of treatment (window of −2 weeks) until 24 week duration.
HR, hormone receptor (estrogen and/or progesterone receptor); HER2, human epidermal growth factor receptor 2; PR, partial response; SD, stable disease; CI, confidence interval; PD, progressive disease.

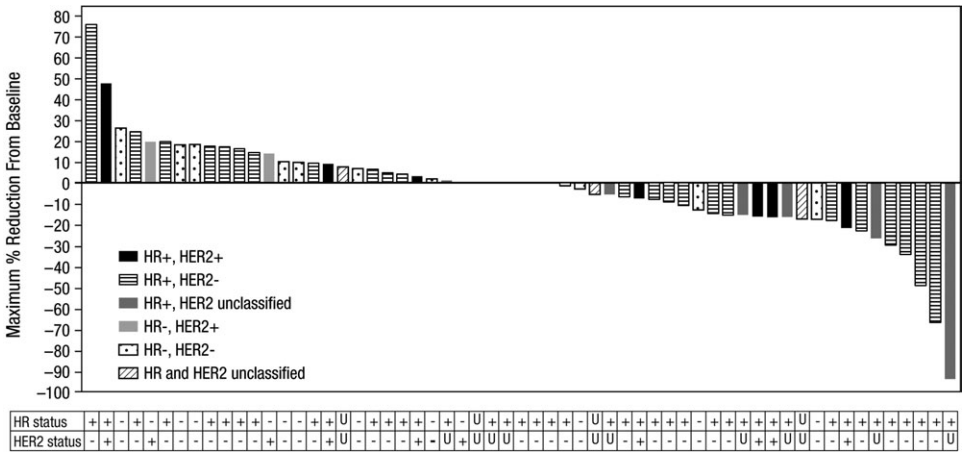

Figure 3. The best response for target lesions per patient for patients with target lesions assessed at baseline and at least one follow-up ($n = 59$). Patients with a negative maximum percent reduction from baseline had a decrease in the size of the target tumor and patients with a positive maximum percent reduction from baseline had an increase in tumor size. HR, hormone receptor (estrogen and/or progesterone receptor); HER2, human epidermal growth factor receptor 2; U, unclassified.

8%). Onset of diarrhea occurred early during bosutinib treatment (median, 2 days) and the incidence and severity decreased over time (Figure 4). Less than 20% of patients had diarrhea in week 2 or later. No grade 3 diarrhea occurred after month 1. Five patients had a dose reduction due to diarrhea and one patient terminated bosutinib treatment due to diarrhea.

During bosutinib treatment, 12 (16%) patients had grade 3–4 elevations in alanine aminotransferase (ALT) levels and 10 (14%) patients had grade 3–4 elevations in aspartate aminotransferase (AST) levels (14 patients had grade 3–4 elevations in ALT and/or AST levels) as measured by laboratory tests. Grade 1 elevations occurred in the greatest percentage of patients as the maximum toxicity (ALT: grade 1, 25%; grade 2, 8%; grade 3, 12%; grade 4, 4%; AST: grade 1, 26%; grade 2, 11%; grade 3, 12%; grade 4, 1%). Elevations of ALT or AST were generally observed within the first 4 months of bosutinib

treatment, with no grade 3–4 elevations occurring after 4 months of treatment (Figure 5). Of the 14 patients with grade 3–4 ALT and/or AST elevations, 6 (43%) had at least one liver lesion identified at baseline. Thirteen (93%) patients recovered to normal or grade 1 levels during bosutinib treatment or during follow-up after treatment discontinuation; 8 (57%) patients recovered to normal or grade 1 levels without bosutinib dose delay or reduction. No follow-up information was available for one patient, who discontinued due to disease progression in the lungs and liver. One patient terminated bosutinib treatment due to a grade 4 ALT elevation, which resolved to grade 1 within 3 weeks of stopping treatment.

Four (6%) patients had anemia and two (3%) had neutropenia, both of which were considered unrelated to bosutinib treatment by investigators. Thrombocytopenia was not reported. Eight (11%) patients had peripheral edema; one patient was considered to have edema related to bosutinib treatment. Two (3%) patients had pleural effusion that was considered unrelated to bosutinib treatment.

A single dose reduction of bosutinib was required for eight (11%) patients because of adverse events. Eighteen (25%) patients had at least one dose delay lasting 3 or more days because of adverse events. Patients discontinued bosutinib treatment because of disease progression (75%), adverse events (12%), withdrawal of consent (7%), death (3%), symptomatic deterioration (1%), and a failure to return (1%; Figure 1).

Table 3. Treatment-emergent adverse events reported in at least 10% of the 73 treated patients

Adverse event, n (%)	Any grade	Grade 3–4
Diarrhea	48 (66)	4 (6)
Nausea	40 (55)	1 (1)
Vomiting	34 (47)	1 (1)
Fatigue	19 (26)	3 (4)
Asthenia	14 (19)	4 (6)
Anorexia	14 (19)	0
Infections and infestations	12 (16)	2 (3)
Rash	10 (14)	0
Headache	10 (14)	1 (1)
Arthralgia	9 (12)	1 (1)
Abdominal pain	9 (12)	1 (1)
Back pain	9 (12)	3 (4)
Peripheral edema	8 (11)	0
Cough	8 (11)	0
Dyspnea	8 (11)	0
Weight decreased	8 (11)	0

bone turnover analysis

The bone resorption marker CTX and the bone formation markers BSAP, osteocalcin, and P1NP were consistently higher in patients with bone disease than in those with no bone disease (data not shown). However, no consistent changes in levels of each marker relative to time or direction of change during bosutinib treatment were observed (data not shown).

discussion

In this phase II study, unselected pretreated patients with locally advanced or metastatic breast cancer were treated with a single daily oral dose of bosutinib 400 mg. Bosutinib had moderate antitumor activity. In the ITT population, the primary end point, the PFS rate at 16 weeks, was 39.6% and median PFS was 9.9 weeks. The PFS rate at 16 weeks was 25.0%, 41.7%, and 43%, respectively, for patients with triple-negative, HER2-positive, and HR-positive disease. Four patients with HR-positive disease achieved a confirmed PR.

These results compare favorably with those of another small-molecule Src/Abl inhibitor, dasatinib, which has been studied in two phase II trials as a treatment of metastatic breast cancer patients who had triple-negative or HR-positive and/or HER2-positive disease [18, 19]. In both trials, >90% of patients had received no more than two prior chemotherapy regimens. The PFS rate at 17 weeks was 14%–22%. Two patients with HR-positive disease, one with HER2-positive disease, and two with triple-negative disease had confirmed PRs. While direct comparisons of clinical trials must be interpreted with caution because of differences in patient populations, the results of our study suggest that bosutinib showed at least comparable

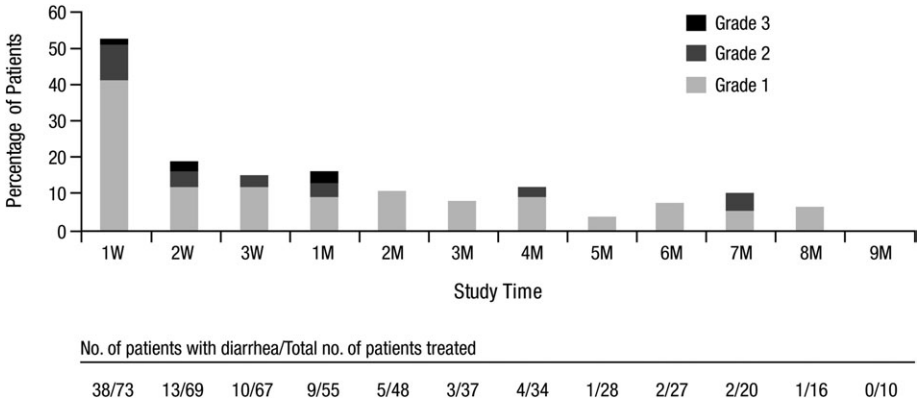

Figure 4. Occurrence of diarrhea per time period. The maximum grade toxicity per time period was reported for each patient. W, weeks; M, months.

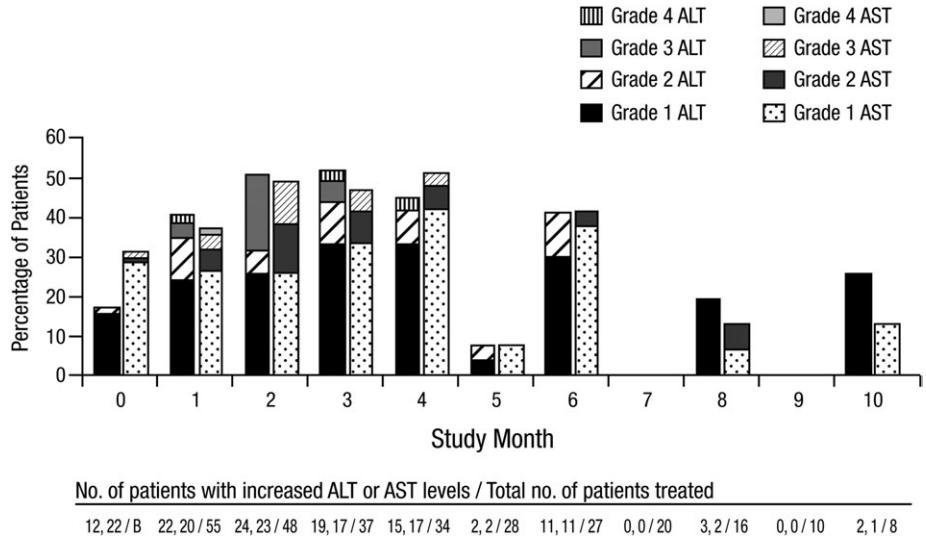

Figure 5. Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) per time period. The maximum grade elevation per time period was reported for each patient. Per protocol, laboratory tests were not scheduled for months 5, 7, and 9. B, number of patients with nonmissing values at baseline, $n = 73$ and $n = 72$ for ALT and AST elevations, respectively.

efficacy to dasatinib in pretreated metastatic breast cancer patients with HR-positive disease.

Bosutinib was generally tolerable in this patient population, with a different toxicity profile from that of dasatinib. Although diarrhea and fatigue were common toxic effects of both bosutinib and dasatinib [18, 19], the incidence of anemia in metastatic breast cancer patients treated with bosutinib (6%) was much lower than that in similar patients treated with dasatinib (66%) [18]. Similarly, the incidence of neutropenia in bosutinib-treated patients (3%) was much lower than in dasatinib-treated patients (41%). Bosutinib-related peripheral edema was reported in one (1%) patient and pleural effusion was reported in no patients. In contrast, dasatinib-related generalized edema and pleural effusion were reported in 7% and 26%–39% of patients, respectively [18, 19]. Bosutinib induced reversible elevations in ALT and AST in this study, which has not been reported for dasatinib-treated patients [18, 19].

The different toxic effects associated with bosutinib or dasatinib treatment could be explained by the different specificities of the drugs. Bosutinib specifically inhibits the Src and Abl tyrosine kinases, while dasatinib inhibits these as well as c-Kit and platelet-derived growth factor receptor (PDGFR)-β [20, 21]. Because c-Kit has a role in normal hematopoiesis [22], the inhibition of c-Kit by dasatinib may explain the much higher incidence of anemia and neutropenia in dasatinib-treated breast cancer patients than in similar bosutinib-treated patients. Furthermore, the role of PDGFR-β in the control of tissue interstitial fluid pressure [23] may explain why fluid accumulation occurred in many more dasatinib-treated breast cancer patients than in similar bosutinib-treated ones.

Capecitabine has been used for the treatment of metastatic breast cancer patients who have previously received treatment with anthracyclines and/or taxanes and at least two prior chemotherapy regimens. Synergy has been shown to exist between dasatinib and capecitabine in triple-negative breast cancer cell lines [24]. Thus, a phase I/II study is ongoing to evaluate the combination of bosutinib and capecitabine in patients with solid tumors (http://ClinicalTrials.gov).

In conclusion, bosutinib as a monotherapy showed a tolerable safety profile and moderate antitumor activity in pretreated patients with locally advanced or metastatic breast cancer. PRs were observed in patients with HR-positive disease. Given these results in a challenging unselected patient population, further studies with bosutinib in combination with other agents are warranted following implementation of an appropriate method of patient selection.

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disclosure

NB, EL, KT, and CZ are employees of Wyeth Research/Pfizer Inc, the developer of bosutinib and study sponsor; NB also holds stock in Pfizer Inc. The other authors have no conflicts of interest.

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