TBCRC-010: Phase I/II Study of Dasatinib in Combination with Zoledronic Acid for the Treatment of Breast Cancer Bone Metastasis

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Statement of Translational Relevance

The skeleton is the most common site of metastases from breast cancer. Breast cancer bone metastases are sustained through src kinase mediated release of osteoclast activating growth factors. This study evaluated the safety and efficacy of dasatinib, a src kinase inhibitor, in combination with zoledronic acid, an osteoclast activation inhibitor, in patients with bone predominant breast cancer metastases. The combination was well tolerated and responses in bone were noted in patients with hormone receptor positive, low grade tumors and high baseline bone turnover markers. Interestingly, in patients who continued inactive hormonal therapy beyond progression, the addition of dasatinib and zoledronic acid was effective at achieving objective responses. This represents a proof of principle of reversing endocrine resistance in bone using agents targeting bone metastases.
Abstract

Purpose

Osteoclast mediated bone resorption through src kinase releases growth factors, sustaining bone metastases. This trial determined the recommended phase 2 dose (RP2D) and clinical efficacy of the src-kinase inhibitor dasatinib combined with zoledronic acid (ZA) in bone predominant, HER2-negative breast cancer metastases.

Experimental Design

A 3+3 lead in phase I design confirmed the recommended phase 2 dose (RP2D) allowing activation of the single arm, phase II trial. ZA was administered IV on day 1 and dasatinib was given po once daily for 28 days each cycle as twice daily administration caused dose limiting toxicity. Response was assessed every 3 cycles. N-telopeptide (NTx) was serially measured.

Results

25 patients were enrolled. No DLTs were noted at the RP2D of dasatinib=100 mg/day. Common adverse events (AEs) were grade 1-2: rash (9/25, 36%), fatigue (9/25, 36%), pain (9/25, 36%), nausea (6/25, 20%). The objective response rate in bone was 5/22 (23%), all partial responses (PRs). The clinical benefit rate (PRs + stable disease (SD) ≥ 6 months) in bone was 8/22 (36%). Median time to treatment failure was 2.70 months (95% CI: 1.84 – 5.72) in the general cohort, 3.65 months (95% CI: 1.97 – 7.33) in patients with hormone receptor (HR)-positive breast cancer and 0.70 months (95% CI: 0.30 – NA) in those with HR-negative disease. Factors associated with response in bone included lower tumor grade, HR positive status, and pre-treatment high NTx levels.

Conclusion

Combination therapy was well tolerated, and produced responses in bone in patients with HR-positive tumors.
Introduction

The skeleton is one of the most common sites of breast cancer metastases. Approximately 70% of patients who die from breast cancer will have bone metastasis on autopsy. Bone metastases occur more commonly in lower grade, hormone receptor (HR)-positive tumors (1). Patients with distant metastases only to bone also have an improved survival compared to patients who have non-osseous metastases (2, 3). Skeletal related events (SREs) occur in as high as 51% of women with skeletal metastases (4). Breast cancer osteolytic metastases are sustained through a vicious cycle of tumor induced osteoclast bone resorption, growth factor release and tumor growth (5-8). Platelet derived growth factor (PDGF) has been shown to induce osteoclast activation and bone resorption, and elevated PDGF levels correlate with poorer outcomes in patients with breast cancer (9-14). Multiple studies have identified Src kinase as an essential factor for normal osteoclast function, and for the development of bone metastases through the parathyroid hormone-related protein (PTHRP) mediated effect on osteoclasts (15-19). Src kinase is overexpressed in breast cancer tissue compared to normal breast tissue, and has been associated with an increased risk of metastasis, recurrence and shortened survival (20-22).

Dasatinib is a potent multitargeted kinase inhibitor including src and PDGFR receptor, among others (23-25). It is approved for the treatment of newly diagnosed chronic phase chronic myelogenous leukemia and imatinib-resistant or -intolerant chronic myelogenous leukemia or Philadelphia positive acute lymphoblastic leukemia. (26, 27). Single agent studies of dasatinib in breast cancer have yielded low response rates across all breast cancer subtypes (28, 29). A phase 1 study of dasatinib in combination with capecitabine in 40 metastatic breast cancer patients reported 9 partial responses (PR), 8 of which were in HR-positive breast cancer (30). The combination of dasatinib and letrozole as first line therapy in patients with metastatic HR-positive breast cancer extended the progression-free survival (PFS) to 20.1 months from 9.9 months for letrozole alone (31). A placebo-controlled phase 2 study of exemestane +/- dasatinib reported higher PFS in a subset of patients with symptomatic bone metastases (32).

Zoledronic acid use has been shown to reduce SREs in patients with breast cancer skeletal metastases. (33, 34). Despite preclinical data supporting increased cell death and reversal of epithelial-mesenchymal-transition, zoledronic acid has not been shown to improve survival of patients with breast cancer (35-38). Taken together, this data supports using the combination of
dasatinib with zoledronic acid in synergy to reduce osteoclast mediated bone resorption and prevent tumor growth and proliferation.

Materials and Methods

This study was sponsored by the Translational Breast Cancer Research Consortium, and was conducted at three institutions: The University of Texas MD Anderson Cancer Center, The University of Chicago and Duke Cancer Institute. The study protocol and informed consent were approved by the institutional review board at all three institutions. The trial was registered with the National Cancer Institute, protocol number NCT00566618.

Patient eligibility

Patients were consented and enrolled in the trial if they met the following eligibility criteria: had a confirmed pathological diagnosis of invasive carcinoma of the breast that was HER2-negative (0-1+ by immunohistochemistry or 2+ and non-amplified by FISH), who carried a diagnosis of metastatic disease with predominant bone involvement defined as bone metastases detected on imaging studies in the presence or absence of visceral involvement (if visceral involvement was present, patients had to be asymptomatic from visceral disease and have no metastases in visceral organs that measured >3cm in size). Patients had to be ≥18 years of age and have a performance status ECOG ≤2, and could have received one prior line of chemotherapy. Patients were required to have adequate hematologic, renal, and hepatic function prior to enrollment. Patients with HR-positive breast cancer were also required to have had one prior hormonal therapy for metastatic disease, and have documented progression of disease on hormonal therapy prior to enrolment. Patients had to have completed previous radiation therapy at least 2 weeks (8 weeks for brain radiation) prior to study enrolment. Patients with irradiated tumor as the only site of evaluable disease were not eligible for protocol therapy unless there was documented disease progression within the previously radiated site. All patients had to have recovered to grade ≤1 from all acute toxicity of previous therapy. Patients were excluded if they required concurrent radiation, had an active infection requiring the use of intravenous antibiotics, had another malignancy (other than breast cancer) that required radiotherapy or systemic treatment within the past 5 years, had active cardiac disease, had concurrent medical conditions which may increase the risk of toxicity (pleural or pericardial effusion, bleeding diathesis), were unwilling or unable to use an
acceptable method of contraception for the entire study period and for at least 4 weeks after cessation of study drug, were pregnant or breastfeeding, or had untreated or uncontrolled brain metastasis. Patients were also excluded if they had active dental problems, recent or planned dental or jaw surgery within 8 weeks of enrolment, and known hypersensitivity to zoledronic acid or aspirin. Patients were not allowed to receive any concurrent bisphosphonate therapy other than that prescribed by the study.

Treatment plan and dose escalation

This study was conducted as an open label, phase 1/2 dose escalation study to evaluate the safety and tolerability of dasatinib in combination with zoledronic acid in patients with metastatic breast cancer to bone. Zoledronic acid was administered using standard dosing as a 15 minute intravenous infusion on day 1 of a 28 day cycle. Dasatinib was taken by mouth daily on days 1-28 of the cycle. Dasatinib was given continuously unless patients developed toxicities requiring dose adjustment or treatment interruption.

The phase 1 part of the study used a step down design that initially evaluated the first 3 patients treated on dose level 1 and, if DLT was not seen, enrolled an additional 3 patients to confirm the RP2D. If unacceptable DLT was seen, subsequent dosing stepped down to the -1 dosing cohort with subsequent accrual planned for up to 2 lower dosing cohorts as indicated by incidence of DLT. The RP2D was defined as the dose at which ≤1/6 patients developed a DLT. DLT was defined as a toxicity which occurred during cycle 1, suspected to be drug related and included any of the following: grade 4 non-hematological toxicity, grade 4 neutropenia lasting > 7 days or any febrile neutropenia, grade 3 non-hematological toxicity that persists >72 hours despite adequate supportive care, grade 2 or greater neutropenia (ANC<1.5x10^9/L) or thrombocytopenia (PLT<75x10^9/L) which failed to revert to ≤grade 1 by the time of the scheduled start of cycle 2, 50% decrease in calculated creatinine clearance, or a diagnosis of osteonecrosis of the jaw. Initially, dose level 1 administered dasatinib at 70 mg by mouth twice daily; however, when the first enrolled patient developed grade 3 pleural and pericardial effusions, the study was modified for dose level 1 to administer dasatinib at 100 mg daily due to a more favorable toxicity profile seen in other clinical trials treating solid tumors and chronic myelogenous leukemia.
In the phase 2 part of the study, patients were treated with the dose of dasatinib found to be safe in combination with zoledronic acid in the phase 1 part of the study. Patients were stratified into two cohorts based on N-telopeptide (NTx) levels obtained prior to initiation of therapy: low NTx levels (< 50nM/mmol), and moderate (50-99nM/mmol) or high (≥100nM/mmol) NTx levels. Treatment was continued until disease progression or until development of unacceptable toxicities. To determine the effect of dasatinib in reversing resistance to hormonal therapy in HR-positive breast cancer, patients who developed disease progression on hormonal therapy were allowed to continue the ‘inactive’ hormonal therapy while receiving dasatinib and zoledronic acid on this trial.

Safety and efficacy

During the phase 1 part of the study, patients were monitored for toxicity every week during the first cycle of therapy and on day 1 (+/- 48 hours) prior to therapy for subsequent cycles. ECG and laboratory assessments were performed weekly during the first cycle. ECG was performed on day 1 (+/- 48 hours) of cycle 2 only. Laboratory assessments were performed on day 1 (+/- 48 hours) prior to therapy during cycle 2 and all subsequent cycles.

During the phase 2 part of the study, patients were monitored for toxicity on day 1 (+/- 48 hours) prior to therapy during subsequent cycles. Physical exams and laboratory assessments were performed monthly on day 1 (+/- 48 hours) prior to initiation of the next cycle of therapy. Measurement of NTx was planned at baseline (up to 7 days prior to therapy), at day 28 (+/- 48 hours) of cycle 1 and at day 28 (+/- 48 hours) of every 3rd cycle of therapy.

Zoledronic acid was dosed based on the serum creatinine level obtained within 2 weeks of drug administration. Toxicity was assessed using the NCI Common Toxicity Criteria (CTC) Scale, version 3.0. Dasatinib was held for treatment related toxicities ≥ grade 2.

Response was assessed every 2 cycles using MD Anderson criteria (39) for bone disease and RECIST v1.1 for non-bone disease. Patients who completed one cycle of therapy were evaluable for response. Response rate (RR) was defined as the percentage of patients achieving a complete response (CR) or partial response (PR); clinical benefit rate (CBR) was defined as the percentage of patients with CR, PR or stable disease (SD) at 6 months. Patients were taken off study if they
had evidence of progressive disease either in bone or non-bone metastases using the response criteria for each disease site.

Statistical design and methods

The phase 1 part of the study was designed to determine the recommended RP2D of dasatinib in combination with zoledronic acid. The phase 2 part of the study aimed at determining the clinical efficacy of the combination of dasatinib and zoledronic on bone disease, and correlate RR, CBR and time to progression (TTP) with tumor marker status. Patients in both phase 1 and phase 2 parts of the trial were included in the efficacy analysis if treated at the RP2D.

The primary efficacy analysis measured disease response in bone. The primary endpoint was the response rate in bone. Interim efficacy monitoring was conducted using a Simon’s two-stage design using the minimax criterion.

It was assumed that dasatinib in combination with zoledronic acid would have a target response rate in bone of 25%. A response rate of 5% or lower would be considered a failure. A Simon’s two stage design was incorporated to close the study due to lack of efficacy if none of the first 15 patients enrolled developed a response to therapy. When at least one of the first 15 patients responded to the treatment, 10 additional patients were entered in the study to reach a total of 25 patients. This design yields a type 1 error rate of 0.05 when the true response rate is 5% and power of 90% when the true response rate is 0.25. By the end of the study, the new regimen would be rejected if response rate in bone was less than or equal to 3 out of 25 patients and would be accepted otherwise. If the trial continued to the second stage (i.e., accrual = 25) and 5 of 25 patients responded for a point estimate of 20.0%, the exact binomial 95% confidence interval would be (6.8%, 40.7%).
Results

Patients

Between 2/1/2008 and 9/17/2012, 25 patients were enrolled and treated on protocol at the three recruiting sites. Patient characteristics are summarized in table 1. Median age was 45 years (range 36-74), 21 patients (84%) had HR-positive disease and 4 patients (16%) had HR-negative disease. No patients had HER2-amplified breast cancer. Sixteen patients (64%) had low (<50nM/mmol), 3 (12%) patients had moderate (50-99nM/mmol), and 4 patients (16%) had high (≥100nM/mmol) NTx level at baseline.

Phase 1: MTD/RP2D

The first patient treated on protocol developed pleural and pericardial effusions in cycle 1 using dasatinib 70 mg twice daily. Following that, the dasatinib dose was changed to 100 mg daily for the 6 patient phase 1 run-in cohort. There were no reported DLTs at this dose level, and the MTD/RP2D was set as dasatinib 100 mg daily in combination with zoledronic acid 4 mg IV on day 1 of a 28 day cycle.

Phase 2

Safety and toxicity

The most common AEs reported were grade 1-2 and included: fatigue in 9/25 patients (36%), rash in 9/25 patients (36%), pain in 9/25 patients (36%) and nausea in 6/25 patients (20%). Grade 3 AEs included anemia in 1/25 patients (4%) and pain in 1/25 patients (4%). There were no grade 4 AEs. The complete list of AEs is summarized in table 2.

Clinical efficacy

Responses in bone were noted after the first 15 patients were enrolled, and the trial moved to stage 2 to enroll 10 additional patients. Twenty-two patients completed at least one cycle of therapy and were evaluable for treatment response in bone (Table 3). By central review assessment, RR in bone was 23% (5/22 patients) and CBR in bone was 36% (8/22 patients) with 3 patients achieving SD ≥6 months as best response. By site review, RR in bone was 27% (6/22 patients) and CBR in bone was 32% (7/22 patients) with 1 patients achieving SD ≥6 months as best response. There were no CR, all responses being confirmed PRs. Of note, one patient left the country after 2 cycles of therapy. She had an unconfirmed PR at that time, and continued to take dasatinib with her local physician outside the country and did not return for follow up scans until she developed progression 8 months later.

Eight patients had non-bone metastases at study entry and were evaluable for overall response in all sites. By central review, overall RR was 13% (1/8 patients with PR), and overall CBR was 38% (3/8 patients) with 2 patients achieving SD ≥ 6 months. Of note, all 3 patients with CBR had
stable disease in bone at the time of visceral progression (which occurred >6 months after starting protocol therapy). The remaining five patients with visceral disease at study entry had progressive disease as best overall response.

Median time to treatment failure was 2.70 months (95% CI: 1.84 – 5.72) in the general cohort, 3.65 months (95% CI: 1.97 – 7.33) in patients with HR-positive breast cancer and 0.70 months (95% CI: 0.30 – NA) in those with HR-negative disease. Factors associated with response in bone were HR-positive disease (p = 0.02), low grade disease (p = 0.006), and high baseline NTx (p=0.036). Prior bone modifying agent use, the type (hormonal therapy, chemotherapy, or combination) and number of prior lines of therapy in the metastatic setting were not associated with clinical benefit in bone to the combination of dasatinib and zoledronic acid.

Fourteen patients with HR-positive disease continued their ‘inactive’ hormonal therapy on protocol and were evaluable for response in bone. Median duration on hormonal therapy prior to progression and enrolment on study for these patients was 4.1 months (2.6 – 34.5 months). By central review, RR in bone was 29% (4/14 patients), and CBR in bone was 43% (6/14 patients) with 2 patients achieving stable disease ≥6 months as best response. By site review, RR in bone was 29% (4/14 patients), and CBR in bone was 36% (5/14 patients) with 1 patient achieving SD≥6 months as best response. The duration of hormonal therapy prior to enrolment was not associated with treatment benefit (p=0.34).

**Response by NTx level at baseline**

Three patients had moderate baseline NTx. One patient completed one cycle of therapy and had progression of disease (PD) as best response in bone, the other two patients withdrew during cycle 1 of therapy. Four patients had high NTx level at baseline, 2 had PR and 2 PD as best response in bone. The two patients with PRs had an 82% and 87% decline in NTx levels at 28 days, compared with 27% decrease and 40% increase in patients with PD. Both patients with an NTx response had not received bisphosphonate therapy for greater than 6 months prior to enrolling on the study. One patient had received pamidronate for 4 months prior to the study, and one started zoledronic acid on protocol.

NTx levels at baseline and at day 28 on protocol were available for 16 patients. Figure 1 shows a waterfall plot of the change in NTx level between baseline and day 28. There was no difference in the change in NTx levels between the patients who achieved a PR and those who had PD (p=0.1033).
Discussion

In this study, the combination of dasatinib 100 mg daily and zoledronic acid was well tolerated. No DLTs were reported at this dose level, and the majority of AEs were grades 1 and 2, consistent with prior studies of dasatinib in solid tumors (40, 41). Responses in bone were noted in 23% of patients by central review, all PRs. These were exclusively in patients with HR-positive breast cancer, with 0/4 patients with HR-negative disease deriving clinical benefit from the combination. A multivariable model for clinical benefit in bone including hormone receptor status and other covariates was not feasible in this study as the sample size was small with only 25 subjects, of whom 7 patients achieved clinical benefit in bone by site review and 8 subjects with clinical benefit in bone by central review. In addition, there were only 4 patients with HR-negative disease, none of whom achieved clinical benefit in bone. A logistic regression model including hormone receptor status would have resulted in a possible quasi-complete separation of data points.

Despite preclinical studies showing that dasatinib can inhibit the growth of triple-negative breast cancer cells (42), results from clinical trials of dasatinib in breast cancer, including our study, have failed to reproduce these results. When used in combination with chemotherapy (30) or with hormonal therapy in this study, clinical efficacy was noted only in HR-positive tumors. This study also aimed at evaluating the ability of dasatinib to reverse endocrine resistance in bone in tumors progressing on hormonal therapy. Patients were allowed to continue hormonal therapy and zoledronic acid upon progression and dasatinib was added to the treatment regimen. In this subgroup of patients, PRs in bone were noted in 29% of patients, CBR in bone in 43% of patients. This provides clinical evidence suggesting that dasatinib may be able to overcome endocrine resistance in bone; however, confirmation is needed by larger, randomized clinical trials. In addition, the inhibition of pathways shown to be important in the development of bone metastasis suggested that dasatinib may be more effective at targeting bone metastases compared to visceral metastases (43). Further investigation of optimal dasatinib dosing for both bone and/or visceral metastasis is warranted. In this study, we observed that 3 patients were taken off study due to visceral progression at a time whereas bone disease remained stable. Similar findings were reported in a phase 2 study evaluating dasatinib vs placebo added to exemestane in
metastatic breast cancer resistant to non-steroidal aromatase inhibitors. In that study, the subgroup of patients with symptomatic bone metastases derived the greatest CBR and PFS (32).

The evaluation of tumor response in bone remains challenging and patients with bone only disease are often excluded from participating in clinical trials. These limitations signaled the need for validation of bone resorption biomarkers as markers of response in patients with skeletal metastasis. NTx, a marker of bone resorption, was found to be elevated in the majority of breast cancer patients with bone metastases (44). NTx levels have been correlated to clinical outcomes in breast cancer patients with bone predominant disease, with high and moderate levels associated with a significant increase in SREs, progression of disease and reduced benefit from second line hormonal therapy (44-46). The reduction in NTx levels following bisphosphonate therapy has been shown to translate into a significant reduction in fractures and progression of disease (47, 48). In this study, the required number of patients with moderate and high NTx levels needed to be recruited was not reached to evaluate NTx as a predictive or prognostic biomarker; it was rather evaluated as a correlative biomarker. Of the 4 patients with high NTx levels at baseline, the 2 patients with PR had a more impressive decrease in NTx levels compared to the 2 patients with PD. These numbers hint at the possibility of NTx being a predictive biomarker, but are too small to derive conclusions.

Despite multiple studies evaluating dasatinib in breast cancer, biomarkers identifying the optimal patient population that will derive the greatest benefit from this agent have not been identified. A study evaluating gene-signature guided dasatinib therapy in unselected breast cancer patients was closed for futility (49, 50). Paul et al reported a significant increase in PFS for dasatinib in combination with letrozole (20.1 months) compared to letrozole alone (9.9 months) in patients with metastatic HR-positive breast cancer. In that study, no aromatase inhibitor use in the metastatic setting was allowed, <5% of patients in each arm had received Tamoxifen for metastatic disease, and approximately 40% of patients had de novo metastatic disease. In addition, approximately 70% of patients had bone predominant metastatic disease (31). In contrast, studies of dasatinib in combination with fulvestrant or exemestane in metastatic breast cancer patients who had progressed on aromatase inhibitor therapy did not report any improvement in PFS (31, 32). Our results as well as previous studies demonstrate that dasatinib seems to have clinical activity in early metastatic HR-positive, bone predominant breast cancer.
The SWOG S0622 study evaluating two schedules of dasatinib in bone predominant metastatic breast cancer has been completed and is awaiting publication. This larger study in a similar patient population to ours should provide a better indication of efficacy and biomarker analysis for dasatinib monotherapy. The SWOG S0622 study did not allow continuation of hormonal therapy beyond progression, and thus will not address the issue of endocrine resistance reversal seen in a proportion of our patients on this study.

In conclusion, the combination of dasatinib and zoledronic acid was well tolerated in breast cancer patients with bone predominant metastatic disease. There appears to be a clinical benefit for bone metastases in patients with HR-positive, low grade disease with elevated NTx levels at baseline. The role of dasatinib in the treatment of metastatic HR-positive breast cancer today is unclear, especially with the recent approvals of mTOR/PI3K inhibitors and CDK 4/6 inhibitors for this disease. Both these agents have been reported to cause myelosuppression, a side effect that can limit their use in patients with bone predominant disease. The efficacy and safety profile of dasatinib may make it an attractive option for HR-positive metastatic breast cancer patients who often will receive multiple lines of therapy before requiring cytotoxic chemotherapy. Further investigation of dasatinib for metastatic bone predominant breast cancer may be warranted as a potentially effective and well tolerated therapy.

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References


Figure Legend:

Figure 1. Waterfall Plot of the Change in NTx Levels between Baseline and Day 28.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patients (N)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Median Age, (Range)</td>
<td>45, (36-74)</td>
</tr>
<tr>
<td>Phase 1</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Hormone receptor</td>
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<tr>
<td>Positive</td>
<td>21 (84%)</td>
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<tr>
<td>Negative</td>
<td>4 (16%)</td>
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<tr>
<td>Grade</td>
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</tr>
<tr>
<td>1</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>2</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>3</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Initial Sites of Metastases</td>
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</tr>
<tr>
<td>Bone Only</td>
<td>17 (68%)</td>
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<tr>
<td>Lung</td>
<td>5 (20%)</td>
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<tr>
<td>Lymph Nodes</td>
<td>4 (16%)</td>
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<tr>
<td>Liver</td>
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<tr>
<td>Prior Endocrine Therapy for Metastatic Disease</td>
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<tr>
<td>0</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>1</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>≥2</td>
<td>3 (12%)</td>
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<tr>
<td>Prior Chemotherapy for Metastatic Disease</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>1</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>NTx at baseline</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>16 (64%)</td>
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<tr>
<td>Moderate</td>
<td>3 (12%)</td>
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<tr>
<td>High</td>
<td>4 (16%)</td>
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<tr>
<td>Reason for discontinuation*</td>
<td></td>
</tr>
<tr>
<td>Progression of Disease</td>
<td>22 (88%)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>2 (8%)</td>
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*1 patient left the country and was taken off the study, had unconfirmed PR as best response at the time of study discontinuation
Table 2. Adverse Events at Recommended Phase 2 Dose

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>N=25 patients</th>
<th>Grade 1-2 events</th>
<th>Grade 3-4 events</th>
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<tbody>
<tr>
<td><strong>Hematological events</strong></td>
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<tr>
<td>Anemia</td>
<td>2</td>
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<td>1</td>
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<td>Thrombocytopenia</td>
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<tr>
<td><strong>Non hematological events</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Respiratory</td>
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<td>Vasomotor symptoms</td>
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<td>Constipation</td>
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<td>Xerostomia</td>
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</tr>
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<td>Infections (non neutropenic)</td>
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<td>Edema</td>
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<tr>
<td>Paresthesia</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>8</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3. Response to therapy in bone

<table>
<thead>
<tr>
<th>Response in bone</th>
<th>Central review</th>
<th>Site review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (CR+PR)</td>
<td>5/22 (23%)</td>
<td>6/22 (27%)</td>
</tr>
<tr>
<td></td>
<td>ITT* = 5/25 (20%)</td>
<td>ITT = 6/25 (24%)</td>
</tr>
<tr>
<td>SD≥ 6 months</td>
<td>3/22 (13%)</td>
<td>1/22 (5%)</td>
</tr>
<tr>
<td></td>
<td>ITT = 3/25 (12%)</td>
<td>ITT = 1/25 (4%)</td>
</tr>
<tr>
<td>CBR (CR+PR+SD≥6 months)</td>
<td>8/22 (36%)</td>
<td>7/22 (32%)</td>
</tr>
<tr>
<td></td>
<td>ITT = 8/25 (32%)</td>
<td>ITT = 7/25 (28%)</td>
</tr>
</tbody>
</table>

*ITT= intent to treat analysis of all patients
Table 4. Response to therapy in bone for patients who progressed on hormonal therapy and continued the same therapy with dasatinib

<table>
<thead>
<tr>
<th>Response in bone</th>
<th>Central review</th>
<th>Site review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (CR+PR)</td>
<td>4/14 (29%)</td>
<td>4/14 (29%)</td>
</tr>
<tr>
<td>SD≥ 6 months</td>
<td>2/14 (14%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td>CBR (CR+PR+SD≥ 6 months)</td>
<td>6/14 (43%)</td>
<td>5/14 (36%)</td>
</tr>
</tbody>
</table>
Figure 1. Waterfall Plot of the Change in NTx Levels between Baseline and Day 28

PR: Partial Response; PD: Progressive Disease

*NTX levels at day 28 were not available for 1 patient with PR and 3 patients with SD ≥6 months by central review. These patients were not included in the waterfall plot.
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