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Phase I study of erlotinib and metformin in metastatic triple negative breast cancer

Kathleen Fenn^a, Matthew Maurer^b, Shing M. Lee^c, Katherine D. Crew^a, Meghna S. Trivedi^a,
Melissa K. Accordino^a, Dawn L. Hershman^a, Kevin Kalinsky^a

^aDepartment of Medicine, Columbia University Irving Medical Center, 161 Fort Washington Avenue, New York NY 10032;

^bBristol-Myers Squibb, 100 Nassau Park Blvd #300, Princeton, NJ 08540;

^cDepartment of Biostatistics, Mailman School of Public Health, Columbia University, 722 W 168th St, New York, NY 10032

Abstract

Purpose: Epidermal growth factor receptor (EGFR) is frequently overexpressed in metastatic triple negative breast cancer (mTNBC). One strategy for overcoming resistance to EGFR inhibition is concomitant inhibition of downstream signaling. The antidiabetic drug metformin inhibits both MAPK and PI3K/mTOR pathway signaling. We evaluated the combination of erlotinib and metformin in a phase 1 study of patients with mTNBC.

Patients and Methods: Patients with mTNBC who had received at least one prior line of therapy for metastatic disease were eligible. Erlotinib dose was fixed at 150 mg daily. Metformin dose escalation was planned according to a 3+3 design. Dose-limiting toxicities (DLT) were assessed during the first five weeks of therapy. The primary objective was to determine the maximum tolerated dose (MTD) of metformin with fixed dose erlotinib. Secondary endpoints were response rate, stable disease rate, and progression free survival (PFS).

Results: Eight patients were enrolled. Median number of prior therapies for metastatic disease was 2.5 (range 1–6). No DLT events were reported during the DLT assessment period. A majority of adverse events were grade 1/2. Grade 3 diarrhea despite maximum supportive care required dose reduction of metformin in one patient. Grade 3 rash led to study withdrawal in one patient. No grade 4 AEs were reported. The best observed response was stable disease in two patients (25%). Median PFS was 60 days (range 36–61).

Corresponding Author: Kevin Kalinsky, MD, MS, Assistant Professor of Medicine, Division of Hematology & Oncology, Columbia University Irving Medical Center, 161 Fort Washington, Room 1069, New York, New York 10032, Telephone: 212-305-1945, Fax: 212-305-0178 kk2693@columbia.edu.

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DATA AVAILABILITY

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conclusion: Erlotinib and metformin were well tolerated in a population of pre-treated mTNBC patients but did not demonstrate efficacy in this population.

MicroAbstract

There is an urgent need to develop more effective therapies to treat metastatic triple negative breast cancer (mTNBC). Preclinically, the combination of erlotinib and metformin has shown efficacy in TNBC cell lines and mouse models. In this phase I study, 8 patients with mTNBC who had received at least one prior therapy for metastatic disease were treated with the combination of erlotinib and metformin; dose escalation of metformin was performed according to a 3+3 design. Erlotinib and metformin were well tolerated with no dose-limiting toxicities, but no objective responses were seen in the study group.

Keywords

metastatic breast cancer; triple negative breast cancer; targeted therapy; erlotinib; metformin

Introduction:

Triple negative breast cancer (TNBC) is associated with a comparatively aggressive clinical course and poorer prognosis compared to other breast cancer subtypes.^{1, 2} While the IMpassion130 trial provides support for the benefit of first-line chemoimmunotherapy approaches in PD-L1 positive patients, eventually patients with metastatic triple negative breast cancer (mTNBC) progress on first-line therapy.³ Cytotoxic chemotherapy remains the standard of care for second-line systemic treatment, and no molecularly targeted therapies are currently approved for clinical use in mTNBC. Response rates to conventional chemotherapy are low. There remains an unmet need for more effective and less toxic regimens in this population.

Activating mutations in the epidermal growth factor receptor (EGFR) are relatively rare in TNBC, ranging from 0 to 11 percent in published studies.⁴⁻⁶ However, the rate of EGFR overexpression in TNBC is considerably higher at approximately 30 to 60 percent, depending on the antibody used.⁷⁻⁹ EGFR overexpression is associated with high-grade disease in breast carcinomas and is associated with significantly worse overall survival in patients with operable TNBC.^{7, 10} EGFR copy number variations are associated with EGFR overexpression in TNBC and are predictive of poorer disease-free survival.¹¹ To date, however, there is only modest evidence for the efficacy of EGFR-directed agents in mTNBC.¹² For example, the chimeric EGFR-targeted monoclonal antibody cetuximab did not significantly improve outcomes when added to platinum agents in two separate phase II studies, though the addition of cetuximab was associated with a numerically higher but nonsignificant increase in overall response rate in the larger BALI-1 study.^{13, 14}

One potential strategy for overcoming resistance to EGFR inhibition is concomitant inhibition of downstream signaling. Metformin is a liver kinase B1 (LKB1)-dependent AMP-activated protein kinase (AMPK) activator that inhibits both mitogen-activated protein kinase (MAPK) and Akt pathways. As a single agent, metformin has been shown to inhibit breast cancer cell growth *in vitro* and to reduce levels of EGFR in TNBC cell lines.^{15, 16}

Preclinical studies performed at our institution demonstrate that the combination of the EGFR inhibitor erlotinib with metformin synergistically induces apoptosis in TNBC cell lines.¹⁷ In the same study, our group showed that dual therapy with erlotinib and metformin decreases tumor burden in mouse xenograft models of PTEN-null EGFR-amplified basal-like breast cancer (BC), further supporting the potential clinical activity with this regimen. These data serve as the rationale for evaluating the safety and tolerability of the combination of erlotinib and metformin in a phase 1 study of patients with mTNBC.

Subject and Methods:

Major eligibility criteria

Patients between 18 and 80 years of age with a confirmed diagnosis of mTNBC were eligible. Patients with HER2 negative disease by ASCO-CAP guidelines and ER positive disease with immunohistochemistry (IHC) staining of 1 to 9 percent were eligible regardless of PgR status.¹⁸ Prior diagnosis of ER positive, HER2 negative disease was allowed, provided that ER expression on the patient's most recent biopsy was <10%. Patients must have received at least one prior treatment for metastatic disease. Measurable or non-measurable metastatic disease per RECIST 1.1 criteria was allowed. Participation required an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2, life expectancy of greater than 12 weeks, absolute neutrophil count (ANC) $\geq 1250/\text{mm}^3$, platelets $\geq 75,000/\text{mm}^3$, Hgb ≥ 8.5 g/dL, total bilirubin ≤ 1.5 x the upper limit of normal (ULN), AST and ALT levels ≤ 3.0 x ULN, alkaline phosphatase ≤ 2.5 ULN, and estimated creatinine clearance ≥ 60 mL/min (Cockcroft-Gault formula). Patients with a history of central nervous system (CNS) metastases or cord compression must have remained clinically stable and off corticosteroids for at least 6 weeks since completion of definitive treatment. Concomitant use of medications known to be inducers or inhibitors of CYP3A4 was not permitted. Patients with diabetes or fasting blood glucose level ≥ 126 mg/dL were ineligible. Patients who had previously received metformin or EGFR-targeted therapy were ineligible. Patients who had used tobacco or nicotine products or medications during the previous three months were ineligible given the potential effects on erlotinib drug levels.¹⁹ Patients with a condition thought to increase the risk of metformin-associated acidosis were ineligible; examples of such conditions included New York Heart Association class III or IV congestive heart failure, history of acidosis of any type, or regular intake of three or more alcoholic beverages per day.

Study design and treatment

The primary aims were to determine the maximum tolerated dose (MTD) of metformin in combination with a fixed dose of erlotinib at 150 mg daily and to determine the clinical benefit at the combined MTD. The MTD was defined as the highest dose level of metformin at which ≤ 1 of a maximum of 6 patients experienced a dose limiting toxicity (DLT). Clinical benefit was defined as partial response or stable disease per RECIST 1.1 at the time of the second tumor response assessment (126 $\pm$ 6 days after cycle 1 day 1). The primary endpoint was dose limiting toxicity (DLT). Secondary endpoints were response rate, stable disease rate, and progression free survival (PFS).

The dose of erlotinib was fixed at 150 mg daily, the FDA-approved dose for patients with EGFR mutant non-small cell lung cancer. Two doses of metformin were evaluated, 850 twice daily and 850 three times daily (Table 1). Metformin dose escalation was performed according to a 3+3 design. Given the frequent incidence of gastrointestinal upset in patients initiating treatment with metformin, the metformin dose was uptitrated to the assigned dose level. One dose de-escalation to 500 mg twice daily was allowed. The study drugs were administered in 21-day continuous treatment cycles. Patients were removed from the protocol in the event of disease progression, DLT after dose reduction to the lowest dose level, or in the event of withdrawal of consent. DLTs were assessed during the first five weeks of therapy, given that the metformin dose was uptitrated after week 1. DLTs were defined as any grade 3 non-hematologic toxicity that the patient did not recover from or was not reversed with supportive care within 4 days, or any grade 4 or higher hematologic or non-hematologic toxicity deemed possibly, probably, or definitely related to study drugs.

The study was approved by the institutional review board at Columbia University Irving Medical Center (CUIMC). Informed consent was obtained from all participants in the study. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01650506) identifier was [NCT01650506](https://clinicaltrials.gov/ct2/show/study/NCT01650506).

Evaluations

Screening assessments were performed within 14 days prior to study enrollment and included a history and physical exam, performance status assessment, and laboratory assessment (beta-HCG, complete blood count, comprehensive metabolic panel, fasting glucose and fasting insulin). Within seven days prior to study initiation, fasting insulin and lactate were drawn.

Response assessments were planned every three cycles (63 $\pm$ 3 days) with a CT chest/abdomen/pelvis with oral and intravenous contrast and a bone scan. For patients with available tissue, molecular profiling using commercial CLIA-approved assays was performed; panels included FoundationOne®, Caris Target Now/Molecular Intelligence®, and Columbia Combined Cancer Panel (CCCP).^{20–22}

Statistical considerations

Descriptive statistics including medians, ranges, and percentages were calculated for variables including demographic and clinical parameters, safety events, and response rates. Progression-free survival, defined as date of registration to date of first observation of progressive disease, discontinuation of study drugs due to toxicity, or death due to any cause, was estimated using the Kaplan-Meier method. Response evaluation was performed according to RECIST 1.1 criteria for patients with measurable disease.

Results:

Patient characteristics

Between March 2013 and May 2015, nine patients were screened. Eight patients met eligibility criteria and were enrolled. One patient was deemed ineligible due to uncontrolled brain metastases. Three patients were assigned to receive metformin at 850 mg BID and five

patients were assigned to receive metformin at 850 mg TID. Based on an expected maximum tolerated metformin dose of 850 mg TID, the original study design anticipated enrollment of 9 patients in the dose escalation phase 1 portion and an additional 8 patients in the extended phase 1 portion. If one patient met the primary endpoint of clinical benefit among the 14 patients treated at the MTD, the regimen would be considered worthy of further investigation.²³ However, the accrual rate was slower than anticipated and the study stopped early due to funding completion. Baseline patient characteristics, including sites of disease and previous lines of therapy, are summarized in Table 2. The median number of prior therapies received for metastatic disease was 2.5 (range 1–6). All patients had ER-negative disease. Three patients (37.5%) had PgR-positive disease; PgR expression levels for these patients ranged from 3 to 40 percent. The most common sites of metastatic disease at the time of enrollment were lung (62.5%), lymph nodes (50%), and bone (25%). One patient had brain metastases. Median duration of the most recent treatment regimen prior to study enrollment was 3.26 months (range 0.49–8.74).

Laboratory assessments

Baseline median fasting glucose was 91.5 mg/dL (range 69–116) and median fasting insulin was 11 uIU/mL (range 2–30). In order to monitor for metformin-induced lactic acidosis, venous lactate levels were measured at baseline and periodically during the study. Median baseline lactate was 1.1 mmol/L (range 0.5–2.8). One patient developed an elevated lactate to 2.9 mmol/L (grade 1) on day 28 which resolved without intervention to 1.7 mmol/L when rechecked on day 30. Study drugs were continued during this event. No other incidents of lactic acidosis were observed.

Safety data

No DLTs were reported in either of the dose cohorts during the DLT assessment period. In Table 3, any adverse events (AE) at least possibly related to treatment occurring in two or more patients and any grade 3 AE are listed. No grade 4 AEs were reported. The combination of erlotinib and metformin was generally well-tolerated. The majority of AEs were grade 1 or 2 at both dose levels of metformin. The most common AEs were rash (88%), weight loss (75%), dry skin (75%), diarrhea (75%), nausea (63%), vomiting (50%), and dry mouth (50%).

Grade 3 toxicities were reported in three patients (38%), one at metformin 850 mg BID and two at 850 mg TID. Grade 3 hyponatremia deemed possibly related to the study drugs occurred in one patient and resolved after administration of intravenous normal saline. The same patient experienced grade 3 rash starting in cycle 1; the rash was refractory to oral steroids, leading to study withdrawal after cycle 2. The patient was censored at the time the study drugs were held on day 43. Skin biopsy confirmed a hypersensitivity reaction; it was unclear whether erlotinib or metformin was the inciting agent.

Grade 3 diarrhea occurred in 2 patients (25%). In one of these patients, diarrhea despite maximum supportive care occurred during cycle 2 and necessitated dose reduction of metformin from 850 mg TID to 850 mg BID. The patient was censored at the time of the dose reduction on day 35. All patients received education from the research nursing staff at

the start of treatment on the use of anti-diarrheal medications, such as loperamide, to manage medication-related diarrhea. The maximum documented number of loperamide tablets that a patient took in a 24-hour period was 8.

Efficacy

Median progression-free survival was 60 days (range 36–61). Six patients (75%) experienced progression of disease either prior to or at the time of the first scheduled response assessment (Figure 1). The one patient with brain metastases was noted to have progression of disease in the brain at the time of the first response assessment. No objective tumor responses were observed. Per RECIST v1.1, the best observed response was stable disease in two patients (25%).

Of the two patients with stable disease, one patient had stable disease at the time of the first assessment but was later found to have progression of a bony metastasis on MRI on day 79, prompting study withdrawal. The second patient withdrew from the study after 57 days due to grade 3 rash consistent with hypersensitivity reaction. This patient had an oncologic history notable for metastatic renal cell carcinoma to the liver, previously treated with sunitinib, followed by everolimus at progression of disease. While on everolimus, she was diagnosed with stage I TNBC, initially treated with partial mastectomy and XRT. Sixteen months after her BC diagnosis, she was diagnosed with a mTNBC to her liver. She stopped everolimus and was treated with paclitaxel/bevacizumab. Progression of disease in the liver was noted after 2.1 months, and she began treatment with gemcitabine/carboplatin/bevacizumab. She remained on this regimen for 4.8 months at which point gemcitabine was discontinued due to persistent grade 2–3 thrombocytopenia. She received one dose of cisplatin/bevacizumab but thrombocytopenia persisted and she subsequently enrolled on our study. After she was taken off study and censored due to toxicity, her disease remained stable off any treatment for an additional 37.2 months, at which point she had biopsy-confirmed recurrence of TNBC in a paratracheal lymph node.

Immunohistochemical and mutational profiling

Tumor tissue for five enrolled patients was sent for extended IHC-based protein expression analysis, mutational analysis, or both at some point during the treatment course. PTEN expression was assessed by IHC for three patients on pre-treatment biopsies (Caris); of these, one patient had intact PTEN expression and two demonstrated loss of expression. EGFR amplification by FISH was assessed in one patient and was negative (Caris). Tumor mutational profiling on pre-treatment tissue was performed for three patients. In one patient, analysis identified mutations in *PIK3CA*, *TP53* and *NFI* along with variants of unknown significance in *CREBBP* and *RAD50* (CCCP). In another, only a *TP53* mutation was identified (FoundationOne). In the third patient, no mutations were identified based on a limited panel (*PIK3CA*, *c-KIT*, *BRAF*, *KRAS*, *NRAS*; Caris). Among these patients, three had progression of disease at the time of the first response assessment. One patient had stable disease but was removed from study due to grade 3 rash (see Efficacy section); this patient was found to have *TP53* mutation and PTEN loss (FoundationOne, Caris).

Extended IHC analysis and limited mutational profiling was performed for one patient on post-treatment tissue. IHC analysis demonstrated intact PTEN expression (Caris). No pathogenic mutations were identified. This patient had progression of disease at the time of first response assessment.

Discussion:

This phase I study evaluated the EGFR inhibitor, erlotinib, in combination with the biguanide antidiabetic agent, metformin, in patients with pre-treated mTNBC. Overall, we found that the combination was fairly well tolerated in this population with no unexpected toxicities.

The adverse events reported in this study correspond to toxicities commonly seen with erlotinib and metformin when used as monotherapy. Rash is the most common adverse event associated with erlotinib, with rates of up to 85% reported in clinical studies.^{24, 25} Rash is infrequently associated with metformin.²⁶ All patients in this study reported rash, though only one patient had grade 3 rash. That patient had a biopsy-proven hypersensitivity reaction which prompted treatment discontinuation; it was not clear whether erlotinib or metformin was the culprit drug.

After rash, diarrhea is the most common adverse effect associated with erlotinib.²⁷ Additionally, gastrointestinal distress is the most common toxicity associated with metformin use.²⁸ Symptoms may be more severe at the onset of treatment and can include nausea, vomiting, diarrhea, bloating, and abdominal pain. To minimize gastrointestinal side effects, patients were initially started on a metformin dose lower than the intended dose level, which was uptitrated after week 1 if tolerated. Moreover, the protocol provided detailed recommendations regarding supportive care and drug administration to minimize gastrointestinal side effects. Despite these measures, all patients reported diarrhea. Compared to the lower dose level, a higher proportion of patients receiving the maximum dose of metformin experienced vomiting, anorexia, and weight loss. Two patients in the higher dose group reported grade 3 diarrhea, one of whom required dose reduction of metformin after the DLT period.

Toxicities were similar to those reported in a phase I-II trial of erlotinib and metformin in patients with metastatic non-small cell lung cancer.²⁹ In that study, twelve patients received metformin at a maximum daily dose of 2000 mg plus erlotinib at 150 mg daily; grade 3 diarrhea was reported as a DLT at a metformin dose of 2000 mg daily. These results suggest that additive gastrointestinal toxicity may prevent uptitration of metformin when co-administered with erlotinib, further emphasizing the importance of early and aggressive supportive care should this combination be explored in future studies.

With regards to efficacy, no clinical responses were seen, as defined by the protocol. One patient who was removed from study for grade 3 rash experienced stable disease off treatment for over three years after discontinuation of the study regimen. Subsequent IHC analysis on a pre-treatment biopsy revealed loss of PTEN expression. Notably, in our

group's preclinical work, PTEN loss was found to sensitize BC cells to the combination of erlotinib and metformin.¹⁷

Metformin as monotherapy has shown activity against BC cell lines in preclinical studies, prompting interest in its potential clinical role.^{15, 30} Furthermore, population-based studies have demonstrated an association between metformin use in diabetic postmenopausal women and a lower incidence of invasive BC.³¹ Proposed mechanisms of action for the activity of metformin include indirect activation of AMPK signaling as well as improvement in metabolic parameters such as insulin, glucose, leptin, and C-reactive peptide.³² Since metformin is orally administered, widely available, and generally well tolerated, it has been an attractive agent for clinical investigation. Unfortunately, clinical studies of metformin in patients with an established diagnosis of invasive BC have been disappointing thus far, particularly in TNBC.³³ In the metastatic setting, the randomized phase II MYME trial did not show an improvement in PFS with the addition of metformin to chemotherapy in patients with HER2-negative metastatic BC.³⁴ Metformin continues to be investigated in combination with other agents, particularly in overweight and obese patients in whom its metabolic effects may be most beneficial; however, the combination of metformin, exemestane, and everolimus was recently shown to have only modest efficacy in a phase II trial of overweight and obese patients with hormone receptor-positive metastatic BC.³⁵ Results are pending from MA.32, a randomized trial of metformin versus placebo in early stage BC. This study is anticipated to yield important data on the potential benefit of adjuvant metformin in HER2- BC.³⁶ Meanwhile, the lack of clinical response seen in our study of metformin with erlotinib further adds support to the idea that metformin-based approaches may be less efficacious than previously anticipated in metastatic disease.

Our study adds to a body of literature suggesting limited efficacy for EGFR inhibition in metastatic BC. With regards to small molecule inhibitors, a phase II study of erlotinib in combination with bevacizumab demonstrated minimal activity in unselected patients with pretreated metastatic BC, as did a separate study of gefitinib monotherapy in this population.^{37, 38} In the former study, the level of EGFR expression was not predictive of response to therapy. The combination of EGFR-targeted monoclonal antibodies with chemotherapy has led to somewhat more promising results. Notably, the BALI-I study yielded a nearly double, though statistically nonsignificant, increase in overall response rate when cetuximab was added to cisplatin in patients with mTNBC (20% vs 10%).¹⁴ In another phase II study, cetuximab in combination with carboplatin and irinotecan yielded an overall response rate of 49% in patients with mTNBC.³⁹ It may be worthwhile for future studies to investigate whether newer generation EGFR tyrosine kinase inhibitors combine with metformin with limited toxicity and potentially improved clinical benefit. It is also possible that the efficacy of erlotinib and metformin might be augmented by the addition of cytotoxic chemotherapy, though this must be weighed against the likelihood of increased toxicity.

Unfortunately, there are no validated predictive biomarkers for response to EGFR-targeted therapy in BC. Similar to previous studies of EGFR inhibition in mTNBC, inclusion criteria for this study did not require evidence of EGFR overexpression. EGFR gene amplification was assessed by FISH for only one patient prior to study enrollment and was negative. While it is possible that the combination of erlotinib and metformin may be effective in a subset of

TNBC patients with alterations in the pathways of interest, our small sample size limits the ability to identify predictive markers in this trial.

There are several limitations to our study. There was slow accrual to this trial, and the study was stopped early due to funding completion. Accordingly, the limited sample size precluded the formal assessment of the potential for clinical benefit as well as further pharmacodynamic studies. Nevertheless, our study offers important data on the safety and efficacy of the study drug combination.

Conclusions:

In summary, this phase I study demonstrated that the combination of erlotinib and metformin was fairly well tolerated in a population of pre-treated patients with mTNBC. The most common AEs were rash and gastrointestinal toxicity; no unexpected AEs occurred. Insufficient clinical activity was seen to justify further investigation of this combination alone in an unselected population of patients with mTNBC.

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Clinical Practice Points:

- The epidermal growth factor receptor (EGFR) is frequently overexpressed in metastatic triple negative breast cancer (mTNBC). However, EGFR monotherapy has shown limited efficacy in this disease.
- Resistance to EGFR inhibition may be overcome by concomitant inhibition of downstream signaling. The antidiabetic drug metformin inhibits both the MAPK and PI3K/mTOR pathways. Previous preclinical studies have shown that the combination of erlotinib and metformin is effective in both TNBC cell lines and mouse models.
- We conducted a phase I study of erlotinib and metformin in pretreated mTNBC patients.
- We demonstrated that this combination is safe at a dose of erlotinib 150 mg daily and metformin 850 mg three times daily. The most common adverse events were rash and gastrointestinal toxicity.
- However, no objective responses were seen in our study cohort.
- Our findings do not support further investigation of this treatment combination alone in an unselected population of patients with mTNBC.

Figure 1: Swimmer plot depicting time on study, response assessments, and toxicity events for each patient enrolled. Green bars denote patients assigned to metformin 850 mg BID; blue bars denote patients assigned to metformin 850 mg TID.

*Color should be used for figure in print.

Table 1:

Dosing of Metformin and Erlotinib

Dose level	Metformin [total daily dose]	Erlotinib
-1	500 mg daily week 1, 500 mg twice daily thereafter [1000 mg]	150 mg daily
0	850 mg daily week 1, 850 mg twice daily thereafter [1700 mg]	150 mg daily
1	850 mg daily week 1, 850 mg twice daily week 2, 850 mg three times daily thereafter [2550 mg]	150 mg daily

Table 2:

Clinical and Pathologic Features

	N=8
Age – median (range)	48 (37–79) years
BMI – median (range)	27.03 (20.97–34.18) kg/m ²
ECOG PS	
0	2 (25%)
1	6 (75%)
Race or ethnic group	
Non-Hispanic white	4 (50%)
Black or African American	2 (25%)
Hispanic	1 (12.5%)
Unknown	1 (12.5%)
Number of prior metastatic regimens	
2	4 (50%)
>2	4 (50%)
Sites of disease	
Lung	5 (62.5%)
Lymph node	4 (50%)
Bone	2 (25%)
Liver	1 (12.5%)
Brain	1 (12.5%)
HR status	
ER–/PgR+	3 (37.5%)
ER–/PgR–	5 (62.5 %)

Table 3:

Adverse Events

Event	Metformin 850 mg BID n=3			Metformin 850 mg TID n=5		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Rash	1 (33)	1 (33)	1(33)	3 (60)	2 (40)	--
Weight loss	1 (33)	--	--	3 (60)	2 (40)	--
Dry skin	--	1 (33)	--	5 (100)	--	--
Diarrhea	--	3 (100)	--	--	3 (60)	2 (40)
Nausea	1 (33)	1 (33)	--	4 (80)	--	--
Vomiting	1 (33)	--	--	3 (60)	--	--
Dry mouth	1 (33)	--	--	2 (40)	--	--
Dysgeusia	1 (33)	--	--	2 (40)	--	--
Increased creatinine	2 (66)	--	--	1 (20)	--	--
Fatigue	--	1 (33)	--	2 (40)	--	--
Anorexia	1 (33)	--	--	1 (20)	1 (20)	--
Hyponatremia	--	--	1 (33)	--	--	--
Flatulence	1 (33)	--	--	1 (20)	--	--
Sore throat	1 (33)	--	--	--	--	--
Increased bilirubin	1 (33)	--	--	1 (20)	--	--
Dyspepsia	1 (33)	1 (33)	--	1 (20)	--	--
Alopecia	1 (33)	--	--	1 (20)	--	--
Mucositis	--	--	--	2 (40)	--	--
Abdominal pain	--	--	--	2 (40)	--	--
Increased ALT	--	--	--	2 (40)	--	--