Published in final edited form as:

Cancer Chemother Pharmacol. 2013 January ; 71(1): 63–72. doi:10.1007/s00280-012-1977-9.

Phase I trial of exemestane in combination with metformin and rosiglitazone in non-diabetic obese postmenopausal women with hormone receptor–positive metastatic breast cancer

Francisco J. Esteva^a, Stacy L. Moulder^a, Ana M. Gonzalez-Angulo^a, Joe Ensor^b, James L. Murray^a, Marjorie C. Green^a, Kimberly B. Koenig^a, Mong-Hong Lee^c, Gabriel N. Hortobagyi^a, and Sai-Ching Yeung^{d,e}

^aDepartment of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

^bDepartment of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

^cDepartment of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

^dDepartment of Emergency Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

^eDepartment of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Purpose—Obese women with breast cancer have worse prognosis than women with normal body mass index. Endocrine therapy resistance is in part mediated by insulin resistance in obese women with breast cancer. We investigated the tolerability and pharmacokinetics of exemestane in combination with metformin and rosiglitazone in non-diabetic overweight and obese postmenopausal women with hormone receptor positive metastatic breast cancer.

Methods—Patients had previously received chemotherapy and endocrine therapy for breast cancer. Exemestane was given as 25 mg orally per day. Metformin (M) and rosiglitazone (R) were given twice daily. Dose level 1 consisted of M 1500 mg/day and R 6 mg/day. Dose level 2 consisted of M 2000 mg/day and R 8 mg/day. Plasma concentrations of exemestane were measured on days 1, 8, and 15.

Results—Twenty patients were enrolled. Fourteen patients received exemestane, metformin and rosiglitazone. Six patients received exemestane with metformin only (2000 mg/day). Both regimens were well tolerated at the highest doses tested, and there were no notable changes in plasma exemestane levels. Six patients (30%) had stable disease for 6 months or longer.

Conclusions—Oral daily administration of exemestane (25 mg) and metformin (2000 mg), with and without rosiglitazone (8 mg) daily was well tolerated. Exemestane pharmacokinetics were not altered by metformin and rosiglitazone.

Correspondence: Francisco J. Esteva, MD, PhD, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1354, Houston, Texas 77030, USA. fjesteva@mdanderson.org. Phone: +1-713-792-2817.

DISCLOSURES: NONE

Conflict of interest: None. The Susan G. Komen for the Cure and the National Institutes of Health had no influence on the design, conduct and interpretation of the results of this study.

Keywords

Breast neoplasm; exemestane; metformin; rosiglitazone; phase I trial

Introduction

Obesity is associated with an increased risk of developing postmenopausal breast cancer and is an independent prognostic factor in patients who have been diagnosed with breast cancer [23]. Up to 50% of postmenopausal breast cancer deaths in the United States may be linked to obesity [33]. The effect of obesity on breast cancer risk is mediated by both insulin resistance and estrogen metabolism [35]. Estrogens, both exogenous and endogenous, are etiologic factors for breast cancer [40]. Estrogens stimulate cell proliferation through nuclear receptor-mediated gene regulation as well as other effects that increase mutation rates and aneuploidy. The biosynthesis of estrogens in adipose tissue in postmenopausal women is particularly important in the pathogenesis of estrogen receptor-positive breast carcinoma [30]. Hyperinsulinemia is associated with increased risk of breast cancer [24]. Both retrospective and prospective observational studies support a potential role of insulin-like growth factors (IGFs) in breast carcinogenesis [16, 19, 31]. Obese patients also have elevated serum concentrations of leptin (an adipokine), which contribute to their increased risk of developing breast cancer compared with lean patients with normal leptin levels [15]. A high serum level of adiponectin (another adipokine) is a risk factor for breast cancer in postmenopausal females [37, 38]. Thus, estrogens, adipokines such as leptin and adiponectin, insulin, and IGF-1 have been viewed as important factors in hormone receptor-positive (HR+) breast cancer carcinogenesis [11, 13].

Aromatase inhibitors (AIs) are one of the standard treatments for postmenopausal women with HR+ metastatic breast cancer [4, 8]. These include nonsteroidal, reversible AIs (e.g., anastrozole, letrozole) and the steroidal, irreversible AI (exemestane) [12]. Because most women treated with AI therapy in the adjuvant setting receive anastrozole or letrozole, patients with HR+ breast cancer whose disease progresses after adjuvant treatment often receive exemestane, either front-line or subsequently in the treatment of their metastatic disease [3, 10, 34].

Metformin is approved for the treatment of type 2 diabetes mellitus. In one study of diabetic patients with early-stage breast cancer, those who received neoadjuvant chemotherapy with concomitant metformin had a higher rate of pathologic complete response than did those who received chemotherapy without metformin [20]. The mechanism of action of metformin in breast cancer cells is not fully understood but may involve activation of AMPK, inhibition of respiratory chain complex 1, and activation of G6PDH [26]. Furthermore, metformin can mimic the hepatic gene expression profile of long-term caloric restriction in mice and it can suppress breast cancer carcinogenesis in transgenic mice [2]. The effects on breast cancer after breast cancer has formed in obese mice is under investigation.

Rosiglitazone is a thiazolidinedione that activates PPAR γ receptors [9] to improve insulin resistance and it has been shown to cause a significant redistribution of fat away from viscera and liver with a concomitant increase in insulin sensitivity [27]. In obese women with polycystic ovary syndrome, rosiglitazone increases plasma concentration of adiponectin [28]. In breast cancer cells, thiazolidinediones have antineoplastic activity both in vitro and in vivo [7].

While exemestane decreases estrogen level, metformin and rosiglitazone improve insulin resistance and lower insulin and IGF-1 concentration. In addition, both metformin and rosiglitazone treatment are associated with redistribution of body fat [14]. Furthermore,

experimental data show that metformin and rosiglitazone have direct inhibitory effects on breast cancer cells [1, 2]. On the basis of preclinical evidence of the antitumor activity of metformin and rosiglitazone and the activity of exemestane in the treatment of HR+ metastatic breast cancer, we investigated the tolerability of exemestane in combination with metformin and rosiglitazone in overweight and obese postmenopausal women with HR+ metastatic breast cancer.

Patients and Methods

Patients and Study Design

This was a phase I single-institution, open-label, dose-escalation study (ClinicalTrials.gov identifier, NCT00933309) designed to assess the tolerability of metformin and rosiglitazone in combination with exemestane in postmenopausal overweight or obese women with HR+ metastatic breast cancer. The postmenopausal status was defined by one of the following: a) no spontaneous menses for more than 1 year in women > 55 years old; b) no spontaneous menses within the past 1 year in women ≤ 55 years old with postmenopausal gonadotrophin concentration (luteinizing hormone and follicle-stimulating hormone concentration > 40 IU/L) or postmenopausal estradiol concentration (< 10 pg/mL); or c) bilateral oophorectomy. Overweight and obese are defined by the World Health Organization as a body mass index of 25.0–29.9 kg/m² and ≥ 30 kg/m², respectively. All patients had a history of biopsy-proven estrogen receptor–positive (≥ 10%) and/or progesterone receptor–positive (≥ 10%) breast cancer and clinical evidence of metastatic disease. HER2-positive patients were not excluded. Prior endocrine therapy, biologic therapy, and chemotherapy were allowed, either adjuvantly or for metastatic breast cancer. Prior exemestane, metformin, or rosiglitazone were allowed if taken more than 7 days prior to enrollment. An Eastern Cooperative Oncology Group performance status score ≤ 2 was required for participation. Requirements for adequate organ function included an absolute neutrophil count ≥ 1000/μL; platelets ≥ 75 000/μL; hemoglobin ≥ 8.5 g/dL; serum creatinine < 1.4 mg/dL; bilirubin < 1.8 mg/dL; alanine aminotransferase or aspartate aminotransferase ≤ 2.5 times the upper limit of the normal range if there were no demonstrable liver metastases or ≤ 5 times the upper limit of normal in the presence of liver metastases; alkaline phosphatase < 3 times the upper limit of normal; calcium ≥ 11.0 mg/dL; and international normalized ratio < 1.6. Patients had to be competent to give informed consent and to state that they understood the investigational nature of the proposed treatment.

Patients were ineligible if they had received extensive radiotherapy (≥ 30% of marrow-bearing bone, e.g., whole pelvis or half spine) within the previous 4 weeks or if they had uncontrolled diabetes mellitus (hemoglobin A1C > 9 or random plasma glucose > 400 mg/dL), history of acromegaly, Cushing syndrome, Cushing disease, Addison disease (treated or untreated), unstable angina, or uncontrolled ischemic cardiac disease or symptomatic congestive heart failure (e.g., New York Heart Association class III or IV). Patients were not allowed to take hormone replacement therapy (estrogen with or without progesterone) or other investigational drugs within 3 weeks of registration on the protocol. Patients were excluded if they were known to have chronic liver diseases (e.g., chronic active hepatitis, cirrhosis) or human immunodeficiency virus infection. Patients could not have received chemotherapy within 3 weeks (6 weeks for nitrosourea or mitomycin-C). Acute toxic reactions to prior therapy had to have resolved to grade ≤ 1 with the exception of fatigue, alopecia, or anemia. The protocol was approved by the institutional review board at The University of Texas MD Anderson Cancer Center. Written informed consent was obtained from all patients.

The primary end point was to investigate a safe dosage and tolerance of metformin and rosiglitazone in combination with the FDA-approved dose of exemestane in overweight and

obese postmenopausal women with HR+ metastatic breast cancer. We evaluated the pharmacokinetics of exemestane and the clinical benefit of treatment as secondary end points. Safety assessments were made according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. Dose-limiting toxicity (DLT) was defined as: grade 3 nonhematologic toxicity; grade III nausea/vomiting, skin rash, and/or diarrhea (despite adequate supportive care); grade 3 skin toxicity not reverting to grade 2 within 14 days of the scheduled start date; febrile neutropenia [absolute neutrophil count (ANC) $<1.0 \times 10^9/L$ and fever $\geq 38.5^\circ C$], and/or documented infection (ANC $<1.0 \times 10^9/L$); grade IV thrombocytopenia or bleeding requiring a platelet transfusion.

All patients received 25 mg/day oral exemestane, which is the dose approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic breast cancer. The dose of exemestane was not modified throughout the study. The starting doses of the other agents were 1500 mg/day metformin and 6 mg/day rosiglitazone (2 patients). The dose level was escalated to dose level 2 (12 patients), as shown in Table 1, if no DLT was observed and de-escalated if DLT was observed. Dose level 2 was considered the maximum tolerated dose if no DLT occurred. The first 14 patients enrolled received metformin plus rosiglitazone as the combination tablet Avandamet (GlaxoSmithKline, Research Triangle Park, NC). Six additional patients received single-agent 2000 mg/day metformin (Glucophage XR, Bristol-Myers Squibb Company, New York, NY). A cycle was defined as 28 days. Treatment was continued until disease progression or intolerable toxic reactions occurred.

On each patient visit to the outpatient clinic, we obtained a medical history and conducted a physical examination. We evaluated vital signs and results of laboratory examinations, including complete blood cell count with differential, lipid profile, and concentration of blood urea nitrogen, creatinine, random glucose, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, and hemoglobin A1C (in patients with a history of diabetes mellitus). These tests were completed at baseline; at weeks 4, 8, and 12; and every 3 months (± 7 days) thereafter. An electrocardiogram was obtained at baseline. Tumor assessment data using standard diagnostic imaging tests was required prior to registration to confirm metastatic disease. Re-staging imaging studies were completed every 2–3 months at the discretion of the treating physician.

Tolerability and Efficacy Evaluations

The study was conducted using a continual reassessment method (CRM) with a cohort size of 2 patients initially. The CRM is based entirely on a Bayesian decision framework. The Department of Biostatistics at MD Anderson has extensive experience with this methodology and has produced software implementing this method. The MD Anderson–developed CRM software assumes that the probability of toxicity at dose i (π_i) is modeled as $\pi_i = p_i^{\exp(\alpha)}$, where p_i is a constant and α is distributed a priori as a normal random variable with mean 0 and variance 2. The CRM software requires the investigator to specify the prior mean probability of toxicity at each of the four doses under consideration (s_i , $i = 1, 2, 3, 4$). The CRM model assumes that toxicity increases with dose, and thus, the s_i values must increase as i increases. The values p_i in the probability model are selected so that $E[p_i^{\exp(\alpha)}] = s_i$. After the first cohort, each successive cohort is given the dose whose posterior probability of toxicity, given the data collected thus far, is closest to the target toxicity (the software does not allow an untried dose to be skipped). Thus, as information accumulates, the model is continually updated posteriorly and decisions are made on the basis of the posterior distribution. As a result, no data are lost, and there is the assurance that the decision to increase or decrease the dose level is consistently reassessed as more information becomes available.

We began enrolling patients in our trial in September 2009. In September 2010 the FDA announced that it would restrict the use of rosiglitazone to patients with type 2 diabetes that could not be controlled by other medications. These new restrictions were implemented in response to data suggesting an elevated risk of cardiovascular events, such as heart attack and stroke, in diabetic patients treated with rosiglitazone [25]. Because of concerns regarding the unlikely future use of rosiglitazone in nondiabetic populations and the increasing interest in metformin's potential as a treatment for breast cancer, we amended our protocol. The last six patients enrolled received exemestane in combination with metformin (2000 mg/day), without rosiglitazone.

Patients were assessed every 12 weeks for tumor response using standard clinical criteria. The clinical benefit rate was determined by the number of patients who achieved an objective response according to the Response Evaluation Criteria in Solid Tumors[18] plus those who had stable disease for at least 24 weeks. Complete response was defined as the disappearance of all known lesions for at least 4 weeks. Partial response was defined as 30% decrease in the sum of the longest diameters of all measurable lesions.

Pharmacokinetic Sampling, Assay, and Analysis

Thirteen patients participated in the pharmacokinetic part of this study. Of these, five were overweight and eight were obese. These patients' mean height was 164 ± 6.01 cm, their mean weight was 85.9 ± 11.1 kg, and their mean body mass index was 31.9 ± 4.54 kg/m² (Table 2).

Two of the patients in the pharmacokinetic study were treated on dose level 1, and eleven were treated at dose level 2. On day 1, blood samples (5 mL) were drawn predose and at 1, 3, 6, 12, and 23 hours postdose. Blood samples were also drawn on days 8 and 15 at the same time points as day 1. Plasma samples were prepared from each blood sample and stored at -20°C until shipment to PRA International (Lenexa, KS) for pharmacokinetic analysis.

Exemestane concentrations in plasma were determined by solid phase extraction followed by ultra performance liquid chromatography coupled with tandem mass spectrometry (MS/MS, API 4400, Applied Biosystems Inc., Foster City, CA). The lower limit of quantitation was 0.1 ng/mL.

Pharmacokinetic parameters of exemestane were determined by noncompartmental analysis of plasma concentration versus time data using WinNonlin version 5.2 (Pharsight, Mountain View, CA). The area under the curve (AUC_{0-24}) was calculated using the linear trapezoidal rule up to the last quantifiable concentration (C_{last}) and extrapolated to infinite time ($\text{AUC}_{0-\text{inf}}$) by adding $C_{\text{last}}/K_{\text{el}}$ to AUC_{0-24} , where K_{el} is the slope of the regression line. The half-life of the terminal decay phase ($t_{1/2,z}$) was determined by linear regression analysis of the natural logarithm (ln) concentration versus time curve: $t_{1/2,z} = \ln 2/K_{\text{el}}$. Oral clearance (CL/F) was calculated as oral dose/ $\text{AUC}_{0-\text{inf}}$. Volume of distribution (Vz/F) was calculated as $\text{CL}/F/K_{\text{el}}$.

Results

Patient Characteristics

We enrolled 20 eligible patients between September 2009 and February 2011. The median body mass index was 33 (Table 3). All primary tumors were estrogen receptor-positive, and 14 were progesterone receptor-positive. Nineteen of the patients had clinical evidence of visceral and/or bone metastasis; one patient had soft tissue metastasis only. All patients had received prior chemotherapy or endocrine therapy for breast cancer. Nineteen patients had

received prior chemotherapy for breast cancer. Six patients had received a nonsteroidal inhibitor in the adjuvant setting, and four received prior exemestane for metastatic disease.

Tolerability

Throughout the treatment period, we observed drug-related adverse events (definite or probable) in most patients. These included mild (grade 1–2) nausea and diarrhea, similar to what would be expected for single-agent exemestane. We found no difference in toxicities between dose level 1 and dose level 2. No DLT was noted, and no dose reductions occurred. On a few occasions, at the attending physician's request the rosiglitazone and metformin treatment was suspended for a few days in one of the patients because of grade 2 diarrhea. None of the patients developed hypoglycemia.

We observed grade 3 adverse events, which were not drug related, in five patients. A patient who developed grade 3 nausea and vomiting was found to have progressive disease with worsening pleural effusions as well as renal insufficiency. One patient with a history of inflammatory bowel syndrome experienced grade 3 nausea. One patient with liver and bone metastases was enrolled with grade 2 anemia (9.8 g/dL), and she developed grade 3 anemia while receiving treatment. Another patient experienced grade 3 diarrhea and fatigue secondary to lymphocytic colitis. One patient had intermittent grade 3 fatigue, which was attributed to worsening depression related to her diagnosis and prognosis.

Pharmacokinetics

Plasma concentration versus time values were captured on days 1, 8, and 15 and can be found in Figure 1. Plasma pharmacokinetic parameters are found in Table 5. On day 1, $t_{\max}$, the time after administration at which exemestane reached its maximum concentration ($C_{\max}$), was a mean 2.54 ± 1.81 hours (range, 1.00–6.00 hours). After reaching $C_{\max}$, exemestane concentration declined in a biexponential manner, with a terminal oral half-life of 4.87 ± 1.13 hours (range, 3.47–7.64 hours). Exposure to exemestane (both $C_{\max}$ and AUC) was highly variable (Figure 2). The mean $C_{\max}$ was 12.1 ± 11.6 ng/mL (range, 2.2–39.3 ng/mL), while AUC_{0-24} was 48.6 ± 29.5 h*ng/mL (range, 11.0–127.0 h*ng/mL) and $AUC_{0-\infty}$ was 50.9 ± 30.0 h*ng/mL (range, 12.6–131.0 h*ng/mL). Apparent CL/F was 663 ± 440 L/hour (range, 191–1979 L/hour), while the apparent terminal phase V_z/F was 4405 ± 2299 L (range, 1426–9922 L).

On days 8 and 15, $t_{\max}$ occurred somewhat more rapidly, with the median $t_{\max}$ decreasing to 1.92 ± 1.04 hours (range, 1.0–3.0) and 1.36 ± 0.81 hours (range, 1.0–3.0 hours), respectively. Exposure to exemestane changed very little during 15 days of treatment. The mean $C_{\max}$ was 11.30 ± 8.26 ng/mL (range, 3.05–25.50 ng/mL) and 15.4 ± 17.0 ng/mL (range, 5.09–64.5 ng/mL) for days 8 and 15, respectively. AUC_{0-24} was 48.1 ± 36.7 h*ng/mL (range, 11.7–142 h*ng/mL) and 52.1 ± 46.7 h*ng/mL (range, 20.63–190 h*ng/mL) for days 8 and 15, respectively. As was the case for day 1, only a small fraction (about 6% on average) of AUC_{0-24} was extrapolated to $AUC_{0-\infty}$. $AUC_{0-\infty}$ was 52.6 ± 39.0 h*ng/mL (range, 13.2–147 h*ng/mL) and 55.2 ± 48.1 h*ng/mL (range, 22.4–195 h*ng/mL) on days 8 and 15, respectively. As on day 1, $C_{\max}$ and AUC_{0-24} varied considerably on days 8 and 15 (Figure 2).

The mean half-life ($T_{1/2}$) of exemestane was 5.69 ± 2.40 hours (range, 1.69–10.4 hours) on day 8 and 6.65 ± 2.34 hours (range, 3.00–11.50 hours) on day 15, slightly longer compared to that observed on day 1. This increase appeared to be partly due to a somewhat larger V_z/F . On day 8, the mean V_z/F was 5364 ± 3001 L (range, 1238–10 375 L), increasing slightly to 5812 ± 2924 L (1051–10 893 L) on day 15. In contrast, CL/F appeared to change little on

days 8 and 15 compared with day 1. CL/F was 730 ± 482 L/hour (170–1900 L/hour) on day 8 and 613 ± 255 L/hour (128–1116 L/hour) on day 15.

Figure 3 depicts the accumulation ratio (R_A) for $C_{\max}$ and AUC_{0-24} . $R_{A(C_{\max})}$ or $R_{A(AUC)}$ is defined as the ratio of $C_{\max}$ or AUC_{0-24} on day 15 to that on day 1. The mean $R_{A(C_{\max})}$ was 1.50 ± 0.92 (range, 0.35–3.06) while the mean $R_{A(AUC_{0-24})}$ was 1.20 ± 0.70 (range, 0.42–3.05), suggesting little, if any, accumulation of exemestane from day 1 to day 15.

Efficacy

None of the patients achieved a complete or partial response. Six patients (30%) had stable metastatic disease for 6 months or longer (range, 6–18 months). Four patients received metformin and rosiglitazone and achieved SD for 6, 6, 18, 18 months, respectively. Two patients received metformin alone and achieved SD for 10 and 11 months, respectively. One patient who had received prior anastrozole and exemestane for metastatic breast cancer achieved stable disease for 11 months with exemestane and metformin treatment. None of the other three patients who had received prior exemestane derived clinical benefit from the combination.

Discussion

This study showed that oral administration of exemestane is safe in combination with metformin and rosiglitazone in overweight and obese nondiabetic postmenopausal women with HR+ metastatic breast cancer. The treatment was well tolerated, and no DLT was observed. Most patients experienced mild (grade 1–2) drug-related adverse events, mainly nausea and diarrhea, similar to what would be expected for single-agent exemestane. The combination was associated with clinical benefit in 30% of patients who had had disease progression subsequent to previous conventional chemotherapy and endocrine therapy.

Upon its administration to postmenopausal overweight women with breast cancer, exemestane was rapidly absorbed and then eliminated in a biexponential manner with a mean half-life of 5–7 hours. Exemestane had a rather high apparent terminal volume of distribution, which averaged about 4400–5800 L, consistent with wide distribution throughout body water and tissues. Although metabolites were not followed in this study, exemestane is known to be extensively metabolized by multiple cytochrome p450 (CYP) enzymes, including CYP3A4 [17, 39], CYP1A2, CYP2B6, and CYP4A11 [22]. The oxidative metabolites 17-hydroxexemestane and 6-hydroxyexemestane are the major metabolites of exemestane [5, 6]. Exemestane and its metabolites are ultimately excreted in the urine and feces [29].

Several studies were reviewed in which exemestane was administered to patients at a dose of 25 mg/day for various time periods with at least some pharmacokinetic data [5, 6, 17, 21, 29, 39]. As seen in Table 6, the pharmacokinetic parameters of exemestane determined in this study proved comparable to the values obtained in prior studies, suggesting they were not affected by the addition of metformin and rosiglitazone in this population.

In the present study of exemestane administered concomitantly with obesity medications rosiglitazone and metformin, no treatment group received only exemestane; therefore it was not possible to determine whether any drug interactions occurred with these two agents. However, it is known that rosiglitazone is mainly metabolized by CYP2C8 and, to a lesser extent, CYP2C9 [32]. Furthermore, metformin is rapidly eliminated through active secretion by the kidneys, and it is neither metabolized nor protein bound in plasma [36]. Thus, given that exemestane is mainly cleared by CYP3A4 metabolism, an important interaction with these two agents would not be expected. Several of the studies cited above measured

exemestane pharmacokinetics in the presence of concomitant medications, including raloxifene [39], celecoxib [6] and tamoxifen [17] - also with no apparent drug interactions. This may be due to the fact that multiple CYPs play a role in exemestane metabolism.

A phase III randomized trial (MA.32) is in progress in North America to determine the efficacy and tolerability of adjuvant metformin in patients with early-stage breast cancer. However, significant questions regarding antineoplastic clinical benefits of metformin and/or thiazolidinediones still remain for obese/overweight breast cancer patients in the metastatic setting. The tolerability and pharmacokinetic data of exemestane supports further testing of aromatase inhibitors and metformin combinations in the metastatic setting for overweight postmenopausal women with HR+ metastatic breast cancer.

Acknowledgments

This work was supported by a PROMISE grant from the Susan G. Komen for the Cure and by the National Institutes of Health through MD Anderson's Cancer Center Support Grant (CA016672). The authors thank Bryan Tutt from the Department of Scientific Publications at MD Anderson Cancer Center for editorial assistance. We also thank Martijn Hilhorst and Thomas Thompson from PRA International (Lenexa, KS) for measurements of exemestane in human plasma and interpretation of pharmacokinetics data, respectively. The pharmacokinetics sampling was performed in the U.T. MD Anderson Cancer Center Clinical and Translational Research Center (CTRC) and was supported by the Center for Clinical and Translational Sciences, which is funded by National Institutes of Health Clinical and Translational Science Award UL1 RR024148 and by the National Institutes of Health Cancer Center Support Grant (CCSG) award CA016672 to MD Anderson Cancer Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health."

References

1. Alimova IN, Liu B, Fan Z, et al. Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro. *Cell Cycle*. 2009; 8:909–15. [PubMed: 19221498]
2. Anisimov VN, Berstein LM, Egormin PA, et al. Effect of metformin on life span and on the development of spontaneous mammary tumors in HER-2/neu transgenic mice. *Exp Gerontol*. 2005; 40:685–93. [PubMed: 16125352]
3. Benson JR, Jatoi I, Keisch M, et al. Early breast cancer. *Lancet*. 2009; 373:1463–79. [PubMed: 19394537]
4. Brewster AM, Hortobagyi GN, Broglio KR, et al. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst*. 2008; 100:1179–83. [PubMed: 18695137]
5. Corona G, Elia C, Casetta B, et al. A liquid chromatography-tandem mass spectrometry method for the simultaneous determination of exemestane and its metabolite 17-dihydroexemestane in human plasma. *J Mass Spectrom*. 2009; 44:920–8. [PubMed: 19214962]
6. Dirix LY, Ignacio J, Nag S, et al. Treatment of advanced hormone-sensitive breast cancer in postmenopausal women with exemestane alone or in combination with celecoxib. *J Clin Oncol*. 2008; 26:1253–9. [PubMed: 18323548]
7. Elstner E, Williamson EA, Zang C, et al. Novel therapeutic approach: ligands for PPARgamma and retinoid receptors induce apoptosis in bcl-2-positive human breast cancer cells. *Breast Cancer Res Treat*. 2002; 74:155–65. [PubMed: 12186376]
8. Esteve FJ. Monoclonal antibodies, small molecules, and vaccines in the treatment of breast cancer. *Oncologist*. 2004; 9:4–9. [PubMed: 15163841]
9. Esteve FJ, Glaspy J, Baidas S, et al. Multicenter phase II study of oral bexarotene for patients with metastatic breast cancer. *J Clin Oncol*. 2003; 21:999–1006. [PubMed: 12637463]
10. Esteve FJ, Hortobagyi GN. Locally advanced breast cancer. *Hematol Oncol Clin North Am*. 1999; 13:457–472. [PubMed: 10363140]
11. Esteve FJ, Hortobagyi GN. Prognostic molecular markers in early breast cancer. *Breast Cancer Res*. 2004; 6:109–18. [PubMed: 15084231]

12. Esteve FJ, Hortobagyi GN. Comparative assessment of lipid effects of endocrine therapy for breast cancer: implications for cardiovascular disease prevention in postmenopausal women. *Breast*. 2006; 15:301–312. [PubMed: 16230014]
13. Esteve FJ, Sahin AA, Cristofanilli M, et al. Molecular prognostic factors for breast cancer metastasis and survival. *Semin Radiat Oncol*. 2002; 12:319–328. [PubMed: 12382190]
14. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA*. 2000; 283:1695–702. [PubMed: 10755495]
15. Han C, Zhang HT, Du L, et al. Serum levels of leptin, insulin, and lipids in relation to breast cancer in china. *Endocrine*. 2005; 26:19–24. [PubMed: 15805581]
16. Hankinson SE, Schernhammer ES. Insulin-like growth factor and breast cancer risk: evidence from observational studies. *Breast Dis*. 2003; 17:27–40. [PubMed: 15687675]
17. Hutson PR, Love RR, Havighurst TC, et al. Effect of exemestane on tamoxifen pharmacokinetics in postmenopausal women treated for breast cancer. *Clin Cancer Res*. 2005; 11:8722–7. [PubMed: 16361559]
18. Jaffe CC. Measures of response: RECIST, WHO, and new alternatives. *J Clin Oncol*. 2006; 24:3245–51. [PubMed: 16829648]
19. Jin Q, Esteve FJ. Cross-talk between the ErbB/HER family and the type i insulin-like growth factor receptor signaling pathway in breast cancer. *J Mammary Gland Biol Neoplasia*. 2008; 13:485–98. [PubMed: 19034632]
20. Jiralerspong S, Palla SL, Giordano SH, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol*. 2009; 27:3297–302. [PubMed: 19487376]
21. Johannessen DC, Engan T, Di Salle E, et al. Endocrine and clinical effects of exemestane (PNU 155971), a novel steroidal aromatase inhibitor, in postmenopausal breast cancer patients: a phase I study. *Clin Cancer Res*. 1997; 3:1101–8. [PubMed: 9815789]
22. Kamdem LK, Flockhart DA, Desta Z. In vitro cytochrome P450-mediated metabolism of exemestane. *Drug Metab Dispos*. 2011; 39:98–105. [PubMed: 20876785]
23. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol*. 2001; 2:133–40. [PubMed: 11902563]
24. Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: findings from the British Women's Heart and Health Study. *Cancer Causes Control*. 2004; 15:267–75. [PubMed: 15090721]
25. Lenihan DJ, Esteve FJ. Multidisciplinary strategy for managing cardiovascular risks when treating patients with early breast cancer. *Oncologist*. 2008; 13:1224–34. [PubMed: 19091778]
26. Leverve XM, Guigas B, Demaille D, et al. Mitochondrial metabolism and type-2 diabetes: a specific target of metformin. *Diabetes Metab*. 2003; 29:6S88–94. [PubMed: 14502105]
27. Lu M, Sarruf DA, Talukdar S, et al. Brain PPAR-gamma promotes obesity and is required for the insulin-sensitizing effect of thiazolidinediones. *Nat Med*. 2011; 17:618–22. [PubMed: 21532596]
28. Majuri A, Santaniemi M, Rautio K, et al. Rosiglitazone treatment increases plasma levels of adiponectin and decreases levels of resistin in overweight women with PCOS: a randomized placebo-controlled study. *Eur J Endocrinol*. 2007; 156:263–9. [PubMed: 17287417]
29. Mauras N, Lima J, Patel D, et al. Pharmacokinetics and dose finding of a potent aromatase inhibitor, Aromasin (exemestane), in young males. *J Clin Endocrinol Metab*. 2003; 88:5951–6. [PubMed: 14671195]
30. Morris PG, Hudis CA, Giri D, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. *Cancer Prev Res (Phila)*. 2011; 4:1021–9. [PubMed: 21622727]
31. Nahta R, Hortobagyi GN, Esteve FJ. Growth factor receptors in breast cancer: Potential for therapeutic intervention. *Oncologist*. 2003; 8:5–17. [PubMed: 12604728]
32. Park JY, Kim KA, Shin JG, et al. Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol*. 2004; 58:397–402. [PubMed: 15373932]

33. Petrelli JM, Calle EE, Rodriguez C, et al. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. *Cancer Causes Control*. 2002; 13:325–32. [PubMed: 12074502]
34. Rivera E, Valero V, Syrewicz L, et al. Phase I study of stealth liposomal doxorubicin in combination with gemcitabine in the treatment of patients with metastatic breast cancer. *J Clin Oncol*. 2001; 19:1716–1722. [PubMed: 11251001]
35. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. *Obes Rev*. 2004; 5:153–65. [PubMed: 15245384]
36. Sirtori CR, Franceschini G, Galli-Kienle M, et al. Disposition of metformin (N,N-dimethylbiguanide) in man. *Clin Pharmacol Ther*. 1978; 24:683–93. [PubMed: 710026]
37. Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. *Clin Chem*. 2008; 54:e11–79. [PubMed: 19042984]
38. Tian YF, Chu CH, Wu MH, et al. Anthropometric measures, plasma adiponectin, and breast cancer risk. *Endocr Relat Cancer*. 2007; 14:669–77. [PubMed: 17914097]
39. Traina TA, Poggese I, Robson M, et al. Pharmacokinetics and tolerability of exemestane in combination with raloxifene in postmenopausal women with a history of breast cancer. *Breast Cancer Res Treat*. 2008; 111:377–88. [PubMed: 17952589]
40. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. *N Engl J Med*. 2006; 354:270–82. [PubMed: 16421368]

Figure 1a.

Figure 1b.

Figure 1. Mean exemestane concentration versus time on days 1, 8, and 15 after oral administration of 25 mg exemestane to postmenopausal breast cancer patients. a) arithmetic scale; b) logarithmic scale.

Figure 2a.

Figure 2b.

Figure 2. Comparison of a) maximum concentration (C_{max}) or b) area under the curve (AUC_{0-24}) on days 1, 8, and 15 after oral administration of 25 mg/day exemestane to postmenopausal breast cancer patients.

Figure 3.

Accumulation ratio¹ of maximum concentration (C_{max}) and area under the curve (AUC_{0-24}) after administration of 25 mg/day exemestane to postmenopausal breast cancer patients.

¹ The accumulation ratio is defined as the ratio of C_{max} or AUC_{0-24} on day 15 to that on day 1

Table 1

Exemestane, rosiglitazone, and metformin dosing

Dose Level	Exemestane dose	Rosiglitazone/metformin ^a dose
–2	25 mg once a day	1 tablet once a day (Total 2 mg/500 mg per day)
–1	25 mg once a day	1 tablet twice a day (Total 4 mg/1000 mg per day)
1	25 mg once a day	2 tablets in am, 1 tablet in pm (Total 6 mg/1500 mg per day)
2	25 mg once a day	2 tablets twice a day (Total 8 mg/2000 mg per day)

^aRosiglitazone (2 mg) and metformin (500 mg) were given as a combination tablet.

\$watermark-text

\$watermark-text

\$watermark-text

Table 2

Demographics of patients who underwent exemestane pharmacokinetic studies

Patient No.	Height (cm)	Weight (kg)	Body mass index (kg/m ²)	Ethnicity	Rosiglitazone/metformin ^a daily dose
1	166	112.0	40.9	Black	2 tablets in am, 1 tablet in pm (Total 6 mg/1500 mg per day)
2	165	92.9	34.1	Black	
3	163	92.2	34.7	White	2 tablets twice a day (Total 8 mg/2000 mg per day)
4	160	84.1	32.9	White	
5	158	93.3	37.6	White	
6	169	95.7	33.5	White	
7	166	75.3	27.3	White	
8	160	76.0	26.4	White	2 tablets twice a day (Total 8 mg/2000 mg per day)
9	167	73.7	26.5	White	
10	179	85.0	26.5	Black	
11	158	73.2	29.5	White	
12	159	83.8	33.4	White	
13	160	80.0	31.3	White	
Mean	164	85.9	31.9		
SD	6.01	11.1	4.54		
%CV	3.67	12.9	14.2		

All patients received exemestane 25 mg daily.

^aRosiglitazone (2 mg) and metformin (500 mg) were given as a combination tablet.

Table 3

Patient characteristics at baseline

Characteristic	No. of patients	% of patients
Age (years)		
Median	61	
Range	48–77	
Body mass index (kg/m²)[AU: OK?]		
Median	33	
Range	23.44–50.27	
Adjuvant systemic therapies		
Anthracycline	7	35
Taxane	6	30
Other chemotherapy	3	15
Tamoxifen	7	35
Nonsteroidal aromatase inhibitor	6	30
Prior systemic therapy for metastatic breast cancer		
Anthracycline	5	25
Taxane	7	35
Other chemotherapy	19	95
Tamoxifen	4	20
Nonsteroidal aromatase inhibitor	13	65
Other hormonal treatments (megestrol, fluoxymestrone, fulvestrant)	9	45
Exemestane	4	20
ER		
Positive	20	100
Negative	0	0
PR		
Positive	14	70
Negative	6	30
Positive	0	0
Negative	0	100
Race/ethnicity		
White	16	80
Black	4	20
Hispanic	0[AU: Please check. Table 2 has 1 Hispanic patient.]	

Characteristic	No. of patients	% of patients
Other	0	0
Sites of metastasis		
Liver	5	25
Lung	5	25
Bone	13	65
Soft Tissue	8	40

Table 4

Overall drug-related nonhematologic adverse events

Toxic reaction	Grade 1		Grade 2		Grade 3	
	No. of patients	%	No. of patients	%	No. of patients	%
Nausea	8	40	1	5	2	10
Fatigue	7	35	0	0	2	10
Diarrhea	6	30	3	15	1	5
Hot flashes	6	30	0	0	0	0
Myalgia	2	10	0	0	0	0
Anorexia	2	10	1	5	0	0
Cough	2	10	0	0	0	0
Dizziness	2	10	0	0	0	0
Taste alteration	2	10	0	0	0	0
Indigestion	1	5	0	0	0	0
Headaches	3	15	0	0	0	0
Vomiting	1	5	1	5	1	5
Abdominal pain/cramping	0	0	3	15	0	0
Weight loss	0	0	1	5	0	0
Sweating	1	5	0	0	0	0
Vision changes	1	5	0	0	0	0
Elevated creatinine	3	15	1	5	0	0
Elevated bilirubin	1	5	0	0	0	0
Lymphopenia	0	0	1	5	0	0
Leukopenia	1	5	0	0	0	0
Anemia	9	45	1	5	1	5
Elevated alkaline phosphatase	2	10	0	0	0	0
Neutropenia	0	0	1	5	0	0
Hypoalbuminemia	1	5	0	0	0	0
Hyperkalemia	1	5	0	0	0	0
Hypercholesterolemia	1	5	0	0	0	0
Hypertriglyceridemia	2	10	0	0	0	0

NOTE: there were no grade 4 adverse events.

\$watermark-text

\$watermark-text

\$watermark-text

Table 5

Mean ($\pm$ SD) of selected pharmacokinetic parameters of exemestane after oral administration of a 25 mg/day dose to postmenopausal breast cancer patients for 15 days.

Day	parameter	t _{max} (hr)	C _{max} ng/mL	AUC ₀₋₂₄ (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	t _{1/2} (hr)	Vz/F (L)	CL/F (L/hr)
1	N	13	13	13	13	13	13	13
	Mean	2.54	12.1	48.6	50.9	4.87	4405	663
	SD	1.81	11.6	29.5	30.0	1.13	2299	440
	CV%	71.2	95.9	60.7	59.0	23.3	52.2	66.5
	Min	1.0	2.20	11.0	12.6	3.47	1426	191
	Max	6.0	39.3	127	131	7.64	9922	1979
	Median	3.0	6.80	37.5	39.3	4.71	3744	637
8	N	13	13	13	12	12	12	12
	Mean	1.92	11.3	48.1	52.6	5.69	5364	730
	SD	1.04	8.26	36.7	39.0	2.40	3001	482
	CV%	54.0	73.4	76.2	74.1	42.3	55.9	66.0
	Min	1.0	3.05	11.7	13.2	1.69	1238	170
	Max	3.0	25.5	142	147	10.4	10375	1900
	Median	1.0	7.44	33.8	38.5	5.57	5684	666
15	N	11	11	11	11	11	11	11
	Mean	1.36	15.4	52.1	55.2	6.65	5812	613
	SD	0.81	17.0	46.7	48.1	2.34	2924	255
	CV%	59.3	111	89.7	87	35.2	50.3	41.6
	Min	1.0	5.09	20.63	22.4	3.00	1051	128
	Max	3.0	64.5	190	195	11.5	10893	1116
	Median	1.0	9.8	37.1	38.6	6.14	5257	647

\$watermark-text

\$watermark-text

\$watermark-text

Table 6

Summary of selected literature of pharmacokinetic values for exemestane (25 mg/day)

Author	Time	N	T _{max} (h)	C _{max} ng/mL	AUC _{0-t} (hr*ng/mL)	Half-life (h)	V _z /F (L)	CL/F (L/h)	Concomitant medications
Present study	1 day		2.54 ± 1.81	12.1 ± 11.6	48.6 ± 29.5	4.87 ± 1.13	4405 ± 2299	663 ± 440	
	8 days	13 female patients	1.92 ± 1.04	11.3 ± 8.26	48.1 ± 36.7	5.69 ± 2.40	5364 ± 3001	730 ± 482	rosiglitazone, metformin
	15 days		1.36 ± 0.81	15.4 ± 17.0	52.1 ± 46.7	6.65 ± 2.34	5812 ± 2924	613 ± 255	
Traina et al. [21]	2 weeks	5 female patients	--	7.9 ± 4.8 6.0 ± 1.9	52.0 ± 28.2 49.1 ± 24.0	--	--	--	none raloxifene
Corona et al. [24]	8 weeks	1 female patient	1.0	24.4	74.5	10.1			Not specified
Dirix et al. [23]	29 days	5 female patients	2	36.4 ± 10.2	121	--	--	--	none
		12 female patients	--	27.7 ± 19.1	98				celecoxib
Mauras et al. [25]	1 day	10 healthy males	--	16.1 ± 8.0	36.4 ± 10.2	8.9 ± 5.3		725 ± 186	none
Hutson et al. [20]	8 weeks	32 female patients	--	--	41.5	--	--	602	tamoxifen

t_{max}, the time after administration at which exemestane reached its maximum concentration

C_{max}, maximum concentration

AUC, area under the curve

V_z/F, volume of distribution

CL/F, oral clearance