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PHASE II STUDIES

Efficacy and safety of the combination of metformin, everolimus and exemestane in overweight and obese postmenopausal patients with metastatic, hormone receptor-positive, HER2-negative breast cancer: a phase II study

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Summary

Background Increased adiposity is thought to result in worse clinical outcomes in patients with breast cancer through increased estrogen production, hyperinsulinemia, insulin resistance, and activation of the phosphatidylinositol-3-kinase/AKT/mammalian target of rapamycin (mTOR) pathway. Thus, we hypothesized that the addition of metformin to everolimus and exemestane, could lead to better outcomes in overweight and obese patients with metastatic, hormone receptor-positive, HER2-negative breast cancer. We conducted a phase II trial to evaluate the efficacy and safety of the combination of metformin, everolimus and exemestane in overweight and obese postmenopausal women with metastatic, hormone receptor-positive, HER2-negative breast cancer. *Methods* Twenty-two patients with a body mass index ≥25 kg/m^2 were treated with metformin 1000 mg twice daily, everolimus 10 mg daily and exemestane 25 mg daily. Median progression-free (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. *Results* Median PFS and OS were 6.3 months (95% confidence interval [CI]: 3.8–11.3 months) and 28.8 months (95% CI: 17.5–59.7 months), respectively. Five patients had a partial response and 7 had stable disease for ≥24 weeks yielding a clinical benefit rate of 54.5%. Compared with overweight patients, obese patients had an improved PFS on univariable ($p = 0.015$) but not multivariable analysis ($p = 0.215$). Thirty-two percent of patients experienced a grade 3 treatment-related adverse event (TRAE). There were no grade 4 TRAEs and 7 patients experienced a grade 3 TRAE. *Conclusion* The combination of metformin, everolimus and exemestane was safe and had moderate clinical benefit in overweight and obese with patients metastatic, hormone receptor-positive, HER2-negative breast cancer.

Keywords Metformin · Everolimus · Exemestane · Obesity · Metastatic breast cancer

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Introduction

Obesity is associated with an increased risk of breast cancer in postmenopausal women [1] and heralds a poorer prognosis [2–5]. Although the mechanism by which obesity contributes to worse outcomes in postmenopausal women with breast cancer has not been fully unraveled, several pathways have been implicated. Obesity is thought to result in increased estrogen production and consequent stimulation of estrogen-dependent tumor growth in postmenopausal women with hormone receptor-positive breast cancers as adipocytes are the main source of the enzyme aromatase, which is responsible for converting androgens to estrogens [6]. In addition, increased adiposity may lead to insulin resistance and

hyperinsulinemia, which in turn results in higher levels of insulin-like growth factor-1 (IGF1) leading to increased proliferation of breast cancer cells [7, 8], thought to be mediated, in part, by IGF1-dependent activation of the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway [9]. Thus, in an integrated manner, adipokine secretion, hyperinsulinemia, estrogen signaling, inflammation, and activation of the PI3K/AKT/mTOR pathway play important roles in promoting breast cancer progression [10].

Metformin is an orally administered drug that has been used to treat type II diabetes mellitus (DM) and reduces resistance to insulin [11]. In addition, metformin has been shown to inhibit breast cancer cell proliferation in vitro [12] and its use has been associated with improved outcomes in patients with breast cancer [13, 14]. Moreover, promising signals of activity were observed in obese mouse models of estrogen receptor (ER)-positive breast cancer treated with the combination of metformin and everolimus, an mTOR inhibitor [10]. Together with these data, the relatively favorable toxicity profile of metformin supports its development as a key component of novel combinatorial treatment approaches in breast cancer.

The combination of everolimus with exemestane, an aromatase inhibitor, was associated with a significant improvement in progression-free survival (PFS) when compared with exemestane alone in patients with advanced, hormone receptor-positive breast cancer in a randomized, phase III trial [15]. In addition, the combination of everolimus and exemestane has limited overlapping toxicity with metformin. Further, we had previously conducted a phase I study demonstrating that concurrent administration of metformin and exemestane was well tolerated and had no significant impact on the pharmacokinetic profile of exemestane [16]. Thus, given the association between obesity and poorer outcomes in postmenopausal breast cancer, potentially due in part to hyperinsulinemia, increased IGF1 levels and activation of the PI3K/AKT/mTOR pathway, we conducted a prospective phase II study to evaluate the safety and efficacy of the novel combination of metformin, everolimus and exemestane in overweight or obese postmenopausal women with metastatic, hormone receptor-positive, human epidermal growth factor receptor-2 (HER2)-negative breast cancer.

Methods

Eligibility

Postmenopausal women with hormone receptor-positive, HER2-negative breast cancer and clinical evidence of metastatic disease were eligible for the study if they had a body-mass index (BMI) ≥ 25 kg/m^2. Patients were considered postmenopausal if they met any of the following criteria: (1) lack of spontaneous menstrual periods for at least 12 consecutive months and age ≥ 55 years; (2) lack of spontaneous menstrual periods for at least 12 consecutive months with postmenopausal gonadotrophin levels (luteinizing hormone and follicle-stimulating hormone levels >40 IU/L) or postmenopausal estradiol levels; or (3) history of bilateral oophorectomy. ER- and progesterone receptor-positivity was defined as ≥10% staining of invasive carcinoma cells of any intensity by immunohistochemistry (IHC). Patients who were ER- and/or progesterone receptor-positive were considered to be hormone receptor-positive and eligible for the study. Patients were required to have a fasting cholesterol level of ≤300 mg/dL and a fasting triglyceride level ≤ 2.5 times the upper limit of normal with or without lipid-lowering therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 as well as adequate organ and marrow function.

Patients were allowed to have received prior chemotherapy and/or hormonal therapy for metastatic disease. Concurrent bisphosphonate therapy was permitted for the management of bone loss and/or bone metastases. Localized radiotherapy was allowed prior to the initiation of study medications if deemed not to influence the signal of evaluable lesions.

Patients were excluded from the study if they had HER2-positive disease, defined as 3+ staining on IHC or a HER2/chromosome ratio of ≥2 and average HER2 copy number ≥ 4 by in situ hybridization. Other exclusion criteria included active treatment for DM, hemoglobin A1C $\geq 6.5\%$, random plasma glucose >200 mg/dL, metformin use within 30 days prior to study enrollment, prior treatment with exemestane or mTOR inhibitors, metastatic disease involving the central nervous system, bilateral diffuse pulmonary lymphangitic carcinomatosis, and the presence of life-threatening visceral metastatic disease.

The study protocol was reviewed and approved by The University of Texas MD Anderson Cancer Center Institutional Review Board and all patients signed written informed consent. The study is registered at ClinicalTrials.gov (NCT01627067).

Study design and treatment

The primary objective of this single-institution prospective phase II trial was to evaluate the efficacy of exemestane and everolimus in combination with metformin in overweight and obese (BMI ≥ 25 kg/m^2) postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer. Exemestane and everolimus were administered orally at a dose of 25 mg and 10 mg once daily, respectively. The starting dose of metformin was 500 mg once daily orally. The dose of metformin was increased by 500 mg every three days until the target dose of 1000 mg twice daily was reached.

Evaluations before and during treatment included a complete medical history, physical examinations, toxicity

assessments and appropriate laboratory and imaging studies every 8 weeks. Patients remained on study until disease progression, unacceptable toxicity, or withdrawal of consent. Full supportive care was provided to all patients during this study.

Safety monitoring and dose modifications

While on study, patients were evaluated for toxicity every 4 weeks for the first 12 weeks and every 8 weeks thereafter. Severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. A treatment-related adverse event was defined as an adverse event thought to be possibly, probably or definitely related to the study treatment. Interim monitoring of adverse events was conducted and enrollment was to be terminated if there was a more than 92.5% chance that the rate of dose-limiting toxicities was greater than 30%.

Grade 2 and grade 3 non-infectious pneumonitis thought to be related to everolimus were managed with a 50% dose reduction and holding of everolimus, respectively, until recovery to grade 1 or less. If recovery to grade 1 or less did not occur within 3 weeks, study treatment was discontinued. Grade 4 non-infectious pneumonitis thought to be related to everolimus was an indication for permanent discontinuation of everolimus. Corticosteroids were used for non-infectious pneumonitis as clinically indicated.

Grade 2 stomatitis thought to be related to everolimus was managed by holding everolimus until resolution to grade 1 or less, at which point, everolimus was restarted at the same dose. Grade 3 stomatitis was similarly managed with a dose interruption but also required a 50% dose reduction of everolimus at the time when treatment was to be resumed. Everolimus was discontinued for grade 4 stomatitis.

Everolimus and metformin were held for all other grade 2 or higher treatment-related adverse events until resolution to grade 1 or less, with the exception of fatigue and grade 2 diarrhea in the absence of maximal antidiarrheal medication use. Upon resolution of the treatment-related adverse event to grade 1 or less, everolimus and metformin were to be restarted either at the same dose (grades 2 and 3) or with a 50% dose reduction (grade 4). With the exception of non-infectious pneumonitis, study treatment was discontinued if a treatment-related adverse event did not resolve to grade 1 or less within 4 weeks of symptom onset.

Disease monitoring

All patients in this study were evaluated with appropriate cross sectional imaging and nuclear bone scans at baseline and every 8 weeks thereafter. For patients with measurable disease at baseline, complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were defined and assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [17]. For patients without measurable disease at baseline, CR, non-CR/non-PD and PD were defined according to RECIST 1.1. All CRs and PRs required confirmation by repeat assessments done no less than 4 weeks from the initial scan where response was documented. All responses were reviewed by an independent radiologist at the time of study completion.

Statistical methods

The planned enrollment for this study was up to 40 patients. The primary end point of this study was progression-free survival (PFS), defined as the time from study enrollment to disease progression or death from any cause, whichever occurred first. Data for PFS were censored at the time of a patient's removal from study. With 40 patients accrued at a rate of 2 patients per month, a one-sided alpha of 5%, and a post-accrual follow up of 3 months, we would have 80% power to detect a median PFS of 12 months as being statistically significantly higher than a historical control median PFS of 7 months. All other analyses were post-hoc and should be regarded as such. Overall survival (OS) was defined as the time from study enrollment to death from any cause. Data on vital status were collected after study completion through May 1, 2018 and were used in the determination of OS. The overall response rate (ORR) was defined as the proportion of patients with a best overall response of CR or PR. The clinical benefit rate (CBR) was defined as the proportion of patients with a best overall response of CR, PR or SD (non-CR/non-PD for patients without measurable disease) lasting at least 24 weeks. The exact binomial method was used to calculate 95% confidence intervals (CI) for proportions. For patients with a best overall response of CR or PR, the duration of response (DOR) was defined as the time from first documentation of CR or PR to the time of disease progression. Data on the DOR were censored at the time of a patient's removal from the study. For patients with a best overall response of SD (non-CR/non-PD for patients without measurable disease), the duration of SD (non-CR/non-PD for patients without measurable disease) was defined as the time from study enrollment to the time of disease progression. Median PFS, OS and DOR were estimated using the Kaplan-Meier method. Cox regression analyses were used to calculate hazard ratios (HR) and accompanying 95% CIs. All data were analyzed using STATA v14.0 (STATA, College Station, TX).

Results

Patients

Twenty-two female patients were enrolled from October 2012 through September 2013 and were treated at The University of

Texas MD Anderson Cancer Center. Recruitment was terminated after the first 22 patients were enrolled due to limited accrual rates. Table 1 summarizes the baseline characteristics of the patients on this study. The median age was 57.2 years (range: 37.6–70.5 years). The median BMI was 29.9 kg/m^2 (interquartile range [IQR]: 28.0–35.9 kg/m^2). Sixty-eight percent of patients had an ECOG performance status of 0 and 91% were white. All patients had ER-positive disease and 64% had progesterone receptor-positive disease. Forty-one percent and 59% of patients had received chemotherapy and hormonal therapy, respectively, for the treatment of metastatic disease prior to study enrollment.

Table 1 Baseline patient characteristics

Characteristic ($N = 22$)	Value
Age, years	
Median	57.2
Range	37.6–70.5
ECOG[1] Performance Status, n (%)	
0	15 (68)
1	7 (32)
Race/Ethnicity, n (%)	
White	20 (91)
Black	2 (9)
BMI, kg/m^2	
Median	29.9
Interquartile range	28.0–35.9
BMI category, n (%)	
Overweight (BMI 25–29.9 kg/m^2)	11 (50)
Obese (BMI ≥ 30 kg/m^2)	11 (50)
ER-positive, n (%)	22 (100)
Progesterone receptor-positive, n (%)	14 (64)
Sites of Metastatic Disease, n (%)	
Bone[2]	20 (91)
Viscera[2]	17 (77)
De Novo metastatic disease, n (%)	
Yes	7 (32)
No	15 (68)
Prior chemotherapy for non-metastatic disease	
Yes	15 (68)
No	7 (32)
Prior hormonal therapy for non-metastatic disease	
Yes	14 (64)
No	8 (36)
Number of prior chemotherapy regimens received for metastatic disease, n (%)	
0	13 (59)
1	4 (18)
2	3 (14)
3	2 (9)
Number of prior hormonal therapies received for metastatic disease, n (%)	
0	9 (41)
1	6 (27)
2	5 (23)
3	2 (9)

[1] ECOG: Eastern Cooperative Oncology Group

[2] Some patients had both bone and visceral metastasis

Efficacy

All 22 patients treated on this study were considered evaluable for efficacy. The median PFS and OS for all patients on this study was 6.3 months (95% CI: 3.8–11.3 months, Fig. 1) and 28.8 months (95% CI: 17.5–59.7 months, Fig. 2), respectively. Compared with overweight patients, obese patients had an improved PFS on univariable cox regression analysis (HR: 0.25; 95% CI: 0.08–0.76; $p = 0.015$). However, this benefit was no longer statistically significant on multivariable analysis (adjusted HR: 0.43; 95% CI: 0.11–1.63; $p = 0.215$). Obese patients did not appear to have an improved OS compared to overweight patients on both univariable (HR: 0.60, 95% CI: 0.22–1.62, $p = 0.31$) and multivariable analyses (adjusted HR: 0.56, 95% CI: 0.18–1.74, p = 0.31). In our multivariable model (which included BMI category [overweight vs. obese], age at study enrollment, ECOG performance status, presence of visceral metastases, presence of bone metastases, and de novo metastatic disease), the presence of visceral metastases predicted poorer PFS (adjusted HR: 34.1, 95% CI: 2.3–499.4, $p = 0.010$) while the presence of bone metastases predicted improved PFS (adjusted HR: 0.02, 95% CI: 0.0009–0.58, $p = 0.021$). Using the same multivariable model, we did not identify any statistically significant associations between baseline covariates and OS. Best overall responses are summarized in Table 2. Seventy-three percent of patients had measurable disease at the time of baseline imaging and 27% did

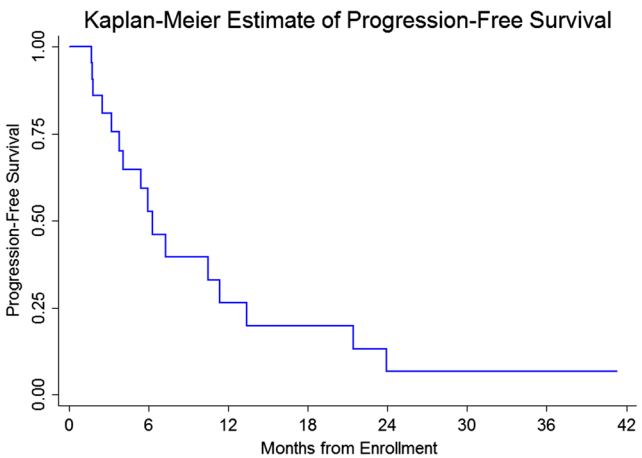

Fig. 1 Kaplan-Meier Estimation of Progression-Free Survival (PFS). A Kaplan-Meier plot of PFS is shown. The median PFS for all patients ($n = 22$) on this study was 6.3 months (95% CI: 3.8–11.3 months)

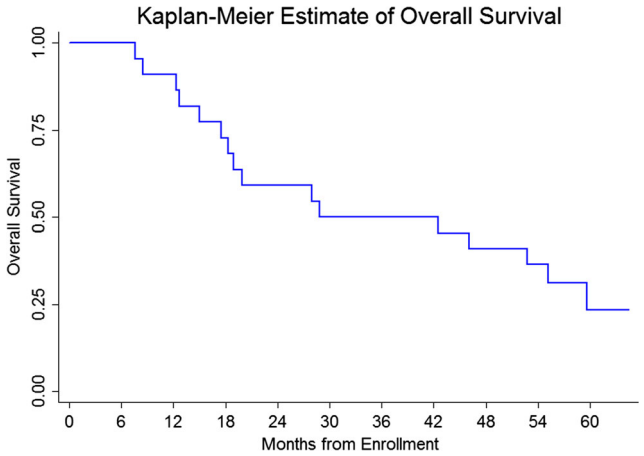

Fig. 2 Kaplan-Meier Estimation of Overall Survival (OS). A Kaplan-Meier plot of OS is shown. The median OS for all patients on this study (n = 22) was 28.8 months (95% CI: 17.5–59.7 months)

not. Five patients had PR, yielding an ORR of 22.7% (95% CI: 7.8–45.4%) and 54.5% (12/22) had SD or non-CR/non-PD. Of the 12 patients with SD or non-CR/non-PD, 7 had SD or non-CR/non-PD lasting at least 24 weeks. Thus, the CBR observed in this study was 54.5% (12/22) (95% CI: 32.2–75.6%). Among the five patients with PRs, the median DOR was 10.5 months (95% CI: 5.4 months-undefined).

Toxicity

All 22 treated patients were considered evaluable for toxicity. No treatment-related deaths occured. Table 3 summarizes the grade 2 and higher treatment-related adverse events. No grade 4 treatment-related adverse events were observed. Grade 3 treatment-related adverse events included weight loss (14%), hyperglycemia (9%), mucositis (5%), fatigue (5%), increased aspartate aminotransferase (5%), increased alanine aminotransferase (5%), and infection (5%). The most common grade 2 treatment-related adverse event was weight loss (45%), followed by mucositis (41%), fatigue (23%), increased aspartate aminotransferase (18%), hyperglycemia (14%), infection (14%), nausea (14%), vomiting (14%) and diarrhea (14%). Two patients (9%) developed grade 1 pneumonitis while on study and no patients had grade 2 or greater pneumonitis.

Table 2 Best overall patient response. Best overall response observed on study by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Response Category	Number (N = 22, %)
Complete Response	0
Partial Response	5 (22.7)
Stable Disease (including non-CR/non-PD[1]) lasting ≥24 weeks	7 (31.8)
Stable Disease (including non-CR/non-PD[1]) lasting <24 weeks	5 (22.7)
Progressive Disease	5 (22.7)
Clinical Benefit[2]	12 (54.5)
Overall Response[3]	5 (22.7)

1) For patients with only non-measurable disease

2) Clinical Benefit = Complete Response + Partial Response + Stable Disease (including non-CR/non-PD) lasting ≥24 weeks

3) Overall Response = Complete Response + Partial Response

Table 3 Treatment-related adverse events. Frequency of grade 2 and greater treatment-related adverse events

Adverse Event, n (%)	Toxicity Grade (Worst per Patient, N = 22)	
	Grade 2	Grade 3
Weight loss	10 (45)	3 (14)
Mucositis	9 (41)	1 (5)
Fatigue	5 (23)	1 (5)
Aspartate aminotransferase increased	4 (18)	1 (5)
Hyperglycemia	3 (14)	2 (9)
Infection	3 (14)	1 (5)
Nausea	3 (14)	0
Vomiting	3 (14)	0
Diarrhea	3 (14)	0
Alanine aminotransferase increased	2 (9)	1 (5)
Anorexia	2 (9)	0
Insomnia	2 (9)	0
Rash	2 (9)	0
Anemia	1 (5)	0
Depression	1 (5)	0
Dyspnea	1 (5)	0
Fever	1 (5)	0
Generalized muscle weakness	1 (5)	0

Discussion

To the best of our knowledge, this is the first reported phase II trial evaluating the novel combination of metformin, everolimus and exemestane in overweight or obese postmenopausal women with metastatic, hormone receptor-positive, HER2-negative breast cancer. The ORR was 22.7% which appears to be higher than the ORR of 9.5% reported in the everolimus plus exemestane arm of the randomized, phase III, BOLERO-2 trial [15]. However, the PFS of 6.3 months reported here does not represent an improvement over the PFS of 6.9 months in the everolimus plus exemestane arm as assessed by local investigators in BOLERO-2 [15]. Likewise, the median OS of 28.8 months reported in this study is similar to the median OS of 31.0 months for patients receiving everolimus plus exemestane in BOLERO-2 [18].

Although the PFS and OS reported in this study do not appear to represent an improvement over the PFS and OS reported for patients randomized to receive everolimus plus exemestane in BOLERO-2, it is important to note that patients in our study were more heavily pretreated, with 41% receiving chemotherapy for metastatic disease prior to study enrollment. In contrast, only 26% of patients in the everolimus plus exemestane arm in BOLERO-2 received chemotherapy for metastatic disease [15]. Further, enrollment on BOLERO-2 was restricted to patients who had received up to one line of chemotherapy for metastatic disease whereas 23% of patients in our study received more than one line of chemotherapy for metastatic disease. In addition, 77% of patients in our study had visceral disease compared with 56% of patients who received everolimus and exemestane in BOLERO-2 [15]. Moreover, enrollment in our study was restricted to patients who were overweight or obese which has been associated with poorer prognosis in breast cancer [19]. Despite enrolling more heavily pretreated patients, having a higher proportion of patients with visceral disease, and selecting for patients with higher BMI, we reported a higher ORR and patients on our study seemed to have similar PFS and OS when compared with patients randomized to receive everolimus plus exemestane in BOLERO-2, suggesting that adding metformin confers a potential benefit in this setting. It is also interesting to note that obese patients in this study were observed to have an improved PFS compared to overweight patients on univariable analysis. Although this difference was no longer statistically significant on multivariable analysis due, in part, to the relatively small number of patients in this study, we hypothesize that the benefit of adding metformin to everolimus and exemestane may be dependent on the degree of adiposity, even in patients with BMI $\geq$25 kg/m^2.

The combination of metformin, everolimus and exemestane was generally well tolerated. Seven patients (32%) experienced a grade 3 treatment-related adverse event and no grade 4 toxicities were observed. Common adverse effects associated with everolimus, such as mucositis and fatigue, were noted in our study and, despite the addition of metformin, we did not observe any grade 3 or higher treatment-related gastrointestinal adverse events. However, 14% of patients on our study had grade 3 weight loss, compared with 1% of patients treated with everolimus plus exemestane in BOLERO-2 [15], possibly due to the satiety-inducing effects of metformin [20]. We also reported a slightly higher rate of grade 3 hyperglycemia compared with patients who were treated on the everolimus plus exemestane arm of BOLERO-2 (9% vs 4%) [15], possibly due, in part, to our selection of patients who were overweight or obese for this study and who were therefore more likely to have impaired glucose metabolism.

Our study has a few limitations. First, the relatively small sample size limits the strength of the inferences that can be drawn from this study and may have restricted our ability to detect clinically meaningful differences in outcomes between our patients and historical controls receiving everolimus plus exemestane. Second, the lack of a contemporary control group of overweight and obese patients treated with everolimus and exemestane (without metformin) implied that it would not be possible to draw strong conclusions about the potential benefits of adding metformin to everolimus and exemestane in this setting. Third, although restricting enrollment on this study to patients who were overweight or obese allowed us to explore the efficacy and safety of metformin in a subset of patients who are at high risk for poor outcomes from their disease, it also limited our ability to generalize findings from this study to patients with low or normal BMI.

In conclusion, this phase II study demonstrated that the combination of metformin, everolimus and exemestane was well tolerated in overweight and obese patients with metastatic, hormone receptor-positive, HER2-negative breast cancer. Despite the strong association between obesity and poor outcomes in breast cancer, the PFS, OS and CBR observed on this study were comparable to findings from studies in patients with hormone receptor-positive, HER2-negative metastatic breast cancer receiving everolimus plus exemestane, and the ORR was notably better. However, the modest signal of efficacy observed in this study is, by itself, insufficient to support further evaluation of this combination. Alternative combinatorial treatment approaches involving metformin in overweight and obese patients should be explored if justified by pre-clinical data.

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Compliance with ethical standards

Conflict of interest FJE has received honoraria from Novartis and Pfizer for consultancy. MCM has received honoraria for serving on the advisory boards of Roche and Pfizer and has received institutional research

funding from Novartis. SCJY has received research funding and grant support from Bristol-Myers Squibb and DepoMed. GNH was the principal investigator of the BOLERO-2 trial and received research funding from Norvatis for conducting the trial and honoraria for chairing the protocol steering committee. VV has received honoraria from Novartis for consultancy. All other authors declare no relevant potential conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Informed consent Informed consent was obtained from all individual participants included in the study.

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