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ORIGINAL REPORT

Metformin and Pathologic Complete Responses to Neoadjuvant Chemotherapy in Diabetic Patients With Breast Cancer

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ABSTRACT

Purpose
Population studies have suggested that metformin use in diabetic patients decreases cancer incidence and mortality. Metformin inhibits the growth of cancer cells in vitro and tumors in vivo. However, there is little clinical data to support this. Our purpose was to determine whether metformin use was associated with a change in pathologic complete response (pCR) rates in diabetic patients with breast cancer receiving neoadjuvant chemotherapy.

Patients and Methods
We identified 2,529 patients who received neoadjuvant chemotherapy for early-stage breast cancer between 1990 and 2007. Patients were compared by groups: 68 diabetic patients taking metformin, 87 diabetic patients not taking metformin, and 2,374 nondiabetic patients. pCR rates were compared between the three groups using χ^2 tests of independence and compared pairwise using a binomial test of proportions. Factors predictive of pCR were assessed using a multivariate logistic regression model.

Results
The rate of pCR was 24% in the metformin group, 8.0% in the nonmetformin group, and 16% in the nondiabetic group ($P = .02$). Pairwise comparisons between the metformin and nonmetformin groups ($P = .007$) and the nonmetformin and nondiabetic groups ($P = .04$) were significant. Comparison of the pCR rates between the metformin and nondiabetic groups trended toward but did not meet significance ($P = .10$). Metformin use was independently predictive of pCR (odds ratio, 2.95; $P = .04$) after adjustment for diabetes, body mass index, age, stage, grade, receptor status, and neoadjuvant taxane use.

Conclusion
Diabetic patients with breast cancer receiving metformin and neoadjuvant chemotherapy have a higher pCR rate than do diabetics not receiving metformin. Additional studies to evaluate the potential of metformin as an antitumor agent are warranted.

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INTRODUCTION

Breast cancer is the second leading cause of death as a result of cancer among women, accounting for approximately 40,000 deaths each year. Most of these deaths result from distant metastatic relapses after potentially curative multimodality therapy (which includes a combination of surgery, systemic therapy, and radiotherapy as appropriate). Improved methods to prevent such relapses are clearly needed.

Neoadjuvant chemotherapy is the standard approach for locally advanced (inoperable) breast cancer and has become an accepted alternative to adjuvant chemotherapy in operable early-stage breast cancer, because it may allow breast conservation. Importantly, it permits assessment of the sensitivity of the tumor to systemic therapy. Pathologic complete response (pCR), defined as absence of tumor in the removed tissue at time of surgery, is a powerful predictor of long-term survival, whereas residual disease correlates with decreased disease-free survival.[1,2]

The prevalence of diabetes is approximately 7% to 8% in the general population, and both prevalence and incidence continue to rise dramatically. The effects of diabetes on breast cancer are complex and have been the subject of recent scrutiny.[3,4] Diabetes has been found to be a risk factor for breast cancer in some but not all studies (as summarized by

Larsson et al[5]), and diabetic patients with breast cancer may have worse outcomes than might their nondiabetic counterparts.[6-8] Obesity is associated with type 2 diabetes and is itself a risk factor for breast cancer[9] and possibly for poorer breast cancer outcomes.[10,11] The common factor linking diabetes, obesity, and metabolic syndrome to cancer may be the insulin resistance and consequent hyperinsulinemia associated with these conditions.[3,12-14] Insulin can promote tumorigenesis directly by affecting epithelial tissues or indirectly by affecting the levels of other modulators, such as insulin-like growth factors, sex hormones, and adipokines.[3,13-16]

Metformin is a widely prescribed oral medication used as first-line therapy for type 2 diabetes. Population studies have suggested that metformin decreases the incidence of cancer and cancer-related mortality in diabetic patients.[17,18] In addition, metformin has been shown to inhibit the growth of cancer cells, including breast cancer, in vitro[19-22] and of tumors in vivo.[21-24] We hypothesized that the antiproliferative effects of metformin might increase the effectiveness of neoadjuvant chemotherapy in diabetic patients with breast cancer. We undertook a retrospective cohort study to evaluate this hypothesis.

PATIENTS AND METHODS

Patients

The Breast Cancer Management System Database at The University of Texas M. D. Anderson Cancer Center was searched, and 3,412 patients with invasive breast cancer who were treated with neoadjuvant chemotherapy from January 1984 to May 2007 were identified. Of these patients, 291 were diabetic. The following exclusion criteria were applied: diabetes diagnosed after the period of neoadjuvant chemotherapy, resolved gestational diabetes, male sex, unknown estrogen receptor (ER) or progesterone receptor (PR) status, unknown human epidermal growth factor receptor 2 (HER-2) status, incomplete records (including medication records), more than 9 months between neoadjuvant chemotherapy initiation and surgery, and second concurrent primary cancer. Medication records from patient record review and pharmacy records were analyzed to divide the diabetic patients into those taking metformin and those not taking metformin during neoadjuvant chemotherapy. The use of other diabetic medications (insulin, thiazolidinediones, and so on) was also tabulated. The final study population consisted of 68 diabetic patients taking metformin during neoadjuvant chemotherapy (metformin group), 87 diabetic patients not taking metformin during neoadjuvant chemotherapy (nonmetformin group), and 2,374 nondiabetic patients (nondiabetic group). The institutional review board approved the retrospective review of the medical records for the purposes of this study.

Pathology

Dedicated breast pathologists at the M. D. Anderson Cancer Center reviewed all pathologic specimens. The histologic type, grade, and immunohistochemical analysis of ER, PR, and HER-2 status were determined as previously described.[25] Briefly, diagnosis of invasive breast cancer was made by core-needle biopsy of the breast tumor. Clinical stage was defined by the sixth edition of the Cancer Staging Manual of the American Joint Committee on Cancer. The histologic type of each tumor was defined according to the classification system of the WHO. Tumor grade was defined according to the modified Black's nuclear grading system. Immunohistochemical analysis to determine ER and PR status was performed using standard immunohistochemistry (IHC) procedures with monoclonal antibodies. Nuclear staining $\geq$ 10% was considered a positive result. Before 1993, the dextran-coated charcoal ligand-binding method was used to determine ER and/or PR status. HER-2 status was evaluated by IHC or by fluorescence in situ hybridization. HER-2–positive tumors were defined as 3+ receptor overexpression on IHC staining and/or gene amplification found on fluorescent in situ hybridization testing. pCR was defined as no evidence of invasive carcinoma in the breast and axillary lymph nodes at time of surgery.

Treatment

In general, all patients received three to six courses of one of the following anthracycline-based chemotherapy regimens: fluorouracil, doxorubicin, and cyclophosphamide; doxorubicin and cyclophosphamide; or fluorouracil, epirubicin, and cyclophosphamide. Additional taxane chemotherapy (paclitaxel or docetaxel) was administered to 1,909 patients (75.5%) for 3 months. At the completion of the neoadjuvant chemotherapy, patients underwent definitive surgery. Eligibility for breast conservation was determined by multidisciplinary evaluation. All patients had axillary staging with axillary lymph node dissection or sentinel node biopsy. Radiation therapy was delivered in the event of breast conservation surgery, locally advanced disease, primary tumor measurement before chemotherapy of $>$ 5 cm, and four or more involved axillary nodes. Adjuvant hormonal therapy was administered according to standard practice.

Statistical Analysis

Baseline patient characteristics were tabulated, and χ^2 tests of independence were used to examine differences in the baseline characteristics between groups (metformin, nonmetformin, and nondiabetic groups). A multivariate logistic regression model was used to examine the relationship between metformin and pCR after adjusting for factors known to affect pCR and for possible confounders related to diabetes and obesity (diabetes status [yes *v* no], age, clinical stage, tumor grade, receptor status, taxane use, and obesity status). To identify where the differences lay, the proportions of patients who experienced pCR for the three groups were compared pairwise using a binomial test of proportions. In an exploratory analysis to examine relapse-free survival (RFS) and overall survival (OS), the time to event or censoring was computed in months since diagnosis for each patient. Survival time was censored at the date of last follow-up during the monitoring period if events were not observed. Three-year survival probabilities and associated CIs were estimated nonparametrically using the Kaplan-Meier product limit method. The survival curves of each group were compared using log-rank tests. Multivariate Cox proportional hazards regression models were used to model survival as a function of metformin use after adjusting for the various confounders. All statistical analyses were performed using Stata 10 software (StataCorp, College Station, TX).

RESULTS

Patient Demographics and Clinical Characteristics

Patients were diagnosed with breast cancer between September 1990 and May 2007. Patient demographics and clinical characteristics are summarized in Table 1. The median age of patients was 49 years (range, 21 to 87 years). Patients in the diabetic groups were older than were those in the nondiabetic group, and consistent with this, these groups had a higher proportion of postmenopausal patients than did the nondiabetic group. Patients in the diabetic groups were also more overweight and obese according to body mass index (BMI) comparisons. The other standard prognostic factors were not significantly different between the three groups (Table 1). Severity of diabetes as judged by hemoglobin A1c levels was not different between the two diabetic groups. We also evaluated the use of other diabetic medications in the diabetic groups, because there is evidence that these—including insulin, as discussed, and thiazolidinediones[26]—may affect tumorigenesis. Insulin use was lower in the metformin group than it was in the nonmetformin group (16% *v* 33%; $P = .02$), whereas thiazolidinedione use was not significantly different between groups ($P = .36$). Finally, neoadjuvant taxane use was higher in the diabetic groups (87% in the metformin group and 84% in the nonmetformin group) compared with the nondiabetic group (75%; $P = .01$).

Table 1. Patient Demographics and Clinical Characteristics by Study Group

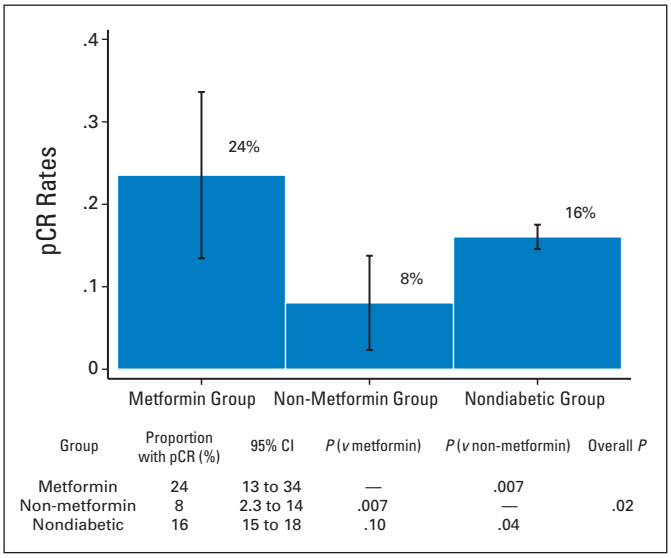
Characteristic	Metformin Group* No.	%	Nonmetformin Group* No.	%	Nondiabetic Group* No.	%	*P*
Age at diagnosis, years							< .001
Median	57.5		57		49		
Range	41-75		34-87		21-83		
< 50	15 of 68	22	20 of 87	23	1,263 of 2,374	53	
≥ 50	53 of 68	78	67 of 87	77	1,111 of 2,374	47	
Menopausal status at diagnosis							< .001
Premenopausal	15 of 68	22	14 of 87	16	1,169 of 2,363	49	
Postmenopausal	53 of 68	78	73 of 87	84	1,194 of 2,363	51	
Hemoglobin A1c level†							.52
Median	7.3		7.8		—		
Range	5.1-13.7		5.4-12.7		—		
BMI							.001
Median	33.8		32.8		26.9		
Range	22.5-61.7		15.9-57.9		16.3-66.0		
Category							
Normal/underweight, ≤ 25	4 of 68	6	12 of 85	14	841 of 2,283	37	
Overweight, 25 to < 30	16 of 68	24	24 of 85	28	724 of 2,283	32	
Obese, ≥ 30	48 of 68	71	49 of 85	58	718 of 2,283	31	
Clinical stage							.18
I	0 of 68	0	1 of 87	1	116 of 2,363	5	
II	38 of 68	56	49 of 87	56	1,309 of 2,363	55	
III	30 of 68	44	37 of 87	43	937 of 2,363	40	
Nuclear grade							.28
1	4 of 66	6	0 of 86	0	77 of 2,314	3	
2	23 of 66	35	28 of 86	33	728 of 2,314	31	
3	39 of 66	59	58 of 86	67	1,509 of 2,314	65	
ER/PR status							.36
Both negative	30 of 68	44	31 of 87	36	848 of 2,374	36	
Either positive	38 of 68	56	56 of 87	64	1,526 of 2,374	64	
HER-2 status							.23
Negative	47 of 68	69	69 of 85	81	1,760 of 2,334	75	
Positive	21 of 68	31	16 of 85	19	574 of 2,334	25	
Lymphovascular invasion							.80
No	48 of 67	72	55 of 82	67	1,548 of 2,282	68	
Yes	19 of 67	28	27 of 82	33	732 of 2,282	32	
Insulin use							.02
No	57 of 68	84	58 of 87	67	—		
Yes	11 of 68	16	29 of 87	33	—		
Thiazolidinedione use							.36
No	48 of 68	71	67 of 87	77	—		
Yes	20 of 68	29	20 of 87	23	—		
Taxane use							.01
No	9 of 68	13	14 of 87	16	597 of 2,374	25	
Yes	59 of 68	87	73 of 87	84	1,777 of 2,374	75	

Abbreviations: BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.
*Because of rounding, figures may not add up to 100%.
†Based on available data of 29 patients in the metformin group and 34 patients in the nonmetformin group.

Metformin and pCR Rates

The proportion of pCR was significantly higher in the metformin group (24%; 95% CI, 13% to 34%) than it was in the nonmetformin group (8.0%; 95% CI, 2.3% to 14%) and the nondiabetic group (16%; 95% CI, 15% to 18%; $P = .02$; Fig 1). Pairwise comparisons revealed a significant difference between the metformin and nonmetformin groups ($P = .007$) and the nonmetformin and nondiabetic groups ($P = .04$). The comparison between the metformin and nondiabetic groups trended toward but did not meet statistical significance ($P = .10$). To evaluate whether differences in amount of chemotherapy delivered caused the difference in pCR rates, we calculated the percentage of planned chemotherapy cycles delivered in the metformin and nonmetformin groups. There was no significant difference; both groups received approximately 90% of the planned cycles of neoadjuvant chemotherapy ($P = .72$). In addition, the average number of cycles delivered per patient was approximately seven in both groups.

Multivariate logistic regression was used to model factors predictive of pCR (Table 2). After adjustment for diabetes status (yes *v* no), BMI, age, stage, grade, ER/PR and HER-2 status, and neoadjuvant taxane use, metformin use during neoadjuvant chemotherapy was



Group	Proportion with pCR (%)	95% CI	P (v metformin)	P (v non-metformin)	Overall P
Metformin	24	13 to 34	—	.007	
Non-metformin	8	2.3 to 14	.007	—	.02
Nondiabetic	16	15 to 18	.10	.04	

Fig 1. Proportions of pathologic complete response (pCR) between study groups. Comparison of pCR rates between the study groups (graph) and pairwise statistical comparisons of pCR rates between the study groups.

found to be an independent predictor of pCR (odds ratio, 2.95; 95% CI, 1.07 to 8.17; $P = .04$). Factors known to be predictive of pCR, such as earlier stage, higher tumor grade, ER-negative and HER-2–positive status, and neoadjuvant taxane use,[25] were confirmed to be so in this analysis. The results for obesity as a predictor of pCR were statistically significant for the comparison of overweight versus nonoverweight status, but not for obese versus nonoverweight status (Table 2).

Because the use of insulin was different in the metformin versus the nonmetformin diabetic groups (16% *v* 33%), we conducted an exploratory analysis of the effect of insulin use on pCR in these groups. In the metformin group, the rate of pCR was not different for insulin use versus no insulin use (27% *v* 23%; $P = .75$). However, in the nonmetformin group, the rate of pCR was significantly different for insulin use versus no insulin use (0% *v* 12%; $P = .05$).

Table 2. Multivariate Logistic Regression Model for Pathologic Complete Response

Variable	Odds Ratio	95% CI	P
Diabetes, yes *v* no	0.44	0.20 to 1.00	.05
Age, ≥ 50 years *v* < 50 years	0.89	0.70 to 1.14	.36
Metformin use, yes *v* no	2.95	1.07 to 8.17	.04
Clinical stage, III *v* I and II	0.60	0.47 to 0.77	< .001
Tumor grade, 3 *v* 1 and 2	2.66	1.89 to 3.73	< .001
Hormone receptor status, ER positive and/or PR positive *v* both negative	0.34	0.26 to 0.44	< .001
HER-2 status, positive *v* negative	2.38	1.86 to 3.05	< .001
Neoadjuvant taxane use, yes *v* no	2.30	1.65 to 3.20	< .001
BMI			
Overweight *v* normal/ underweight	0.77	0.56 to 1.04	.09
Obese *v* normal/ underweight	1.16	0.88 to 1.55	.299

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; BMI, body mass index.

Survival Estimates

At a median follow-up of 37 months (range, 0.6 to 167.3 months), an exploratory analysis of RFS and OS estimates via the Kaplan-Meier method was performed. There were 208 recurrences and 500 deaths. The estimated 3-year RFS rates were 76% (95% CI, 70% to 86%), 66% (95% CI, 52% to 76%), and 73% (95% CI, 71% to 75%), for the metformin, nonmetformin, and nondiabetic groups, respectively, and were not significantly different ($P = .66$). The estimated 3-year OS rates were 81% (95% CI, 65% to 90%), 78% (95% CI, 65% to 86%), and 86% (95% CI, 84% to 87%), for the metformin, nonmetformin, and nondiabetic groups, respectively, and were significantly different ($P = .02$). Cox proportional hazards models were used to analyze factors predictive of RFS and OS. Metformin was not an independent predictor of either RFS or OS after adjusting for diabetes status, BMI, age, stage, grade, ER/PR status, and neoadjuvant taxane use (data not shown).

DISCUSSION

The main finding of our study was that diabetic patients with breast cancer receiving metformin and neoadjuvant chemotherapy have a higher pCR rate than do diabetic patients not receiving metformin (24% *v* 8%; $P = .007$; Fig 1). This was not due to a difference in the amount of chemotherapy delivered, because this was balanced between the two diabetic groups. The multivariate model shows that metformin use was independently predictive of pCR (odds ratio, 2.95; 95% CI, 1.07 to 8.17; $P = .04$) after adjustment for diabetes status, BMI, age, stage, grade, ER/PR and HER-2 status, and neoadjuvant taxane use (Table 2). These results are consistent with epidemiologic data showing metformin use in diabetics decreases both cancer incidence and mortality.[17,18] They are also consistent with the known inhibitory effect of metformin on the growth of cancer cell lines[19-22] and of tumors in animal models.[21-24]

The mechanism of the antiproliferative effect of metformin is a matter of ongoing study. Type 2 diabetes is associated with obesity and metabolic syndrome. Patients with type 2 diabetes are insulin resistant and hyperinsulinemic.[27] There is evidence to suggest that elevated insulin levels and the associated changes in levels of insulin-like growth factors, sex hormones, and adipokines contribute to tumorigenesis.[3,13-16] Metformin partially reverses hyperinsulinemia and may also have antiproliferative effects via this mechanism. In clinical studies, elevated insulin levels have been associated with poorer outcomes in patients with breast cancer.[28-30] Metformin has been shown to reduce insulin levels by 22% in nondiabetic hyperinsulinemic women with early-stage breast cancer.[31] This effect may have been at play in our diabetic population, which was composed largely of overweight or obese patients with type 2 diabetes who were expected to have elevated insulin levels (Table 1).

With regard to this, there is recent evidence for the efficacy of nonpharmacologic interventions in reducing insulin resistance and possibly affecting breast cancer outcomes. For instance, women randomly assigned to 16 weeks of a strength and endurance exercise intervention showed decreases in fasting insulin levels and in insulin resistance.[32] The effects of this intervention on outcome have not yet

been reported. In the Women's Intervention Nutrition Study, in the hormone receptor–negative subset, lower dietary fat intake and weight loss in the intervention group correlated with lower long-term mortality compared with that of the control group (7.5% *v* 18.1%).[33,34] There is no insulin level analysis available, but the result is consistent with the notion that factors other than estrogen, such as insulin, are important in this ER- and PR-negative subset. However, some studies have reported no association between exercise interventions and changes in insulin levels in breast cancer survivors.[35,36]

Interestingly, in our study, the pCR rate was also lower in the nonmetformin diabetic group compared with that in the nondiabetic group (8% *v* 16%; $P = .04$). The rate of 16% in the nondiabetic patients is consistent with other studies of taxane-based neoadjuvant chemotherapy in patients with breast cancer.[1,2,25] The lower rate in the nonmetformin group raises the possibility that other factors particular to this group make the tumors less susceptible to neoadjuvant chemotherapy. The higher rate in the metformin group compared with that in the nonmetformin group suggests these factors may be reversed by metformin.

We examined the possibility that exogenous insulin administration, which may promote tumorigenesis and which was different between the metformin and nonmetformin groups (16% *v* 33%), might have had an effect on the differences in pCR rates between these groups. There was no difference in the pCR rates in the metformin group (27% for insulin use *v* 23% for no insulin use; $P = .75$). However, insulin use was associated with a significant decrease in the pCR rate in the nonmetformin group (0% for insulin use *v* 12% for no insulin use; $P = .05$). These results suggest that part of the difference in pCR rates between the metformin and nonmetformin groups (and between the nonmetformin and nondiabetic groups) may be attributable to insulin use. However, insulin use is only one factor, because patients who were not receiving insulin also seemed to benefit from the addition of metformin (pCR rate increased from 12% to 23%).

Metformin activates the AMP-activated protein kinase (AMPK) pathway in a manner dependent on the upstream kinase LKB1. In hepatocytes, this results in inhibition of gluconeogenesis, and this is the principal mediator of the glucose- and insulin-lowering effects of metformin.[37] Under low-energy and other stress conditions, AMPK phosphorylates a number of targets to inhibit cellular growth and proliferation, including components of the growth-promoting mammalian target of rapamycin pathway.[38-40] Whether the apparent antitumor effect of metformin in our diabetic patients may have been mediated by endogenous insulin or insulin-like growth factors, AMPK, the mammalian target of rapamycin pathway, or other pathways remains to be defined.

An exploratory survival analysis conducted at a median follow-up of 37 months showed no significant difference in 3-year RFS between the three groups ($P = .66$). However, there was a difference in 3-year OS; patients in the diabetic groups were doing worse than were those in the nondiabetic group ($P = .02$). This is consistent with the known worse outcomes of diabetic versus nondiabetic patients with breast cancer.[6-8] In addition, although the pCR rate in the metformin group was threefold that in the nonmetformin group, there was no significant difference in the RFS or OS between these two groups. This can be explained by the modest effect substantial differences in pCR may have on RFS and OS, because the number of patients with pCR is often not large enough to impact the survival of the group as a whole. For example, the National Surgical Adjuvant Breast and Bowel Project B-27 study of neoadjuvant chemotherapy in breast cancer showed no differences in RFS or OS, despite a doubling of the pCR rate in the taxane-containing group (26%) versus the nontaxane-containing group (13%).[1] However, the patients in this study who did achieve pCR had a significant improvement in RFS and OS compared with those who did not.[1] Similar data from a number of other studies have confirmed that pCR is correlated with improved RFS and OS; thus pCR has become a surrogate end point for survival in neoadjuvant studies of breast cancer.[2,41]

To our knowledge, our study has provided the first clinical evidence of the potential efficacy of metformin as an antitumor agent in breast cancer. It was based on one of the largest breast cancer neoadjuvant chemotherapy databases available, although the number of diabetic patients was modest because of the relatively low prevalence of diabetes. Several factors may have differed between the study groups and resulted in bias in the outcome measures. These include potential misclassification of diabetic patients (most were self-identified and taking diabetic medications) and diabetes control (the available A1c data suggested no difference). A number of patients were excluded because of incomplete medication or other records, and the reasons why certain patients were taking particular diabetic medications (such as metformin *v* insulin) are unknown. As with any retrospective study, there remains the possibility of unidentified confounders nonrandomly distributed between the groups of interest.

The main finding of the study—that there is an association between metformin use and higher pCR rates in diabetic patients receiving neoadjuvant chemotherapy—is hypothesis generating and consistent with the idea that metformin may have an antitumor effect in patients with breast cancer. In combination with the growing body of preclinical data, this suggests that this hypothesis deserves to be tested prospectively. We are conducting additional clinical and laboratory studies to evaluate the potential of this interesting and widely used diabetes drug as an antitumor agent.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Provision of study materials or patients: Ana M. Gonzalez-Angulo

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