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Effect of Metformin vs Placebo on Invasive Disease–Free Survival in Patients With Breast Cancer
The MA.32 Randomized Clinical Trial

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IMPORTANCE Metformin, a biguanide commonly used to treat type 2 diabetes, has been associated with potential beneficial effects across breast cancer subtypes in observational and preclinical studies.

OBJECTIVE To determine whether the administration of adjuvant metformin (vs placebo) to patients with breast cancer without diabetes improves outcomes.

DESIGN, SETTING, AND PARTICIPANTS MA.32, a phase 3 randomized, placebo-controlled, double-blind trial, conducted in Canada, Switzerland, US, and UK, enrolled 3649 patients with high-risk nonmetastatic breast cancer receiving standard therapy between August 2010 and March 2013, with follow-up to October 2020.

INTERVENTIONS Patients were randomized (stratified for hormone receptor [estrogen receptor and/or progesterone receptor {ER/PgR}] status, positive vs negative; body mass index, ≤30 vs >30; human epidermal growth factor receptor 2 [*ERBB2,* formerly *HER2* or *HER2/neu*], positive vs negative; and any vs no chemotherapy) to 850 mg of oral metformin twice a day (n = 1824) or oral placebo twice a day (n = 1825) for 5 years.

MAIN OUTCOMES AND MEASURES The primary outcome was invasive disease–free survival in hormone receptor–positive breast cancer. Of the 8 secondary outcomes, overall survival, distant relapse–free survival, and breast cancer–free interval were analyzed.

RESULTS Of the 3649 randomized patients (mean age, 52.4 years; 3643 women [99.8%]), all (100%) were included in analyses. After a second interim analysis, futility was declared for patients who were ER/PgR−, so the primary analysis was conducted for 2533 patients who were ER/PgR+. The median duration of follow-up in the ER/PgR+ group was 96.2 months (range, 0.2-121 months). Invasive disease–free survival events occurred in 465 patients who were ER/PgR+. The incidence rates for invasive disease–free survival events were 2.78 per 100 patient-years in the metformin group vs 2.74 per 100 patient-years in the placebo group (hazard ratio [HR], 1.01; 95% CI, 0.84-1.21; *P* = .93), and the incidence rates for death were 1.46 per 100 patient-years in the metformin group vs 1.32 per 100 patient-years in the placebo group (HR, 1.10; 95% CI, 0.86-1.41; *P* = .47). Among patients who were ER/PgR−, followed up for a median of 94.1 months, incidence of invasive disease–free survival events was 3.58 vs 3.60 per 100 patient-years, respectively (HR, 1.01; 95% CI, 0.79-1.30; *P* = .92). None of the 3 secondary outcomes analyzed in the ER/PgR+ group had statistically significant differences. Grade 3 nonhematological toxic events occurred more frequently in patients taking metformin than in patients taking placebo (21.5% vs 17.5%, respectively, *P* = .003). The most common grade 3 or higher adverse events in the metformin vs placebo groups were hypertension (2.4% vs 1.9%), irregular menses (1.5% vs 1.4%), and diarrhea (1.9% vs 7.0%).

CONCLUSIONS AND RELEVANCE Among patients with high-risk operable breast cancer without diabetes, the addition of metformin vs placebo to standard breast cancer treatment did not significantly improve invasive disease–free survival.

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Visual Abstract

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Metformin, a biguanide commonly used to treat type 2 diabetes, has been associated with improved prognosis across breast cancer subtypes in observational studies involving patients with diabetes, although findings have not been consistent.[1-5] Metformin has also been shown to lower fasting insulin levels and improve obesity associated physiology in patients with breast cancer without diabetes.[6,7] Current understanding of metformin action in cancer includes potential indirect effects resulting from reduced insulin signaling through the phosphatidylinositol 3-kinase (PI3K) and RAS pathways as well as direct antitumor effects (notably liver kinase B1 [LKB1]-mediated activation of AMP-activated protein kinase [AMPK], a negative regulator of PI3K/protein kinase B [AKT]/mammalian target of rapamycin [mTOR] signaling and protein synthesis). Preclinical research provides evidence that metformin may affect all breast cancer subtypes; however, translation to the clinical setting is not straightforward because of the use of supraphysiological concentrations of glucose, insulin, and metformin in the in vitro and in vivo laboratory systems used in the preclinical research.[8,9]

In clinical intervention studies, metformin has been reported to lower intratumoral Ki67 when administered prior to breast cancer excision in some, but not all, studies.[10-13] In a study involving human epidermal growth factor receptor 2 (*ERBB2;* formerly *HER2* or *HER2/neu*)-positive breast cancer, the addition of metformin to neoadjuvant chemotherapy and *ERBB2*-targeted therapy led to higher rates of pathological complete response in patients with at least 1 copy of the *C* allele of the rs11212617 single-nucleotide variant (SNV [formerly single-nucleotide polymorphisms {SNPs}),[14] an allele that has also been associated with enhanced glycemic response and higher metformin blood levels in patients with diabetes.[15]

Based on the above data, it was hypothesized that the use of metformin (vs placebo) given for 5 years would improve invasive disease-free survival and other outcomes in patients with operable breast cancer without diabetes.

Key Points

Question Does the addition of metformin to standard breast cancer treatment improve invasive disease–free survival?

Findings This randomized clinical trial included 3649 patients with high-risk operable breast cancer without diabetes. Treatment with metformin vs placebo resulted in a hazard ratio for an invasive disease–free survival event of 1.01; this was not statistically significant.

Meaning Addition of metformin to standard breast cancer treatment did not significantly improve invasive disease–free survival.

Methods

The protocol and statistical analysis plan for this trial are in Supplements 1 and 2. The study was approved by the Adult Central Institutional Review Board (US National Institutes of Health) and the Ontario Cancer Research Ethics Board and by institutional review boards associated with the participating institutions. All patients provided written informed consent to participate.

MA.32 was an investigator-initiated phase 3 randomized trial conducted by the Canadian Cancer Trials Group (CCTG), in concert with the National Cancer Institute (NCI) US National Clinical Trials Network, UK National Cancer Research Institute, and the Swiss International Breast Cancer Study Group and in accordance with applicable regulatory standards and standard operating procedures. An academic trial committee provided scientific oversight of the trial design, conduct and interpretation of the primary analysis results. Data monitoring, collection, and analysis were performed by the trial sponsor. An independent data and safety monitoring committee reviewed study conduct and safety every 6 months and oversaw the conduct of 2 interim analyses.

Study Population

Patients without diabetes, aged 18 through 74 years, who received standard therapy for a T1 to T3, N0 to N3, M0 breast cancer (excluding T1aN0 and T1bN0) diagnosed during the previous year were enrolled between 2010 and 2013. Those with T1cN0 breast cancer were eligible if they had at least 1 of the following: histologic grade 3, lymphovascular invasion, negative hormone receptors (estrogen receptor and progesterone receptor [ER/PgR−]), *ERBB2* positivity (*ERBB2*+), Oncotype Recurrence Score of 25 or higher, or Ki67 of more than 14%. In May 2012, after 2382 patients were enrolled, amended eligibility criteria mandated triple negative (ER−, PgR−, and *ERBB2*−) status for patients with T1cN0 disease and 1 or more of the above adverse characteristics for those with T2N0 tumors. Patients were required to have a fasting glucose of 126 mg/dL or less (to convert from mg/dL to mmol/L, multiply by 0.0555). Those with a history of diabetes; lactic acidosis; current use of diabetes medication; breast cancer recurrence or previous invasive cancer; habitual intake of 3 or more alcoholic drinks daily; or marked hepatic, kidney, or cardiac dysfunction were excluded. Patients were required to have undergone complete resection of their breast cancer and to have completed neoadjuvant chemotherapy (if given) but could be continuing radiation, adjuvant hormones, *ERBB2*-targeted therapy, other biologics, or bone-targeted therapy (if given) after enrollment. As mandated by the US NCI, patients self-reported information on race and ethnicity using fixed categories.

Randomization

Randomization was 1:1 for metformin to placebo and was stratified for (1) ER and/or PgR+ (ER/PgR+) (≥1%) vs ER/PgR− (<1%), (2) body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or less vs more than 30, (3) *ERBB2* positive vs negative, (4) any vs no chemotherapy and balanced for center. A minimization procedure[16] using the stratification factors was used to allocate patients with equal probabilities to 1 of the 2 treatment groups.

Intervention

Patients received 850 mg of metformin (or an identical-appearing placebo) provided by Apotex Canada (Mississauga) once daily for 4 weeks then twice daily for the balance of 5 years. Study medication was reduced to once daily or discontinued for toxic effects; it was discontinued for 2 to 3 days for radiological investigations requiring intravenous contrast material or receipt of general anesthesia. Patients were asked to resume twice daily dosing as soon as possible after dose reductions or stoppages.

Trial Procedures

Prior to randomization, clinical and radiological assessments were required at diagnosis or later to rule out metastases; blood samples were collected to verify adequate kidney and liver function and to ensure that the fasting glucose value was 126 mg/dL or less. Patients provided consent for collection of tumor and normal breast tissue and fasting blood samples for analyses of metabolic and related factors as previously reported.[7,17-19]

Follow-up was conducted at 6 and 12 months and then annually. Patients provided fasting blood samples at 6 and 60 months. All grade 3 or greater adverse events were recorded at each visit using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 while patients were taking metformin or placebo, and only treatment-related adverse events were recorded thereafter.

Trial End Points

The primary end point was invasive disease-free survival defined as time from randomization to the earliest occurrence of invasive local, regional, or distant recurrences, new primary invasive cancers (breast or nonbreast), and death (from breast cancer, from a nonbreast cancer, or from an unknown cause).[20] Secondary cancer end points included overall survival (time to any death), distant relapse-free survival (time to distant recurrence or death), and breast cancer-free interval (time to any invasive or noninvasive breast cancer event). These end points were centrally verified through a review of supporting documentation (by P.J.G., L.E.S., and W.R.P.). Other secondary end points included new diabetes diagnosis, cardiovascular hospitalizations, quality of life, diet, and physical activity and are not reported in this article.

Sample Size Calculation

The sample size was based on a target hazard ratio (HR) of 0.76, with an estimated 5-year invasive disease-free survival of 85% in the placebo group and 89% in the metformin group; enrolment of 3582 patients with 431 events provided 80% power to detect this HR with a 2-sided α of .05. The minimal detectable difference of 4% (from 85% to 89%) was based primarily on expert consensus of the study investigators; it also reflected the HR seen with a dietary fat reduction intervention in the Women's Intervention Nutrition Study.[21] In 2012, entry was restricted to higher-risk breast cancer, leading to 80% power to detect an HR of 0.785 with 544 events. In 2016, after the second interim analysis, conducted at 29.5 months' median follow-up, once 370 events had occurred, the data and safety monitoring committee, after consultation with an independent statistician, recommended the primary analysis be conducted for the 2533 patients who were ER/PgR+ only (regardless of *ERBB2* status), with a planned analysis at 544 events, which would provide 80% power to detect an HR of 0.78 with a 2-sided $P = .037$. Patients who were ER/PgR− stopped taking the study drug for futility (O'Brien-Fleming $P > .49$) but blinding and follow-up continued with additional analyses of breast cancer outcomes planned. Due to a declining event rate, a time-driven analysis of patients who were ER/PgR+ was approved in 2021; with 466 events at the data lock on October 31, 2020, there was 80% power to detect an HR of 0.757 (3.8% difference between study groups), 2-sided $P = .037$.

Statistical Analysis

Time-to-event survival experiences were described using the Kaplan-Meier method. Two-sided log-rank tests adjusting for stratification factors were the primary method of comparing invasive disease-free survival between groups with patients analyzed according to randomization groups. Cox proportional hazards models were used to identify and adjust for factors significantly related to invasive disease-free survival (*ERBB2* status, BMI, neoadjuvant chemotherapy) and to explore interactions of treatment effect with the rs11212617 SNV. Incidence rates of events per 100 patient-years were calculated in both study groups, recognizing that these numbers reflect averages and that incidence rates may vary over time.

The null hypothesis about the proportional hazards assumption[22] was not rejected in analyses of invasive disease-free survival or overall survival end points (P value = .61 and .83, respectively).

Missing day or month data were imputed using midpoints within the smallest known interval. For categorical variables such as grade, the number and percentage of patients with missing data were reported.

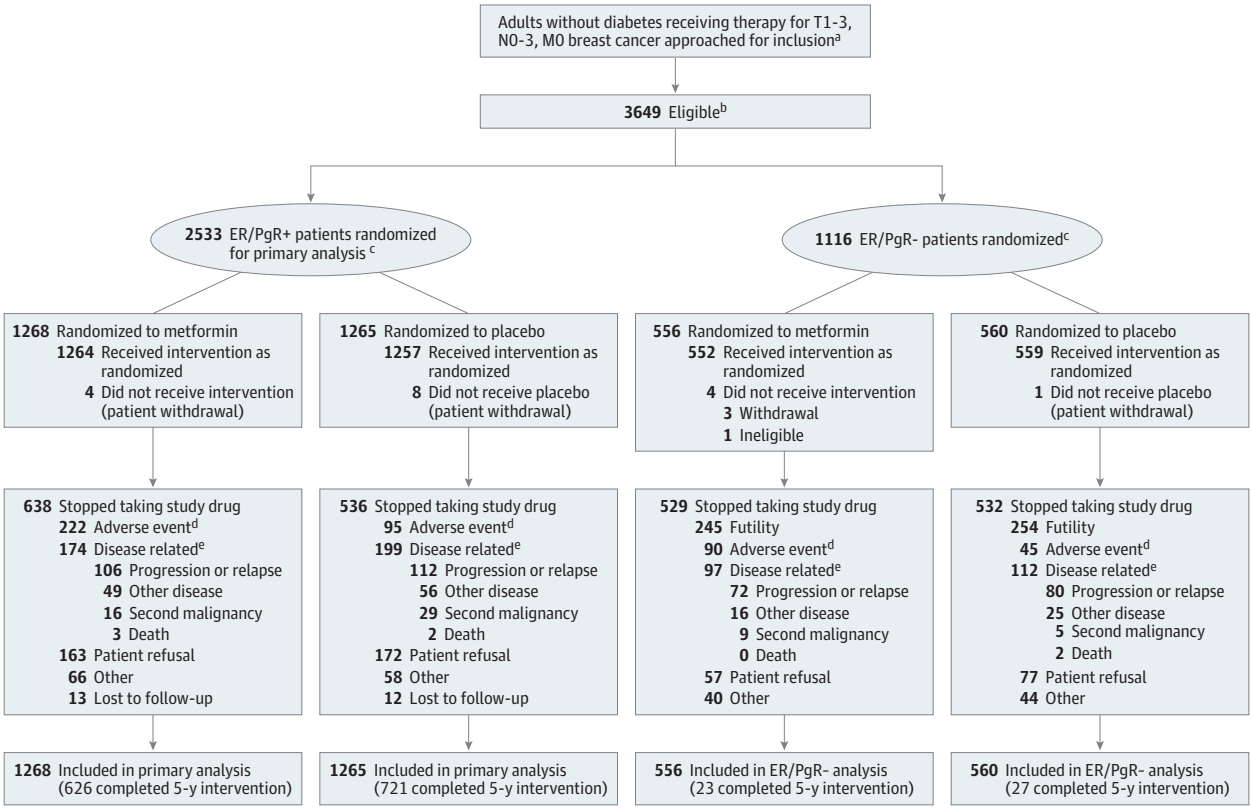
Based on results of the METTEN study,[14] exploratory analyses were conducted in patients with *ERBB2*+ breast cancer. Post hoc tests of interaction of *ERBB2* status (positive vs negative) with the effect of metformin vs placebo on invasive disease-free survival and overall survival end points were performed.

The threshold for significance for the primary analysis was .037; for other analyses it was .05 (both 2-sided). Analyses were performed using SAS version 9.4 (SAS Institute Inc). Because of the potential for type I error due to multiple comparisons, findings of secondary analyses were considered exploratory.

Results

A total of 3649 patients were randomized (mean age, 52.4 years; 3643 women [99.8%]). The Canadian centers enrolled 34% of the patients; the US centers, 60%; and the UK and Swiss centers, 6%. After futility was declared for the 1116 patients with ER/PgR− breast cancer in early 2016, the 2533 patients with ER/PgR+ breast cancer comprised the final primary analysis data set of whom 1268 were randomized to receive metformin and 1265 to receive placebo (**Figure 1**). Twenty-eight patients in the

Figure 1. Study Enrollment and Flow of Patients Without Diabetes With Estrogen Receptor and/or Progesterone Receptor Positive and Negative Breast Cancer Through the MA.32 Trial



[a] Information obtained in screening potential patients was not consistently collected across sites.

[b] Patients were stratified by estrogen receptor and/or progesterone receptor (ER/PgR) status (positive vs negative), body mass index, calculated as weight in kilograms divided by height in meters squared, (<30 vs > 30), human epidermal growth factor receptor 2 (*ERBB2*, formerly *HER2* or *HER2/neu*) status (positive vs negative), and chemotherapy (any vs none).

[c] We originally planned to include all randomized patients in the primary analysis. However, after the second interim analysis, futility was declared for ER/PgR– breast cancer (see the Methods section) causing the cessation of the study drug for these patients. The study was redesigned by an independent statistician for the primary analysis to be conducted for patients with HR+ breast cancer.

[d] Adverse events or complications.

[e] Disease-related events during active treatment.

metformin group and 20 in the placebo group were ineligible; the main reasons for ineligibility were no axillary dissection (n = 18) or an ineligible TNM classification (n =18). The COVID-19 pandemic led to 195 protocol variances (6.2%) that were balanced between study treatment groups. The variances all occurred during posttreatment follow-up: 138 virtual or phone visits, 12 delayed or missed visits, 20 delayed or missed disease assessments, and 25 for other reasons. One patient was excluded from the mean age calculation because their age was not recorded. Twelve patients who did not receive the assigned protocol treatment were excluded from the safety analysis population.

The baseline demographic characteristics and tumor status among patients with ER/PgR+ breast cancer, the primary analysis population, were balanced between treatment groups (median age, 53 years [range, 25-74 years]; 6 men; **Table 1**). Of patients in the ER/PgR+ group, 63 were Asian (2.5%), 9 American Indian or Alaska Native (0.35%), 91 Black (3.6%), 10 Native Hawaiian or Pacific Islander (0.04%), 105 Hispanic (4.1%), and 2217 White non-Hispanic (87.5%). Additionally, 1561 patients (61.6%) were postmenopausal and 2038 (80.5%) had an Eastern Cooperative Oncology Group (ECOG) performance status scale grade of 0; 1700 patients (67.1%) had T2 or T3 tumors; 1569 (61.9%) had involved axillary nodes; 2191 cancers (86.5%) were grade 2 or 3; and 2104 cancers (83.1%) were *ERBB2*–. Of those receiving perioperative treatment, 2150 (84.9%) underwent chemotherapy; 2224 (87.8%), hormone therapy; 434 (17.1%), *ERBB2*-targeted therapy, and 1901 (75.0%), radiotherapy. The median BMI was 27.4 (IQR, 24-32). Overall, randomization occurred a mean (SD) of 276 (69) days after diagnosis.

Primary Outcome

ER/PgR+ Breast Cancer

After a median follow-up of 96.2 months (range, 0.2-121 months), 465 of 2533 patients (18.4%) in the ER/PgR+ group had invasive disease-free survival events (234 metformin group vs 231 placebo group; **Table 2**). Of those, 351 (75.6%) were

Table 1. Baseline Patient and Tumor Characteristics by Study Group of Patients With Breast Cancer Without Diabetes

	No. (%) of patients			
	ER/PgR+		ER/PgR−	
	Metformin (n = 1268)	Placebo (n = 1265)	Metformin (n = 556)	Placebo (n = 560)
Age, median (range), y	52 (25-74)	53 (25-74)	51 (25-74)	52 (23-74)
BMI, median (IQR)	27 (24-32)	28 (24-32)	27 (24-31)	27 (24-32)
Women	1265 (99.8)	1262 (99.8)	556 (100)	560 (100)
Men	3 (0.02)	3 (0.02)	0	0
Race				
No. (%)	1253 (98.8)	1242 (98.2)	548 (98.6)	557 (99.5)
American Indian or Alaska Native	4 (0.3)	5 (0.4)	5 (0.9)	3 (0.5)
Asian	33 (2.7)	33 (2.7)	21 (3.8)	15 (2.7)
Black or African American	36 (3.7)	44 (3.5)	36 (6.6)	40 (7.2)
Hispanic	49 (3.9)	56 (4.5)	35 (6.4)	38 (6.8)
Native Hawaiian or Pacific Islander	4 (0.3)	6 (0.5)	1 (0.2)	2 (0.4)
White non-Hispanic	1119 (89.3)	1098 (88.4)	450 (82.1)	459 (82.4)
Postmenopausal status[a]	787 (62.1)	774 (60.2)	323 (58.1)	353 (63.0)
ECOG performance status[b]				
0	1026 (80.9)	1012 (80.0)	432 (77.7)	446 (79.6)
1	238 (18.8)	250 (19.8)	120 (21.6)	111 (19.8)
2	4 (0.3)	3 (0.2)	4 (0.7)	3 (0.5)
Tumor stage[c]				
cT1	16 (1.3)	26 (2.1)	19 (3.4)	24 (4.3)
cT2	116 (9.1)	122 (9.6)	102 (18.3)	94 (16.8)
cT3	80 (6.3)	89 (7.0)	37 (6.7)	47 (8.4)
pT1	405 (32.0)	385 (30.4)	180 (32.4)	184 (32.9)
pT2	550 (43.3)	563 (44.5)	201 (36.2)	195 (34.8)
pT3	100 (7.9)	80 (6.3)	17 (3.1)	16 (2.9)
pT4	1 (0.1)	0	0	0
Node stage[d]				
cN0	51 (4.0)	78 (6.2)	62 (11.2)	67 (12)
cN1	123 (9.7)	120 (9.5)	73 (13.1)	78 (13.9)
cN2	28 (2.2)	26 (2.1)	12 (2.2)	14 (2.5)
cN3	10 (0.8)	13 (1.0)	11 (2)	6 (1.1)
pN0+pN0(i+)	426 (33.6)	409 (32.9)	252 (45.3)	267 (47.7)
pN1+pN1mi	429 (33.8)	424 (33.5)	99 (17.8)	81 (14.5)
pN2	142 (11.2)	137 (10.8)	30 (5.4)	33 (5.9)
pN3	59 (4.7)	58 (4.6)	17 (3.1)	14 (2.5)
ERBB2+[e]	209 (16.5)	220 (17.4)	105 (18.9)	86 (15.4)
Histologic grade[f]				
1 (low)	164 (12.9)	160 (12.6)	6 (1.1)	0
2 (intermediate)	569 (44.9)	579 (45.8)	75 (13.5)	66 (11.8)
3 (high)	529 (41.7)	514 (40.6)	467 (84)	484 (86.4)
Missing/unknown	6 (0.5)	12 (1.0)	8 (1.4)	10 (1.8)
Adjuvant therapy				
Radiotherapy	936 (73.8)	965 (76.3)	397 (71.4)	405 (72.3)
Chemotherapy	1076 (84.9)	1074 (84.9)	552 (99.3)	556 (99.3)
Hormone therapy	1113 (87.8)	1111 (87.8)	11 (2)	9 (1.6)
Trastuzumab	211 (16.6)	223 (17.6)	103 (18.5)	92 (16.4)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; ECOG, Eastern Cooperative Oncology Group; ER/PgR, estrogen receptor and/or progesterone receptor.

[a] Premenopausal was defined as less than 6 months since last menses and no bilateral oophorectomy or does not meet postmenopausal criteria and age younger than 50 years. Postmenopausal was defined as prior bilateral oophorectomy or more than 12 months since last menses or does not meet premenopausal criteria and age older than 50 years.

[b] The scale assesses how disease affects activities of daily living with a range from 0 (fully active and without restriction compared with predisease status) to 5 (dead). A rating of 3 or higher indicates a need for assistance with self-care.

[c] Tumor stage, as assessed clinically (c) for patients who had received any neoadjuvant therapy and pathologically (p) for those without neoadjuvant therapy.

[d] Nodal stage, as assessed for patients who had received any neoadjuvant therapy (c) and for those without neoadjuvant therapy (p).

[e] *ERBB2* status was classified clinically by pathologists at local centers using a validated classification system. Those not included as positive were considered negative.

[f] Histologic grade was determined for clinical purposes by pathologists at local centers using a validated classification system.

breast cancer related. The incidence rates for invasive disease-free survival events were 2.78 per 100 patient-years in the metformin group and 2.74 per 100 patient-years in the placebo group (HR, 1.01; 95% CI, 0.84-1.21; P = .93; **Figure 2**A).

ER/PgR− Breast Cancer

Although the 1116 patients who had ER/PgR− breast cancer stopped receiving the study drugs in early 2016 (median exposure, 36.7 months; range, 0.07-62.2) when futility was

Table 2. Breakdown of Invasive Disease-Free Survival and Overall Survival Events in Patients With Breast Cancer Without Diabetes[a,b]

	No. (%)			
	ER/PgR+ population		ER/PgR− population	
	Metformin (n = 1268)	Placebo (n = 1265)	Metformin (n = 556)	Placebo (n = 560)
Patients with an invasive disease-free survival event	234 (18.5)	231 (18.3)	122 (21.9)	123 (22.0)
Event type for first event				
Distant recurrence	127 (10.0)	129 (10.2)	55 (9.9)	67 (12)
Local or regional recurrence	32 (2.5)	39 (3.1)	27 (4.9)	29 (5.2)
Invasive contralateral breast tumor	15 (1.2)	9 (0.7)	10 (1.8)	9 (1.6)
New primary (non-breast cancer) malignancy	49 (3.9)	48 (3.8)	25 (4.5)	12 (2.1)
Death (breast cancer)	0	0	0	1 (0.2)
Death (other primary malignancy)	0	1 (0.1)	0	0
Death (primary cardiovascular disease)	3 (0.2)	1 (0.1)	0	0
Death (other and unknown)	8 (0.6)	4 (0.4)	5 (0.9)	5 (0.9)
Patients with a death at any time (before or after an invasive disease-free survival event)	131 (10.3)	119 (9.4)	70 (12.6)	79 (14.1)
Cause of death				
Breast cancer	99 (7.8)	91 (7.2)	56 (10.1)	69 (12.3)
Other primary malignancy	15 (1.2)	15 (1.2)	6 (1.1)	4 (0.7)
Cardiovascular disease	4 (0.3)	2 (0.2)	0	0
Other condition	13 (1.0)	11 (0.9)	8 (1.4)	6 (1.1)

Abbreviation: ER/PgR, estrogen receptor and/or progesterone receptor.

[a] All items shown in the upper section of this table together comprised elements in the composite outcome of invasive disease-free survival.

[b] Median follow-up was 96.2 months in the ER/PgR+ population and 94.1 months in the ER/PgR− population.

declared at the second interim analysis, treatment allocation remained blinded and follow-up continued. Invasive disease-free survival events occurred in 172 patients (15.4%) at the interim analysis and in 245 (22.0%) at the final analysis, which was conducted for a median of 94.1 months (range, 0.03-121.0) of follow-up (Table 2). Compared with patients in the ER/PgR+ group, those in the ER/PgR− group were somewhat younger (Table 1). Reflecting entry criteria, they had smaller but higher-grade cancers with less nodal involvement, and 1108 (99.3%) received adjuvant chemotherapy. The invasive disease-free survival event incidence rate was 3.58 per 100 patient-years in the metformin group vs 3.60 per 100 patient-years in the placebo group (HR, 1.01; 95% CI, 0.79-1.30; *P* = .92; Figure 2C).

Secondary Outcomes

ER/PgR+ Breast Cancer

In the ER/PgR+ population, 190 of 250 deaths (76.0%) were related to breast cancer. Metformin did not significantly affect overall survival: the metformin group had 1.46 deaths per 100 patient-years vs 1.32 deaths per 100 patient-years in the placebo group (HR, 1.10; 95% CI, 0.86-1.41; *P* = .47; Figure 2B). Metformin did not have any effect on distant recurrence-free survival. Both treatment groups had 1.99 distant recurrences or deaths per 100 patient-years (HR, 0.99; 95% CI, 0.80-1.23; *P* = .94). And metformin did not have any effect on breast cancer-free interval. The rates of invasive or noninvasive breast cancer events were 2.15 per 100 patient-years in the metformin group vs 2.18 in the placebo group (HR, 0.98; 95% CI, 0.80-1.20; *P* = .87). rs11212617 SNV status was available for 2334 patients (92.1%) who had ER/PgR+ breast cancer; of those, 1626 (69.7%) had at least 1 *C* allele. Metformin's effect on invasive disease-free survival or overall survival did not vary by any *C* allele (*CC* or *AC* genotypes) vs *AA* genotype (*P* for interaction, .97 and .46, respectively).

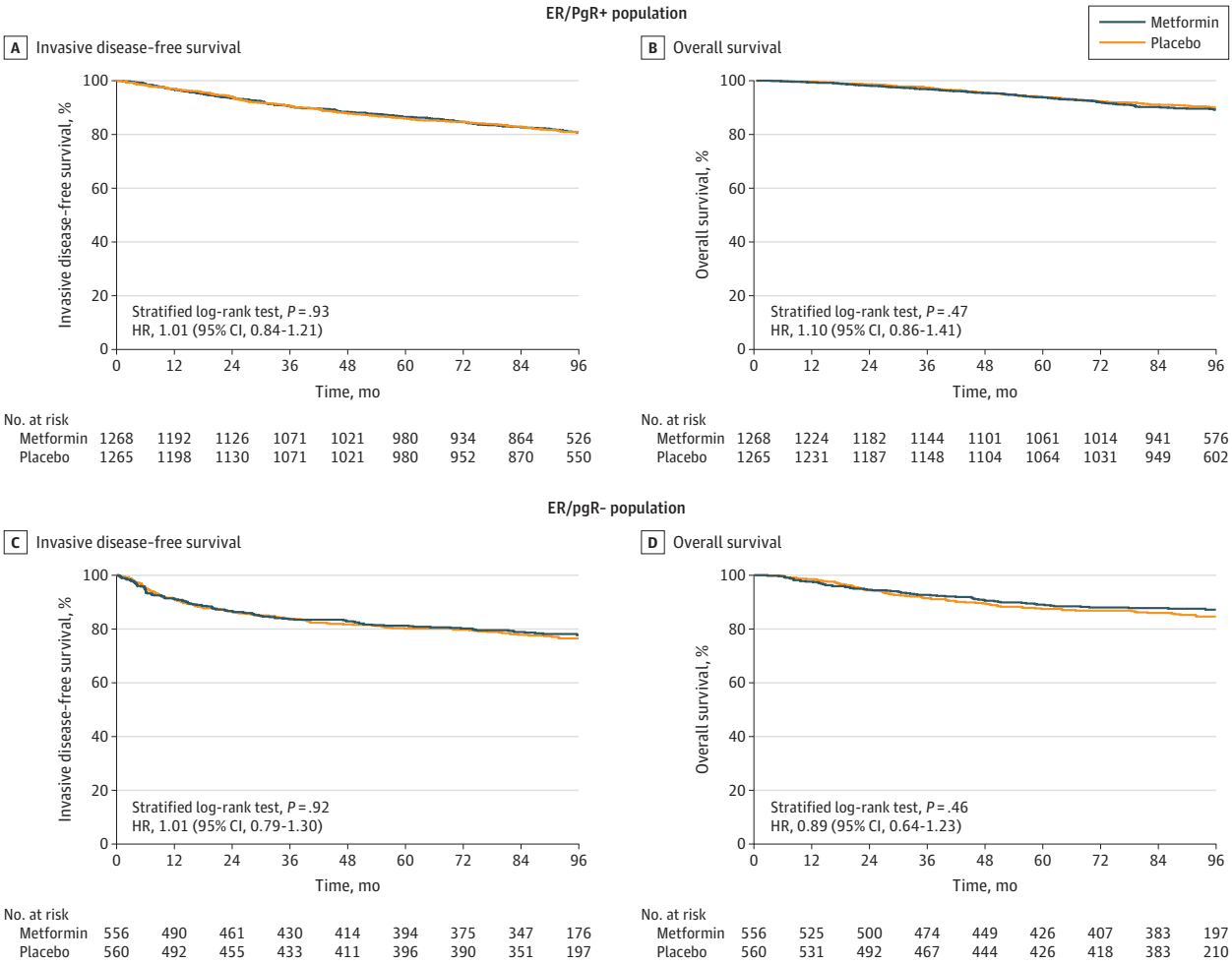
ER/PgR− Breast Cancer

In the ER/PgR− population, there were 1.91 deaths per 100 patient-years in the metformin group vs 2.15 in the placebo group (HR, 0.89; 95% CI, 0.64-1.23; *P* = .46; Figure 2D). Metformin did not have any effect on distant recurrence-free survival (2.35 events per 100 patient-years vs 2.63 in the placebo group; HR, 0.90; 95% CI, 0.67-1.20; *P* = .46); and did not have any effect on breast cancer-free interval (rates of invasive or noninvasive breast cancer events were 2.75 per 100 patient-years vs 3.14 in the placebo group; HR, 0.88; 95% CI, 0.67-1.16; *P* = .35). The effect of metformin on invasive disease-free survival and overall survival did not differ by rs11212617 SNV status (*P* for interaction, .31 and .25, respectively).

Exploratory Analyses in the *ERBB2*+ Population

ERBB2 status did not have a significant impact on the effect of metformin vs placebo on invasive disease-free and overall survival outcomes (*P* for interaction, .59 and .49, respectively). Analyses focused on hypotheses that metformin would be beneficial among those with *ERBB2*+ breast cancer, notably among those with any *C* allele of the rs11212617 SNV. Characteristics of patients by *ERBB2* status and the distribution of outcome events are shown in eTables 1 and 2 in the Supplement 3. The median duration of exposure to the study drug was 58.5 months (range, 0.07-63.8); the median duration of follow-up, 95.4 months (range, 0.03-120.0) among patients with *ERBB2*+ cancers. Patients with *ERBB2*+ breast cancer in

Figure 2. Effect of Metformin vs Placebo on Invasive Disease-Free Survival and Overall Survival



The median duration of follow-up was 96 months (IQR, 86-102) for treatment groups of patients with estrogen receptor and/or progesterone positive (ER/PgR+) breast cancer and was 94 months (IQR, 86-101) for both treatment groups of patients with ER/PgR− breast cancer.

A, Invasive disease-free survival (events include breast cancer recurrence, new primary cancers, or death).

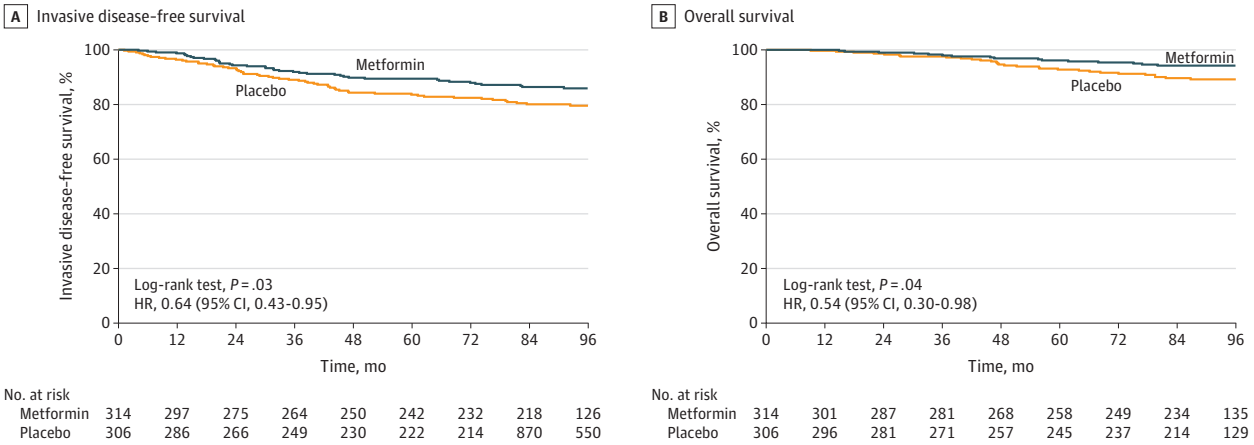
B, Overall survival.

C, Invasive disease-free survival (events include breast cancer recurrence, new primary cancers, or death).

D, Overall survival.

the metformin group vs the placebo group had longer invasive disease-free survival (metformin, 1.93 events per 100 patient-years vs placebo, 3.05 events per 100 patient-years; HR, 0.64; 95% CI, 0.43-0.95; P = .03) and had longer overall survival (metformin, 0.78 deaths per 100 patient-years vs placebo, 1.43 deaths per 100 patient-years; HR, 0.54; 95% CI, 0.30-0.98; P = .04, **Figure 3**). Among patients with *ERBB2*+ breast cancer, there was a significant interaction of rs11212617 SNV status with the effect of metformin on invasive disease-free survival (P for interaction = .05) and overall survival (P for interaction = .02). Invasive disease-free survival events among those with any *C* allele (*CC*, *AC* genotype) were 1.74 per 100 patient-years in the metformin group vs 3.48 in the placebo group (HR, 0.51; 95% CI, 0.31-0.83; P = .007), and there were 0.69 deaths per 100 patient-years in the metformin group vs 1.96 in the placebo group (HR, 0.35; 95% CI, 0.17-0.73; P = .003). Among those with the *AA* genotype, there were 2.50 invasive disease-free survival events per 100 patient-years in the metformin group vs 1.91 in the placebo group (HR, 1.32; 95% CI, 0.58-2.96; P = .51) and 1.18 deaths per 100 patient-years in the metformin group vs 0.53 in the placebo group (HR, 2.15; 95% CI, 0.56-8.36; P = .26; eFigure in the Supplement 3). Metformin did not affect invasive disease-free or overall survival in the patients with *ERBB2*− breast cancer, with a median duration of follow-up of 95.9 months (range, 0.03-121.0); 3.24 invasive disease-free survival events per 100 patient-years occurred in the metformin group vs 2.98 in the placebo group (HR, 1.09; 95% CI, 0.93-1.28; P = .29) and 1.76 deaths per 100 patient-years in the metformin group vs 1.59 in the placebo group (HR, 1.11; 95% CI, 0.90-1.36; P = .34).

Figure 3. Exploratory Analysis of the Effect of Metformin vs Placebo on Invasive Disease-Free and Overall Survival in the Patients With *ERBB2*-Positive Breast Cancer



The median duration of follow-up was 96 months (IQR, 85-101) for both treatment groups of patients with human epidermal growth factor receptor 2 (*ERBB2*, formerly *HER2 or HER2/neu*).

A, Invasive disease-free survival (events include breast cancer recurrence, new primary cancers, or death).
B, Overall survival.

Treatment Continuation and Adverse Events in the Full Study Population

Overall, patient-reported drug continuation in the final year of treatment was 64.3% in the metformin group and 70.9% in the placebo group, excluding those with prior invasive disease-free survival events and those with ER/PgR– breast cancer after they were told to stop taking the study drug prior to the final year of treatment because of futility. Four serious adverse events were reported (1 fetal death in the metformin group; 2 fetal deaths and 1 retinal vascular event in the placebo group). Nonhematological grade 3 or higher adverse events were reported for 391 patients (21.5%) in the metformin and 328 (17.5%) in the placebo group (Fisher exact $P = .003$); the most common adverse events of grade 3 or higher included hypertension (2.4% metformin vs 1.9% placebo), irregular menses (1.5% metformin vs 1.4% placebo), and diarrhea (1.9% metformin vs 0.8% placebo).

Discussion

Among patients with high-risk operable breast cancer without diabetes, the addition of metformin vs placebo to standard breast cancer treatment did not significantly improve invasive disease-free survival or other breast cancer outcomes. These findings do not support adding metformin to standard adjuvant therapy in patients with early-stage breast cancer without diabetes.

The findings reported herein are consistent with randomized trials that failed to identify a beneficial effect of metformin (in addition to standard chemotherapy or hormone therapy) on outcomes in patients with metastatic breast cancer without diabetes.[23-25] These findings suggest the metabolic changes previously reported in this trial population[7,17,19] and any potential direct antitumor effects of metformin were not sufficient to affect breast cancer outcomes.[8,9] They underscore the need for well-conducted randomized trials prior to the clinical adoption of interventions that appear to benefit cancer when they are investigated in observational studies.

Extrapolation of the findings of this trial to patients with diabetes requires caution because of differing metabolic status (eg, glucose control, insulin resistance, obesity) of patients with vs without diabetes, and reports that breast cancer outcomes are poorer in patients with diabetes[26] for reasons that are not fully understood but may be related to the biological effect of diabetes on breast cancer, delayed breast cancer diagnosis, effects of comorbidity, poor treatment adherence, or other factors. Observational studies involving patients with breast cancer and diabetes have reported inconsistent associations of metformin treatment for diabetes with breast cancer outcomes.[1-5] A meta-analysis[1] reported better overall and cancer-specific survival in patients with breast cancer and diabetes who received metformin vs other diabetes treatments; however, all of the included observational studies were susceptible to methodological limitations that may have affected results, notably treatment allocation and survival biases.[27] It has been suggested that metformin may act by alleviating the adverse breast cancer prognosis associated with diabetes,[3,5] possibly through better diabetes control or due to selection of patients with less severe diabetes to receive metformin, rather than through a direct antitumor effect. Because metformin is effective in type 2 diabetes, the results presented herein should not affect the use of metformin to treat diabetes in patients with breast cancer.

The exploratory analyses in *ERBB2*+ breast cancer were informed by the METTEN study,[14] which reported an increased

pathological complete response rate when metformin was added to neoadjuvant chemotherapy and *ERBB2*-targeted therapy in patients with *ERBB2*+ breast cancer with any *C* allele of the rs11212617 SNV (pathological complete response, 81.2% vs 35.3% without metformin); a similar benefit was not seen among those with the *AA* genotype. In the current trial, metformin was associated with longer invasive disease-free and overall survival in the *ERBB2*+ population (96.5% of whom received trastuzumab adjuvant therapy); the benefit was restricted to those with any *C* allele of the rs11212617 SNV. However, these findings should be considered hypothesis generating and require replication, particularly given the absence of a significant interaction of *ERBB2* status with metformin effect.

Limitations

This study has several limitations. First, the focus of the primary analysis on the patients who have ER/PgR+ breast cancer means that observations made about patients with other types of breast cancer should be considered hypothesis generating. For patients with ER/PgR− breast cancer, the conclusion that metformin treatment was not effective at the second interim analysis reflected a priori statistical cut points necessary for a declaration of futility and should be considered definitive; however, the absence of effect of metformin vs placebo with longer follow-up is hypothesis generating. Second, the analyses in *ERBB2*+ breast cancer require replication before clinical practice is changed. Third, the exclusion of patients with diabetes in whom metformin may have different effects does not allow conclusions to be drawn regarding the effect of metformin on breast cancer outcomes in patients with diabetes. Because metformin is beneficial in the treatment of diabetes (including in patients with breast cancer), it should continue to be used for that purpose for these patients. Fourth, the study population was largely White non-Hispanic and North American; this limits the generalizability of our results to other populations.

Conclusions

Among patients with high-risk operable breast cancer without diabetes, the addition of metformin vs placebo to standard breast cancer treatment did not significantly improve invasive disease–free survival.

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