Randomized Trial of Tamoxifen Versus Combined Tamoxifen and Octreotide LAR Therapy in the Adjuvant Treatment of Early-Stage Breast Cancer in Postmenopausal Women: NCIC CTG MA.14

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A B S T R A C T

Purpose
Somatostatin analogs act directly on breast cancer cells and indirectly on insulin and insulin-like growth factor 1 (IGF-1) levels. This trial was undertaken to assess whether octreotide would lower insulin and IGF-1 levels and reduce risk of breast cancer recurrence.

Patients and Methods
The NCIC CTG MA.14 (NCIC Clinical Trials Group MA.14) trial randomly assigned postmenopausal women to 5 years of tamoxifen 20 mg daily (TAM) or TAM plus 2 years of octreotide 90 mg depot intramuscular injections monthly (TAM-OCT) as adjuvant therapy. The primary end point was event-free survival (EFS). Secondary end points were relapse-free survival (RFS), overall survival (OS), toxicity, and effects of treatment on IGF physiology.

Results
Among 667 women with a median follow-up of 7.9 years, 220 events occurred—108 with TAM-OCT and 112 with TAM. Adjusted hazard ratios (HRs; TAM-OCT to TAM) were 0.93 for EFS (95% CI, 0.71 to 1.22; $P = .62$), 0.84 for RFS (95% CI, 0.59 to 1.18; $P = .31$), and 0.97 for OS (95% CI, 0.69 to 1.37; $P = .86$). Among patients with normal baseline gallbladder imaging, cholecystectomy was required in 23.0% of those receiving TAM-OCT but in only 1.4% of those receiving TAM ($P < .001$). At 4 months, TAM-OCT had significantly ($P < .001$) lowered IGF-1, IGF binding protein 3, and C-peptide levels. Older age ($P = .02$), tumor size ($P = .001$), nodal status ($P = .01$), high C-peptide levels ($P < .001$), and higher body mass index (BMI) in models excluding C-peptide ($P < .001$) were associated with poorer EFS in multivariate analysis.

Conclusion
Octreotide-related changes in circulating IGF-1 and C-peptide levels were statistically significant. Octreotide did not add significant clinical benefit. High C-peptide levels (surrogate for insulin secretion rate) and high BMI were associated with poor outcome.

INTRODUCTION

Octreotide LAR is a long-acting somatostatin analog that inhibits secretion of growth hormone by the pituitary and also inhibits secretion of gastroenteropancreatic hormones, including insulin.[1] Somatostatin and its analogs inhibit tumor growth in a variety of animal models and cultured tumor cells.[1,2] Somatostatin receptors (SSTRs) are expressed by several human tumors and their metastases.[2-5] Labeled SSTR agonists have been used to image breast cancer in patients.[6]

Thus, somatostatin and its analogs may have both direct and indirect mechanisms of antitumor action. The direct mechanism is an antiproliferative effect mediated by binding to specific SSTRs on tumor cells.[7] Proposed indirect mechanisms include inhibition of growth hormone secretion, resulting in reduction in circulating insulin-like growth factor 1 (IGF-1)[8] and insulin secretion by pancreatic beta cells. These actions have been proposed as relevant in view of evidence for roles of insulin and IGF-1 in neoplastic growth.[9] When this trial was launched, it was known that IGF-1 levels were reduced in patients administered tamoxifen compared with placebo.[10] Furthermore, a study of IGF-1 levels in patients with metastatic breast cancer randomly assigned to receive tamoxifen or tamoxifen and octreotide showed a significantly greater decrease in

IGF-1 levels from baseline with the combination.[11] Also, data from small clinical studies have shown that somatostatin analogs could produce breast cancer regression[12,13] or stable disease.[13-15] A randomized clinical trial was conducted by the North Central Cancer Treatment Group comparing tamoxifen with tamoxifen plus octreotide in 135 women with metastatic breast cancer. Although terminated early because of accrual difficulties with the three times daily subcutaneous octretotide injection schedule, the trial demonstrated that tamoxifen and octreotide were more potent than either agent alone in reducing IGF-1 levels. This, together with preclinical evidence for benefit of combining octreotide with tamoxifen,[16] led us to hypothesize that the combination of tamoxifen with octreotide, by then available as a monthly depot intramuscular injection, would be more effective than tamoxifen in adjuvant therapy.

PATIENTS AND METHODS

Patient Population

Postmenopausal women who had surgical removal of histologically proven adenocarcinoma of the breast by segmental or total mastectomy with axillary dissection, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, no metastatic disease beyond ipsilateral axillary nodes, and no other malignancies except carcinoma of skin, cervix, endometrium, colon, or thyroid adequately treated 5 or more years before study entry and presumed cured were included. Patients could receive adjuvant chemotherapy before or concurrently with protocol treatment.

Study Design

NCIC CTG MA.14 (NCIC Clinical Trials Group MA.14) was a nonblinded randomized phase III trial comparing 5 years of tamoxifen 20 mg orally daily (TAM) to TAM plus 5 years of octreotide LAR (SMS 201-995 pa LAR) 90 mg depot intramuscular injections monthly (TAM-OCT). Patients were randomly assigned using minimization, with stratification by adjuvant chemotherapy (none, concurrent, sequential), axillary lymph node status (unknown, negative, one to three positive, ≥ four positive), and locally determined estrogen and/or progesterone receptor status (one or both positive, both negative, both unknown). During MA.14, the NSABP B-29 (National Surgical Adjuvant Bowel and Breast Project B-29) study—with a design similar to that of MA.14—was closed in November 1999 because of excess gallbladder toxicity,[17] prompting close review of adverse events in MA.14. We found the risk of cholecystectomy to be 2.2% after 2 years and 8.9% after 3 years.[18] In our trial and the NSABP B-29 study, symptomatic gallbladder disease and surgery increased significantly after 2 years of octreotide. MA.14 was therefore amended to reduce the duration of octreotide to 2 years.

Baseline Assessments

Protocol-specified pretreatment investigations included height, weight, ECOG performance status, full blood count, AST or ALT, alkaline phosphatase (AP), random blood sugar, bilirubin, hemoglobin A1c, thyroid-stimulating hormone, free T4, methylmalonic acid, and serum collection for growth factor studies. Vitamin D levels were subsequently added to the investigations performed on serum collected. Radiologic investigations included chest x-ray; gallbladder ultrasound; bone scan if AP was ≥ 2× normal and/or there were symptoms of metastatic lesions; confirmatory x-ray if results from bone scan were questionable; and abdominal ultrasound, liver scan, or computed tomography of the abdomen, if AST/ALT or AP was ≥ 2× normal. Random assignment occurred within 12 weeks of definitive surgery or 6 weeks of last chemotherapy. Protocol treatment began within 2 working days of random assignment.

Follow-Up

Patients were seen every month for 4 months, every 4 months for 3 years, and every 6 months for the remainder of treatment. Gynecologic evaluation was required annually. Serum was collected for growth factor studies at baseline; every 4 months for 1 year; at months 24, 36, and 60 months; at treatment completion/discontinuation; and at recurrence/second malignancy.

Study Ethics

All patients provided written informed consent before trial participation. Ethics approval was obtained by all participating centers. Study conduct was overseen by an NCIC CTG trial study team, Novartis Canada, which provided the octreotide LAR, and the independent NCIC CTG Data Safety Monitoring Committee (DSMC).

Toxicity Assessment

All patients receiving one or more doses of study treatment were included in safety analyses. Toxicity was graded by NCIC CTG Expanded Common Toxicity Criteria at baseline and each follow-up visit during treatment. Reports were submitted every 6 months to the DSMC.

Quality of Life

Quality of life (QoL) was evaluated using the European Organisation for Research and Treatment of Cancer instrument (Quality of Life Questionnaire C30+1) and a trial-specific checklist, which were administered at baseline; at months 1, 4, 8, and 12; annually until treatment discontinuation; and at recurrence/second malignancy.

Study End Points

The primary end point of this trial was event-free survival (EFS), defined as time from random assignment to time of recurrence of primary disease, second malignancy, or death as a result of any cause. Local and ipsilateral nodal recurrence and metastatic disease were considered recurrence of primary disease. Contralateral breast cancer was considered a treatment failure and EFS event. Secondary end points were relapse-free survival (RFS), defined as time from random assignment to time of recurrence of primary disease, excluding contralateral breast disease; overall survival (OS); toxicity; QoL; effects of treatment on IGF physiology; and relationship between IGF physiology, treatment, and outcome. QoL will be reported separately.

Statistical Design and Analysis

The study was initially designed to accrue 850 eligible women over 4.2 years, with observation of all patients for 5 years before final analysis. Sample-size calculations were based on estimated EFS rate with tamoxifen alone of 73% at 5 years, assuming a 60% to 40% split of node-negative and node-positive patients. To detect TAM/TAM-OCT hazard ratio (HR) of 1.5, with an improvement of 8.2% in EFS in the experimental arm (two-sided $P = .05$; 90% power), we needed 248 events.

Because of concerns regarding gallbladder toxicity, the design was modified to detect the same EFS difference with the same HR of 1.5 with a power of 80%; 191 events were required. Thus, we planned to enroll 650 eligible women over 5 years with 4.7 years of follow-up before final analysis. A test for qualitative interaction (Q-test[19]) was planned between chemotherapy and trial therapy, with subgroup analysis if $P < .1$. We estimated that approximately 80% of patients (most node-negative and 50% of node-positive women) would receive no chemotherapy, with an estimated 5-year EFS of 77%. The study also had 80% power to detect an 8% improvement for the subgroup of patients receiving chemotherapy and TAM-OCT. All efficacy analyses were performed on an intention-to-treat basis. One interim EFS analysis was planned after observing half of the events (96 events). Early termination would be considered if the significance level for the interim analysis was .005 or less.[20] This analysis was performed in October 2002. The DSMC recommended trial continuation.

Protocol-specified analyses included a stratified log-rank statistic, both unadjusted and adjusted for stratification factors, as the primary test statistic for all time-to-event end points. Stepwise Cox proportional hazards regression was used to assess whether factors were multivariately associated with an end point, with a factor added if P was .05 or less by likelihood ratio criterion (approximate χ^2 distribution on 1 degree of freedom). Reported P values are from the final step-wise model. A global treatment by covariate interaction effect under the final Cox model using a likelihood ratio test statistic was planned. A Cox survivor plot whereby arm efficacy was adjusted at mean of stratification and significant factors was used to describe results.

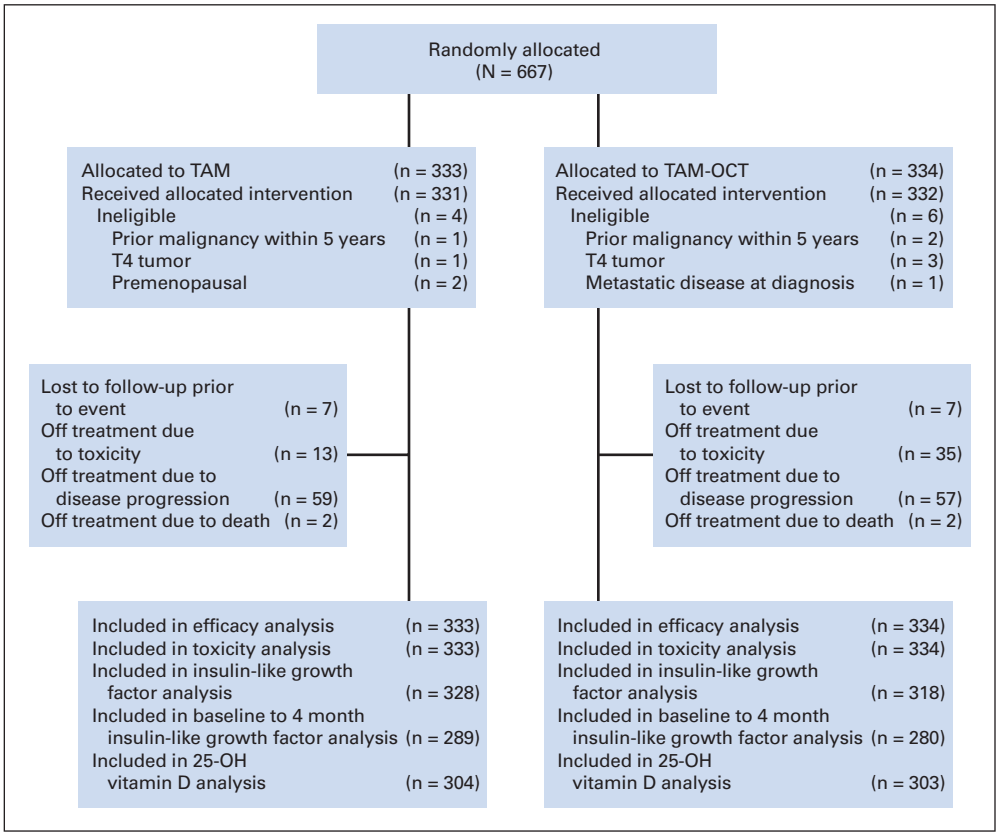

Fig 1. CONSORT diagram. OCT, octreotide; OH, hydroxy; TAM, tamoxifen.

Exploratory investigations were carried out to examine the effects of the following patient characteristics in the primary EFS Cox multivariate analyses: age (< 60, ≥ 60 years), race (white, nonwhite), ECOG status (0, unknown, 1, 2), pathologic T (1, 2, 3A, 4, unknown), pathologic N (0, 1, 2, unknown), and surgery type (total mastectomy, segmental mastectomy, other). IGF-1 (continuous), IGF binding protein 3 (IGFBP-3; continuous), C-peptide (continuous), weight (continuous), and body mass index (BMI; continuous) were examined to assess IGF physiology. We considered effects of baseline 25-hydroxy (OH) vitamin D (continuous) on outcome.

We examined changes in IGF data from baseline to 4 months and BMI changes from baseline to 2 years using a matched by-patient *t*-test to compare change by arm and a pooled across-arms *t*-test to compare differences in change between arms after the protocol-specified logarithmic transformation for IGF-1 and C-peptide. A Box-Cox variance stabilization square-root transformation was indicated for IGFBP-3 and -0.5 power for weight and BMI. No transformation was indicated for baseline 25-OH serum vitamin D. Plots of baseline 25-OH vitamin D were made by month of serum draw and categorized by season of serum draw (May to September, October to April) and level of 25-OH vitamin D (deficient, < 50 nmol/L; insufficient, 50 to 72 nmol/L; sufficient, > 72 to 374 nmol/L; toxic, > 374 nmol/L).

Toxicities were summarized by type of adverse event, worst severity, and relationship to study arm. Fisher's exact test was used to compare toxicities between the two arms by severity (i: none, grade 1, grade 2, grade 3, grade 4, grade 5; ii: none, grades 1 to 2, grades 3 to 5; and iii: none, grades 1 to 5).

RESULTS

Patient Population

From 1996 to 2000, 667 women were accrued from 35 Canadian ($n = 577$) and one US center ($n = 90$; Fig 1). Four of 333 patients allocated to TAM (1.2%) and six of 334 allocated to TAM-OCT (1.8%) were ineligible. Octreotide LAR was administered by intramuscular injection. Compliance was excellent, because the therapy was administered by health care personnel. Patients received a median of 24 doses (range, 0 to 46 doses), and 17% received treatment for 6 months or fewer; 6%, 6 to 12 months; 28%, 12 to 24 months; 30%, 24 to 30 months; 8%, 30 to 36 months; and 10%, longer than 36 months. Table 1 shows baseline patient characteristics, which were well-balanced between arms. Baseline serum was available for IGF-1, IBGBP-3, and C-peptide for 646 patients (96.9%), and 25-OH vitamin D was available for 607 (91%).

Treatment-Related Outcomes

EFS. At final analysis (median follow-up, 7.9 years), 220 events had occurred: 108 with TAM-OCT and 112 with TAM (Fig 2). The EFS-adjusted HR for all enrolled patients (TAM-OCT/TAM) was 0.93 (95% CI, 0.71 to 1.22; $P = .62$; unadjusted $P = .70$). The EFS-adjusted HR for eligible patients was 0.89 (95% CI, 0.67 to 1.17; $P = .39$; unadjusted $P = .54$). Q-statistic test for interaction between chemotherapy and trial therapies was nonsignificant ($P = .39$), so the contingent subgroup analysis was not performed.[19]

RFS. There were 135 recurrences: 63 with TAM-OCT and 72 with TAM. The RFS-adjusted HR was 0.84 (95% CI, 0.59 to 1.18; $P = .31$). Patients allocated to octreotide had an absolute 2.7% lower rate of recurrence during the study period.

OS. There were 68 deaths in each therapy group. The adjusted HR was 0.97 (95% CI, 0.69 to 1.37; $P = .86$).

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	TAM		TAM-OCT		Total	
	No.	%	No.	%	No.	%
Total	333	100	334	100	667	100
Age at allocation, years						
40-49	13	4	8	2	21	3
50-59	151	45	157	47	308	46
60-69	112	34	106	32	218	33
≥ 70	57	17	63	19	120	18
Median	60.1		60.1		60.1	
Race						
Asian	1	0	7	2	8	1
Black	1	0	2	1	3	0
Hispanic	0	0	1	0	1	0
Aboriginal	2	1	2	1	4	1
Other	3	1	4	1	7	1
White	326	98	318	95	644	97
ECOG performance status						
Unknown	1	0	2	1	3	0
0	253	76	264	79	517	78
1	77	23	65	19	142	21
2	2	1	3	1	5	1
T pathologic classification						
1	193	58	194	58	387	58
2	131	39	123	37	254	38
3A	1	0	12	4	13	2
4	3	1	3	1	6	1
In situ	1	0	1	0	2	0
Unknown	4	1	1	0	5	1
N pathologic classification						
0	175	53	177	53	352	53
1	147	44	148	44	295	44
2	4	1	3	1	7	1
Unknown	7	2	6	2	13	2
Breast surgery type						
Other	1	0	0	0	1	0
Segmental mastectomy	212	64	194	58	406	61
Total mastectomy	120	36	140	42	260	39
No. of positive axillary lymph nodes						
0	175	53	177	53	352	53
1-3	112	34	108	32	220	33
≥ 4	39	12	43	13	82	12
Unknown	7	2	6	2	13	2
Estrogen and progesterone receptor status						
Both negative	28	8	31	9	59	9
One positive	304	91	301	90	605	91
Both unknown	1	0	2	1	3	0
Adjuvant chemotherapy						
Concurrent	8	2	10	3	18	3
None	223	67	222	66	445	67
Sequential	102	31	102	31	204	31
IGF-1						
Total	328	98.5	318	95.2	646	96.9
Mean	130		130		130	
SD	55.8		49.7		52.8	
IGFBP-3						
Total	328	98.5	318	95.2	646	96.9
Mean	4,703		4,775		4,738	
SD	1,080		1,120		1,100	
C-peptide						
Total	328	98.5	318	95.2	646	96.9
Mean	3.7		4.0		3.9	
SD	2.2		2.9		2.5	

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Table 1. Patient Demographics and Clinical Characteristics (continued)

Characteristic	TAM		TAM-OCT		Total	
	No.	%	No.	%	No.	%
Weight at baseline						
Total	321	96.4	323	96.7	644	96.6
Mean	73.8		74.2		74.0	
SD	16.2		15.5		15.8	
BMI						
Total	315	94.6	311	93.1	626	93.9
Mean	28.5		28.9		28.7	
SD	5.9		6.1		6.0	
25-OH vitamin D						
Total	304	91.3	303	90.7	607	91.0
Mean	62.4		59.3		60.9	
SD	19.9		18.1		19.1	

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IGF-1, insulin-like growth factor 1; IGFBP-3, IGF binding protein 3; OCT, octreotide; OH, hydroxy; SD, standard deviation; TAM, tamoxifen.

Hormone Levels

Mean baseline IGF-1, IGFBP-3, C-peptide, BMI, and 25-OH vitamin D levels are shown in Table 1. Four-month IGF-1 levels were significantly lower ($P < .001$) than baseline for both study arms; the change was greater in the TAM-OCT arm ($P < .001$), as hypothesized (Fig 3A). IGFBP-3 levels at 4 months were significantly lower ($P < .001$) than baseline for those receiving TAM-OCT but not for those receiving TAM ($P = .85$; Fig 3B). C-peptide levels at 4 months (Fig 3C) and BMI at 2 years (Fig 3D) increased significantly from baseline ($P < .001$) for women allocated to TAM. There was a significant decrease in C-peptide ($P = .04$) and no significant change in BMI ($P = .67$) for those allocated to receive TAM-OCT. 25-OH vitamin D levels varied with month of blood draw (Appendix Fig A1, online only; $P = .007$).

Investigative Factors

In Table 2, we report patient characteristics and insulin and IGF-1 physiology factors, which had a significant effect on EFS. The adjusted Cox stepwise model for all enrolled women indicated longer EFS for women younger than 60 years of age ($P = .02$), with tumors less than T2 ($P = .001$), with N0 disease ($P = .01$), and with lower C-peptide levels ($P < .001$). Lower BMI was significantly associated ($P < .001$) with longer EFS when C-peptide was excluded. No interactions between factor and trial therapy were significant. Figure 4 describes the association between C-peptide, categorized at a median cut point, and EFS ($P = .065$) after adjusting for effects of stratification and other significant factors.

For all patients, tumors T2 or less ($P < .001$) and N0 disease ($P = .01$) were associated with significantly longer RFS in an adjusted Cox model. OS was longer for those younger than 60 years of age ($P = .02$), with tumors T2 or less ($P = .001$), and with lower C-peptide levels ($P < .001$). Interaction between C-peptide and trial therapy was not significant for RFS or OS.

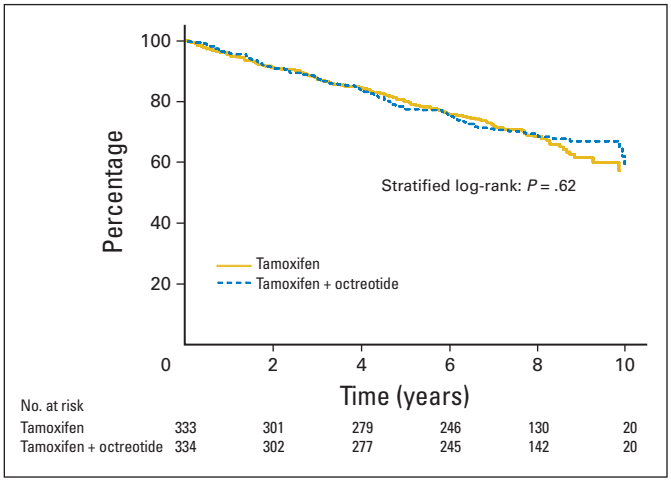

Fig 2. Event-free survival (EFS) by treatment. Effect of tamoxifen with or without octreotide LAR on EFS was adjusted at mean of stratification factors, adjuvant chemotherapy, nodal status, and hormone receptor status; stratified hazard ratio of tamoxifen plus octreotide to tamoxifen was 0.93 (95% CI, 0.71 to 1.22).

Vitamin D

Continuous baseline 25-OH vitamin D was not associated with EFS ($P = .43$) in adjusted Cox modeling, even when adjusted by season (May to September *v* October to April), with levels defined as deficiency/insufficiency versus sufficiency/toxicity (≤ 72 *v* > 72 nmol/L), age (< 60, ≥ 60 years), and tertile BMI.[21] Interactions between baseline 25-OH vitamin D and season, age, and BMI were nonsignificant.

Toxicity

Acute/delayed adverse events are reported in Table 3. Patients allocated to receive TAM-OCT had significantly more diarrhea ($P < .001$) and abdominal pain ($P < .001$) of all grades and experienced local toxicity at the injection site. Patients allocated to receive TAM experienced more edema ($P = .03$) and hot flashes ($P = .004$), although there were no significant differences in grades 3 to 4 edema ($P = .18$) or grades 3 to 4 hot flashes ($P = .40$) by treatment. Those allocated to receive TAM-OCT had more low-grade hyperglycemia ($P = .04$), in keeping with the hypothesized inhibitory effect of octreotide on insulin secretion. In patients with normal baseline gallbladder imaging, abnormal gallbladder imaging was seen after random assignment in 37.9% of patients allocated to receive TAM-OCT but in only

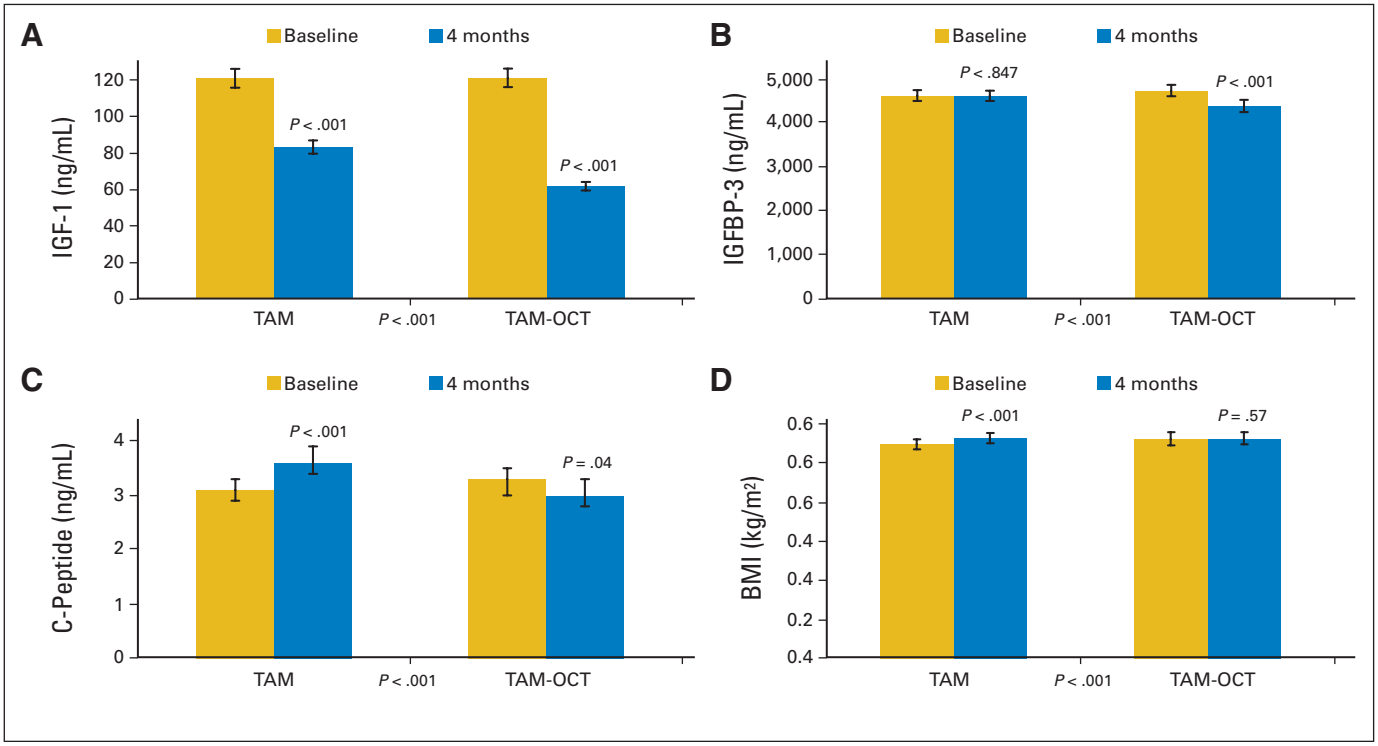

Fig 3. (A) Changes in insulin-like growth factor 1 (IGF-1) from baseline to 4 months; (B) changes in IGF binding protein 3 (IGFBP-3) from baseline to 4 months; (C) changes in C-peptide from baseline to 4 months; (D) changes in body mass index (BMI) from baseline to 2 years. For all, matched *t*-test used to compare patient change by arm, whereas pooled *t*-test of matched patient change used to compare differences between arms. OCT, octreotide; TAM, tamoxifen.

11.5% of those allocated to receive TAM ($P < .001$; Appendix Table A1, online only). Cholecystectomy was required in 23.0% of those allocated to receive TAM-OCT but in only 1.4% of those allocated to receive TAM ($P < .001$). Gallbladder toxicity included sludge, gravel, gallstones, cholecystitis, contracted or distended gallbladder, thickened gallbladder wall, biliary duct dilation, and/or cholecystectomy.

Table 2. Multivariate Effects of Factors on EFS

Factor	Cox Model					
	Adjusted*			Unadjusted†		
	−β‡	SE	P§	−β‡	SE	P§
Age	−0.38	0.15	.01	−0.35	0.14	.01
Tumor size	−0.53	0.15	< .001	−0.64	0.15	< .001
Nodal status	−1.94	0.60	.01	−1.82	0.57	.01
C-peptide	−0.08	0.03	< .001	−0.06	0.03	< .001
BMI‖	—	—	—	−0.29	0.15	< .001

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; ER, estrogen receptor; IGF-1, insulin-like growth factor 1; IGFBP-3, IGF binding protein 3; PR, progesterone receptor.

*Adjusted for effects of stratification factors: adjuvant chemotherapy, nodal status, ER/PR status. Factors not included (*P* for score χ^2): treatment ($P = .75$), race ($P = .76$), ECOG performance status ($P = .45$), surgery type ($P = .99$), weight ($P = .21$), BMI ($P = .06$), IGF-1 ($P = .46$), IGFBP-3 ($P = .93$).

†Factors not included (*P* for score χ^2): treatment ($P = .86$), race ($P = .78$), ECOG performance status ($P = 1.00$), surgery type ($P = .27$), weight ($P = .76$), IGF-1 ($P = .60$), IGFBP-3 ($P = .95$).

‡$-\beta$ is factor effect on EFS; negative direction indicates that patients with higher values (ie, older age) had worse survival.

§Reported *P* values are those in final model for two-sided likelihood ratio criterion; approximate χ^2 distribution on 1 degree of freedom.

‖Lower BMI was significantly associated ($P < .001$) with longer EFS in adjusted models excluding C-peptide.

DISCUSSION

Patients allocated to receive TAM-OCT did not have significantly better EFS than those allocated to receive TAM, nor was there significantly better RFS or OS, suggesting no significant benefit for octreotide on any secondary end point. We found that younger age (<

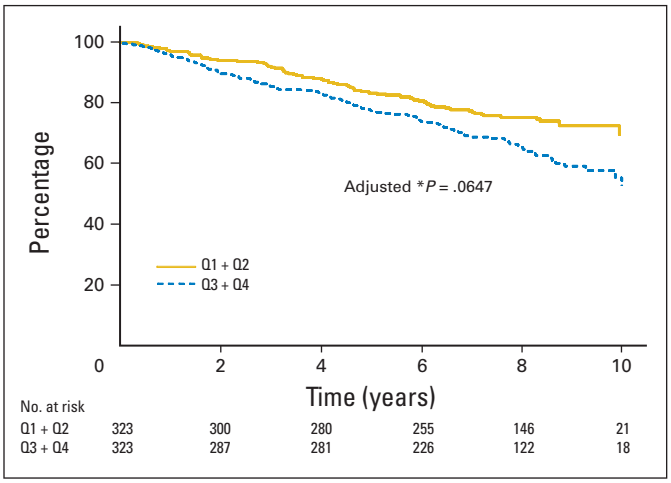

Fig 4. Event-free survival by C-peptide; effect adjusted by trial arm at means for effects of stratification factors and other significant factors, age, and tumor size.

Table 3. Acute/Delayed Adverse Events

Adverse Event	TAM*				TAM-OCT†				*P*‡	
	Grade 1 or 2§	Grade 3 or 4§	Total No.	%	Grade 1 or 2§	Grade 3 or 4§	Total No.	%	1	2
Edema	182	2	184	55	148	7	155	46	.03	.18
Hot flashes	236	43	279	84	213	36	249	75	.004	.40
Diarrhea	67	4	71	21	202	62	264	79	< .001	< .001
GI pain	80	15	95	29	146	58	204	61	< .001	< .001
Hyperglycemia	13	2	15	5	26	3	29	9	.04	1.00
Local toxicity	1	0	1	0	84	0	84	25	< .001	NA

Abbreviations: NA, not available; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; OCT, octreotide; TAM, tamoxifen.
*No. of evaluable patients = 333.
†No. of evaluable patients = 334.
‡*P* values by Fisher's exact test. *P*1, grades 0, 1-5; *P*2, grades 0-2, 3-5.
§Adverse events graded according to NCIC CTG Expanded Common Toxicity Criteria.

60 years; $P = .02$), smaller tumor size ($P = .001$), and lower nodal status ($P = .01$), as reported in other studies, and lower C-peptide levels ($P < .001$) were associated with better prognosis. Lower BMI was also significantly associated with longer EFS in models excluding C-peptide. Therefore, these results add to prior evidence[22,23] that weight and insulin resistance are poor prognostic factors. Interestingly, vitamin D levels were not significant prognostic or predictive factors in this population, although the expected seasonal variation in levels was detected. Supplementation of vitamin D to postmenopausal participants in the Women's Health Initiative did not reduce the incidence of developing invasive breast cancer.[24] However, others who have studied premenopausal women have found an association with outcome.[25.] Classic and more recent studies[9] provide evidence that insulin and IGFs are determinants of breast cancer behavior. When MA.14 was designed, currently available direct pharmaceutical targeting strategies such as antireceptor antibodies, antiligand antibodies, and small-molecule receptor-specific tyrosine kinase inhibitors[9] were not available. In that setting, use of the somatostatin analog octreotide was proposed as a strategy to reduce insulin and IGF-1 ligand levels as well as to activate growth-inhibitory signaling pathways downstream of SSTRs on neoplastic cells. As predicted, IGF-1 levels were lowered by both TAM and TAM-OCT. C-peptide levels and BMI increased significantly from baseline to 4 months for women allocated to receive TAM, whereas those allocated to receive TAM-OCT had a significant decrease in C-peptide and no significant change in BMI. Therefore, women allocated to receive TAM-OCT experienced detectable effects on insulin secretion and IGF-I levels in the hypothesized directions, but these were small in magnitude and were not associated with significant improvement in EFS. We had hypothesized that TAM-OCT would be associated with a 40% to 45% reduction in IGF levels, whereas those receiving TAM would experience a 25% to 30% reduction. Such levels of reduction were observed for IGF-1, although not for IGFBP-3 or C-peptide.

It remains uncertain whether lack of difference in survival end points between arms should be interpreted as evidence that the signaling pathways targeted are irrelevant or simply as evidence that the perturbations in ligand levels achieved were insufficient to have an effect on outcome. We favor the latter possibility, not only because the circumstantial evidence for a role for insulin and/or IGF signaling in breast cancer is strong, but also because in MA.14, as a result of the observed gallbladder toxicity of octreotide, this agent was administered for only 2 years. Therefore, the hormonal differences between the arms were modest in magnitude, and they were maintained for only a small proportion of the follow-up period. It remains a matter of speculation whether longer duration of octreotide would have led to a difference in primary end points. Furthermore, because MA.14 was not powered to allow for subset analysis by degree of decline of IGF-1 or C-peptide, we cannot rule out the possibility of benefit in a subpopulation defined by magnitude of decline in C-peptide or IGF-1.

To better evaluate the hypothesis that targeting insulin/IGF-1 signaling may be of use in breast cancer treatment, it will be useful to study benefits of modern targeting strategies such as antireceptor antibodies and tyrosine kinase inhibitors. Our findings also indirectly support studies of metformin in breast cancer treatment, because this agent—although it has little effect on IGF-1 or insulin levels in normo-insulinemic patients—can lower insulin levels in hyperinsulinemic patients and inhibit signaling pathways downstream of both insulin and IGF-1 receptors in a subset of cancers, provided adequate drug concentrations are present in neoplastic tissue.[24-29]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Weckbecker G, Raulf F, Stolz B, et al: Somatostatin analogs for diagnosis and treatment of cancer. Pharmacol Ther 60:245-264, 1993

2. Coombes RC, Kilburn LS, Snowdon CF, et al: Survival and safety of exemestane versus tamoxifen after 2-3 years tamoxifen treatment (Intergroup Exemestane Study): A randomized controlled trial. Lancet 369:559-570, 2007

3. Lee MT, Liebow C, Kamer AR, et al: Effects of epidermal growth factor and analogues of luteinizing hormone-releasing hormone and somatostatin on phosphorylation and dephosphorylation of tyrosine residues of specific protein substrates in various tumors. Proc Natl Acad Sci U S A 88:1656-1660, 1991

4. Buscail L, Delesque N, Estève J, et al: Stimulation of tyrosine phosphatase and inhibition of cell proliferation by somatostatin analogues: Mediation by human somatostatin receptor subtypes SSTR1 and SSTR2. Proc Natl Acad Sci U S A 91:2315-2319, 1994

5. Lamberts SW: Octreotide. N Engl J Med 334:246-254, 1996

6. van Eijck CH, Krenning EP, Bootsma A, et al: Somatostatin-receptor scintigraphy in primary breast cancer. Lancet 343:640-643, 1994

7. Setyono-Han B, Henkelman MS, Foekens JA, et al: Direct inhibitory effects of somatostatin (analogues) on the growth of human breast cancer cells. Cancer Res 47:1566-1570, 1987

8. Pollak M, Polychronakos C, Guyda H: Somatostatin analogue SMS 201-995 reduces serum IGF-1 levels in patients with neoplasms potentially dependent on IGF-1. Anticancer Res 9:889-892, 1989

9. Pollak M: Insulin and insulin-like growth factor signaling in neoplasia. Nat Cancer Rev 8:915-928, 2008

10. Pollak M, Costantino J, Polychronakos C, et al: Effect of tamoxifen on serum insulin-like growth factor 1 levels in stage 1 breast cancer patients. J Natl Cancer Inst 82:1693-1697, 1990

11. Pollak M, Ingle J, Suman VJ, et al: Enhancement of tamoxifen-induced suppression of serum IGF-1 levels in metastatic breast cancer patients by coadministration of the somatostatin-analogue octreotide. Presented at the 87th Annual Meeting of the American Association of Cancer Research, Washington, DC, April 20-24, 1996 (abstr 1167)

12. Morere JF, Cour V, Breau JL, et al: Stabilizing effect of BIM 23014, a long-acting somatostatin analog, in 30 cases of advanced breast cancer: A phase II study. Proc Am Soc Clin Oncol 8:47, 1989 (abstr 179)

13. Vennin P, Peyrat JP, Bonneterre J, et al: Effect of the long-acting somatostatin analogue SMS 201-995 (Sandostatin) in advanced breast cancer. Anticancer Res 9:153-156, 1989

14. Stolfi R, Parisi AM, Natoli C, et al: Advanced breast cancer: Response to somatostatin. Anticancer Res 10:203-204, 1990

15. Cannata D, Boccardo F, Canobbio L: Somatuline plus tamoxifen in post-menopausal breast cancer patients. Ann Oncol 3:76, 1992 (suppl 5)

16. Weckbecker G, Tolcsvai L, Stolz B, et al: Somatostatin analogue octreotide enhances the antineoplastic effects of tamoxifen and ovariectomy on 7,12-dimethylbenz(alpha)anthracene-induced rat mammary carcinomas. Cancer Res 54:6334-6337, 1994

17. Soran A, Nesbitt L, Mamounas EP, et al: Centralized medical monitoring in phase III clinical trials: The National Surgical Adjuvant Breast and Bowel Project (NSABP) experience. http://www.nsabp.pitt.edu/NSABP_Bibliography.asp

18. Pollak M, Pritchard KI, Whelan T, et al: The NCIC CTG MA.14 experience with the gallbladder toxicity of octreotide pamoate (Oncolar) in a postmenopausal patient population undergoing adjuvant treatment for stage 1-3 breast cancer. Eur J Cancer 38:S93, 2002 (suppl 3)

19. Gail M, Simon R: Testing for qualitative interactions between treatment effects and patient subsets. Biometrics 41:361-372, 1985

20. Gordon Lan KK, DeMets DL: Discrete sequential boundaries for clinical trials. Biometrika 70:659-663, 1983

21. Piura E, Chapman JW, Lipton A, et al: Serum 1-OH vitamin D (D) and prognosis of postmenopausal breast cancer (BC) patients: NCIC-CTG MA14 trial. J Clin Oncol 27:15s, 2009 (suppl; abstr 534)

22. Goodwin PJ, Ennis M, Pritchard KI, et al: Fasting insulin and outcome in early stage breast cancer: Results of a prospective cohort study. J Clin Oncol 20:42-51, 2002

23. Costantino JP, Kuller LH, Ives DG, et al: Coronary heart disease mortality and adjuvant tamoxifen therapy. J Natl Cancer Inst 89:776-782, 1997

24. Chlebowski RT, Johnson KC, Kooperberg C, et al: Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst 100:1581-1591, 2008

25. Goodwin PJ, Ennis M, Pritchard KI, et al: Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. J Clin Oncol 27:3757-3763, 2009

26. Zakikhani M, Blouin MJ, Piura E, et al: Metformin and rapamycin have distinct effects on the AKT pathway and proliferation in breast cancer cells. Breast Cancer Res Treat 123:271-279, 2010

27. Pollak M: Metformin and other biguanides in oncology: Advancing the research agenda. Cancer Prev Res 3:1060-1065, 2010

28. Goodwin PJ, Stambolic V, Lemieux J, et al: Evaluation of metformin in early breast cancer: A modification of the traditional paradigm for clinical testing of anti-cancer agents. Breast Cancer Res Treat 126:215-220, 2011

29. Algire C, Amrein L, Bazile M, et al: Diet and LKB1 expression interact to determine sensitivity to antineoplastic effects of metformin in vivo. Oncogene 30:1174-1182, 2011

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Appendix

Table A1. Gallbladder Imaging After Random Assignment

Imaging	TAM		TAM-OCT	
	No.	%	No.	%
Total No. of patients*	295	100.0	288	100.0
Abnormal imaging report†	34	11.5	109	37.9
Normal imaging report	261	88.5	179	62.2

NOTE. $P < .001$ by Fisher's exact test.
Abbreviations: OCT, octreotide; TAM, tamoxifen.
*Thirty-eight of 333 women receiving TAM and 46 of 344 women receiving TAM-OCT had abnormal gallbladder imaging results at baseline and were not included in these analyses.
†Documentation of cholelithiasis, gallstones, sludge, debris, cholecystitis, adenomyomatiosis, irregular gallbladder wall, wall thickening or thinning, echogenic mass/foci, billiary duct dilation, contracted or distended gallbladder, or polyps.

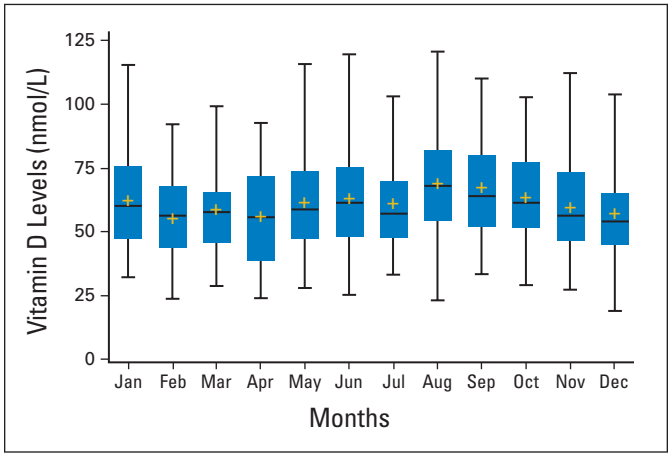

Fig A1. Plots of baseline 25-hydroxy (OH) vitamin D were made by month of serum draw with level of 25-OH vitamin D considered deficient if < 50 nmol/L, insufficient if 50 to 72 nmol/L, sufficient if > 72 to 374 nmol/L, and toxic if > 374 nmol/L.