Octreotide LAR and tamoxifen versus tamoxifen in phase III randomize early breast cancer trials: NCIC CTG MA.14 and NSABP B-29

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Abstract NCIC CTG MA.14 and NSABP B-29 trials examined the addition of Octreotide LAR (OCT) to 5 years of tamoxifen (TAM). Gallbladder toxicity led to B-29 discontinuation of OCT, and MA.14 OCT administration shortened to 2 years. Median follow-up was 9.8 years for 667 MA.14 patients and 6.8 years for 893 B-29 patients. The primary endpoint was disease-free survival (DFS), defined as time from randomization to time of breast cancer recurrence; second primary cancer other than squamous or basal cell skin carcinoma, cervical carcinoma in situ, or lobular breast carcinoma in situ; or death. The primary statistical test was a univariable pooled stratified log-rank test; multivariable assessment was with Cox regression. For MA.14, 97 % of patients were ≥50 years; for B-29, 62 %. MA.14 patients were 53 % lymph node negative (LN−) while B-29 were 100 % LN−; 33 % of MA.14 patients received adjuvant chemotherapy, 2 % concurrently, while B-29 had 53 % concurrent chemotherapy. MA.14 patients were 90% hormone receptor positive; B-29, 100 %. MA.14 patients experienced 5-year DFS of 80 % with TAM, 76 % with TAM + OCT; B-29 patients had 5-year DFS of 88 % for both arms. Pooled univariable TAM + OCT to TAM hazard ratio (HR) was 0.99 (95% CI 0.81–1.20; $p = 0.69$): for MA.14, HR = 0.94 (0.73–1.20; $p = 0.50$); for B-29, HR = 1.09 (0.80–1.50; $p = 0.59$). Multivariable pooled HR = 0.98 (0.81–1.20; $p = 0.84$). Older patients ($p < 0.001$), with higher T stage ($p < 0.001$), and LN + ($p < 0.001$) had shorter DFS. Addition of OCT to TAM did not significantly improve DFS; gallbladder toxicity shortened the additional administration of OCT. This does not negate targeting the insulin–IGF-I receptor family with less toxic therapeutics.

Keywords Early breast cancer · Tamoxifen · Octeotide LAR · Insulin pathway

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Introduction

The discovery of insulin growth factor (IGF) receptors on primary human breast cancers raised the possibility that the paradigm of therapeutic exploitation of hormonal dependence of neoplasia might be extended from gonadal steroids to peptide growth factors [1]. Somatostatin is known to suppress insulin secretion in pancreatic beta cells and to reduce growth hormone secretion by the pituitary gland, which would be expected to reduce insulin-like growth factor 1 (IGF-1) levels. Furthermore, somatostatin receptors are present on a majority of breast cancer cells, and

laboratory evidence suggested that activation of these receptors might be growth inhibitory [2]. While somatostatin has a short half-life, somatostatin analogs were used clinically for the treatment of acromegaly in the 1990s and these were considered worthy of investigation for breast cancer treatment. The two mechanisms of action, "indirect" (via reduction of IGF-1 and insulin levels) or "direct" (via activation of somatostatin receptors on cancer cells) were appealing. Preclinical data suggested mechanisms involving insulin/IGF physiology by which a somatostatin analog and tamoxifen (TAM) combination might be superior to TAM alone for adjuvant breast cancer therapy [3].

Octreotide (SMS 201-995 pa LAR; OCT) was the somatostatin chosen for testing the concept. Five years of combination OCT and TAM therapy (TAM–OCT) was to be tested versus 5 years of TAM. Two randomized phase III clinical trials in early breast cancer were initiated: NCIC Clinical Trials Group (CTG) MA.14 [4] and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-29. Excessive gallbladder toxicity observed in B-29 led to data monitoring committee (DMC)-recommended discontinuation of OCT in B-29 and MA.14 shortening of OCT treatment to two years. Neither trial accrued the protocol-specified number of patients, and in neither trial did TAM-OCT patients receive the planned duration of OCT. Under NCIC CTG data safety monitoring committee (DSMC) supervision, the MA.14 trial was completed to the OCT-revised protocol-specified final analysis at median patient follow-up of 7.9 years [4]. Subsequently, MA.14 data were updated to 9.8 years median follow-up [5]. We examine here the pooled and individual trial experience of adding OCT to TAM.

Methods

NCIC CTG MA.14

The NCIC CTG MA.14 trial (ClinicalTrials.gov Identifier: NCT00002864; CONSORT diagram Fig. 1a) was approved by local ethics review in participating centers. Patients after providing consent were randomized to 5 years of TAM, 20 milligram (mg) orally daily, or 5 years of TAM-OCT, with OCT delivered as monthly 90 mg depot intramuscular injections. MA.14 was designed to accrue 850 postmenopausal women with histologically proven adenocarcinoma of the breast with no restriction on nodal or hormone receptor status, who underwent lumpectomy or total mastectomy [4]. Patients were expected to be accrued in 4.2 years, with all patients followed for 5 years before final analysis. Sample size calculations were based on an estimated 5-year event-free survival (EFS) with TAM alone of 73 %, assuming a 60–40 % split of node negative to node positive patients. Two hundred and forty-eight events were needed to detect, with two-sided alpha level of 5 and 90 % power, a TAM to TAM-OCT hazard ratio (HR) of 1.5, with improved 8.2 % EFS in the experimental arm. Harmonization of MA.14 and B-29 primary endpoints is described below.

Adjuvant chemotherapy was allowed prior to randomization (sequential) or during study treatment (concurrent). Adjuvant radiotherapy was permitted before or after randomization. Patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and tumors with pathologic stage T1, T2, T3a, T4 with dermal involvement on pathology only; Nx, N0, N1, N2; M0; estrogen receptor (ER) and/or progesterone receptor (PgR) positive [$\geq$10 femtomole (fmol)/mg, or positive by immunohistochemistry (IHC)], or negative. Stratification was by adjuvant chemotherapy (none, concurrent, sequential), nodal status (node negative, 1–3 positive, 4+ positive, unknown), and receptor status [ER and/or PgR positive (+), ER and PgR negative, unknown].

MA.14 was activated in September, 1996. In July, 2000, the duration of OCT was reduced to 2 years from 5 years because of concerns that gallbladder toxicity increased significantly after 2 years. Concurrently, the design was modified in July, 2000 to detect, with reduced 80 % power, the same EFS difference and same HR of 1.5; 191 events were required. Enrollment was then to be 650 eligible women accrued over 5 years with 4.7 years of follow-up before final analysis. The trial closed to accrual July 21, 2000. The final efficacy analysis was completed in December 2007 [4], and the final efficacy update used here was completed in January, 2010 [5].

NSABP B-29

The NSABP B-29 trial (ClinicalTrials.gov Identifier: NCT00002967; CONSORT diagram Fig. 1b) had ethics approval and informed patient consent. The primary aim was to determine if the addition of OCT to TAM alone, or to TAM in combination with chemotherapy, prolonged disease-free survival (DFS) in women with histologically axillary node negative (N0), ER+ breast cancer. The trial was designed to accrue 3000 women to allow a comparison of DFS which would have a power of at least 80 % to detect a 25 % decrease in annual event rate in patients treated with OCT, relative to those not receiving OCT, when 400 DFS events were observed.

Women were eligible for B-29 with primary invasive breast cancer, after undergoing lumpectomy and axillary dissection, or total mastectomy and axillary dissection. At the discretion of the treating physician, patients might receive adjuvant chemotherapy in the form of doxorubicin (Adriamycin; A) 60 mg/meter $(m)^2$ intravenous (iv) and

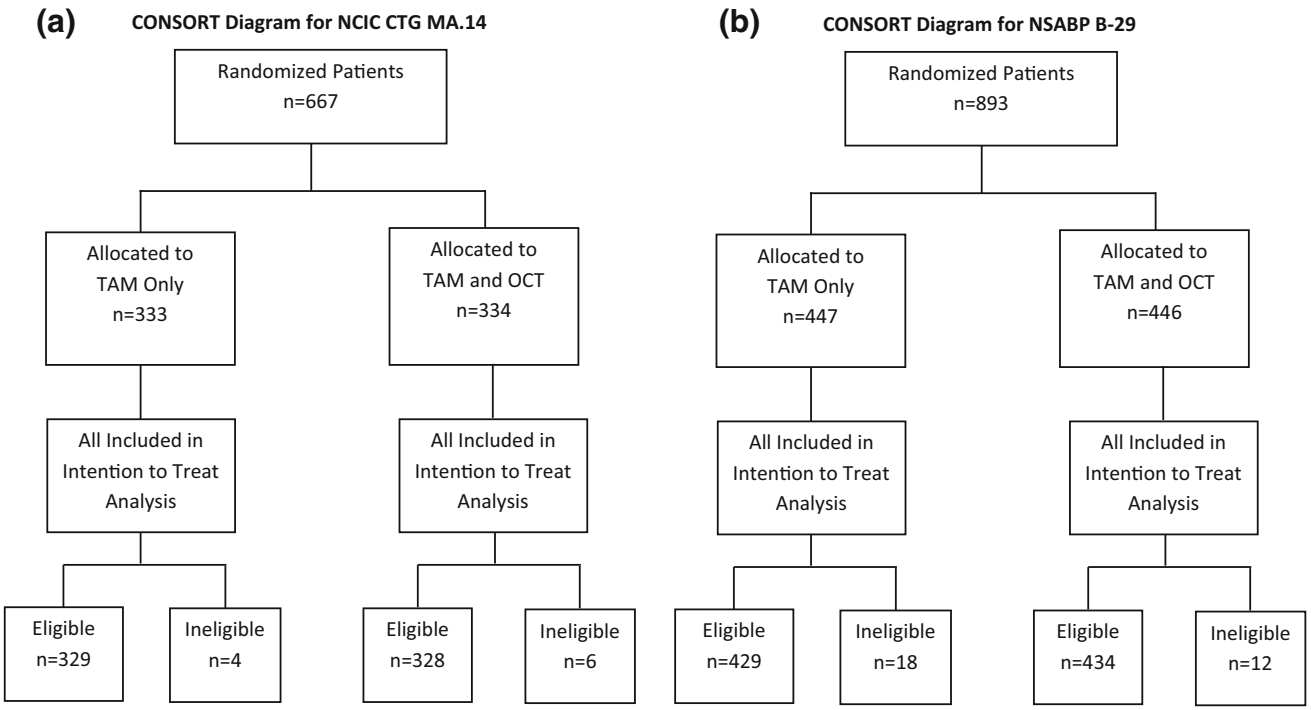

Fig. 1 **a.** CONSORT diagram for NCIC CTG MA.14. **b** CONSORT diagram for NSABP B-29

cyclophosphamide (C) 600 mg/m^2 iv every 21 days for 4 doses, with the decision to administer AC prior to randomization. All chemotherapy was concurrent with trial therapy and received after randomization. All of B-29 radiotherapy was received after randomization and after chemotherapy, if that was given. Stratification within the subgroup receiving AC chemotherapy was by age ($\leq$49, $\geq$50 years); pathologic tumor size [$\leq$2.0, (2.1–4.0), $\geq$4.0 cm (cm)], and institution. Within the subgroup that did not receive chemotherapy, stratification was by age at surgery ($\leq$49, $\geq$50 years), pathologic tumor size [$\leq$2.0, (2.1–4.0), $\geq$4.0 cm], and institution.

The B-29 trial opened accrual on May 1, 1997, with initial patient randomized on May 9, 1997. Due to the occurrence of excessive gallbladder toxicity, the DMC recommended termination of study accrual and treatment with OCT. Consequently, randomization was terminated on December 22, 1999. Follow-up of accrued patients terminated March 2, 2006.

Study end points

The primary endpoint for this pooled analysis was the B-29 primary endpoint of DFS, defined as time from randomization to time of (local, regional, or distant) breast cancer recurrence; second primary cancer other than squamous or basal cell skin carcinoma, cervical carcinoma in situ, or lobular breast carcinoma in situ; or death. The MA.14 EFS primary endpoint differed slightly, and was synchronized to the B-29 DFS endpoint, with removal of second primary cancer events due to squamous or basal cell skin carcinoma, cervical carcinoma in situ, or lobular breast carcinoma in situ.

Statistical analysis

The primary statistical test was a univariable pooled stratified log-rank test, with stratification within trials by applicable stratification factors. B-29 stratification by institution was not used in these analyses. Secondary end points were DFS by individual trials, with assessment by stratified log-rank tests. Graphical depiction was with Kaplan–Meier plots. Unstratified analyses were also performed. Exploratory multivariable effects of treatment were assessed utilizing Cox regression models and the Wald test statistic, with adjustment by applicable investigative factors. Analyses used the intention-to-treat (ITT) populations. All tests were two-sided, with significance indicated by unadjusted $p \leq 0.05$. Analyses were performed with version 9.2 SAS Institute Inc software. We examined the assumption of proportional hazards with plots of log-cumulative hazards against time.

Results

MA.14 accrued 667 patients between 1996 and 2000, 10 of whom were ineligible. The median follow-up time of these patients was 9.8 years. B-29 accrued 893 patients between

1997 and 1999, 30 of whom were ineligible. The median follow-up time for these patients was 6.8 years. All accrued patients were included in these analyses.

Baseline patient characteristics are provided by trial arm for each trial, and pooled across both trials (Table 1). Patients were well-balanced by treatment arms within trials, and hence, by treatment in the pooled data. MA.14 patients were postmenopausal with 97 % ≥50 years of age while 62 % of B-29 women were ≥50 years. Fifty-three percent of MA.14 patients were N0, while B-29 patients were all N0. Thirty-three percent of MA.14 patients received adjuvant chemotherapy, 2 % concurrently, while 53 % of B-29 received concurrent chemotherapy. Ninety percent of MA.14 patients were hormone receptor positive while 100 % of B-29 were ER+. MA.14 patients experienced 5-year DFS rate of 80 % on TAM and 76 % on TAM + OCT (Table 2), while B-29 patients had 5-year DFS of 88 % for both arms. The pooled 5-year rates were 85 and 83 %. The pooled univariable stratified Cox HR of TAM + OCT to TAM was 0.99 [95 % Confidence Interval (CI) 0.81–1.20; $p = 0.69$). The HR for MA.14 was 0.94 (95 % CI 0.73–1.20; $p = 0.50$), and for B-29, was 1.09 (95 % CI 0.80–1.50; $p = 0.59$). Unstratified results were similar (Table 2). Graphical depictions of these results are provided for pooled trial data (Fig. 2), MA.14 (Fig. 3), and B-29 (Fig. 4).

The multivariable HR of TAM + OCT to TAM was not significant after adjustment by other factors (Table 3) with pooled data, or individually for either trial. The pooled HR of TAM + OCT to TAM was 0.98 [95 % CI 0.81–1.20; $p = 0.84$]. Patients who were older ($p < 0.001$) and had higher T stage ($p < 0.001$) with N + disease ($p < 0.001$) had shorter DFS. In MA.14, the HR for TAM + OCT to TAM was 0.93 [95 % CI 0.72–1.20; $p = 0.60$], while for B-29, it was 1.07 [95 % CI 0.78–1.47; $p = 0.65$].

Discussion

MA.14 and B-29 were early breast cancer trials which tested the hypothesis that a somatostatin analog would improve breast cancer outcome. Perhaps two-thirds of breast cancers have somatostatin receptors [2], and preclinical data suggested a somatostatin analog and TAM combination might be superior to TAM [3]. Octreotide (SMS 201-995 pa LAR) was the somatostatin chosen for testing the concept.

Two phase III adjuvant trials were planned. The MA.14 patients were postmenopausal women unrestricted by pathologic nodal status or hormonal receptor status. B-29 patients were node negative with ER + positive tumors, unrestricted by menopausal status. The difference in patient populations led to a lower propensity for administering adjuvant chemotherapy in MA.14; chemotherapy was administered to 53% of B-29 and 33% of MA.14 patients, only 2% of the latter receiving it concurrently. Interestingly, chemotherapy was administered to 31% of women enrolled in the more recent large ($N = 7576$) NCIC CTG MA.27 postmenopausal aromatase inhibitor trial [6]. Thus, there may be general applicability that approximately one-third of postmenopausal women receiving endocrine therapy will be prescribed adjuvant chemotherapy.

In B-29, if administered, a specified regimen of AC chemotherapy and radiotherapy were mandated to take place sequentially during concurrent administration of TAM +/− OCT. The intensity of concurrent adjuvant therapy may have contributed to the earlier observation of significant gallbladder toxicity in B-29. However, in MA.14, the reduced 2-year duration of OCT on MA.14, monitored 6 monthly by the NCIC CTG Data Safety Monitoring Committee, was also found at the final analysis to be associated with significantly higher gallbladder toxicity ($p < 0.001$) [4].

MA.14 patients experienced lower 5-year DFS (80 % on TAM; 76 % on TAM + OCT) compared with B-29 patients, who had 88 % 5-year DFS for both arms. B-29 patients were all node negative so may have been at lower risk of progression than the MA.14 patients, 48 % of whom were node positive. Another reason for lower MA.14 DFS might be the older ages of patients with 97 % of MA.14 patients being at least 50 years of age at randomization, compared with 62 % of B-29 patients. With non-breast cancer deaths included in the DFS primary endpoint, the older women in MA.14 were subject to a substantive competing risk of death from other cause mortality that was neither disease nor treatment related [7–9], which could account in part for lower DFS rates. Alternatively, the more aggressive B-29 concurrent therapy may have decreased the likelihood of relapse.

The pooled analyses show that OCT did not significantly improve DFS for TAM treated patients who had a spectrum of baseline patient characteristics by age, pathologic T, lymph node status, and adjuvant chemotherapy administration, while significantly increasing gallbladder toxicity. No correlative biomarkers were available to determine if somatostatin receptors on breast cancers were in fact activated by OCT, so we are not able to determine if this hypothesized "direct" mechanism operated. However, in MA14, as hypothesized, we did observe small reductions in insulin and IGF-1 levels with OCT exposure [4]. The magnitude of these declines were less than anticipated and insufficient to affect the behavior of any breast cancer clones, even if they were insulin or IGF-1 dependent.

The pooled evidence concerning OCT has limitations since even with both trials combined, the patient count ($N = 1560$) is less than the originally planned B-29 3,000

Table 1 Baseline patient characteristics

Factors	NCIC CTGMA.14 N = 667 (100 %)		NSABP B-29 N = 893 (100 %)		Pooled *N* = 1560 (100 %)	
Treatment	Tamoxifen *N* (%)	Tamoxifen + Octreotide *N* (%)	Tamoxifen*N* (%)	Tamoxifen + Octreotide *N* (%)	Tamoxifen *N* (%)	Tamoxifen + Octreotide *N* (%)
Total	333 (100)	334 (100)	447 (100)	446 (100)	780 (100)	780 (100)
Age at allocation						
0: Age <50	13 (4)	8 (2)	169 (38)	171 (38)	182 (23)	179 (23)
1: Age $\geq$50	320 (96)	326 (98)	278 (62)	275 (62)	598 (77)	601 (77)
Race						
Caucasian	326 (98)	318 (95)	386 (86)	380 (85)	712 (91)	698 (89)
Not Caucasian	7 (2)	16 (5)	61 (14)	66 (15)	68 (9)	82 (11)
Pathologic T						
0: 0, 1, In Situ	194 (58)	195 (58)	334 (75)	325 (73)	528 (68)	520 (67)
1: 2, 3A, 4, Unknown	139 (42)	139 (42)	113 (25)	121 (27)	152 (32)	260 (33)
Number of positive axillary nodes						
0: 0	179 (54)	175 (52)	447 (100)	446 (100)	626 (80)	621 (80)
1: 1–3, 4+, Unknown	154 (46)	159 (48)	0 (0)	0 (0)	154 (20)	159 (20)
Hormone receptor status						
Negative, unknown	31 (9)	34 (10)	0 (0)	0 (0)	31 (4)	34 (4)
Positive	302 (91)	300 (90)	447 (100)	446 (100)	749 (96)	746 (96)
Chemotherapy						
0: None	225 (68)	222 (66)	209 (47)	211 (47)	434 (56)	433 (56)
1: Concurrent, Sequential[1]	108 (32)	112 (34)	238 (53)	235 (53)	346 (44)	347 (44)

[1] NCIC CTG MA.14 patients receiving chemotherapy: 2% received concurrently; NSABP B-29 patients receiving chemotherapy: 100% received concurrently

Table 2 Univariable disease-free survival by treatment

Trials	5 year DFS		Tamoxifen + Octreotide to Tamoxifen			
	Tamoxifen	Tamoxifen + Octreotide	Unstratified		Stratified	
			HR (95% CI)	*P* value*	HR (95% CI)	*P* value*
NCIC CTG MA.14	0.80	0.76	0.93 (0.72–1.19)	0.55	0.94 (0.73–1.20)	0.50
NSABP B-29	0.88	0.88	1.09 (0.80–1.50)	0.59	1.09 (0.80–1.50)	0.59
Pooled	0.85	0.83	0.99 (0.81–1.20)	0.73	0.99 (0.81–1.20)	0.69

* *p* values are based on two-sided log-rank test

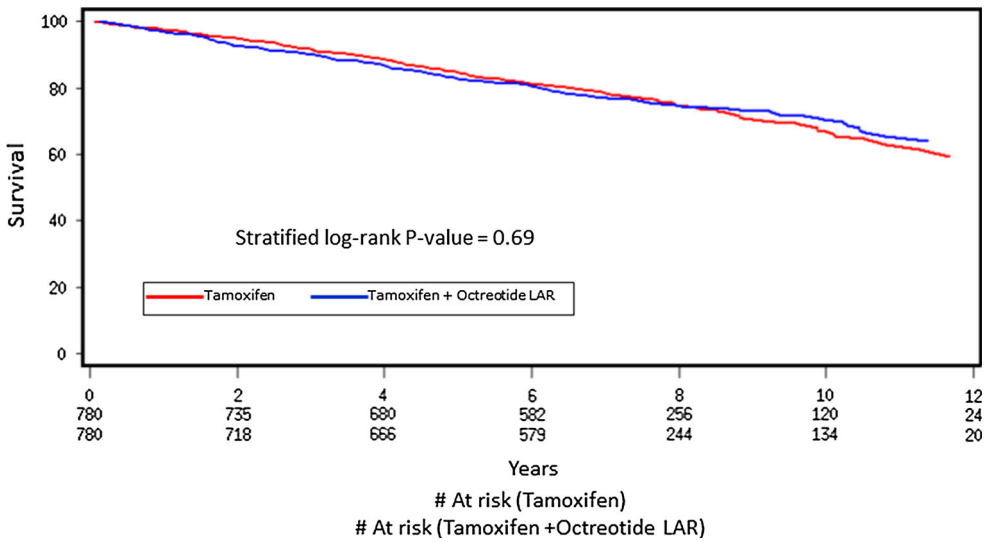

Fig. 2 NCIC CTG MA.14 and NSABP B-29 disease free survival by treatment

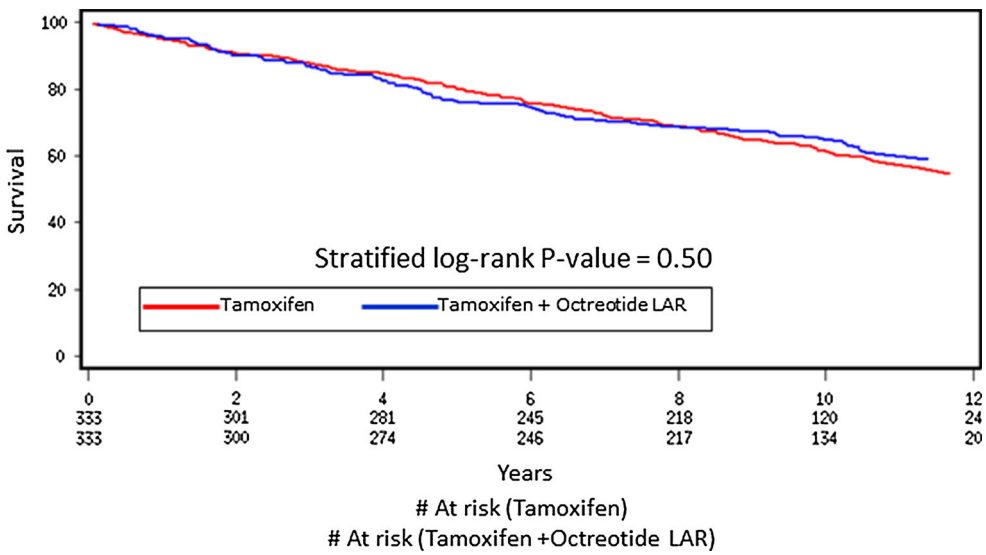

Fig. 3 NCIC CTG MA.14 disease free survival by treatment

sample size, and in neither trial did TAM-OCT patients receive the planned 5-year duration of OCT. Consequently, the pooled analysis is underpowered to detect a significant OCT treatment benefit at the level that was originally planned for either of the studies. It is clear that the level of OCT treatment delivered in these studies was insufficient to achieve a clinically meaningful level of OCT treatment benefit. Moreover, as the excessive gallbladder toxicity

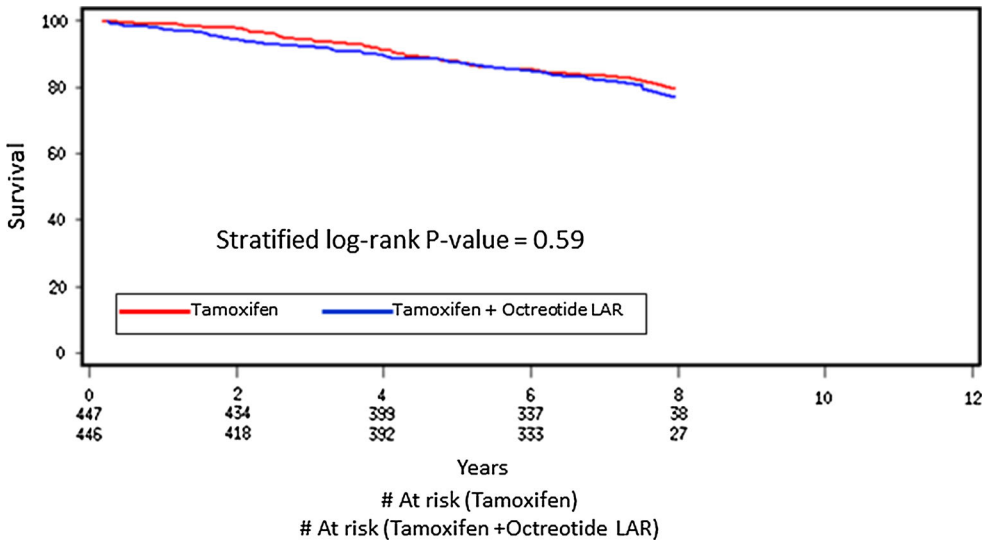

Fig. 4 NSABP B-29 disease free survival by treatment

Table 3 Multivariable effects of factors on DFS

Factor	NCIC CTG MA.14		NSABP B-29		Pooled	
	HR (95% CI)	*p* value*	HR (95% CI)	*p* value*	HR (95% CI)	*p* value*
Tamoxifen + Octreotide versus Tamoxifen	0.93 (0.72–1.20)	0.60	1.07 (0.78–1.47)	0.65	0.98 (0.81–1.20)	0.84
Age $\geq$ 50 versus Age < 50	1.63 (0.66–4.02)	0.28	1.67 (1.15–2.42)	0.008	1.78 (1.28, 2.49)	<0.001
Race non-Caucasian versus Caucasian	0.89 (0.44–1.80)	0.73	1.35 (0.88–2.08)	0.007	1.14 (0.80–1.62)	0.46
Pathologic $\geq$T2 versus <T2	1.55 (1.20–2.00)	0.001	1.62 (1.14–2.30)	0.007	1.60 (1.32–1.95)	<0.001
Node positive versus node negative/unknown	1.31 (1.00–1.72)	0.05	n/a	n/a	1.47 (1.18–1.81)	<0.001
Hormone receptor positive versus negative	0.90 (0.60–1.32)	0.58	n/a	n/a	0.85 (0.58–1.26)	0.42
Chemotherapy none versus concurrent/sequential[†]	1.07 (0.80–1.44)	0.62	0.90 (0.64–1.29)	0.58	0.97 (0.78–1.20)	0.76

* *p* value is based on two-sided Wald statistic

[†] NCIC CTG MA.14 patients receiving chemotherapy: 2 % received concurrently; NSABP B-29 patients receiving chemotherapy: 100 % received concurrently

observed in these patients makes the failed execution of delivering more OCT a moot point, OCT cannot be recommended as a targeted agent against the insulin growth factor pathway for early breast cancer. Importantly, the findings of the MA.14 and B-29 trials should not be used as evidence against the hypothesis that insulin and insulin-like growth factors stimulate breast cancer proliferation. Rather, the trials provide evidence to support the use of agents, including biguanides such as metformin [10] or small molecule antagonists of the insulin–IGF receptor family [11] now being evaluated.

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Compliance with ethical standards

Conflict of interest Dr. Kathleen I Pritchard has declared conflict of interest with AstraZeneca, Pfizer, Roche, Amgen, Novartis, GlaxoSmithKline, and Eisai. Dr. Karen A. Gelmon has declared conflict of interest with Novartis, AstraZeneca, Pfizer, and Roche. No other authors have declared any conflict of interest.

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