clinical trial updates

Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

PURPOSE Five-year data of the phase III trial TAM-01 showed that low-dose tamoxifen at 5 mg once daily administered for 3 years in women with intraepithelial neoplasia (IEN) reduced by 52% the recurrence of invasive breast cancer or ductal carcinoma in situ (DCIS), without additional adverse events over placebo. Here, we present the 10-year results.

METHODS We randomly assigned 500 women with breast IEN (atypical ductal hyperplasia, lobular carcinoma in situ [LCIS], or hormone-sensitive or unknown DCIS) to low-dose tamoxifen or placebo after surgery with or without irradiation. The primary end point was the incidence of invasive breast cancer or DCIS.

RESULTS The TAM-01 population included 500 women (20% atypical ductal hyperplasia, 11% LCIS, and 69% DCIS). The mean (±SD) age at the start of treatment was 54 ± 9 years, and 58% of participants were postmenopausal. After a median follow-up of 9.7 years (IQR, 8.3-10.9 years), 66 breast cancers (15 in situ; 51 invasive) were diagnosed: 25 in the tamoxifen group and 41 in the placebo group (annual rate per 1,000 person-years, 11.3 with tamoxifen *v* 19.5 with placebo; hazard ratio [HR], 0.58; 95% CI, 0.35 to 0.95; log-rank $P = .03$). Most recurrences were invasive (77%) and ipsilateral (59%). Regarding contralateral breast cancer incidence, there were six events in the tamoxifen arm and 16 in the placebo arm (HR, 0.36; 95% CI, 0.14 to 0.92; $P = .025$). The number needed to be treated to prevent one case of breast event with tamoxifen therapy was 22 in 5 years and 14 in 10 years. The benefit was seen across all patient subgroups. There was a significant 50% reduction of recurrence with tamoxifen in the DCIS cohort, which represents 70% of the overall population (HR, 0.50; 95% CI, 0.28 to 0.91; $P = .02$). No between-group difference in the incidence of serious adverse events was reported during the prolonged follow-up period.

CONCLUSION Tamoxifen 5 mg once daily for 3 years significantly prevents recurrence from noninvasive breast cancer after 7 years from treatment cessation without long-term adverse events.

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ASSOCIATED CONTENT

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Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

We conducted a randomized phase III trial in women with excised atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS), and ductal carcinoma in situ (DCIS), showing that tamoxifen 5 mg once daily given for 3 years halved recurrence without exceeding adverse events, resulting in a more favorable cost-benefit profile than 20 mg once daily.[1] In 2019, ASCO Clinical Practice Guidelines included low-dose tamoxifen as an option in women after noninvasive disease[2] and the US Preventative Services Task Force advocated the use of preventive therapy, including low-dose tamoxifen, among women at high risk of breast cancer.[3] Current National Comprehensive Cancer Network guidelines also recommend low-dose tamoxifen after DCIS if the patient is symptomatic on the 20 mg dose once daily or if the patient is unwilling or unable to take the standard dose.[4]

Recent data from US centers show that low-dose tamoxifen is the most popular choice of preventive therapy in women with high-risk lesions, with low

TABLE 1. Main Patient and Tumor Characteristics at Baseline (N = 500)

Characteristic	Tamoxifen (n = 253)	Placebo (n = 247)
Age, years, mean (SD)	54 (9.6)	54 (9.1)
Menopausal status, No. (%)		
Pre	110 (43)	99 (40)
Post	143 (57)	148 (60)
Age at menopause, years, mean (SD)	50 (4.6)	49 (5.8)
Body mass index, kg/m^2, mean (SD)	25.7 (4.8)	25.3 (4.2)
Waist to hip ratio, mean (SD)	0.86 (0.1)	0.86 (0.1)
Endometrial thickness, mm, mean (SD)	5.1 (3.7)	4.7 (3.2)
1st/2nd degree breast/ovarian cancer FH, No. (%)	94 (37)	95 (38)
Histologic type, No. (%)		
ADH (DIN 1b)	51 (20)	50 (20)
LCIS (LIN 2-3)	27 (11)	25 (10)
DCIS grade 1 (DIN 1c)	42 (17)	40 (16)
DCIS grade 2 (DIN 2)	72 (29)	87 (35)
DCIS grade 3 (DIN 3)	60 (24)	45 (18)
Type of surgery, No. (%)		
Conservative (Q/L)	213 (84)	203 (82)
Mastectomy	40 (16)	44 (18)
Comedo, No. (%)	29 (12)	24 (10)
Necrosis, No. (%)	64 (25)	60 (24)
Multifocal neoplasia, No. (%)	73 (29)	67 (27)
ER %, median (IQR)	90 (60-95)	90 (65-95)
PgR %, median (IQR)	70 (20-90)	60 (14-90)
HER2/neu, No. (%)		
0-2	79 (79)	89 (81)
3+	21 (21)	21 (19)
Ki67%, median (IQR)	10 (5-20)	10 (5-18)
Radiotherapy, No. (%)	108 (45)	107 (45)

NOTE. n = 1 patient with invasive breast cancer at baseline was not eligible. Menopausal status was recalculated from the data of the initial paper[1] and redefined as amenorrhea for at least 3 months, serum FSH levels above 45 mIU/mL, and serum estradiol levels below 10 pg/mL.[7] A woman with axillary dissection was re-evaluated as a conservative surgery. Percentages were calculated excluding missing data.

Abbreviations: ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; DIN, ductal intraepithelial neoplasia; ER, estrogen receptor; FH, family history; FSH, follicle-stimulating hormone; HER2, human epidermal growth factor receptor 2; LCIS, lobular carcinoma in situ; LIN, lobular intraepithelial neoplasia; PgR, progesterone receptor; Q/L, quadrantectomy/lumpectomy; SD, standard deviation.

discontinuation rates at 1 year compared with the standard dose and other preventive drugs.[5,6] To confirm the durability of the effect and assess long-term safety associated with 3 years of low-dose tamoxifen, here, we report the 10-year analyses of the TAM-01 trial .

METHODS

The TAM-01 designs and conduct have previously been described.[1] The present report focused on further follow-up of up to 10 years with annual clinical visit or telephone contact and mammography. Cataract and endometrial polyps were included given their association with tamoxifen. Statistical analyses followed previous reports.[1,7]

RESULTS

The TAM-01 population included 500 women (20% ADH, 11% LCIS, and 69% DCIS) randomly assigned to either low-dose tamoxifen (253 patients) or placebo (247 patients) for 3 years (Table 1 and Data Supplement [online only]). At database lock (September 15, 2022), the median follow-up was 9.7 years (IQR, 8.3-10.9 years). Overall, about two thirds of patients met criteria for study compliance (65% in the tamoxifen arm and 61% in the placebo arm had treatment adherence ≥85% at 2.5 years in the study). Sixty-six breast cancers (15 in situ and 51 invasive) were diagnosed: 25 in the tamoxifen group and 41 in the placebo group (annual rate per 1,000 person-years, 11.3 with tamoxifen *v* 19.6 with placebo; hazard ratio [HR], 0.58; 95% CI, 0.35 to 0.95; log-rank $P = .03$). Figure 1 shows the cumulative incidence of the primary end point (invasive breast cancer or DCIS) and contralateral breast events in the two arms. Regarding contralateral breast cancer incidence, there were six events in the tamoxifen arm and 16 in the placebo arm (HR, 0.36; 95% CI, 0.14 to 0.92; $P = .025$). The benefit was seen across all patient subgroups (Data Supplement). There was a significant 50% reduction of recurrence with tamoxifen in the DCIS cohort, which represents 70% of the overall population (Data Supplement). The characteristics of the 66 breast neoplastic events are given in the supplemental data (Data Supplement). Most recurrences were invasive (77%) and ipsilateral (59%). There was no evidence for a different stage and biology of tumors occurring in the tamoxifen arm compared with the placebo arm. The number needed to be treated to prevent one case of breast event with tamoxifen therapy was 22 in 5 years and 14 in 10 years. Table 2 shows adverse events. There were 35 serious adverse events in the tamoxifen arm and 22 in the placebo arm, including one deep vein thrombosis and one stage I endometrial cancer in the tamoxifen arm versus one pulmonary embolism in the placebo arm (rate, 0.45 per 1,000 person-years). There was no significant difference in the number of cancers other than breast cancer (16 [6.4%] *v* 9 [3.7%]). Endometrial polyps occurred in 8.0% on tamoxifen and 5.3% on placebo ($P = .28$). Similarly, there was no excess of cataract in the tamoxifen arm. No changes were observed in BMI and waist-to-hip ratio at 3 years, whereas the mean endometrial thickness in postmenopausal women increased significantly by 1.2 mm while on tamoxifen, as previously reported.[1] There were 10 deaths during the study (six in the tamoxifen group and four in the placebo group). Causes of death in the tamoxifen and placebo groups were breast cancer (1 *v* 2) and

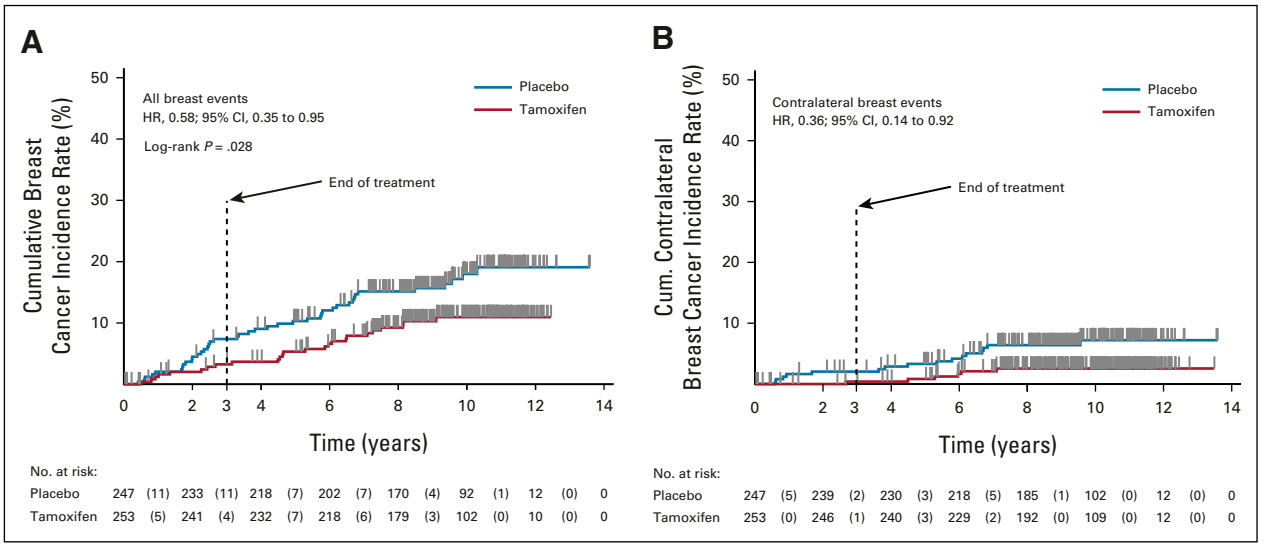

FIG 1. Kaplan-Meier estimates of (A) cumulative incidence of breast cancer events (invasive breast cancer or DCIS) and (B) contralateral breast cancer events in the overall ITT by allocated arm. Numbers in parentheses represent the number of events that occurred within each time interval by treatment arm. The dotted line indicates the time of treatment cessation (3 years). The log-rank test was used to draw inferences. The estimate of the HR was based on a univariable Cox proportional hazards regression model (ie, with only the treatment arm variable). DCIS, ductal carcinoma in situ; HR, hazard ratio; ITT, intention-to-treat population.

other causes (5 *v* 2), respectively. None was adjudicated as treatment-related.

DISCUSSION

In the initial report in 2019, we described a significant 52% reduction in the risk of breast cancer recurrence with a once-daily dose of 5 mg tamoxifen administered for 3 years after a diagnosis of intraepithelial neoplasia.[1] We now report that during an extended follow-up period of 10 years, there was a durable reduction in the incidence of breast cancer, mostly invasive. This result illustrates the carryover benefit of tamoxifen, even at a low dose, up to at least 7 years after treatment cessation, a result that has a meaningful value since it is accompanied by an optimal safety profile. Notably, menopausal symptoms reported by women were almost the same in the two arms, except for a nearly extra daily hot flash in the tamoxifen arm (the frequency was 1.5-fold higher with tamoxifen compared with placebo).[1] By contrast, tamoxifen at standard doses is associated with at least a doubling of vasomotor symptoms and sexual problems compared with a placebo.[8]

Serious adverse events were not increased during low-dose tamoxifen therapy. Specifically, there was no increase in deep vein thrombosis and pulmonary embolism, different from the three-fold increased risk reported by the NSABP P-1 trial with tamoxifen at standard dose.[9]

Similarly, we observed only one stage I endometrial cancer in the tamoxifen arm, with a mean rate of 0.45 per 1,000 person-years, compared with 2.24 per 1,000-person years of the full dose reported in the NSABP P-1 trial.[9] Importantly, the low risk of breast cancer death at 10 years (3 of 500, 0.6%) demonstrates the excellent prognosis of this cohort and supports recent trends in treatment de-escalation in DCIS.[10] Finally, there were no significant excess of endometrial polyps and cataract with low-dose tamoxifen, two less severe but frequent adverse events with full-dose tamoxifen.[11,12]

The favorable risk-to-benefit ratio makes low-dose tamoxifen a valid option in different scenarios.

First, in the adjuvant treatment of DCIS after surgery followed by radiotherapy. In this setting, the prevention of any ipsilateral recurrence would also avoid complications related to breast reconstruction of a previously irradiated breast.[13]

Second, the prevention in women with high-risk lesions, including ADH, atypical lobular hyperplasia, and LCIS, corroborates the recent chemopreventive strategies adopted by several centers that started offering low-dose tamoxifen.[5,6] Finally, the 64% significant reduction of the onset of contralateral breast cancer observed in our trial suggests a strong primary preventive potential in healthy women at high risk. Recent results from other groups are in line with this concept. The phase II KARISMA trial reported a noninferior mammographic density reduction and lower menopausal symptoms after tamoxifen therapy at 2.5, 5, and 10 mg once daily versus the standard dose of 20 mg once daily among premenopausal women undergoing breast cancer screening mammography,[14] thereby reducing the proportion of interval cancers in a screening model.[15]

Limitations of our study include the absence of a vis-a-vis comparison with 20 mg once daily. However, such a noninferiority trial would necessitate a prohibitively large sample size and the risk of low acceptance rate of the standard dose by participants would make this study outdated.[16] Another

TABLE 2. Adverse Events by Allocated Arm

Adverse Event	Tamoxifen (n = 249)	Placebo (n = 246)	*P*
Deep vein thrombosis or pulmonary embolism, No. (%)	1 (0.4)	1 (0.4)	1.0
Superficial phlebitis, No. (%)	2 (0.8)	0	.50
Coronary heart disease, No. (%)	2 (0.8)	2 (0.8)	1.0
Bone fracture, No. (%)	4 (1.6)	2 (0.8)	.69
Cataract, No. (%)	5 (2.0)	5 (2.0)	1.0
Endometrial polyps, No. (%)	20 (8.0)	13 (5.3)	.28
Endometrial cancer, No. (%)	1 (0.4)	0	1.0
Other malignancies, No. (%)	16 (6.4)	9 (3.7)	.22
Thyroid	1	2	
Parathyroid	1	1	
Lungs	1	1	
Melanoma	3	2	
Kidney	—	1	
Bladder	1	—	
Colon	1	—	
Appendiceal	1	—	
Cervix	1	—	
Ovary	1	2	
Lymphoma	4	—	
Myeloma	1	—	
Death from breast cancer, No. (%)	1 (0.4)	2 (0.8)	.62
Death from other causes, No. (%)	4 (2.0)	3 (1.2)	.45
Lung cancer	1	—	
Ovarian cancer	1	—	
Pneumonia	—	1	
Acute renal failure	1	—	
Myocardial infarction	—	1	
Car accident	1	1	
Other serious adverse events, No. (%)	3 (1.2)	6 (2.4)	.34

NOTE. The safety analysis included all patients who received at least one dose of the drug or placebo (495 patients). *P* values were calculated using Fisher's exact test or the Mann-Whitney exact test.

limitation is the lack of a 5-mg tablet on the market as opposed to 10- or 20-mg tablets. On the basis of our prior data and the long half-life of tamoxifen, cutting the tablet into two or one 10 mg tablet every other day may be reasonable.[17]

In conclusion, our findings provide strong support for the use of low-dose tamoxifen after a diagnosis of noninvasive neoplasia and open the door for new studies in the primary prevention of breast cancer in high-risk women.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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