Quality of Life From Canadian Cancer Trials Group MA.17R: A Randomized Trial of Extending Adjuvant Letrozole to 10 Years

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ABSTRACT

Purpose

MA.17R was a Canadian Cancer Trials Group–led phase III randomized controlled trial comparing letrozole to placebo after 5 years of aromatase inhibitor as adjuvant therapy for hormone receptor–positive breast cancer. Quality of life (QOL) was a secondary outcome measure of the study, and here, we report the results of these analyses.

Methods

QOL was measured using the Short Form-36 (SF-36; two summary scores and eight domains) and menopause-specific QOL (MENQOL; four symptom domains) at baseline and every 12 months up to 60 months. QOL assessment was mandatory for Canadian Cancer Trials Group centers but optional for centers in other groups. Mean change scores from baseline were calculated.

Results

One thousand nine hundred eighteen women were randomly assigned, and 1,428 women completed the baseline QOL assessment. Compliance with QOL measures was > 85%. Baseline summary scores for the SF-36 physical component summary (47.5 for letrozole and 47.9 for placebo) and mental component summary (55.5 for letrozole and 54.8 for placebo) were close to the population norms of 50. No differences were seen between groups in mean change scores for the SF-36 physical and mental component summaries and the other eight QOL domains except for the role-physical subscale. No difference was found in any of the four domains of the MENQOL.

Conclusion

No clinically significant differences were seen in overall QOL measured by the SF-36 summary measures and MENQOL between the letrozole and placebo groups. The data indicate that continuation of aromatase inhibitor therapy after 5 years of prior treatment in the trial population was not associated with a deterioration of overall QOL.

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INTRODUCTION

Hormone therapy directed against the estrogen axis is the mainstay of therapy for receptor-positive breast cancer.¹ The chronic nature of relapses in this subtype of breast cancer provides the rationale for the evaluation of extended endocrine therapy as a therapeutic strategy. We reported the results of a Canadian Cancer Trials Group (CCTG)–led phase III trial that compared 10 years versus 5 years of aromatase inhibitor (AI) therapy in postmenopausal women with receptor-positive breast cancer that demonstrated a 4% improvement in the primary outcome measure of

disease-free survival (DFS) after a median follow-up of 6.3 years favoring the extended endocrine therapy intervention versus placebo (hazard ratio, 0.66; $P = .01$; 5-year DFS, 95% v 91%, respectively; ClinicalTrials.gov identifiers: NCT00003140 and NCT00754845).² Quality of life (QOL) was a secondary outcome measure. We prospectively collected QOL data to compare overall QOL and AI-related QOL using overall QOL and menopause-specific QOL (MENQOL) measures. Although the highlights of the QOL analysis were presented in the main efficacy article,² the full analysis is presented in the current article. As exploratory analyses, we also compared baseline QOL with that of the

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general population, explored the effect of time on QOL, and examined the impact of letrozole according to age groups.

METHODS

Details of study methods have been previously published and are outlined here briefly.² MA.17R was a phase III, randomized, double-blind, placebo-controlled trial where postmenopausal women with hormonal receptor-positive breast cancer who received 4.5 to 6 years of adjuvant therapy with an AI were randomly assigned to a further 5 years of letrozole (2.5 mg orally daily) or placebo. Women were stratified according to lymph node status, prior adjuvant chemotherapy, duration of any prior adjuvant tamoxifen, and interval between the last dose of AI and random assignment. The majority of women (68.5%) had previously participated in MA.17, which randomly assigned women to 5 years of letrozole or placebo after 5 years of tamoxifen. Women were eligible if they were randomly assigned within 2 years of completing AIs, had a performance status of ≤ 2 on the Eastern Cooperative Oncology Group scale, and had a minimum life expectancy of at least 5 years. The primary outcome of the study was DFS, which was defined as time from random assignment to recurrence of breast cancer or development of contralateral breast cancer. Secondary outcomes included overall survival, toxicity, and QOL. MA.17R was a North American Intergroup trial led by the CCTG with participation of the Cancer and Leukemia Group B, the Southwest Oncology Group, the Eastern Cooperative Oncology Group, and the North Central Cancer Treatment Group.

QOL was measured using the Short Form-36 (SF-36) Health Survey (two summary scores and eight subscales) and MENQOL (four symptom domains) at baseline and every 12 months up to 60 months using a paper format. QOL assessment was mandatory for CCTG centers but optional for centers from other groups.

Given that women were 5- to 10-years survivors of breast cancer and in relatively good health, we were interested in whether continuing AI use for 5 additional years had an adverse impact on general well-being. We hypothesized that continuing an AI for an additional 5 years would have minimal impact on QOL in patients who already been on AIs for 5 years. We also hypothesized that QOL would decrease in both groups over time as a result of aging and that older women would have worse QOL than younger women. We used a generic (non-disease-specific) QOL questionnaire. The SF-36 is a general health status questionnaire used in a wide variety of diseases and with normative data available.³ It is composed of 36 items that are grouped in eight subscales and summarized in the following two summary scales: the physical component summary (PCS; composed of the physical functioning, role-physical, bodily pain, and general health domains) and the mental component summary score (MCS; composed of the vitality, social functioning, role-emotional, and mental health domains). The SF-36 is scored from 0 to 100, with a higher number representing a better or favorable QOL. The PCS and MCS are normalized so that the mean score for a representative sample of the US population is 50 with a standard deviation of 10.

To test the hypothesis that continued use of AI therapy would negatively impact QOL specifically related to the impact on menopause-related health, we used the MENQOL questionnaire, a specific measure designed for this domain.⁴ The questionnaire consisted of a 29-item symptom checklist and a response scale representing the level of discomfort on each symptom. The MENQOL asks patients to indicate if they had a particular symptom (yes or no) and to evaluate the bother level of the symptom on a scale from 0 to 6. Symptoms include hot flashes, night sweats, feeling depressed, aches muscles or joints, difficulty sleeping, waking, dry skin, vaginal dryness, and sexual dysfunction. The 29 items yield four specific domains (vasomotor, physical, psychosocial, and sexual). Each item is scored from 1 to 8, with the final score for each domain representing a mean of the items in that domain. Higher scores on the scale indicate greater degree of symptom discomfort or less favorable QOL. Both

questionnaires have been shown to be valid, reliable, and responsive to change in the target population^{3,5,6} and were used in the MA.17 trial.⁷ To compare QOL with the general population, we used data from the CCTG chemoprevention trial Mammary Prevention 3 (MAP.3; which used the SF-36 and the MENQOL)⁸ and also from a Canadian population-based survey that used the SF-36.⁹

Statistical Analyses

The data were analyzed according to a prescribed framework developed by the CCTG Quality of Life Committee.¹⁰ The approach, which aimed at minimizing bias, involved the following steps: informal comparisons of completion rates for questionnaires between groups and the baseline scores for QOL summary scales, subscales, and domains between groups; formal comparisons for change of score from baseline over time between groups using longitudinal linear mixed models; and lastly, comparisons of proportions of women who had clinically important changes (better or worse) from baseline using χ^2 tests.

In the statistical modeling of change scores from baseline over time, time from random assignment, treatment group, and interaction between time and treatment group were treated as fixed covariates in the linear mixed models. If an interaction was significant at the $P = .05$ level, cross-section analyses of change scores at each assessment time point were performed using the Wilcoxon test. Otherwise, the P values for the coefficients of treatment group and time from random assignment in the reduced models without the interaction term were used to assess the treatment difference and time effect, respectively.

For the proportions of women who had clinically important changes from baseline, minimally clinically important differences of 5 for the change scores of the SF-36 summary scale and subscales¹¹ and 0.5 for the change scores of MENQOL were used, as in the MA.17 QOL analysis.⁷ Given this is a trial of stopping a medication versus continuing, priority was given to detecting improvement in women randomly assigned to placebo (and thus ceasing active treatment). Women were considered as improved for an SF-36 subscale or summary scale if they had an improvement of at least 5 points (ie, at least one change score that is > 5) at any time during follow-up. For women not improving, those with a deterioration of 5 points or more (ie, at least one change score that is ≤ -5) were considered deteriorated. Women who neither improved nor deteriorated were considered stable. This analysis was repeated for each of MENQOL domains using a cutoff of 0.5 points. χ^2 tests were used to compare difference in the proportions of women with improved, stable, and deteriorated QOL. For exploratory analyses, no formal statistical comparisons were done between MA.17R, MAP.3, and Canadian normative data. To explore whether the association of change in QOL on continuing or stopping letrozole varied according to age group, women were divided into three groups (< 60 , 60 to 70, and > 70 years), and a linear mixed model was applied with age, treatment, and their interaction as fixed covariates.

All analyses were conducted by intent-to-treat principle by including all women with baseline data and at least one postbaseline data point in the primary analyses. For cross-sectional analyses, women with data at a specific time point were used. A $P \leq .05$ was considered statistically significant, and no adjustment was made for multiple comparisons.

RESULTS

A total of 1,918 patients were randomly assigned in MA.17R, and 1,506 patients were on the QOL substudy (Appendix Fig A1, online only). Patient baseline characteristics for all the women randomly assigned in this study and for the women who participated in the QOL analyses are listed in Table 1. Patient characteristics were similar. Among the QOL substudy population, the median age was 65.8 years in the letrozole arm and 64.7 years in the placebo arm. More than 50% of patients in each arm had lymph node

Table 1. Baseline Patient, Tumor, and Treatments Characteristics and Compliance With Baseline QOL Questionnaire Completion

Characteristic	All Patients (n = 1,918)	Patients in QOL Substudy	
		Letrozole (n = 714)	Placebo (n = 714)
Median age, years (range)	65.1 (43-92.2)	65.8 (43-89.2)	64.7 (43-89.6)
Age, years, No. (%)			
< 60	478 (24.9)	162 (22.7)	190 (26.6)
60-69	850 (44.3)	307 (43.0)	325 (45.5)
≥ 70	590 (30.8)	245 (34.3)	199 (27.9)
Positive receptor status, No. (%)	1,895 (98.8)	705 (98.7)	707 (99.0)
Positive node status at diagnosis, No. (%)	986 (51.4)	377 (52.8)	363 (50.8)
Prior surgery, No. (%)			
Lymph node dissection	1,733 (90.4)	655 (91.7)	655 (91.7)
Mastectomy	931 (48.5)	348 (48.7)	344 (48.2)
Prior adjuvant chemotherapy	1,118 (58.3)	404 (56.6)	402 (56.3)
Time from initial pathologic diagnosis to the date of random assignment, years			
Median, range	10.6 (0.6-22.3)	10.6 (4.6-21.4)	10.6 (0.6-22.3)
No. (%)			
5-9	548 (28.6)	187 (26.2)	182 (25.5)
≥ 10	1,356 (70.7)	522 (73.1)	529 (74.1)
Years on tamoxifen			
Median (range)	5.0 (0-10.8)	5.0 (0-9.0)	5.0 (0-10.8)
No. (%)			
0	397 (20.7)	131 (18.3)	136 (19.0)
< 2-4.5	152 (7.9)	53 (7.4)	50 (7.0)
4.5-5.5	1,315 (68.6)	510 (71.4)	507 (71.0)
> 5.5	54 (2.8)	20 (2.8)	21 (2.9)
Years on aromatase inhibitor			
Median (range)	5.0 (4.5-8.6)	5.0 (4.5-8.6)	5.0 (4.5-6.2)
No. (%)			
< 4.5	5 (0.3)	2 (0.3)	0 (0)
4.5-5.5	1,828 (95.3)	684 (95.8)	683 (95.7)
> 5.5	84 (4.4)	28 (3.9)	31 (4.3)
Time between last dose of AI and random assignment, days (range)*	18 (0-789)	15 (0-763)	18 (0-789)
Interval between last dose of aromatase inhibitor and random assignment, No. (%)			
< 6 months	1,727 (90.0)	660 (92.4)	658 (92.2)
6 months to 2 years	162 (8.4)	50 (7.0)	54 (7.6)
Race and ethnicity			
White (not of Hispanic origin)	1,762 (91.9)	655 (91.7)	658 (92.2)
Hispanic	24 (1.3)	9 (1.3)	6 (0.8)
Black (not of Hispanic origin)	60 (3.1)	23 (3.2)	15 (2.1)
Asian or Pacific Islander	40 (2.1)	15 (2.1)	19 (2.7)
Native North American or Native Alaskan	9 (0.5)	3 (0.4)	6 (0.8)
Other	8 (0.4)	2 (0.3)	5 (0.7)
Unknown or refusal	15 (0.8)	7 (1.0)	5 (0.7)
ECOG performance status			
0	1,708 (89.1)	631 (88.4)	632 (88.5)
1	195 (10.2)	79 (11.1)	76 (10.6)
2	15 (0.8)	4 (0.6)	6 (0.8)
QOL questionnaire compliance			
Baseline		714 (95.3)	714 (94.3)
Month 12		645 (91.2)	646 (89.3)
Month 24		604 (88.7)	599 (89.7)
Month 36		567 (88.9)	563 (88.7)
Month 48		530 (89.4)	530 (88.5)
Month 60		481 (86.7)	472 (85.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; QOL, quality of life.

*There were eight patients whose duration between last dose of aromatase inhibitor and random assignment was longer than 2 years. These patients were considered as ineligible but included in the analysis on the basis of the intent-to-treat principle.

involvement. More than 70% of patients took tamoxifen for 5 years before their initial 5 years of AIs. The median number of days between the last dose of AI and random assignment was 15 in the letrozole arm and 18 in the placebo arm. In terms of ethnic representation, > 90% of patients were white, with a small

proportion of Hispanic, black, Asian or Pacific Islander, and native North American patients. Overall, compliance rates were > 85% and were similar between the two arms.

Mean baseline scores for PCS and MCS were similar between the groups at baseline (Table 2). The mean PCS was just below the

Table 2. Baseline QOL Scores for MA.17R Women and Healthy Women in MAP.3 and a Population-Based Survey

Measure	Mean (SD)				
	MA.17R Letrozole	MA17.R Placebo	MAP.3 Exemestane ⁸	MAP.3 Placebo	Canadian Normative Data ⁹
Age, years	65.8*	64.7*	62.5*	62.4*	63.1
SF-36					
Physical component summary	47.5 (9.4)	47.9 (9.3)	49.7 (8.2)	50.0 (7.9)	49.7 (9.4)
Mental component summary	55.5 (7.5)	54.8 (7.8)	52.5 (6.3)	52.0 (6.2)	50.9 (9.6)
Physical functioning	75.9 (24.2)	77.4 (22.7)	81.1 (20.1)	81.9 (19.0)	83.5 (21.2)
Role-physical	82.5 (32.3)	81.8 (32.6)	84.4 (21.2)	85.5 (19.6)	78.7 (35.5)
Bodily pain	74.5 (22.1)	74.2 (21.6)	71.4 (22.0)	71.4 (21.6)	73.3 (23.3)
General health	75.0 (17.1)	74.9 (18.0)	78.4 (16.3)	78.8 (16.4)	76.4 (17.7)
Vitality	66.7 (18.8)	65.5 (19.1)	64.5 (13.7)	65.1 (13.5)	62.9 (18.4)
Social function	92.1 (15.9)	91.8 (16.0)	92.0 (15.9)	91.7 (16.0)	84.3 (20.7)
Role-emotional	89.1 (26.9)	87.8 (28.0)	90.6 (17.0)	91.0 (16.6)	81.2 (33.7)
Mental health	81.8 (14.6)	81.2 (14.4)	72.6 (12.0)	72.9 (11.7)	76.1 (15.7)
MENQOL					
Vasomotor	2.4 (1.7)	2.5 (1.7)	2.3 (1.6)	2.4 (1.6)	
Psychosocial	2.2 (1.2)	2.3 (1.3)	2.2 (1.2)	2.2 (1.2)	
Physical	2.6 (1.2)	2.7 (1.2)	2.6 (1.2)	2.5 (1.1)	
Sexual	2.4 (2.0)	2.7 (2.1)	2.1 (1.6)	2.1 (1.6)	

Abbreviations: MAP.3, Mammary Prevention 3; MENQOL, menopause-specific quality of life; SD, standard deviation; SF-36, Short Form-36.

*These values represent medians.

norm and the mean MCS was slightly above the norm for the US female population (the PSC and MSC are overall scores normalized to the US population with a mean of 50 and a standard deviation of 10). The mean baseline scores for the SF-36 subscales were similar between groups. The mean baseline scores for the MENQOL domains were also similar between groups and relatively favorable (all mean scores were < 3).

For the main hypotheses addressing the change in mean QOL scores over time by intent to treat, no differences were observed between groups for the SF-36 PCS or MCS scores (Table 3 and Figs 1A and 1B). For other SF-36 subscales and MENQOL domains, a statistically significant difference between treatment groups was

seen only for the SF-36 role-physical scale in the reduced model, with a deterioration of −3.2 points ($P = .009$; Table 3 and Fig 1C) in the letrozole arm compared with the placebo arm. A statistically significant interaction between time and treatment arm was found for the SF-36 bodily pain and role-emotional subscales ($P = .03$ for both; Table 3). For these two subscales, cross-sectional analyses were conducted. As can be seen in Figure 1D, for SF-36 bodily pain, no significant difference was seen at any time point. For SF-36 role-emotional, more women deteriorated in the placebo arm than the letrozole arm at month 60 ($P = .01$; Fig 1E). The significant results observed from this analysis may become insignificant after adjustment of testing for multiple scales and domains.

Table 3. Longitudinal Linear Mixed Model of Change Scores

Measure	Model 1				Model 2		
	Time		Treatment		Time P	Treatment P	Interaction P
	E	P	E	P			
SF-36							
Physical component summary	−0.04	< .001	−0.37	.18	< .001	.27	.94
Mental component summary	−0.02	< .001	−0.42	.12	< .001	.02	.07
Physical functioning	−0.09	< .001	−0.76	.24	< .001	.35	.89
Role-physical	−0.13	< .001	−3.19	.009	< .001	.02	.71
Bodily pain	−0.05	< .001	−0.95	.19	< .001	.02	.03
General health	−0.04	< .001	−0.17	.73	< .001	.97	.62
Vitality	−0.06	< .001	−1.02	.06	< .001	.01	.08
Social function	−0.07	< .001	−0.61	.34	< .001	.16	.28
Role-emotional	−0.08	< .001	−2.31	.03	< .001	.003	.03
Mental health	−0.02	.003	−0.67	.16	.001	.049	.15
MENQOL							
Vasomotor	−0.006	< .001	0.007	.87	< .001	.74	.69
Psychosocial	0.0007	.15	0.03	.37	.09	.21	.35
Physical	0.001	.002	0.03	.29	.02	.38	.96
Sexual	−0.005	< .001	0.08	.22	< .001	.56	.30

NOTE. Model 1 is a linear mixed model for change score from baseline with time from random assignment and treatment as covariates. Model 2 is a linear mixed model for change score from baseline with time from random assignment, treatment, and their interaction as covariates. In all models, P value represents the significance of the effect. For SF-36, negative values indicate deterioration, and for the MENQOL, negative values indicate improvement.

Abbreviations: E, estimate of effect; MENQOL, menopause-specific quality of life; SF-36, Short Form-36.

Fig 1. Quality of life (QOL) of letrozole (LET) versus placebo (PLA). (A) Short Form-36 (SF-36) physical component summary. Time, $P < .001$; treatment group, $P = .18$. (B) SF-36 mental summary component. Time, $P < .001$; treatment group, $P = .12$. (C) SF-36 role-physical. Time, $P < .001$; treatment group, $P = .009$. (D) SF-36 bodily pain. Time, $P < .001$; interaction $P = .03$; $P \geq .05$ at each time point. (E) SF-36 role-emotional. Time, $P < .001$; interaction $P = .03$; $P \geq .05$ at each time point except at month 60, where $P = .01$. (F) Menopause-specific QOL (MENQOL) vasomotor domain. Time, $P < .001$; treatment group, $P = .87$. (G) MENQOL sexual domain. Time, $P < .001$; treatment group, $P = .22$.

The proportions of women who had clinically important changes from baseline are presented in Figure 2. Some borderline and statistically significant differences were observed. In the SF-36 PCS, 27% of women improved, 31% were stable, and 42%

deteriorated in the letrozole arm compared with 31%, 33%, and 36% of women, respectively, in the placebo arm (*P* = .05; Fig 2A, SF-36 response analysis). For the bodily pain subscale, 48% of women improved, 9% were stable, and 43% deteriorated in the

Fig 3. Selected quality of life (QOL) subscales by age group. (A) Short Form-36 (SF-36) physical functioning. (B) SF-36 bodily pain. (C) Menopause-specific quality of life (MENQOL) vasomotor domain. (D) MENQOL sexual domain.

letrozole arm compared with 54%, 11%, and 35% of women, respectively, in the placebo arm ($P = .005$; Fig 2A, SF-36 response analysis). For menopausal symptoms, a difference was found in the vasomotor domain, with 44% of women improved, 32% stable, and 25% deteriorated in the letrozole arm compared with 50%, 30%, and 20% of women, respectively, in the placebo arm ($P = .03$; Fig 2B, MENQOL response analysis).

For our exploratory objectives, baseline QOL of women enrolled onto MA.17R was compared with baseline QOL for women without a history of cancer enrolled onto MAP.3 (a chemoprevention trial of exemestane v placebo⁸; Table 2). When comparing MA.17R data to baseline MAP.3 data, it can be seen that women on MA.17R had slightly better QOL as measured by the SF-36 MCS, bodily pain, and mental health scales. It was slightly worse for the SF-36 PCS, physical functioning, role-physical, and general health scales and the sexual domain of the MENQOL. Compared with the Canadian normative data⁹ (population-based data with no information on the history of cancer or not), QOL was better in the MA.17R population for most domains except for the SF-36 PCS score and the physical functioning and general health domains.

To look at effect of time, we used a linear mixed model with only time and treatment as the covariates (model 1 in Table 3). There was a statistically significant deterioration over time for the two SF-36 summary scales and the eight subscales. For the

MENQOL, there was a statistically significant improvement for the vasomotor and sexual domains over time and deterioration for the physical domain over time.

To explore the associated differences in QOL according to age group, we analyzed the following subscales on which continuing an AI could have more impact: the SF-36 physical functioning and bodily pain subscales and the MENQOL vasomotor and sexual domains (Appendix Table A1, online only). As expected for the SF-36 physical functioning subscale, we did observe a worsening of QOL by increasing age group (Fig 3). In addition, the interaction term for age and treatment was significant ($P = .02$; Appendix Table A1), but further cross-sectional analyses by age group did not find any point where there was a significant difference between women in the two treatment groups. SF-36 bodily pain subscales showed worsening by increasing age and no interaction by treatment group. Vasomotor symptoms and sexual dysfunction were reported less by older women, and no significant differences by treatment group were observed.

DISCUSSION

In view of the improvement in the primary outcome measure of DFS of 4%, it is reassuring that no significant detrimental effect on

QOL was seen in continuing an AI versus stopping it after 5 years of AI treatment. There was no difference in QOL between letrozole and placebo in the majority of the SF-36 subscales; in the SF-36 role-physical subscale, there was a slight deterioration, which was less than the usually accepted clinically significant threshold. When the proportions of women who improved or worsened were studied, the placebo group (stopping the AI) was more likely to improve for the SF-36 PCS, the bodily pain subscale, and the MENQOL vasomotor symptoms domain. These results are consistent with other trials comparing AI versus placebo. In both the adjuvant⁷ and chemoprevention settings,⁸ overall QOL was similar between the AI arm versus the placebo arm, except for few domains where small expected differences were seen (pain and vasomotor and sexual symptoms). In the National Surgical Adjuvant Breast and Bowel Project B-33 trial (extended exemestane v placebo after 5 years of tamoxifen), numerically worse scores on the four domains of the MENQOL were seen at 24 months, but none were statistically significant.¹²

We found that, 5 to 10 years after diagnosis, survivors of breast cancer have a QOL that is similar to that of other women of the same age with no history of breast cancer, except for slightly lower QOL in regard to physical domains and sexual symptoms. Given the mechanism of action of AI, which decreases the level of circulating estrogens, these differences are not surprising.

As expected, we observed that as women age, there is a slight deterioration in QOL and that older women have a worse QOL in the physical functioning subscale. In a population-based study where SF-36 was administered over a 5-year period, it was also found that there was a greater deterioration in QOL in older age groups, especially in the physically oriented domains.¹³ Overall, however, within an age group, there was no significant effect on QOL of continuing letrozole versus stopping it.

A few caveats regarding this study must be kept in mind. First, these results must be interpreted in light of the selected patient population who participated in the study because self-selection on the basis of prior tolerance of AI therapy was likely. Second, there was heterogeneity in the study population, with some patients entering the study at 10 years after diagnosis (the MA.17 study population) and others entering after completion of 5 years of AI

therapy after diagnosis. Third, the interval off AI therapy allowed for the study participation was up to 2 years, although there seemed to be little difference in median time off therapy between the two arms, and only 8.4% of patients had been off AI for longer than 6 months. Finally, no adjustment was made for multiple testing.

In conclusion, our data found that in women who already tolerated 5 years of an AI, continuing therapy for another 5 years was not associated with a significant deterioration in QOL despite the fact that symptoms associated with estrogen deprivation (eg, vasomotor) improved slightly after stopping the AI. These results, in combination with the data on disease control and toxicity, will assist health care providers and women with breast cancer to make an informed decisions regarding continuing AI therapy beyond 5 years.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Appendix

Fig A1. CONSORT flow diagram. LET, letrozole; PLAC, placebo.

Table A1. Longitudinal Linear Mixed Model of Change Scores for the Effect of Age

Measure	Age		Treatment		Age-Treatment	
	E	P	E	P	E	P
SF-36						
Physical functioning	−0.06	< .001	11.1	.02	−0.16	.02
Bodily pain	−0.025	.011	0.77	.88	−0.027	.74
MENQOL						
Vasomotor	−0.0046	< .001	−0.47	.16	0.0089	.08
Sexual	−0.004	< .001	−0.40	.42	0.009	.23

NOTE. Linear mixed model for change score from baseline with age, treatment, and their interaction as covariates. In all models, *P* value represents the significance of the effect.

Abbreviations: E, estimate of effect; MENQOL, menopause-specific quality of life; QOL, quality of life; SF-36, Short Form-36.