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ORIGINAL REPORT

Efficacy, Toxicity, and Quality of Life in Older Women With Early-Stage Breast Cancer Treated With Letrozole or Placebo After 5 Years of Tamoxifen: NCIC CTG Intergroup Trial MA.17

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ABSTRACT

Purpose
National Cancer Institute of Canada Clinical Trials Group trial MA.17 randomly assigned 5,187 postmenopausal, hormone-receptor–positive patients with early breast cancer who completed 5 years of tamoxifen to receive either letrozole or placebo. At 30 months median follow-up, letrozole significantly improved disease-free survival (DFS) in all patients and overall survival (OS) in node-positive patients. Breast cancer incidence increases with age and more than 1,300 women age 70 years or older were enrolled onto MA.17, making it ideal to explore the benefits, toxicities, and quality of life (QOL) impact of letrozole on older women.

Patients and Methods
In this study, 5,169 randomly assigned patients were divided into three age groups: younger than 60 years (n = 2,152), 60 to 69 years (n = 1,694), and ≥ 70 years (n = 1,323). Log-rank test was used to compare differences in DFS, distant-disease–free survival, and OS between age and treatment groups, and Cox models were used to estimate hazard ratios and associated 95% CIs. QOL was measured using the Medical Outcomes Short Form-36 and the Menopause-Specific Quality-of-Life questionnaire.

Results
At 4 years, DFS demonstrated statistically significant differences favoring letrozole only in patients age younger than 60 years (hazard ratio = 0.46; $P = .0004$); there was no interaction between age and treatment, indicating a similar effect of letrozole among all age groups. There was no difference in toxicity or QOL at 24 months among letrozole- and placebo-treated patients age ≥ 70 years.

Conclusion
Healthy patients age 70 years and older completing 5 years of tamoxifen should be considered for extended adjuvant therapy with letrozole.

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INTRODUCTION

In the United States, breast cancer incidence and mortality rates rise dramatically with age, and today most women who die of breast cancer are 65 years or older. While the risk of breast cancer is about 1 in 230 for women younger than 39 years old, it rises to 1 in 13 for women between 60 to 79 years of age.[1] Extensive data indicate that older age is frequently associated with poorer treatment that can lead to shortened survival.[2-4] Life expectancy has dramatically improved in North America, and in the United States the average life expectancy for a woman is now 80 years. Tumor biology in older women is more favorable than in younger patients, but after adjusting for stage, mortality rates are similar among older and younger women except for those younger than age 35 years and older than age 80 years; the latter groups have poorer survival rates.[5]

At least 70% to 80% of women 65 years or older have hormone-receptor–positive breast cancers, and in this group, the use of adjuvant tamoxifen therapy has significantly improved disease-free survival (DFS) and overall survival (OS).[6] However, even in women taking tamoxifen for 5 years, more than half of all breast cancer relapses occur between 5 and 15 years,[6] and at least two large trials have failed to show benefit for tamoxifen therapy

exceeding 5 years.[7-9] Ongoing trials are still exploring the optimal duration of tamoxifen use (see www.cancer.gov for details of Adjuvant Tamoxifen Longer Against Shorter and CRC-TU-Adjuant Treatment Tamoxofen Offers More trials), but at present most clinicians limit treatment to 5 years. Aromatase inhibitors (AIs) have emerged as highly effective endocrine therapies in postmenopausal patients, decreasing relapse rates by approximately 3% when compared with tamoxifen; survival, however, has not been convincingly improved in these trials but follow-up is still short.[10-13] Because of the high relapse rate after 5 years of tamoxifen therapy, we designed National Cancer Institute of Canada Clinical Trials Group trial (NCIC CTG) MA.17 to test the efficacy of the AI letrozole in postmenopausal patients who were disease free after 5 years of tamoxifen. At 30 months median follow-up, the hazard ratio (HR) for letrozole compared with placebo-treated patients on NCIC CTG MA.17 was 0.58 (95% CI, 0.45 to 0.76; $P = .00004$) for DFS, and 0.60 (95% CI, 0.43 to 0.84; $P = .002$) for distant-disease–free survival (DDFS). OS was significantly improved for letrozole patients in the node-positive (HR = 0.61, range, 0.38 to 0.98; $P = .04$) but not in the node-negative cohort.[14]

Currently, a 65-year-old woman in average health can expect to live another 20 years, a 75-year-old woman can expect to live 13 more years, and an 85-year-old woman can expect to live another 7 more years.[15] Little data are available on older patients treated with adjuvant AIs. More than 1,300 patients age ≥ 70 years participated in this placebo-controlled trial, making it an ideal study to explore the benefits and toxicities of letrozole in older patients. In addition, the trial included an extensive quality-of-life (QOL) assessment that further explored the effects of AI therapy on other important survivorship domains in addition to standard toxicity grading.[16] The analysis we report here was performed to determine whether there were age-dependent differences in DFS, DDFS, and OS,

Table 1. Baseline Patient and Breast Cancer Characteristics by Age Group

	Patient Age (years)						*P*	
	< 60 (n = 2,152)		60-69 (n = 1,694)		≥ 70 (n = 1,323)			
Characteristic	No.	%	No.	%	No.	%	Univariate	Multivariate
Treatment							.40	.09
Letrozole	1,065	49	835	49	682	52		
Placebo	1,087	51	859	51	641	48		
Race/ethnicity							.11	.11
White	1,963	91	1,521	90	1,224	93		
Black	72	3	58	3	49	4		
Other	94	4	77	5	32	2		
Unknown	13	1	20	1	11	1		
Missing	10	0	18	1	7	1		
Performance status							< .0001	< .0001
0	2,035	95	1,558	92	1,053	80		
1	115	5	131	8	253	19		
2	1	0	4	0	17	1		
Missing	1	0	1	0	0	0		
Axillary lymph node status							< .0001	< .0001
Negative	1,000	46	899	53	669	51		
Positive	1,103	51	731	43	525	40		
Unknown	42	2	59	3	125	9		
Missing	7	0	5	0	4	0		
Hormone receptor status							.54	.82
Positive (ER and/or PR)	2,098	97	1,653	98	1,283	97		
Negative	3	0	1	0	4	0		
Unknown	31	1	30	2	30	2		
Missing	20	1	10	1	6	0		
Duration of tamoxifen treatment							.17	.69
≤ 5	1,009	47	745	44	613	46		
> 5	1,141	53	948	56	705	53		
Missing	2	0	1	0	5	0		
Median		5.00	5.01		5.00			
Prior adjuvant chemotherapy							< .0001	< .0001
No	666	31	1,070	63	1,083	82		
Yes	1,483	69	622	37	238	18		
Missing	3	0	2	0	2	0		
Prior surgery								
Lumpectomy/segmental mastectomy	1,301	60	971	57	709	54	.0007	< .0001
Mastectomy	1,112	52	836	49	713	54	.12	.81

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

toxicity, or QOL among older and younger patients in this large placebo-controlled trial.

PATIENTS AND METHODS

Study Design

Details of the study design, eligibility criteria, and the patient population of the NCIC CTG Intergroup trial MA.17 have been previously described.[14,17] This trial was a phase III, randomized, double-masked, placebo-controlled trial, the primary objective of which was to determine the efficacy of letrozole in preventing disease recurrence in postmenopausal women with primary breast cancer who had completed about 5 years (range, 4.5 to 6 years) of adjuvant tamoxifen. Patients were randomly allocated to letrozole (2.5 mg by mouth daily) or placebo for 5 years and stratified by hormone-receptor status, nodal involvement, and chemotherapy use. In accordance with the protocol-specified guidelines, MA.17 was terminated in 2003 on the recommendation of the data and safety monitoring committee after the first interim analysis demonstrated a statistically significant effect on DFS for patients treated with letrozole as compared with placebo.[17]

Detailed QOL analyses, also part of this trial, have been published previously.[16] Eligibility for the QOL substudy included willingness to complete QOL questionnaires before randomization and fluency in English or French. QOL was measured using the Medical Outcomes Short Form 36-item general health questionnaire (SF-36), a multipurpose QOL measure. SF-36 contains eight subscales (domains), which are summarized into two global scores, the physical and mental component summary (PCS and MCS).[18] The eight subscales include physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The instrument has been used extensively in cancer and noncancer populations, and is scored from 0 to 100, with a higher number representing a higher QOL. The PCS and MCS are normalized so that the mean score for a representative sample of the US female population is 50, with a standard deviation of 10. The Menopause-Specific QOL Questionnaire (MENQOL) was chosen specifically to assess menopausal related symptoms that might be worsened by the use of AIs.[19] It contains 29 items under four domains (vasomotor, psychosocial, physical, and sexual). The instrument scoring for the MENQOL ranges from 1 to 8, with the higher numbers representing greater symptom discomfort and less favorable QOL. Both instruments have been shown in previous studies to be valid, reliable, and sensitive to change. The instruments were administered before randomization, at 6 months postrandomization, and then yearly. In this unplanned subset analysis that focuses on age, women randomly assigned onto MA.17 were divided into one of the following three age groups: younger than 60 years, 60 to 69 years, and $\geq$ 70 years.

Patient Population

Women were eligible for the main trial if they were at least 50 years of age at the start of adjuvant tamoxifen therapy, if they were younger than 50 years but were postmenopausal or had undergone a bilateral oophorectomy before initiation of tamoxifen therapy, if they had become amenorrheic since initiation of tamoxifen therapy, or if they had postmenopausal levels of luteinizing or follicle-stimulating hormone. Other criteria included a histologically confirmed diagnosis of primary hormone receptor–positive breast cancer with no evidence of metastatic disease, discontinuation of tamoxifen less than 3 months before enrollment, ECOG performance status of 0 to 2, and a life expectancy of more than 5 years. Exclusion criteria included concomitant treatment with hormone replacement therapy or a selective estrogen receptor modulator. Intermittent treatment with vaginal estrogens was permitted. All patients gave written informed consent, meeting international guidelines to participate in the trial.

Statistical Analysis

DFS was defined as the time from randomization to the time of recurrence (in breast, chest wall, nodal, or metastatic sites) or the development of new contralateral primary breast cancer. Death without recurrence and secondary malignancy were not considered as events. Secondary end points included OS (defined as time to death from any cause), QOL, and long-term safety. Adverse events were assessed by the National Cancer Institute Common Toxicity Criteria (version 2.0). Safety and study drug exposure were analyzed on all patients who received at least one dose of study medication. The χ^2 test was used to perform univariate analyses for the association between age groups and binary variables such as a clinical characteristic, discontinuation of treatment, and toxicities, and the analysis of variance to perform multivariate analyses to identify independent characteristics associated with age. For the time-to-an-event variable, the log-rank test was used to compare the difference between age or treatment groups, and the Cox model was used to estimate the HRs and associated 95% CIs. All *P* values are two-sided.

RESULTS

The study group totaled 5,187 randomly assigned patients, but due to noncompliance with the Good Clinical Practice Guidelines, 17 patients (10 receiving letrozole and seven receiving placebo), all from

Table 2. Analysis of Outcomes for All Patients by Age

Characteristic	Univariate Analysis				Multivariate Analysis†		
	4-Year Outcome (%)	HR*	95% CI	Log-Rank *P*	HR*	95% CI	*P* From Cox Regression
Disease-free survival by age, years				.74			
< 60, n = 2,152	92.4	1.00	NA		1.00	NA	NA
≥ 60 and < 70, n = 1,694	91.4	1.12	0.84 to 1.50		1.15	0.85 to 1.57	.36
≥ 70, n = 1,323	92.5	1.04	0.76 to 1.43		1.08	0.75 to 1.55	.67
Distant disease-free survival by age, years				.57			
< 60, n = 2,152	96.0	1.00	NA		1.00	NA	NA
≥ 60 and < 70, n = 1,694	94.3	1.21	0.83 to 1.77		1.34	0.90 to 2.00	.14
≥ 70, n = 1,323	95.0	1.16	0.78 to 1.74		1.37	0.86 to 2.16	.18
Overall survival by age, years				< .0001			
< 60, n = 2,152	97.4	1.00	NA		1.00	NA	NA
≥ 60 and < 70, n = 1,694	96.2	1.48	0.85 to 2.57		1.45	0.81 to 2.62	.21
≥ 70, n = 1,323	90.6	4.06	2.51 to 6.55		4.04	2.35 to 6.95	< .0001

Abbreviations: HR, hazard ratio; NA, not available.
*HR *v* < 60 years.
†Adjusting for letrozole or placebo treatment, duration of prior tamoxifen, nodal status, and prior chemotherapy.

Table 3. Outcomes by Age, Treatment, and Nodal Status

Group	Letrozole		Placebo		Hazard Ratio	95% CI	*P**
	No. of Patients	4-Year DFS (%)	No. of Patients	4-Year DFS (%)			
< 60 years	1,065	94.5	1,087	90.2	0.46	0.30 to 0.70	.0004
Node positive	543	92.9	560	87.5	0.52	0.31 to 0.85	.0096
Node negative	500	96.3	500	92.8	0.34	0.14 to 0.81	.014
≥ 60 and < 70 years	835	93.8	859	89.1	0.68	0.44 to 1.04	.078
Node positive	354	92.1	377	81.3	0.61	0.35 to 1.07	.082
Node negative	444	94.9	455	94.3	0.76	0.37 to 1.55	.45
≥ 70 years	682	94.7	641	90.2	0.67	0.41 to 1.11	.12
Node positive	273	91.4	252	87.8	0.78	0.43 to 1.42	.42
Node negative	348	97.9	321	93.7	0.22	0.06 to 0.80	.021

Group	Letrozole		Placebo		Hazard Ratio	95% CI	*P**
	No. of Patients	4-Year DDFS (%)	No. of Patients	4-Year DDFS (%)			
< 60 years	1,065	97.0	1,087	95.1	0.53	0.30 to 0.92	.025
Node positive	543	95.2	560	92.3	0.54	0.29 to 1.01	.053
Node negative	500	98.9	500	97.8	0.49	0.15 to 1.63	.24
≥ 60 and < 70 years	835	96.5	859	92.0	0.59	0.34 to 1.03	.062
Node positive	354	95.2	377	83.9	0.39	0.20 to 0.79	.009
Node negative	444	97.7	455	97.5	1.24	0.42 to 3.69	.70
≥ 70 years	682	96.2	641	93.8	0.72	0.39 to 1.34	.30
Node positive	273	94.2	252	87.8	0.72	0.35 to 1.48	.37
Node negative	348	98.1	321	97.3	0.30	0.06 to 1.48	.14

Group	Letrozole		Placebo		Hazard Ratio	95% CI	*P**
	No. of Patients	4-year OS (%)	No. of Patients	4-year OS (%)			
< 60 years	1,065	97.6	1,087	97.3	0.78	0.34 to 1.79	.56
Node positive	543	95.6	560	95.9	0.81	0.32 to 2.06	.66
Node negative	500	99.6	500	98.9	1.00	0.14 to 7.10	1.00
≥ 60 and < 70 years	835	96.7	859	95.8	0.75	0.36 to 1.59	.56
Node positive	354	95.5	377	93.4	0.64	0.23 to 1.80	.39
Node negative	444	97.8	455	97.1	0.85	0.26 to 2.79	.79
≥ 70 years	682	90.8	641	90.6	0.82	0.50 to 1.35	.44
Node positive	273	89.1	252	80.2	0.50	0.20 to 0.96	.038
Node negative	348	91.5	321	97.9	2.31	0.82 to 6.49	.11

Abbreviations: DFS, disease-free survival; DDFS, distant-disease–free survival; OS, overall survival.
*From the Cox model for the comparison between letrozole and placebo.

one center, were excluded from all analyses. Of the 5,170 patients remaining, one had age information missing and was excluded, leaving 5,169 patients for these analyses. Twenty-one patients (seven randomly assigned to letrozole and 14 to placebo) never received study medication, and the safety analysis therefore included 5,149 patients. The median follow-up of patients was 30 months, with a range of 1.5 to 61.4 months. The median age of patients enrolled onto the trial was 62 years, with a range of 32 to 95 years. Of the 5,169 patients, 2,152 (42%) were younger than 60 years, 1,694 (33%) were 60 to 69 years, and 1,323 (26%) were ≥ 70 years of age. Among those 70 years and older, 54% (712 patients) were age 70 to 74 years, 31% (411 patients) were age 75 to 79 years, 12% (164 patients) were age 80 to 84 years, and 3% (36 patients) were ≥ 85 years of age. Table 1 lists key baseline patient and disease characteristics based on age groups. Both univariate and multivariate analyses demonstrate that a higher proportion of younger women had better performance status, positive lymph nodes, chemotherapy, and lumpectomy or segmental mastectomy. Discontinuation of treatment due to either refusal of further treatment, toxicity, or other reasons was noted in 24% of older patients and was higher than in younger patients (18% of those 60 years and younger, and 19% of those 61 to 69 years; $P = .0003$), but there were no differences in the percent of older patients who discontinued treatment in the letrozole or placebo groups (24% *v* 23%; $P = .63$). In those younger than 60 years of age, significantly more patients receiving letrozole discontinued treatment for toxicity (5% letrozole *v* 3% placebo; $P = .008$), whereas more patients receiving placebo discontinued treatment for other reasons (3% letrozole *v* 5% placebo; $P = .03$); refusal was 10% for both the letrozole and placebo groups. Among those 60 to 69 years and ≥ 70 years of age, there was no difference in the reasons for treatment discontinuation among the letrozole and placebo arms.

Table 2 lists estimates of 4-year DFS, DDFS, and OS by age group. There was no significant difference in DFS and DDFS between the three age groups. As expected, the OS was significantly different

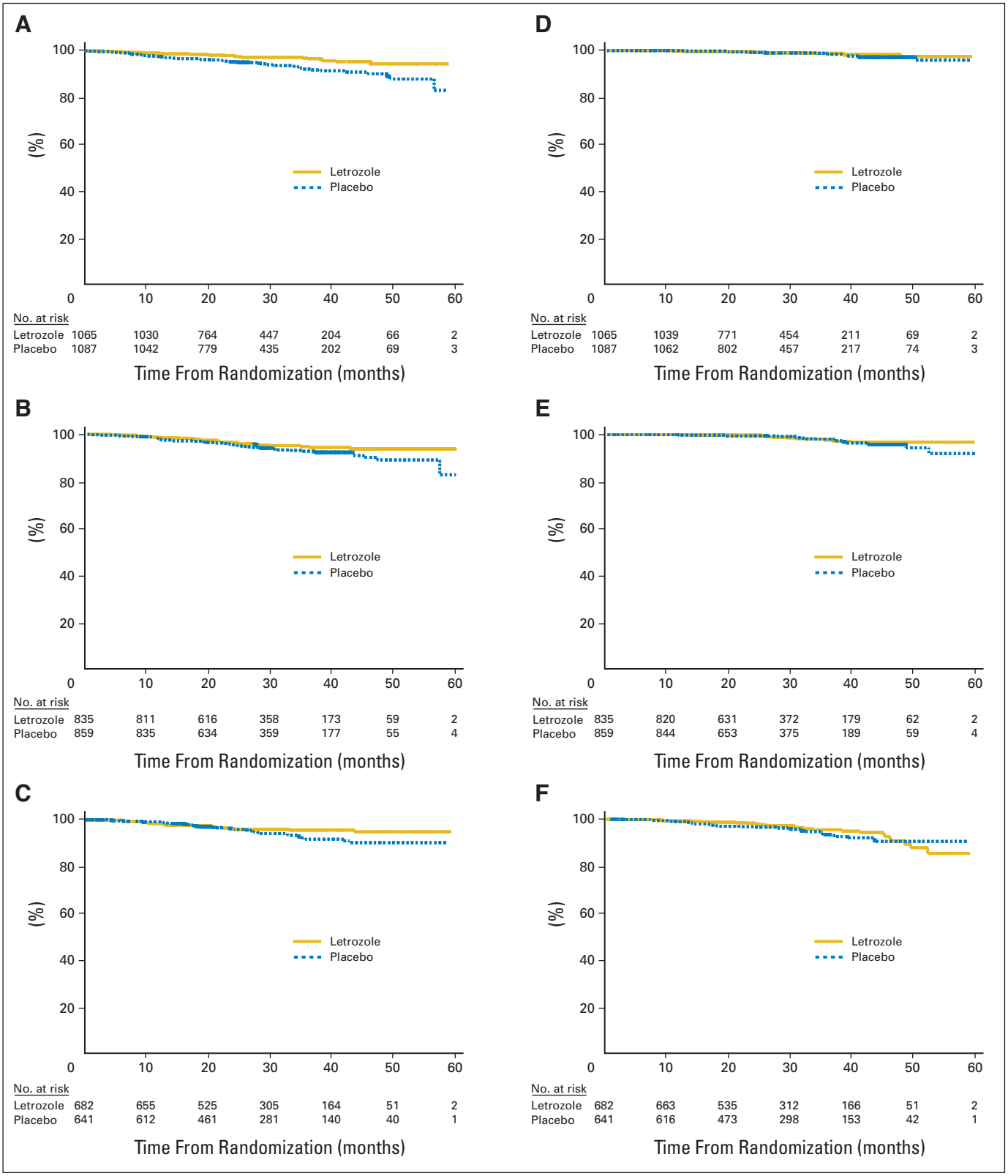

Fig 1. (A, B, C) Disease-free survival by age: (A) 60 years and younger; (B) 61 to 69 years; (C) 70 years or older. (D, E, F) Overall survival by age: (D) 60 years and younger; (E) 61 to 69 years; (F) 70 years or older.

between these three age groups due to an increased risk of non–breast cancer-related death with increasing age. The results remain the same after adjusting for other potential prognostic factors such as letrozole or placebo treatment, duration of prior tamoxifen, nodal status, and prior chemotherapy. Table 3 lists the 4-year estimates for the comparison between letrozole and placebo for DFS, DDFS, and OS within each of the three age subgroups and by lymph node status. Figure 1 shows the Kaplan-Meier estimates for DFS and OS by treatment and age. Although statistically, letrozole significantly improved both DFS and DDFS only in women younger than 60 years of age, the interaction between age and treatment was not statistically significant for any of these three outcomes ($P = .36$, 0.77, and 0.98 for DFS, DDFS, and OS, respectively), indicating no evidence of a heterogeneous effect of letrozole among age groups. Letrozole significantly improved DFS compared with placebo for both node-negative and node-positive patients younger than 60 years and for patients with negative nodes $\geq$ 70 years old. In node-positive patients, letrozole compared with placebo led to a significant improvement in DDFS in those age 60 to 69 years, and a significant improvement in OS for those age $\geq$ 70 years.

Toxicity data are summarized in Table 4 and include any reported adverse event with a 1% or greater difference among the letrozole and placebo groups or noted in 5% or more of either group. The vast majority of reported toxicities were grade 1 and grade 2 (data not shown). As a group, women $\geq$ 70 years of age had significantly higher incidences of edema, hypertension, fatigue, anorexia, constipation, diarrhea, arthritis, dizziness, and dyspnea but lower incidences of hot flushes, sweating, vaginal bleeding, high cholesterol, insomnia, headache, and vaginal dryness compared with younger women. Compared with placebo, women receiving letrozole who were younger than 60 years had a significantly lower incidence of vaginal bleeding and higher incidence of arthralgia; women receiving letrozole who were age 60 to 69 years had a statistically significantly higher incidence of hot flushes, insomnia, arthralgia, and alopecia. In women $\geq$ 70 years of age there was no significant difference in toxicities between the letrozole and placebo groups. Unrelated to treatment, women $\geq$ 70 years of age had significantly higher incidences of fracture, new osteoporosis, and cardiac disease (data not shown). However, in this age group there were no significant differences between the two treatment groups in fractures (6% letrozole *v* 8% placebo), the development of osteoporosis (10% letrozole *v* 8% placebo), or cardiac disease (10% letrozole *v* 11% placebo).

The QOL analyses by treatment and age for the eight dimensions and two overall scales (physical and mental overall) in the SF-36 and four domains in the MENQOL are summarized in Table 5 for women 70 years of age and after 24 months of follow-up. Although fewer women completed follow-up QOL assessments, compliance rates from our previous QOL analysis[16] indicate that they represented approximately 90% of women who were expected to complete these assessments. Women age 70 years and older who received letrozole had significantly worse QOL versus those receiving placebo on the vitality score at 6 months (-5.6 *v* -3.5; $P = .03$), and in bodily pain (-3.2 *v* -7.6; $P = .01$), physical scale (-1.3 *v* -3.3; $P = .009$), and

Table 4. Percent of Patients With Acute Toxicities (grade 1 to 4) by Age and Treatment

	Patient Age (years)								
	< 60			60-69			≥ 70		
Toxicity	Letrozole	Placebo	*P*	Letrozole	Placebo	*P*	Letrozole	Placebo	*P*
No. of patients	1,063	1,089		834	860		681	642	
Edema	20	18	.25	22	19	.14	25	27	.31
Hypertension	3	4	.28	7	6	.38	6	6	.86
Hot flushes	68	66	.18	59	52	.003	40	35	.09
Fatigue	35	36	.50	39	37	.49	45	44	.84
Sweating	37	35	.29	30	28	.61	20	20	.95
Anorexia	4	2	.14	6	5	.63	9	6	.11
Constipation	13	14	.64	13	15	.35	16	16	.84
Diarrhea	6	5	.32	7	7	.75	8	10	.19
Nausea	11	12	.51	14	11	.06	10	13	.10
Vaginal bleeding	8	12	.007	4	6	.08	4	3	.47
Infection w/o neutropenia	5	4	.45	5	4	.47	5	5	.91
Arthritis	4	4	.44	7	6	.40	9	7	.15
High cholesterol*	16	16	.63	17	18	.73	15	14	.55
Dizziness	16	16	.85	18	14	.07	21	23	.40
Insomnia	7	7	.51	7	4	.014	4	4	.86
Depression	6	5	.61	5	5	.80	5	5	.62
Headache	30	30	.93	28	28	.86	22	19	.11
Arthralgia	27	19	< .001	26	20	.005	21	24	.24
Myalgia	15	12	.03	15	12	.09	14	12	.26
Bone pain	5	4	.41	6	7	.27	5	6	.70
Dyspnea	4	5	.37	6	5	.33	9	10	.73
Alopecia	5	4	.24	5	3	.03	4	3	.21
Vaginal dryness	8	8	.93	5	4	.16	2	1	.15

*Change from normal to high from χ^2 test for the comparison in the incidence of toxicity between letrozole and placebo.

MENQOL vasomotor domain (0.03 *v* −0.37; $P = .001$) at 12 months. The only significant difference in QOL at 24 months for the age group 70 years and older was increased MENQOL vasomotor symptoms (0.07 *v* −0.3; $P = .02$), which became similar to placebo at 36 months (−0.3 *v* −0.4; $P = 1.0$). For the SF-36 domains, the differences observed ranged between 2 and 4 points on a 100-point scale, or 0.1 and 0.2 of a standard deviation. For the MENQOL domains, the differences observed were 0.4 points on a 7-point scale, or less than 0.3 of a standard deviation.

DISCUSSION

Although letrozole was found to be significantly better than placebo for both DFS and DDFS only in women younger than 60 years, and numerical estimates in Tables 2 and 3 indicate that the benefits in terms of DFS and DDFS are greatest in the younger group, there was no statistically significant interaction between age and treatment for DFS, DDFS, or OS, indicating that the effect of letrozole is homogenous among age groups. Moreover, MA.17 showed an OS

Table 5. Effect of Letrozole Versus Placebo in Women ≥ 70 Years on Quality of Life (SF-36) and Menopausal Symptoms (MENQOL) at Baseline and 24 Months

	Letrozole			Placebo			
Domain and Scale	No. of Patients	Mean	SD	No. of Patients	Mean	SD	*P*
SF-36							
Physical health							.66
Baseline	485	64	27	438	65	27	
24 months*	225	−6.4	19	188	−6.0	23	
Role function, physical							.33
Baseline	484	70	38	439	74	36	
24 months	221	−8.7	43	187	−12.0	44	
Bodily pain							.05
Baseline	489	72	24	441	75	22	
24 months	229	−2.0	21	189	−7.0	23	
General health							.99
Baseline	484	72	17	435	73	18	
24 months	223	−3.0	17	182	−4.0	18	
Vitality							.51
Baseline	488	63	20	440	62	20	
24 months	227	−5.3	17	188	−4.7	18	
Social function							.49
Baseline	488	91	16	439	91	19	
24 months	228	−6.9	22	187	−4.8	23	
Role function, emotional							.87
Baseline	477	85	30	434	84	30	
24 months	220	−11.5	38	182	−11.9	41	
Mental health							.52
Baseline	488	91	16	440	81	15	
24 months	227	−4.4	16	188	−3.8	15	
Physical, overall							.18
Baseline	470	43	11	426	45	10	
24 months	211	−1.5	8	171	−2.5	9	
Mental, overall							.33
Baseline	470	56	7	426	55	8	
24 months	211	−2.8	9	171	−2.2	9	
MENQOL							
Vasomotor							.02
Baseline	473	1.8	1.3	423	2.0	1.5	
24 months	209	0.1	1.3	177	−0.3	1.2	
Psychosocial							.72
Baseline	472	2.0	1.0	419	2.1	1.0	
24 months	209	0.1	1.0	170	0.2	1.1	
Physical							.98
Baseline	470	2.6	1.1	423	2.6	1.1	
24 months	208	0.1	1.0	178	0.1	1.1	
Sexual							.26
Baseline	386	1.6	1.2	343	1.6	1.3	
24 months	152	0.0	1.3	111	−0.2	1.0	

Abbreviations: SF-36, Medical Outcomes Short Form 36-item questionnaire; MENQOL, Menopause-Specific Quality-of-Life questionnaire; SD, standard deviation.
*Increase (positive value) or decrease (negative value) from baseline.

advantage for all node-positive patients. In this age-directed subset analysis, only node-positive patients age ≥ 70 years had significant improvements in OS without significant improvements in DFS and OS—an observation likely due to chance. Overall, our data do suggest that healthy elders should be considered for extended adjuvant endocrine therapy as they are more likely to have both hormone-receptor positive and lower grade tumors.[20,21]

It has been shown that younger postmenopausal women experience a higher frequency of menopausal symptoms with endocrine therapy than older postmenopausal women.[22] In women age ≥ 70 years in this trial, toxicity was similar among letrozole- and placebo-treated patients. This is noteworthy, given that overall, letrozole-treated patients were more likely to have more hot flushes, arthralgia, myalgia, and alopecia—adverse effects related to estrogen depletion. Although fractures and new osteoporosis were similar in older patients receiving letrozole and placebo, follow-up was short and elders should be monitored carefully because bone mass decreases with age, making them more vulnerable for clinical consequences of bone loss. The effects of AIs on bone metabolism and recommendations for monitoring and managing these patients have been extensively reviewed.[23] Guidelines for monitoring bone density have also been developed by the American Society of Clinical Oncology.[24] It is important to note that all women randomly assigned to MA.17 had completed 5 years of prior tamoxifen therapy. Thus women highly intolerant of any form of endocrine therapy or who could not tolerate tamoxifen may not be represented in this trial. Similarly, women with significant osteoporotic or cardiovascular risk factors may have declined trial participation. For example, it is possible that the 5 years of tamoxifen therapy that preceded letrozole in this trial was associated with better bone density than in patients who receive AIs as initial therapy.

QOL for older patients on this trial was initially poorer in those receiving letrozole but only a mild increase in vasomotor symptoms for letrozole-treated patients was noted at 36 months. This is noteworthy because for all patients on this trial, our prior analysis showed a significant worsening in QOL for patients who experienced bodily pain (51% letrozole *v* 47% placebo) or vasomotor symptoms (29% letrozole *v* 22% placebo).[16] Discontinuation of treatment was noted in 24% of older patients and was significantly higher than in younger patients, but there was no difference in the percent of older patients who discontinued treatment in the letrozole or placebo groups. It is well understood that comorbidity increases with age.[25] As age increases, the likelihood of dying of a nonbreast cancer cause increases irrespective of breast cancer stage.[26] It is most likely that the higher rate of treatment discontinuation for older women in this trial was due to the development or worsening of other serious illness that minimized the risk of breast cancer relapse and led to discontinuation of treatment.

The decision to use letrozole after 5 years of tamoxifen therapy is an important one, and requires a frank discussion between the patient and health care provider. Many older patients with life expectancies of more than 5 years, if offered letrozole, are likely to take it for a small percentage reduction in the chance of relapse. Our data show no interaction between the benefits of letrozole and age, and for patients 70 years or older there is no increase in any reported toxicities compared with placebo. QOL assessment in these older patients showed only a modest decrease with letrozole treatment compared with placebo, and these changes are not likely to have a major effect on function. In summary, letrozole was well tolerated by older women in this trial, and healthy older patients who have completed 5 years of tamoxifen should be considered for extended adjuvant endocrine therapy with letrozole.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Jemal A, Tiwari RC, Murray T, et al: Cancer statistics, 2004. CA Cancer J Clin 54:8-29, 2004

2. Hébert-Croteau N, Brisson J, Latreille J, et al: Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. J Clin Oncol 22:3685-3693, 2004

3. Bouchardy C, Rapiti E, Fioretta G, et al: Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol 21: 3580-3587, 2003

4. Eaker S, Dickman PW, Bergkvist L, et al: Differences in management of older women influence breast cancer survival: Results from a population-based database in Sweden. PLoS Med 3:e25, 2006

5. Tai P, Cserni G, Van De SJ, et al: Modeling the effect of age in T1-2 breast cancer using the SEER database. BMC Cancer 5:130, 2005

6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1665-1666, 2005

7. Stewart HJ, Prescott RJ, Forrest AP: Scottish adjuvant tamoxifen trial: A randomized study updated to 15 years. J Natl Cancer Inst 93:456-462, 2001

8. Fisher B, Dignam J, Bryant J, et al: Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor- positive tumors. J Natl Cancer Inst 88:1529-1542, 1996

9. Delozier T, Spielmann DT, Janvier M, et al: Optimal duration of adjuvant tamoxifen (TAM) in early breast cancer (EBC): Ten year results of a randomized trial (TAM-01) of the FNCLCC Breast Group. Breast Cancer Res Treat 94:S10, 2005 (abstr 14)

10. Howell A, Cuzick J, Baum M, et al: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365:60-62, 2005

11. Coates AS, Keshaviah A, Thurlimann B, et al: Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1-98. J Clin Oncol 25:486-492, 2007

12. Coombes RC, Hall E, Gibson LJ, et al: A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 350:1081-1092, 2004

13. Jakesz R, Jonat W, Gnant M, et al: Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 366:455-462, 2006

14. Goss PE, Ingle JN, Martino S, et al: Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17. J Natl Cancer Inst 97:1262-1271, 2005

15. National Center for Health and Statistics: Tables on trends in health and aging; life expectancy. http://www.cdc.gov

16. Whelan TJ, Goss PE, Ingle JN, et al: Assessment of quality of life in MA. 17: A randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. J Clin Oncol 23:6931-6940, 2005

17. Goss PE, Ingle JN, Martino S, et al: A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 349:1793-1802, 2003

18. Ware JE, Kosinski M, Keller SD: SF-36 Physical and Mental Summary Scales: A Users Manual (ed 3). Boston, MA, The Health Institute, New England Medical Center, 1994

19. Hilditch JR, Lewis J, Peter A, et al: A menopause-specific quality of life questionnaire: Development and psychometric properties. Maturitas 24:161-175, 1996

20. Diab SG, Elledge RM, Clark GM: Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 92:550-556, 2000

21. Daidone MG, Coradini D, Martelli G, et al: Primary breast cancer in elderly women: Biological profile and relation with clinical outcome. Crit Rev Oncol Hematol 45:313-325, 2003

22. Day R: Quality of life and tamoxifen in a breast cancer prevention trial: A summary of findings from the NSABP P-1 study—National Surgical Adjuvant Breast and Bowel Project. Ann N Y Acad Sci 949: 143-150, 2001

23. Chien AJ, Goss PE: Aromatase inhibitors and bone health in women with breast cancer. J Clin Oncol 24:5305-5312, 2006

24. Hillner BE, Ingle JN, Chlebowski RT, et al: American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 21:4042-4057, 2003

25. Yancik R, Wesley MN, Ries LA, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285: 885-892, 2001

26. Schairer C, Mink PJ, Carroll L, et al: Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 96:1311-1321, 2004