

Letrozole, a New Oral Aromatase Inhibitor for Advanced Breast Cancer: Double-Blind Randomized Trial Showing a Dose Effect and Improved Efficacy and Tolerability Compared With Megestrol Acetate

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Purpose: To compare two doses of letrozole and megestrol acetate (MA) as second-line therapy in postmenopausal women with advanced breast cancer previously treated with antiestrogens.

Patients and Methods: Five hundred fifty-one patients with locally advanced, locoregionally recurrent or metastatic breast cancer were randomly assigned to receive letrozole 2.5 mg (n = 174), letrozole 0.5 mg (n = 188), or MA 160 mg (n = 189) once daily in a double-blind, multicenter trial. Data were analyzed for tumor response and safety variables up to 33 months of follow-up evaluation and for survival up to 45 months.

Results: Letrozole 2.5 mg produced a significantly higher overall objective response rate (24%) compared with MA (16%; logistic regression, $P = .04$) or letrozole 0.5 mg (13%; $P = .004$). Duration of objective response was significantly longer for letrozole 2.5 mg compared with MA (Cox regression, $P = .02$). Letrozole 2.5 mg

was significantly superior to MA and letrozole 0.5 mg in time to treatment failure ($P = .04$ and $P = .002$, respectively). For time to progression, letrozole 2.5 mg was superior to letrozole 0.5 mg ($P = .02$), but not to MA ($P = .07$). There was a significant dose effect in overall survival in favor of letrozole 2.5 mg ($P = .03$) compared with letrozole 0.5 mg. Letrozole was significantly better tolerated than MA with respect to serious adverse experiences, discontinuation due to poor tolerability, cardiovascular side effects, and weight gain.

Conclusion: The data show letrozole 2.5 mg once daily to be more effective and better tolerated than MA in the treatment of postmenopausal women with advanced breast cancer previously treated with antiestrogens.

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ENDOCRINE THERAPY is an important option in the treatment of advanced breast cancer, with tamoxifen the most widely used first-line drug. Approximately 40% of patients who relapse after tamoxifen may achieve further clinically useful tumor control with second-line therapy,^{1,2} but the optimum choice of second-line treatment has not yet been defined. Progestins and aromatase inhibitors (AIs) are both commonly used; progestins (megestrol acetate [MA] and medroxyprogesterone acetate) can cause edema, weight gain, vaginal bleeding, hypertension, and thromboembolic problems,² while aminoglutethimide, until recently the most commonly used AI, can cause rash, drowsiness, and lethargy.²

Lately, more selective AIs³⁻⁸ have been developed, including letrozole (CGS 20267), a new orally active, potent, highly selective, nonsteroidal competitive inhibitor of the aromatase enzyme.⁹ It has been reported to be approximately 10,000 times as potent as aminoglutethimide in vivo, with no evidence of inhibition of progesterone or corticosterone synthesis at doses required to inhibit estrogen synthesis.¹⁰ In animal models, it has been shown to lead to almost complete regression of estrogen-dependent dimethylbenzanthracene (DMBA)-induced mammary tumors.¹⁰ Phase I studies have shown letrozole to be effective in suppressing estrone, estradiol, and estrone sulfate by more than 75% to 80% at doses of 0.1 mg to 5 mg/d, with no clinically relevant

effects on other hormones of the endocrine system (including glucocorticoids, mineralocorticoids, and thyroid hormones).¹¹⁻¹⁴ Objective tumor response rates of approximately 25% have been obtained in postmenopausal patients with advanced breast cancer after failure of previous therapy. Tolerability was excellent, with minimal side effects.¹³⁻¹⁶

This study reports the results of a multicenter, international, double-blind, randomized trial to compare the efficacy and safety of two doses of letrozole versus MA as second-line therapy in the treatment of women with advanced breast cancer previously treated with an antiestrogen. The dose of letrozole 0.5 mg was selected because it was the lowest dose to achieve maximal estrogen suppression. The dose of 2.5 mg was chosen because it was still selective and well tolerated and could perhaps achieve a higher degree of aromatase inhibition at the level of the tumor. The two doses differ by a factor of five to ensure that a dose effect, if present, could be detected.¹⁷

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PATIENTS AND METHODS

Patients

Postmenopausal women with histologically or cytologically confirmed breast cancer and with measurable or assessable locally advanced or locoregionally recurrent or metastatic disease were eligible for the study. Postmenopausal status was defined by no spontaneous menses for at least 5 years; spontaneous menses within the past 5 years, but amenorrheic (eg, spontaneous or secondary to chemotherapy or hysterectomy) for at least 12 months, and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels greater than 40 IU/L (or according to the definition of the postmenopausal normal range of the laboratory involved); bilateral oophorectomy; or radiation castration and amenorrheic for at least 3 months. Patients had to have tumors with positive or unknown estrogen or progesterone receptor status. Patients were regarded as estrogen or progesterone receptor-positive if any assay (cytochemical, immunochemical, immunohistochemical, or radioimmunoassay) of primary or secondary tumor tissue was positive. Patients were regarded as receptor unknown if no assay was known to be positive or negative. Patients with estrogen receptor-negative, but progesterone receptor-positive status, or vice versa, were considered as receptor-positive and were included in the trial. Patients were required to have failed to respond to previous antiestrogen therapy either by relapsing on adjuvant therapy (given for ≥ 6 months) or within 12 months of stopping treatment, or by progressing on first-line antiestrogen treatment for metastatic disease. Previous treatment with chemotherapy as neoadjuvant or adjuvant treatment or for advanced disease (no more than one regimen) was allowed. Other inclusion criteria were a World Health Organization (WHO) performance status ≤ 2 , total bilirubin level less than 1.5 and/or transaminases less than 2.6 times upper limit of normal, creatinine concentration less than 1.5 times upper limit of normal, WBC count $\geq 3.0 \times 10^9/L$, neutrophil count $\geq 1.5 \times 10^9/L$, hemoglobin ≥ 10 g/dL, platelets $\geq 75 \times 10^9/L$, and total serum calcium level less than 2.75 mmol/L.

Exclusion criteria were rapidly progressive disease (CNS involvement, or diffuse lymphangitis carcinomatosa of the lung); inflammatory breast cancer; disease limited to hilar enlargement, pleural effusion, or ascites; hepatic metastases that involved more than one third of the liver; concurrent or previous malignant disease (other than contralateral breast carcinoma, in situ carcinoma of the cervix treated by cone biopsy, or adequately treated basal or squamous cell skin carcinoma); history of deep vein thrombosis or pulmonary embolism; uncontrolled cardiac disease or diabetes mellitus; adrenal insufficiency; or Cushing's syndrome.

Adjuvant endocrine therapy other than antiestrogens, oophorectomy, or radiation castration, and previous first-line endocrine therapy other than antiestrogens for advanced disease, were not allowed. Systemic corticosteroids for more than 15 days, investigational drugs, and concomitant anticancer treatment, except for radiotherapy to areas not being evaluated, were not permitted during the trial. Bisphosphonates started in the 6 months before or during the trial were not allowed if bone metastases were the sole manifestation of disease.

All patients gave written consent to participate in the study, which was approved by the relevant local ethical review board and the Freiburger Ethik-Kommission International. The study was conducted according to Good Clinical Practice requirements.

Study Design

This randomized, double-blind, comparative trial was conducted in 91 centers in 10 countries. Letrozole 2.5 mg or 0.5 mg once daily, or MA

160 mg once daily, were assigned equally, using the double-dummy technique, to patients who met the inclusion criteria.

Randomization was stratified for each participating country. Within each country, treatments were assigned and packed 1:1:1 according to computer-generated permuted blocks of size 6 or size 3. Those countries that would include small centers had a block size of 3, and all countries had a block size of 3 for "reserve" supplies (ie, after enrollment of the planned number of patients had been completed in the center, additional patients could be enrolled following the reserve supplies). Each patient enrolled was assigned the treatment pack with the lowest available randomization number at a center.

Patients were seen for tumor evaluation before the start of trial treatment and every 3 months during the trial. All patients were enrolled over 18 months from March 1993 to September 1994. Patients were monitored for tumor response and safety variables for up to 33 months (median, ≈ 5.5 months) and for up to 45 months for survival (median, 18 to 20).

At each visit, superficial or palpable lesions were measured, chest x-ray was performed, and severity of pain, performance status, and adverse experiences were recorded. In addition, pulse rate, blood pressure, weight, and routine hematology and biochemistry parameters were measured. ECG was performed at baseline and at 3 and 12 months (or when the patient discontinued the study).

Bone scans and/or skeletal surveys, liver ultrasonograms, or computed tomographic (CT) scans were performed at baseline and at 6 months and repeated every 3 months if positive at baseline. A quality-of-life questionnaire, the QLQ-C30 of the European Organization for Research and Treatment of Cancer (EORTC),¹⁸ was completed by patients at baseline and at each visit while on trial treatment.

The primary efficacy end point was overall objective tumor response (complete response [CR] and partial response [PR]), assessed using International Union Against Cancer (UICC) criteria.¹⁹ Measurable disease was defined as the presence of metastatic lesions measurable in one or two dimensions using radiographic methods (x-ray, CT scan, ultrasonogram, or nuclear magnetic resonance) or physical methods (ie, palpation and measurement by calipers). Osteolytic bone lesions were considered as assessable, but nonmeasurable. Osteoblastic lesions or mixed blastic/lytic lesions at the same site and with no other site of metastatic disease, pleural effusion, hilar enlargement, and ascites were regarded as nonassessable, nonmeasurable disease. Hilar enlargement evaluated by CT scan was accepted as assessable, but nonmeasurable disease. Nonassessable, nonmeasurable lesions could not be monitored for response, but their continued presence would downgrade a CR to a PR in measurable lesions, and any increase in extent of such lesions or the appearance of new nonassessable, nonmeasurable lesions constituted disease progression (PD). The overall tumor response of each patient was verified by independent blinded external peer review (two medical oncologists and one radiologist). Peer review assigned an assessment of overall tumor response: CR, PR, stabilization of disease (NC), PD, or not assessable (NA). CR, PR, and NC had to be confirmed on two occasions at least 4 weeks apart (generally, at the next scheduled 3-month assessment). Other end points included time to progression (TTP) of disease (interval between start of trial therapy [date of randomization] and the earliest diagnosis of PD validated by peer review whereby patients who died before any on-treatment tumor staging could be performed were counted as having progressed), time to treatment failure (TTF; interval between start of trial therapy [date of randomization] and the earliest event of PD, withdrawal of trial therapy for any reason, death for any cause, withdrawal of consent, or loss to follow-up), and time to death, as well as duration of objective response (CRs and PRs). Duration of clinical benefit (CR, PR, and NC ≥ 6

months) was subsequently added in accordance with current standards of reporting.

Safety and tolerability were assessed using the National Cancer Institute common toxicity criteria.

Statistical Methodology

Assuming a significance level of 5% (two-tailed), the total sample size was calculated on the basis of overall objective tumor response as 540 patients, with 146 patients per arm, increased by approximately 23% to allow for each pair of treatments to be compared, and for a small proportion of patients being lost to follow-up without having an assessment of tumor response. The sample size had approximately 80% power to detect a 13% absolute superiority of one of the letrozole arms over MA, assuming an overall objective tumor response rate of 15% for MA.

No interim analysis was planned. The core trial data were analyzed 9 months after the end of enrollment. Six months later, the extension data for all variables were analyzed. Overall survival is updated every 6 months until 90% of all enrolled patients have died. These subsequent analyses were performed mainly to confirm the core trial results and to obtain more mature estimates of time events. The extension data and most recent survival data are presented here.

The primary end point (overall objective tumor response) was analyzed by logistic regression, presenting odds ratios with 95% confidence intervals (CI). Time to progression, time to treatment failure, and overall survival were analyzed using Cox proportional hazards regression models presenting risk ratios with 95% CIs. Treatment comparisons were adjusted for the following baseline covariates: age, body-mass index, receptor status, dominant site of disease, extent of disease (anatomical locations), disease-free interval, prior antiestrogen therapy, response to prior antiestrogen therapy, previous chemotherapy, previous or concomitant bisphosphonates, and performance status. Significance levels were not adjusted for multiple comparisons or multiple end points. The main comparison of interest was letrozole 2.5 mg versus MA.

Duration of overall objective response (CRs and PRs), duration of clinical benefit, TTP, TTF, and time to death were estimated by the Kaplan-Meier product-limit method. Treatment comparisons of duration of response and duration of clinical benefit were not adjusted for baseline covariates, because of confounding with response.

Analyses were performed on the intent-to-treat data set, which included all patients who received study medication. The analysis of safety data was descriptive, presenting 95% CIs of differences between treatments. Where appropriate, Fisher's exact test or a χ^2 test was used.

RESULTS

Patients

A total of 551 patients took study medication and were included in the intent-to-treat analyses (letrozole 2.5 mg, n = 174; letrozole 0.5 mg, n = 188; MA, n = 189). Table 1 shows that the three treatment arms were similar with respect to demographic and baseline characteristics.

Efficacy

Overall survival. Figure 1 shows the Kaplan-Meier estimates for time to death. The median time to death was

Table 1. Patient Demographics and Baseline Data

Variable	% of Patients		
	Letrozole 0.5 mg (n = 188)	Letrozole 2.5 mg (n = 174)	MA (n = 189)
Age, years (mean \pm SD)	64.6 \pm 10.5	63.6 \pm 9.1	64 \pm 9.5
Age class, years			
\leq 55	20.2	19.0	16.4
56-69	44.7	54.6	55.0
\geq 70	35.1	26.4	28.6
Dominant site*			
Soft tissue	30.3	25.3	25.4
Bone	30.9	29.9	31.7
Viscera	37.2	42.5	40.7
Anatomic sites*			
1	62.8	58.6	51.3
2	29.3	30.5	37.0
3	6.4	8.6	9.5
Disease-free interval			
0 (stage IV)	11.2	7.5	11.6
< 24 months	25.5	31.6	30.2
\geq 24 months	63.3	60.9	58.2
Overall receptor status			
ER+PgR+	36.7	32.8	37.0
ER+ or PgR+	18.6	24.7	21.7
ER \neq PgR \neq	44.7	42.5	41.3
Performance status			
0	50.0	51.1	46.0
1	38.3	34.5	45.0
2	11.7	14.4	9.0
Prior chemotherapy			
None	60.6	69.0	59.8
Adjuvant only	21.8	20.7	21.7
Therapeutic \pm adjuvant	17.6	10.3	18.5
Prior antiestrogen			
Adjuvant only	34.6	32.8	32.3
Therapeutic \pm adjuvant	65.4	67.2	67.7
Response to antiestrogen therapy			
CR + PR	21.3	19.0	21.2
PD + unknown < 6 months†	8.0	12.1	13.8
Adjuvant antiestrogens	38.8	33.9	34.9
Biphosphonates before trial entry or concomitantly	4.3	2.3	3.7
Radiotherapy to areas not being evaluated for tumor response	8.0	10.3	9.0

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

*Dominant site and number of anatomic sites do not sum to 100% as peer review considered that some patients did not have evidence of malignant disease at baseline.

†PD or response is unknown, but antiestrogen was given for <6 months.

654 days (21.5 months) for letrozole 0.5 mg, 655 days (21.5 months) for MA, and 770 days (25.3 months) for letrozole 2.5 mg. There was a significant dose effect in favor of letrozole 2.5 mg compared with letrozole 0.5 mg ($P = .03$). There was no significant difference between letrozole 0.5 mg and MA ($P = .4$) or between letrozole 2.5 mg and MA ($P = .15$). These results are listed in Table 2.

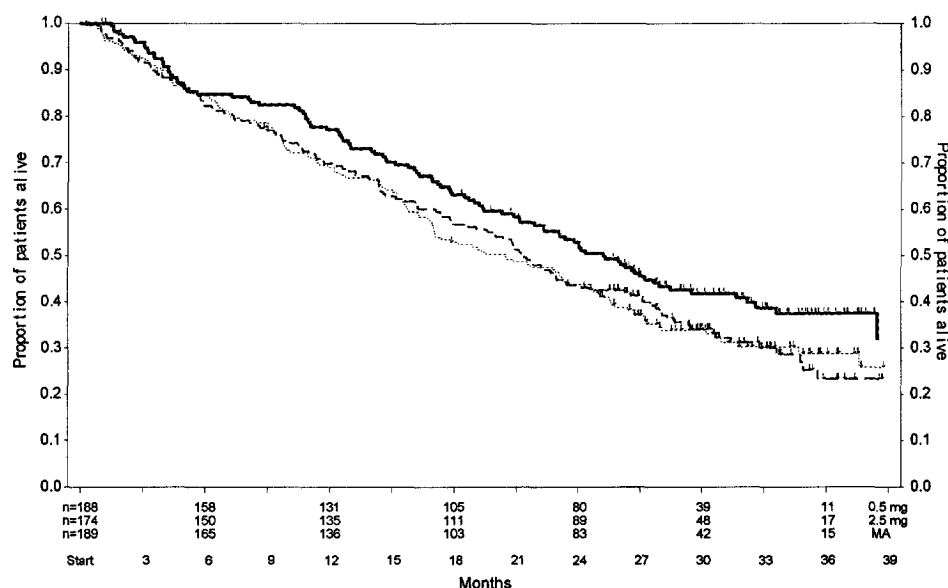


Fig 1. Kaplan-Meier estimates for time to death: letrozole 0.5 mg (- - -), letrozole 2.5 mg (—), MA (· · ·) (Plot curtailed when <5 patients/treatment arm). Deaths: 126 (67.0%) on letrozole 0.5 mg, 103 (59.2%) on letrozole 2.5 mg, 128 (67.7%) on MA. Arrows indicate censored observations.

TTP. The median TTP was 5.6 months for letrozole 2.5 mg, 5.5 months for MA, and 5.1 months for letrozole 0.5 mg (Fig 2). There was no significant difference between letrozole 2.5 mg and MA ($P = .07$), although the strong trend

Table 2. Summary of Analysis of Main End Points

End Point	Treatment Comparison		
	0.5 mg:2.5 mg	0.5 mg:MA	2.5 mg:MA
Overall survival			
Risk ratio	1.34	1.12	0.82
95% CI	1.02 to 1.76	0.87 to 1.44	0.63 to 1.08
P	.03	.38	.15
TTP			
Risk ratio	1.35	1.04	0.80
95% CI	1.04 to 1.75	0.81 to 1.32	0.62 to 1.02
P	.02	.78	.07
TTF			
Risk ratio	1.47	1.08	0.77
95% CI	1.15 to 1.89	0.86 to 1.36	0.61 to 0.99
P	.002	.52	.04
Objective response (CR + PR)			
Odds ratio	0.42	0.60	1.82
95% CI	0.23 to 0.76	0.32 to 1.12	1.02 to 3.25
P	.004	.11	.04
Duration of CR + PR*			
Risk ratio	1.32	0.58	0.42
95% CI	0.54 to 3.23	0.25 to 1.34	0.20 to 0.86
P	.54	.19	.02
Duration of CR + PR + NC \geq 6*			
Risk ratio	1.22	0.52	0.44
95% CI	0.68 to 2.19	0.30 to 0.89	0.26 to 0.73
P	.50	.01	.001

Abbreviations: 0.5 mg, 0.5 mg letrozole; 2.5 mg, 2.5 mg letrozole; MA, 160 mg MA.

*Unadjusted for baseline covariates; all other comparisons adjusted according to the protocol and analysis plan.

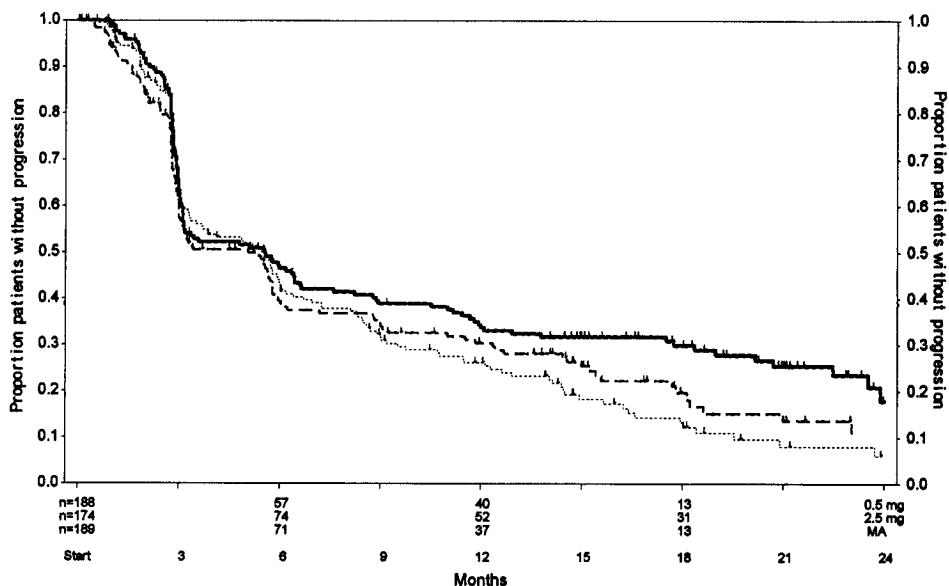
favoring letrozole 2.5 mg (95% CI suggested as great as a 38% reduction in the risk of progressing with letrozole 2.5 mg to a 2% increase in the risk compared with MA), or between letrozole 0.5 mg and MA acetate ($P = .8$) in overall TTP. The treatment difference between letrozole 2.5 mg and letrozole 0.5 mg was significant ($P = .02$). These results are listed in Table 2.

TTF. The median TTF was longest for letrozole 2.5 mg (5.1 months) compared with MA (3.9 months) and letrozole 0.5 mg (3.2 months). Letrozole 2.5 mg was significantly superior to MA in overall TTF ($P = .04$). The dose effect in favor of letrozole 2.5 mg compared with letrozole 0.5 mg was also significant ($P = .002$). There was no significant difference between letrozole 0.5 mg and MA (Table 2).

Objective response. Table 3 lists the objective response rates and associated CIs for the three treatment arms. There was a significant dose effect in favor of letrozole 2.5 mg compared with letrozole 0.5 mg ($P = .004$), and a significant superiority of letrozole 2.5 mg over MA ($P = .04$). There was no significant difference between letrozole 0.5 mg and MA (Table 2).

Duration of objective response was significantly longer for letrozole 2.5 mg compared with MA ($P = .02$). The median duration of objective response was not reached for letrozole 2.5 mg, compared with 17.9 months for MA, and 18.2 months for letrozole 0.5 mg. Covariates predictive for overall objective response were dominant site of disease and performance status. Patients with soft tissue as the predominant site of disease and good performance status (0 or 1) were more likely to respond to one of the three treatments than patients with bone or visceral involvement and perfor-

Fig 2. Kaplan-Meier estimates for TTP: letrozole 0.5 mg (- -), letrozole 2.5 mg (—), MA (· · ·) (Plot curtailed when <5 patients/treatment arm). Disease progression: 128 patients (68.1%) on letrozole 0.5 mg, 120 (69.0%) on letrozole 2.5 mg, 145 (76.7%) on MA. Arrows indicate censored observations.



mance status 2 (data not shown). Patients with predominantly soft tissue disease achieved an objective response rate of 48% with letrozole 2.5 mg and 40% with MA. For patients with predominantly bone metastases, the objective response rate was 15% with letrozole 2.5 mg and 10% with MA. For patients with visceral involvement, an objective response rate of 16% was observed with letrozole 2.5 mg and of 8% with MA. In addition, letrozole 2.5 mg appeared to be more efficacious than letrozole 0.5 mg or MA in patients who did not respond to first-line antiestrogen treatment (response rates, 29%, 7%, and 15%, respectively).

Response rates, including patients with stable disease for ≥ 6 months, were 27% for letrozole 0.5 mg, 35% for letrozole 2.5 mg, and 32% for MA. There was no significant difference among the three treatment arms. There was overall a significant difference between treatments in dura-

tion of response, including stable disease ≥ 6 months (log-rank, $P = .001$), with both doses of letrozole being superior to MA (Cox regression, $P = .001$ for 2.5 mg and $P = .01$ for 0.5 mg; Table 2). The median duration of clinical benefit was 18.1 months for letrozole 0.5 mg, 23.5 months for letrozole 2.5 mg, and 14.5 months for MA.

Subjective assessments. Slightly fewer patients (41%) in the letrozole-2.5 mg arm had a worsening of pain during treatment compared with the low-dose letrozole (50%) and MA (49%) arms. Fewer patients experienced a deterioration in WHO performance status in the group that received letrozole 2.5 mg group (41%) compared with MA (55%) (χ^2 , $P = .01$). No major differences in quality of life were apparent between treatments over time. The higher incidence of dyspnea in the MA arm (adverse experiences) was reflected in consistently higher dyspnea scores in the MA arm in the quality-of-life scale. Similarly, patients in the MA arm scored worse in physical functioning than in the 2.5-mg letrozole arm, with intermediate scores for patients on 0.5 mg letrozole, which reflects the higher levels of worsening of performance status in patients on MA. The early nausea that occurs in some patients with letrozole was noted in the nausea and vomiting subscale in the quality-of-life instrument, but the symptom disappeared with time.

Table 3. Overall Tumor Response

Variable	Letrozole 0.5 mg (n = 188)		Letrozole 2.5 mg (n = 174)		MA (n = 189)	
	No.	%	No.	%	No.	%
Objective response	24	12.8	41	23.6	31	16.4
95% CI	8.0-17.6		17.2-29.9		11.1-21.7	
CR	6	3.2	12	6.9	8	4.2
PR	18	9.6	29	16.7	23	12.2
NC	27	14.4	19	10.9	29	15.3
PD	105	55.9	93	53.4	106	56.1
Not assessable*	32	17.0	21	12.1	23	12.2

*Patients with incomplete documentation of tumor lesions, patients judged by peer review not to have evidence of malignant disease, or patients who had PRs or NC that was not confirmed at least 4 weeks later.

Tolerability and Safety

Table 4 lists the type and frequency of adverse experiences, irrespective of relationship to trial medication, reported during the follow-up period of up to 33 months. The lowest frequency of adverse experiences occurred in the arm

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