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Switching to Anastrozole Versus Continued Tamoxifen Treatment of Early Breast Cancer: Preliminary Results of the Italian Tamoxifen Anastrozole Trial

Francesco Boccardo, Alessandra Rubagotti, Matteo Puntoni, Pamela Guglielmini, Domenico Amoroso, Angela Fini, Giuseppe Paladini, Mario Mesiti, Domenico Romeo, Michela Rinaldini, Simona Scali, Mauro Porpiglia, Chiara Benedetto, Nunzio Restuccia, Franco Buzzi, Roberto Franchi, Bruno Massidda, Vito Distante, Dino Amadori, and Piero Sismondi

From the National Cancer Research Institute; University of Genoa, Genoa; S. Orsola-Malpighi Hospital, Bologna; Institute of Oncology, University of Messina, Messina; San Donato Hospital, Arezzo; S. Anna Hospital; University of Turin; University and Mauriziano Hospital, Turin; Institute of Oncology S. Luigi-S. Currò, Catania; S. Maria Hospital, Terni; Civic Hospital, Casalpusterlengo; University of Cagliari, Cagliari; University of Florence, Florence; Pierantoni Hospital, Forlì, Italy.

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Address reprint requests to Francesco Boccardo, MD, National Cancer Research Institute and the University of Genoa, Italy, Largo R. Benzi 10, 16132 Genoa, Italy; e-mail: f.boccardo@unige.it.

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ABSTRACT

Purpose
Tamoxifen, which is actually the gold standard adjuvant treatment in estrogen receptor–positive early breast cancer, is associated with an increased risk of endometrial cancer and other life-threatening events. Moreover, many women relapse during or after tamoxifen therapy because of the development of resistance. Therefore new approaches are required.

Patients and Methods
We conducted a prospective randomized trial to test the efficacy of switching postmenopausal patients who were already receiving tamoxifen to the aromatase inhibitor anastrozole. After 2 to 3 years of tamoxifen treatment, patients were randomly assigned either to receive anastrozole 1 mg/d or to continue receiving tamoxifen 20 mg/d, for a total duration of treatment of 5 years. Disease-free survival was the primary end point. Event-free survival, overall survival, and safety were secondary end points.

Results
Four hundred forty-eight patients were enrolled. All women had node-positive, estrogen receptor–positive tumors. At a median follow-up time of 36 months, 45 events had been reported in the tamoxifen group compared with 17 events in the anastrozole group ($P = .0002$). Disease-free and local recurrence-free survival were also significantly longer in the anastrozole group (hazard ratio [HR] = 0.35; 95% CI, 0.18 to 0.68; $P = .001$ and HR = 0.15; 95% CI, 0.03 to 0.65; $P = .003$, respectively). Overall, more adverse events were recorded in the anastrozole group compared with the tamoxifen group (203 *v* 150, respectively; $P = .04$). However, more events were life threatening or required hospitalization in the tamoxifen group than in the anastrozole group (33 of 150 events *v* 28 of 203 events, $P = .04$).

Conclusion
Switching to anastrozole after the first 2 to 3 years of treatment is well tolerated and significantly improves event-free and recurrence-free survival in postmenopausal patients with early breast cancer.

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INTRODUCTION

For many years, tamoxifen has represented the gold standard adjuvant treatment for endocrine-responsive early breast cancer.[1,2] Treatment with this agent significantly reduces the risk of recurrence and death in virtually all patients with estrogen receptor–positive tumors receiving treatment for an appropriate period of time.[3] However, several trials[4,5] and the most recent Early Breast Cancer Trialists' Collaborative Group overview[3] have confirmed that 5 years of tamoxifen treatment increases risk of endometrial

carcinoma and other life-threatening conditions such as thromboembolic events. Moreover, many women with estrogen receptor–positive tumors do not benefit from tamoxifen because they are primarily resistant to tamoxifen or develop resistance to this treatment after initially benefiting from it.[6] Tamoxifen resistance and, in particular, tamoxifen-induced tumor growth, which is a form of resistance well documented in experimental models,[7] are likely reasons why prior attempts to improve the efficacy of tamoxifen adjuvant therapy by prolonging treatment beyond 5 years have failed.[8,9]

Aromatase inhibitors inhibit breast cancer growth by reducing systemic and tumor estradiol levels.[10] The third-generation aromatase inhibitors are as effective as, if not superior to, tamoxifen when used as first-line treatment for advanced disease.[11-13] They are also of benefit to many women with advanced breast cancer who have been initially treated with tamoxifen.[14,15] After the positive results in the treatment of advanced disease, the efficacy of aromatase inhibitors has also been investigated in the adjuvant setting, including head to head as an alternative to tamoxifen, combined with tamoxifen, or as a switch after a few years of tamoxifen or after a standard 5-year course of tamoxifen as postadjuvant treatment.[16-20] Switching women currently receiving tamoxifen to an aromatase inhibitor may offer advantages over continued tamoxifen treatment because it allows women who have been receiving an established treatment to receive a second different type of drug that may pre-empt the development of tamoxifen resistance and, thus, reduce relapse rates and may also offer tolerability benefits. Therefore, patients have the opportunity to receive 5 years of endocrine treatment while limiting the exposure to both tamoxifen and the aromatase inhibitor.

A preliminary study was conducted to investigate the efficacy of this approach using a sequence of tamoxifen and aminoglutethimide (the only available aromatase inhibitor at that time).[16] Although no effect on recurrence rate was observed in the aminoglutethimide group,[16] the effects on pattern of recurrence and mortality encouraged us to recruit patients into a companion trial using the third-generation aromatase inhibitor anastrozole.

PATIENTS AND METHODS

Study Design

The Italian Tamoxifen Anastrozole (ITA) trial was a phase III, randomized, multicenter trial including postmenopausal women who had already received 2 to 3 years of tamoxifen treatment. Patients were randomly assigned to receive continued tamoxifen treatment (20 mg/d) or to be switched to anastrozole (1 mg/d) for a period of time that would result in a total of 5 years of endocrine treatment. Before randomization, women were stratified according to prior chemotherapy and participating center.

Study Population

Eligible patients were postmenopausal women (ie, women missing regular menses for at least 1 year) or women more than 50 years of age who had undergone hysterectomy. Women who were confirmed to be amenorrheic as a consequence of chemotherapy were also permitted. When menopausal status was unclear, plasma follicle-stimulating hormone and estradiol levels were evaluated before inclusion. Other inclusion criteria were histologically confirmed primary breast cancer, tumor estrogen receptor positivity (confirmed by immunohistochemical analysis; progesterone receptor assessment was not required), positive axillary nodes, and no evidence of recurrent or metastatic disease (assessed using imaging studies and blood tests).

Patients with a history or presence of any other cancer (except adequately treated skin cancer or carcinoma-in-situ of the cervix) and patients with any condition that may jeopardize their compliance to treatment or follow-up were excluded. The ethics committee at each center approved the study protocol, and written informed consent was obtained from all patients.

Study Protocol Evaluations

During the first year after random assignment, patients underwent clinical examinations every 3 months; subsequent examinations were performed every 6 months. At each visit, patients were asked to report any tolerability issues; blood counts and biochemical tests were also performed up to 5 years after randomization. Ultrasound examination of the liver, bone scan, and chest x-rays were usually performed on an annual basis. Mammography of the ipsilateral and/or the contralateral breast was performed annually or every 2 years, according to local policy.

Study End Points

The primary end point was disease recurrence, including both locoregional and distant recurrences (except contralateral breast cancer). Locoregional recurrences had to be cytologically and/or hystologically confirmed and included tumor relapse in the ipsilateral breast, thoracic wall, axilla, and other locoregional nodes. For estimates of event-free survival, events included any of the following: locoregional recurrence (as previously defined), distant metastases, second primary tumors (including contralateral breast cancer), and breast cancer–unrelated deaths (ie, deaths occurring in the absence of disease recurrence).

The incidence of deaths, whatever the cause, and adverse events were secondary end points. All second primary tumors (except contralateral breast cancer) were included among serious adverse events. Serious adverse events included all lethal or life-threatening events or those events causing disability or requiring hospitalization.

Statistical Methods

Disease-free survival and event-free survival were defined as the time from random assignment to the occurrence of disease recurrence or any of the previously defined events. Survival was defined as the time from random assignment to death, independently of cause. Curves were constructed using the Kaplan-Meier method[21] and compared using the log-rank test.[22] All P values were two-tailed. Multivariate models were constructed including variables known to be predictive of risk of relapse in univariate models.[23] Forest plot was performed to describe the interaction of each treatment with the variables within each strata.[24] The χ^2 test or Fisher's exact test were used to compare the incidence of adverse events in each group.

Sample Size

Aromatase inhibitors are known to benefit women with advanced breast cancer who experience failure with first-line treatment with tamoxifen. Approximately 50% of women formerly responsive to tamoxifen derive clinical benefit (tumor response or stable disease ≥ 24 weeks) from subsequent treatment with aromatase inhibitors.[25] Therefore, we hypothesized that switching patients to anastrozole may result in a 50% reduction in the risk of recurrence. Originally, a more conservative 30% decrease in the annual risk of recurrence was assumed to calculate the sample size. Under these conditions and with an $\alpha = .05$, it was estimated that a total of 996 patients (498 per arm) would be required to give the trial a statistical power of an 80% chance of detecting such a difference in favor of anastrozole. However, this study accrued approximately half this number of patients because of the existence of competitive trials in Italy that discouraged the participation of some of the centers that had, in principle, agreed to participate in the ITA trial.

RESULTS

Patients

A total of 448 patients were enrolled onto the trial between March 1998 and December 2002, and all of the patients were included in an intent-to-treat analysis. The median follow-up (from randomization) was 36 months (range, 1 to 70 months). Nineteen patients in the tamoxifen group and 18 patients in the anastrozole group were withdrawn from treatment. Patient baseline demographics are listed in Table 1. One patient in each group was found to have no histologic involvement of axillary nodes, and two patients in the anastrozole group had estrogen receptor–negative tumors. Hormone receptor status was unknown for 14% of the patients continued on tamoxifen and for 8% of patients who were switched to anastrozole. Prior radiotherapy mostly consisted of irradiation of the residual breast in women who had undergone conservative surgical procedures (approximately half of the patients in each treatment group). Few women (seven in the tamoxifen group and two in the anastrozole group) had received thoracic wall irradiation after mastectomy. There were no significant differences between groups regarding variables.

Efficacy

At the time of this analysis, 32 women (14.2%) in the tamoxifen group had disease recurrence compared with 12 women (5.4%) in the anastrozole group. Women in the tamoxifen group also developed more second primary tumors compared with the anastrozole group (10 *v* five

Table 1. Patient Baseline Demographics

Demographic	Tamoxifen (n = 225)		Anastrozole (n = 223)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	63		63	
Range	43-77		38-76	
Tumor size, cm				
≤ 2	99	44	110	49
> 2	115	51	109	49
Missing	11	5	4	2
Tumor grade				
1-2	149	66	140	63
3	43	19	54	24
Undetermined or missing	33	15	29	13
Receptor status				
Estrogen receptor–positive	194	86	203	91
Estrogen receptor–negative	—	—	2	1
Undetermined or missing	31	14	18	8
No. of involved nodes				
≤ 3	132	59	152	68
> 3	91	40	71	32
Missing	2	1	—	—
Treatment of primary				
Mastectomy	123	55	116	52
QUAD/tumorectomy plus axillary dissection	102	45	107	48
Prior radiotherapy	110	49	120	54
Prior adjuvant chemotherapy	150	67	149	67
Time on tamoxifen at randomization, months				
Median	28		28	
Range	20-39		23-40	

Abbreviation: QUAD, quandrantectomy.

tumors, respectively), including five endometrial cancers, and three women in this group died in the absence of clinically detectable disease recurrence. Thus, in total, there were 45 events in the tamoxifen group and 17 events in the anastrozole group (Table 2). There were 10 deaths in the tamoxifen group, seven of which were a result of breast cancer, and four deaths in the anastrozole group, all of which were breast cancer related ($P = .1$). Significant benefits in terms of event-free (Fig 1) and recurrence-free survival (Fig 2) were observed in the women switched to anastrozole (hazard ratio [HR] = 0.35; 95% CI, 0.20 to 0.63; $P = .0002$ and HR = 0.35; 95% CI, 0.18 to 0.68; $P = .001$, respectively). The 3-year difference in recurrence-free survival was 5.8% (95% CI, 5.2% to 6.4%). Women in the anastrozole group also had significantly longer locoregional recurrence-free survival (HR = 0.15; 95% CI, 0.03 to 0.65; $P = .003$), whereas the difference in distant metastases–free survival approached statistical significance (HR = 0.49; 95% CI, 0.22 to 1.05; $P = .06$; Figs 3 and 4).

Multivariate analysis confirmed that switching to anastrozole resulted in a significant reduction in the risk of developing an event or a disease recurrence and that this effect was independent of the other variables (Table 3). The benefit (in terms of risk of recurrence) of switching to anastrozole seemed to be consistent across the strata analyzed (Fig 5).

Safety

Adverse events occurring in each treatment group are listed in Table 4. Eighty-one patients in the tamoxifen group (36.0%) and 98 patients in the anastrozole group (43.9%) experienced one or more adverse events ($P = .1$). More patients treated with anastrozole, compared with the tamoxifen group, experienced more than one adverse event (47 *v* 32 patients, respectively; $P = .06$), and overall, more events were recorded in this group (203 *v* 150 events, respectively; $P = .04$). However, more patients in the tamoxifen group experienced serious adverse events than patients in the anastrozole group (29 of 225 patients, 12.9% *v* 24 of 223 patients, 10.8%, respectively). Although this difference was not statistically significant ($P = .5$), in total, significantly more serious adverse events occurred in the tamoxifen group than the anastrozole group (33 of 150 events, 22.0% *v* 28 of 203 events, 13.9%, respectively; $P = .04$). It is worth noting that the percentage of patients requiring treatment discontinuation because of adverse events was small and comparable in the two groups (4.0% and 4.4% in the tamoxifen and anastrozole groups, respectively).

Table 2. No. and Distribution of Events

Event	Tamoxifen (n = 225; No.)	Anastrozole (n = 223; No.)
Tumor recurrences		
Locoregional recurrences*	13	2
Distant metastases, with or without locoregional recurrences	19	10
Second primary tumors		
Contralateral breast	2	1
Endometrium	5	1
Other sites	3	3
Death without relapse	3	—
Total events	45	17

*See also Results.

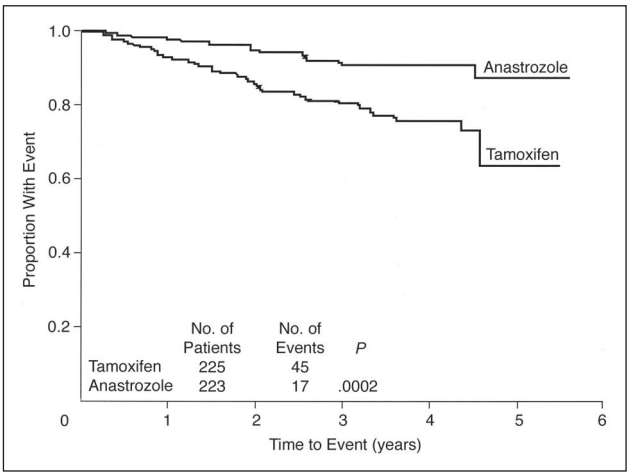

Fig 1. Kaplan-Meier estimates of event free-survival. See Results for hazard ratios.

DISCUSSION

Aromatase inhibitors are becoming increasingly important in the management of early breast cancer.[16-20] Our group was the first one to conceive the idea of switching women

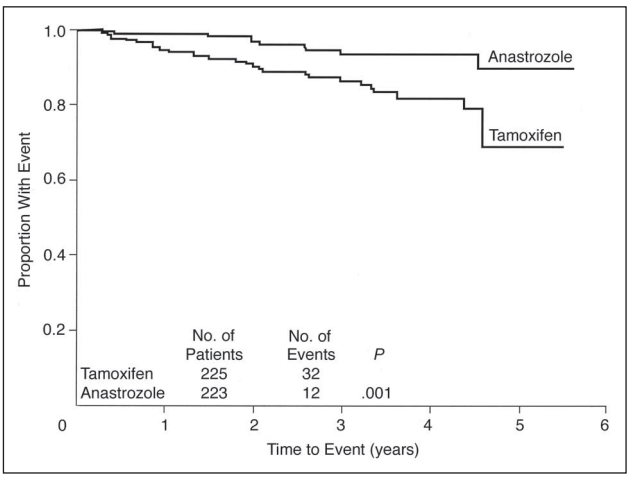

Fig 2. Kaplan-Meier estimates of recurrence-free (locoregional plus distant) survival. See Results for hazard ratios.

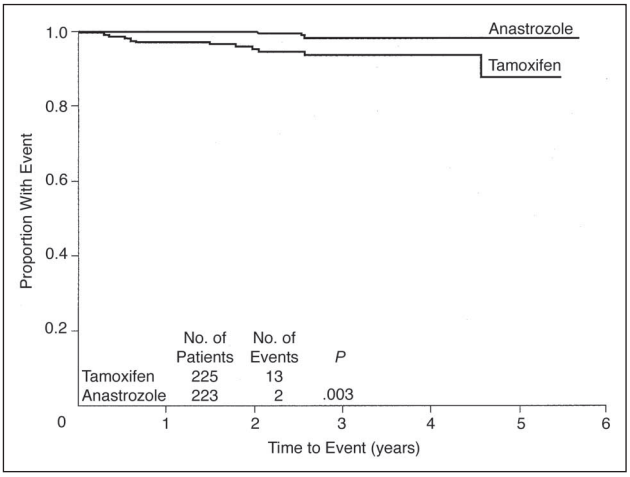

Fig 3. Kaplan-Meier estimates of locoregional recurrence-free survival. See Results for hazard ratios.

already on treatment with adjuvant tamoxifen to an aromatase inhibitor and to show that this approach might produce a valuable benefit.[16] This preliminary experience prompted us to go on testing the potentialities of the new strategy with new-generation aromatase inhibitors. Unfortunately, the new trial was closed before we were able to enroll the number of patients originally planned for the reasons that are described in the following paragraph.

Although only interim analyses of safety were originally planned, an interim efficacy analysis was performed in October 2002, when 443 patients had been enrolled onto the study. This analysis, which included the first 426 assessable patients, was decided by all participants in view of the preliminary results of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial, which had become available in 2001, suggesting the putative superiority of anastrozole over tamoxifen in hormone-naive, hormone receptor–positive women.[17] The interim analysis confirmed that switching to anastrozole might provide additional benefit over continuing on tamoxifen, namely concerning recurrence-free survival, with a $P = .015$. Because it had taken approximately 5 years to accrue half of the patients who were originally thought to be required, it seemed that it would not be realistic and probably would not be ethical to continue to recruit patients for another 5 years to reach the expected size. However, although preliminary and limited to a substantially smaller number of patients than expected, the interim analysis had the statistical power (81%) that was originally deemed to be necessary. Therefore, all investigators unanimously decided that recruitment should be closed, and December 31 of the same year was arbitrarily fixed, without adopting any specific stopping rule. This allowed five more patients to be randomly assigned.

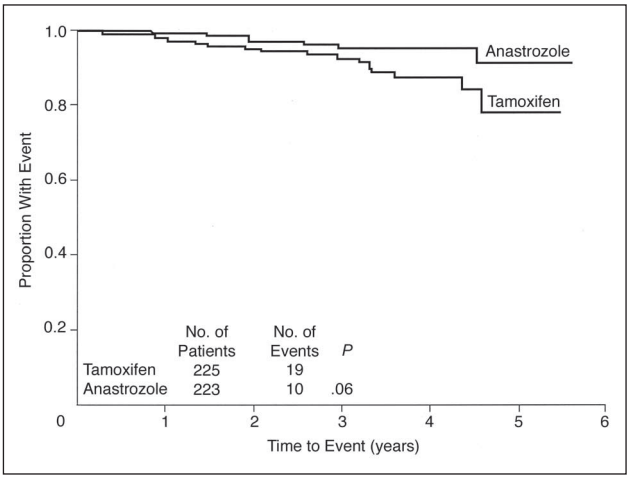

Fig 4. Kaplan-Meier estimates of distant metastases–free survival. See Results for hazard ratios.

It was decided that the preliminary nature of results and the missing of any statistically significant evidence of a survival benefit would not allow for automatically switching to anastrozole the patients who had been randomly assigned to continue with tamoxifen and who were still on study. These patients represented approximately 25% of the patients randomly assigned to continue on tamoxifen up to the fifth year, and all of these patients were actually maintained on tamoxifen treatment. The results of the subsequent analysis, which was performed 1 year later and forms the subject of the present article, confirmed the trends of the interim analysis with an even higher statistical power (89%). Nonetheless, these results are still premature, and we should be cautious in extrapolating them to all women currently receiving adjuvant tamoxifen treatment because of the small size of this trial. However, data are provocative and deserve some comment in the context of previous trials.

With respect to our previous switching trial,[16] we expected anastrozole treatment to be more effective than aminoglutethimide. The two trials had similar designs and patient selection criteria; however, the median follow-up was longer in the previous trial. The previous trial also used a low aminoglutethimide dose (250 mg/d) and a shorter duration of treatment. Nonetheless, the results of both trials suggest benefits for patients switching to the aromatase inhibitor. In particular, women who were switched to anastrozole in the ITA trial gained significant benefits in terms of risk of recurrence, which is a difference that was not observed in the Gruppo di Ricerca in Oncologia Clinica e Terapie Associate 04 trial.[16] However, a more favorable pattern of relapse (fewer visceral failures and longer survival after recurrence) was observed in women who were switched to aminoglutethimide in the previous trial.[16] Because of the relatively small size of both trials, it is possible that the observed differences in disease recurrence may be a result of chance. However, the results of trials comparing the new imidazolic aromatase inhibitors with aminoglutethimide in women with advanced disease[25,26] and the proven

Table 3. Hazard of Developing Any Event or Disease Recurrence After Multivariate Analysis

Factor	Any Event			Disease Recurrence		
	HR	95% CI	*P*	HR	95% CI	*P*
Treatment						
Tamoxifen	1.0		.0004	1.0		.002
Anastrozole	0.36	0.21 to 0.63		0.35	0.18 to 0.69	
Tumor size, cm						
≤ 2	1.0		.03	1.0		.1
> 2	1.86	1.06 to 3.27		1.67	0.86 to 3.24	
Tumor grade						
1-2	1.0		.4	1.0		.2
3-Gx	1.23	0.73 to 2.06		1.44	0.79 to 2.63	
No. of involved nodes						
≤ 3	1.0		.15	1.0		.1
> 3	1.48	0.86 to 2.52		1.64	0.87 to 3.07	
Prior adjuvant chemotherapy						
No	1.0		.4	1.0		.1
Yes	1.29	0.71 to 2.35		1.87	0.86 to 4.06	

Abbreviations: HR, hazard ratio; Gx, grade undetermined or missing.

superiority of these compounds over aminoglutethimide in inhibiting aromatase activity and estradiol synthesis[27] support the assumption that observed differences may reflect the superior biologic and clinical activity of anastrozole.

We also expected anastrozole to be better tolerated than aminoglutethimide and to allow better compliance with treatment. Indeed the number of withdrawals caused by adverse events was considerably higher with aminoglutethimide[16] (14.0%) compared with anastrozole (4.0%). Although anastrozole was better tolerated than aminoglutethimide, even in the present trial, switching was associated with some side effects in approximately 40% of patients. Compared with patients who were continued on tamoxifen, more patients in the anastrozole group experienced lipid disorders and gastrointestinal complaints, but five of these patients had hiatus hernia at baseline. These effects were somewhat expected in view of previous findings with these agents in advanced breast cancer[11,12] and the differential effects on lipid metabolism exerted by tamoxifen[28] and the aromatase inhibitors.[29] Because tamoxifen treatment results in reduced plasma cholesterol levels and anastrozole has been shown to be lipid neutral,[30,31] it is likely that the

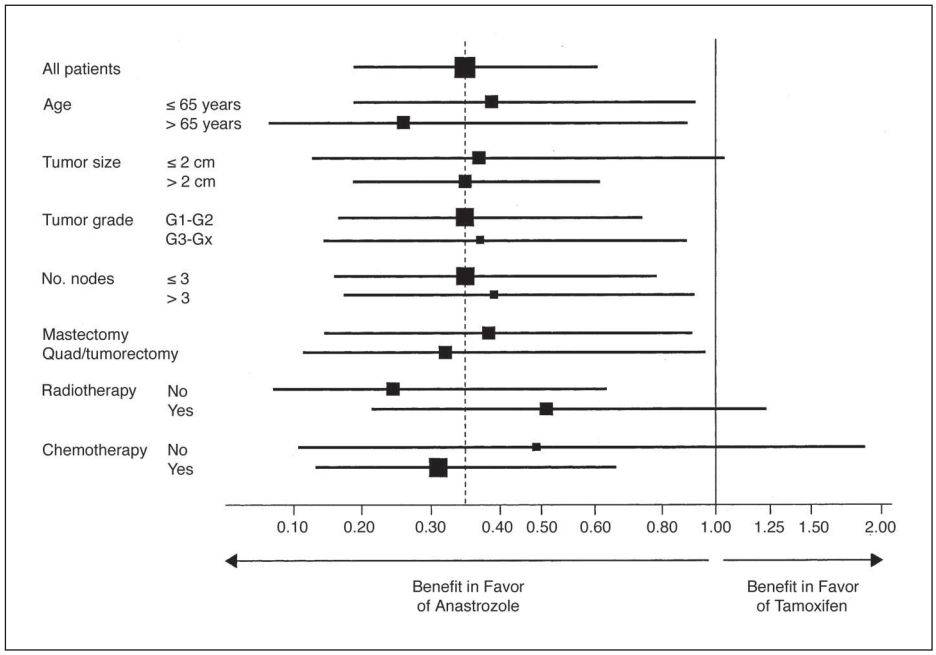

Fig 5. Subgroup analysis of the risk of recurrence. The hazard ratio given for all patients was adjusted for tumor size, tumor grade, number of involved nodes, and treatment of primary tumor. The size of the squares is proportional to the size of the subgroups.

Table 4. Type and Incidence of Adverse Events

Event	Tamoxifen		Anastrozole		
	No.	%	No.	%	*P*
GI symptoms	4	2.7	16	7.9	.03
GI disorders	8	5.3	9	4.4	.4
CNS symptoms	8	5.3	14	6.9	.4
CNS disorders	—	—	3	1.5	.2
Fatigue	—	—	4	2.0	.1
Venous disorders	9	6.0	5	2.5	.08
Lipid metabolism disorders	6	4.0	19	9.3	.04
Glycemic disorders	3	2.0	10	4.9	.1
Musculoskeletal disorders	18	12.0	17	8.4	.2
Bone fractures	2	1.3	2	1.0	.6
Gynecologic symptoms	12	8.0	15	7.4	.5
Gynecologic changes, including endometrial carcinoma	17	11.3	2	1.0	.0002
Cardiovascular diseases	14	9.3	16	7.9	.4
Lower urinary tract disorders	7	4.7	9	4.4	.6
Skin disorders/symptoms	4	2.7	9	4.4	.3
Infectious diseases	8	5.3	14	6.9	.4
Second primary tumors, other than endometrial carcinoma	3	2.0	3	1.5	.5
Other	27	18.0	36	17.7	.5

changes in serum lipids in the anastrozole group are a result of the effects of tamoxifen withdrawal. No differences in the incidence of musculoskeletal disorders or bone fractures were evident in the present trial; however, our results are preliminary, based on a small number of events, and follow tamoxifen therapy, so differences may arise after longer follow-up. Furthermore, switching to anastrozole resulted in a significant reduction in the incidence of gynecologic changes, particularly endometrial cancer; and in total, serious adverse events were less common in this group.

Three other recent trials suggest that aromatase inhibitors have a valuable role to play in the management of early breast cancer.[17-20] The ATAC trial enrolled 9,366 postmenopausal women in a prospective, double-blind, randomized study comparing 5 years of tamoxifen treatment with anastrozole alone or in combination with tamoxifen. The first analysis showed that anastrozole alone, but not the combination, was superior to tamoxifen and also better tolerated.[17] An updated analysis of this trial (median follow-up of 47 months) confirmed the superiority of anastrozole, particularly in women with hormone receptor–positive tumors, in whom a 22% decrease in the risk of recurrence ($P = .007$) was observed.[18]

The ITA data presented here are supportive of the overall results seen in ATAC, illustrating the efficacy and tolerability benefits of anastrozole over tamoxifen. However, differences in trial design, trial size, and patient demography prevent full comparison of the two trials.

The MA-17 trial, which was performed by the National Cancer Research Institute of Canada, recruited 5,187 women who had received an average of 5 years of adjuvant tamoxifen.[19] These women were randomly assigned to a further 5 years of treatment with either letrozole or placebo. However, an interim analysis showed that the HR for local recurrence, distant metastasis, and new contralateral breast cancers favored letrozole ($P = .00008$), so recruitment of patients ceased after a median follow-up of 2.4 years.[19] Again, differences in study design and size render it difficult to compare ITA with MA-17; however, both trials show the benefit of aromatase inhibitor treatment after tamoxifen in postmenopausal women with early breast cancer (although the results were preliminary for both trials and the comparison is against a placebo, rather than an active drug, in the MA-17 trial).

More recently, the results of an international cooperative trial of exemestane after 2 or 3 years of tamoxifen therapy in postmenopausal women (Intergroup Exemestane Study [IES]) have been reported.[20] This trial accrued 4,742 patients, of whom 2,362 have been randomly assigned to switch to exemestane and 2,380 have been assigned to continue to receive tamoxifen.

The unadjusted HR in the exemestane group compared with the tamoxifen group was 0.68 (95% CI, 0.56 to 0.82; $P < .001$), implying an absolute 3-year benefit in disease-free survival of 4.7% (95% CI, 2.6% to 6.8%). Although this trial shares exactly the same design as our trial, it is also difficult to compare the two trials. The two trials differ in regard to their size (the IES trial accrued approximately 10-fold the patients recruited in the ITA trial), patient selection (approximately half of the patients enrolled onto the IES trial were node negative), the proportion of patients previously treated with adjuvant chemotherapy (which was more than twice larger in our trial), and the type of aromatase inhibitor. Indeed, no major differences are likely to

be expected between anastrozole and exemestane in terms of efficacy. However, there is no doubt that the two drugs act via different mechanisms,[10,25] are partially non–cross resistant,[10,25] and have different pharmacodynamic effects and toxicologic profiles.[32] Unfortunately, direct comparisons between the two drugs are not available yet, and indirect comparisons are not reliable.

Despite previous differences, the two trials produced comparable results. It is interesting to note that the size of the benefit observed in both trials was in the same range of that reported in the MA-17 trial, and, on average, the benefit achieved in the ITA, IES, and MA-17 trials (all of which tested the value of an aromatase inhibitor after 2, 3, or more years of tamoxifen) was apparently superior to the benefit achieved by anastrozole in the ATAC trial, in which the aromatase inhibitor was used as an alternative to tamoxifen since the beginning.

Currently, there are no clinical data directly comparing switching with initiating treatment with an aromatase inhibitor. However, recent research on tamoxifen action and resistance suggests that, biologically, timing and sequencing of treatments may be crucial. Berstein et al[33] have reviewed the results of several experiments that suggest that tamoxifen resistance can be the result of either genetic or adaptive changes. According to their model, different stages can be identified relating to time-dependent increases in aromatase activities in breast cancer cell lines exposed to tamoxifen. Aromatase activity is low in the early stages of exposure, but it progressively increases up to the fourth month and tends to decline thereafter. These changes may help explain the differences in size of the effects achieved with aromatase inhibitors in previous trials. For example, in the present trial and in the IES trial,[20] the aromatase inhibitor was administered, on average, after 2.4 years of tamoxifen treatment. According to Bernstein's model, a significant proportion of the tumor cells will show increased aromatase activity at this stage. The elegant experiment performed by Brodie[34] in the aromatase-overexpressing MCF-7 breast cancer xenograft model shows that switching to an aromatase inhibitor after 16 weeks of tamoxifen treatment reduces the rate of tumor growth by more than 80% compared with animals that receive tamoxifen up to week 28.[34] This confirms the effectiveness of switching in a model where aromatase activity is artificially increased and is highly evocative of the situation that may have occurred in the switching studies performed in breast cancer patients.

Larger, recently closed and ongoing adjuvant trials will be crucial not only to further define the role of aromatase inhibitors in the treatment of early breast cancer but also in defining whether sequencing aromatase inhibitors and tamoxifen might really be superior to monotherapy with aromatase inhibitors from the beginning.[35] While awaiting for the results of these trials, both the ITA and IES trial results seem to provide enough evidence to suggest that switching to an aromatase inhibitor is a valuable option for women currently treated with tamoxifen. However, the prematurity of results with respect to mortality and long-term safety require some caution and suggest limiting this option to women who have become intolerant to tamoxifen and/or have developed clinical conditions (ie, venous disorders, gynecologic changes, ocular problems, and so on) that might contraindicate the continued use of tamoxifen.

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Appendix

Participating Center*	Main Investigators
Ospedale San Donato, Arezzo	M. Rinaldini, S. Scali
Azienda Ospedaliera di Bologna-Policlinico S. Orsola Malpighi, Bologna	G. Paladini, A. Fini
Policlinico Universitario Monserrato, Cagliari	B. Massidda, M.T. Ionta
Instituto Oncologico S. Luigi-S. Currò, Catania	N. Restuccia, R. Bordonaro, D. Giuffrida
Presidio Ospedaliero di Casalpusterlengo, Casalpusterlengo	R. Franchi, G. Tansini
Università degli Studi "G. D'Annunzio," Chieti	S. Iacobelli, L. Irtelli, M.T. Martino
Arcispedale S. Anna, Ferrara	M. Indelli, C. Modenesi
Università degli Studi, Firenze	V. Distante, R. Simoncini
Ospedale L. Pierantoni, Forlì	D. Amadori, P. Serra, D. Casadei Giunchi
Università degli Studi e Istituto Nazionale per la Ricerca sul Cancro, Genova	F. Boccardo, D. Amoroso
E.O. Ospedali Galliera, Genova	L. Gallo, C. Caroti
Ospedale Umberto I, Lugo	G. Cruciani, E. Montanari, A. Piancastelli
Azienda Policlinico G. Martino, Messina	M. Mesiti, D. Romeo
Istituto Scientifico San Raffaele, Milano	E. Villa, D. Aldrighetti, P. Zucchinelli
Arnas Ospedale Oncologico M. Ascoli, Palermo	B. Agostana, A. Traina, M.P. Cusimano
Fondazione Maugeri, Pavia	G. Bernardo, A. Bernardo
Università Cattolica del S. Cuore "A. Gemelli," Roma	R. Bellantone, S. Mancuso, C. Barone, C. De Crea, E. Foti, C. Battelli, G. Di Leonardo
Azienda ULSS 18-Presidio Ospedaliero di Rovigo, Rovigo	E. Ferrazzi, D. Menon
Ospedale Civile, USL 1 Imperiese, Sanremo	E. Campora, D. Guarneri
Presidio Ospedaliero di Saronno, Saronno	G. Schieppati, G. Di Lucca, C. Verusio
Università degli Studi, Sassari	A. Farris, G. Sanna, M.G. Sarobba
Azienda Ospedaliera S. Maria, Terni	F. Buzzi, S. Catanzani
Ospedale S. Anna, Torino	M. Porpiglia, C. Benedetto, P. Sozzani
Ospedale Mauriziano Umberto I, Torino	P. Sismondi, R. Ponzone, N. Biglia
Ospedale Edoardo Agnelli, Pinerolo Torino	L. Galletto, M. Sussio, L. Verra
Centro Oncologico "Mario Lovenati," Trieste	G. Mustacchi, R. Ceccherini
Ospedale San Bortolo, Vicenza	V. Fosser, M. Magazù, L. Merlini

Abbreviations: ULSS/USL, Unitá Sanitaria Locale.
*The centers and investigators listed in the Appendix contributed to patient accrual.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors have completed the disclosure declaration, the following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
Francesco Boccardo			AstraZeneca (A)					
Dino Amadori			Intalfarmaco (A); Novartis (A); Eli-Lilly (B)		Bristol-Myers Squibb (A); Bayer (A); Elan (A)	Elan (A)		

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