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ORIGINAL REPORT

Phase III, Double-Blind, Controlled Trial of Atamestane Plus Toremifene Compared With Letrozole in Postmenopausal Women With Advanced Receptor-Positive Breast Cancer

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ABSTRACT

Purpose
To compare time to progression (TTP) with a steroidal aromatase inhibitor (AI) atamestane (ATA) combined with toremifene (TOR; complete estrogen blockade) versus letrozole (LET) in receptor-positive advanced breast cancer (ABC).

Patients and Methods
Eligibility included postmenopausal receptor-positive ABC and adjuvant hormonal therapy completed more than 12 months prior to study entry. Participants received daily ATA 500 mg with TOR 60 mg (ATA + TOR), or letrozole 2.5 mg (LET). The primary end point was TTP, whereas secondary objectives included objective response (OR), overall survival (OS), and time to treatment failure (TTF). The study had 80% power to detect a 25% increase in TTP assuming a TTP of 9.4 months in the LET population.

Results
A total of 865 patients were randomly assigned (434 to ATA + TOR and 431 to LET) in 60 centers in the United States, Canada, Russia, and Ukraine. Baseline characteristics were balanced. Median TTP was identical in the two arms at 11.2 months ($P < .92$). Median TTF was similar at 9.24 months (ATA + TOR) versus 10.44 months (LET). The hazard ratios (LET/ATA + TOR) were 1.00 (95% CI, 0.92 to 1.08) for TTP, 0.99 (95% CI, 0.92 to 1.06) for TTF, and 0.98 (95% CI, 0.87 to 1.11) for OS. OR occurred in 30% of patients receiving ATA + TOR and in 36% of patients receiving LET ($P < .1$). Adverse events (AEs) were similar for patients receiving ATA + TOR versus LET, and serious AEs were 10% *v* 11%, respectively.

Conclusion
TTP for patients receiving ATA + TOR was identical to that for patients receiving LET, representing the first endocrine therapy comparable to LET in ABC. Unlike in the Anastrozole, Tamoxifen, and Combined trial, addition of an antiestrogen did not decrease efficacy of the AI. Future studies of AIs in combination with more effective selective estrogen receptor modulators or selective receptor downregulators is warranted.

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INTRODUCTION

Inhibiting extragonadal peripheral estrogen synthesis with third-generation aromatase inhibitors (AIs) has become standard first-line therapy in postmenopausal women with hormone receptor–positive, locally advanced, or metastatic breast cancer.[1] The nonsteroidal AIs, anastrozole and letrozole (LET) have been approved for this indication and show longer times to disease progression (TTP) than tamoxifen. Exemestane, a steroidal inhibitor, also yielded impressive response rates, although it is not approved as first-line treatment.[2-7] The patient population selected for this study was similar to that in the seminal LET versus tamoxifen trial, which showed LET to be superior to tamoxifen in median TTP (9.4 *v* 6.5 months).[8,9] AIs are distinct from tamoxifen in their antiestrogen effects; they inhibit synthesis of extragonadal estrogens in postmenopausal women, whereas tamoxifen blocks estrogen from binding and interacting with the estrogen receptor (ER).[10-12]

It has been shown in vitro that even low levels of estrogen may stimulate breast cancer cell growth,[13] and monotherapy with an antiestrogen may therefore not be sufficient. Clinical observations suggest

that human breast tumors can adapt to endocrine therapy by developing hypersensitivity to estradiol.[14]

Combining an AI with a selective estrogen receptor modulator (SERM) tamoxifen, to create a complete estrogen blockade has been attempted in at least one large adjuvant trial with a view to preventing low levels of estrogen from stimulating breast cancer growth. The Anastrozole, Tamoxifen, and Combined adjuvant trial compared 5 years of tamoxifen versus anastrozole and to the combination of tamoxifen plus anastrozole.[15] Somewhat surprisingly, the combination yielded a result no better than that for tamoxifen, and statistically inferior to that for anastrozole administered as monotherapy.[16] The explanation for this somewhat counterintuitive result is unknown, but tamoxifen is a mixed partial estrogen agonist and antagonist, and the prevailing hypothesis is that in the low estrogen environment created by anastrozole, tamoxifen is stimulatory rather than antiestrogenic, which counteracts the antiestrogenic intent of the combination. Preclinical data support this hypothesis. In the immature rat uterine assay, the tamoxifen analog, toremifene, is 40-fold less estrogenic than tamoxifen, at clinically relevant doses and at estrogen concentrations achieved with concurrent aromatase inhibition.[17] These findings led us to hypothesize that a combination endocrine therapy, employing an AI with toremifene (TOR), would yield a more complete estrogen blockade than would be achieved by an inhibitor in combination with tamoxifen and that such a combination would be superior to an AI alone.

Atamestane (ATA) is a novel potent, specific steroidal irreversible inactivator of aromatase comparable in efficacy to other third-generation AIs in current clinical use. Its two principal metabolites are weak inhibitors of aromatase.[18] In a phase II study in 120 women with advanced disease who experienced progression while receiving tamoxifen, ATA yielded an overall response rate, a clinical benefit rate, and TTP of 15%, 49%, and 7 months, respectively (comparable to exemestane, LET, and anastrozole in this setting). Our phase III trial reported here compared ATA plus TOR versus LET. The trial committee in consultation with the US Food and Drug Administration decided that the control arm could not be ATA monotherapy, given that it is an investigational agent, nor could the control arm be TOR, because although approved as first-line therapy, its use in this setting has been replaced by AI monotherapy. We therefore elected to test the combination against LET, because LET had the strongest phase III data compared with tamoxifen, the statistical power of which was based on a superiority design rather than a noninferiority design of the anastrozole and exemestane trials. We report here the results of our phase III trial.

PATIENTS AND METHODS

Study Design

The study was a two-arm, randomized, double-blind, active control, multinational, multicenter phase III clinical trial conducted in 60 investigative centers and four countries. It was designed to assess safety and efficacy of ATA in combination with TOR in treating postmenopausal women with advanced breast cancer. Patients in one arm received one 60-mg capsule of TOR in the morning and five 100-mg tablets of ATA daily, three before or after breakfast and two before or after dinner. Patients in the second arm received one 2.5-mg capsule of LET in the morning and five tablets of placebo daily, three before or after breakfast and two before or after dinner. TOR and LET tablets were overencapsulated to prevent unblinding of the treatment by patients or the treating physicians. TOR in capsules was identical in appearance to capsules containing LET. Atamestane or placebo tablets were identical in appearance. Randomization was accomplished by assignment of treatment to patient number in blocks of four, stratified by study center. Randomization was performed centrally by the statistical service provider after verification of inclusion/exclusion criteria. Sites were notified by fax. The clinical sites were not provided with the random code; any emergency unblinding (eg, to allow the investigator to determine whether a given patient should receive a nonsteroidal AI after progression and removal from the study) was performed by an independent statistician at a contract research organization not otherwise involved with the study. Patients, investigators, and the sponsor remained blinded toward the treatment assignment until the unblinding of the study after database lock. All analyses are reported for all 865 patients randomly assigned: 434 patients were randomly assigned to receive ATA plus TOR and 431 patients were randomly assigned to receive LET.

Patients continued treatment until progression of disease (PD) or until other reasons, such as toxicity or withdrawal of consent, necessitated discontinuation. Treatment after PD was at the discretion of the individual investigator. All patients were observed for overall survival (OS).

Eligibility Criteria

Inclusion criteria included postmenopausal women age $\geq$ 18 years with locally recurrent, locally advanced, or locally metastatic breast cancer not amenable to radiation therapy or surgery, and/or distant metastatic disease; pathologic or histologic confirmation of breast cancer at initial diagnosis or at the time of metastases; Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and a predicted life expectancy of 12 weeks or more; postmenopausal status (defined as luteinizing hormone/follicle-stimulating hormone levels in the postmenopausal range in women whose menopause occurred less than 5 years before random assignment); ER-positive and/or progesterone receptor–positive status for all tumors; disease measurable in two dimensions (defined as follows: one diameter either at least 2 cm or at least two times the computed tomography [CT]/magnetic resonance imaging [MRI] slice/reconstruction thickness for bone/soft tissue/visceral disease as assessed by CT/MRI scan [to include spiral CT technique]; one diameter at least 2 cm for lesions other than bone lesions assessed by conventional x-ray techniques; or one diameter at least 1 cm for bone lesions assessed by conventional x-ray techniques). Administration of bisphosphonates in patients with bone metastases was allowed, as long as the drug was started before random assignment of the patient; written informed consent was obtained from all study participants.

Patients were excluded from study for any one of the following reasons: prior hormonal therapy to treat locally recurrent, locally advanced, or metastatic disease; prior adjuvant therapy with AIs or antiestrogens/SERMs within 12 months before enrollment; PD during therapy with antiestrogens (including SERMs administered for prevention of osteoporosis); life-threatening locally recurrent, locally advanced, or metastatic disease, or disease requiring chemotherapeutic intervention; history of known CNS metastases, significant neurological dysfunction including active seizures, or clinical signs of other significant neurological diseases; other active malignancy (except basal cell carcinoma of the skin or in situ cervical cancer; patients with previous malignancies had to have been without evidence of disease for at least 5 years); laboratory-based abnormalities (creatinine $>$ 2.0 mg/dL; ALT, AST, or serum bilirubin $>$ 2.5 $\times$ the upper limit of normal; hemoglobin $<$ 9 g/dL; platelets less than 100,000/mm3, WBC $<$ 2,000/μL); premenopausal endocrine status; pregnant or lactating status; usage of an investigational drug within the 30 days before enrollment; or the planned usage of an investigational drug other than the study medication during the course of the current study; contraindication to use of TOR, ATA, LET, or any of the inactive components of their formulations; or prior enrollment onto this study.

Assessment of Efficacy and Safety

The defined primary efficacy end point was TTP (in years), defined as the number of days from the random assignment date to the first documented onset of PD divided by 365. For patients with no documented onset of PD, TTP was censored at the date of the last completed tumor assessment.

TTP was analyzed on the intent-to-treat population. PD was defined according to International Union Against Cancer criteria as an increase of greater than 25% in the size of all measurable tumor areas as measured by the sum of the products of the longest diameter and greatest perpendicular diameter of all measurable lesions or marker lesions, as compared with the smallest diameters achieved during the course of therapy, or the appearance of any new lesion(s) or progression of any marker lesion. Progression of a single lesion was defined as greater than 50% increase in the area of a lesion with initial area $\leq 2\ cm^2$ or greater than 25% increase in the area of a lesion more than $2\ cm^2$. Death as a result of metastatic disease was also considered PD. Response of disease was assessed on at least two assessments separated by at least 4 weeks as follows: complete response was a total disappearance of all measurable and assessable clinical evidence of cancer in the case of bone lesions. For lytic lesions complete response was the complete disappearance or signs of complete reorganization of all lesions on x-ray. For blastic lesions, complete response was the complete disappearance of all lesions on bone scan and complete disappearance of all lesions on x-ray. Partial response was at least a 50% reduction in the size of all measurable lesions or marker lesions. Stable disease was determined when a patient failed to qualify for either a response or PD.

If patients received bisphosphonates for the treatment of bone lesions, lytic bone lesions were considered nonassessable for objective response; likewise, bone lesions treated with radiotherapy were also nonassessable. Tumor assessment required the use of the technique applied to document the extent of the disease at the time of enrollment (x-ray, bone scan, MRI, or CT scan). PD was determined by the local investigators and documentation of PD using imaging was required. Copies of all images (duplicate originals) were made available for source data verification and external review. CT and MRI scans were archived digitally. All other images were digitized and stored in a centralized database for an independent evaluation by a blinded evaluator.

Adverse events were defined as any undesirable experience regarding the health of a patient occurring during the trial, whether or not it was considered related to the study treatments. This included events not reported at baseline, intercurrent illnesses, hypersensitivity reactions, toxicities, injuries, and clinically relevant laboratory abnormalities. All adverse events were graded according to the National Cancer Institute Common Toxicity Criteria.[19]

Statistical Analysis

The study had 80% power to detect a 25% increase in TTP with a two-sided type I error of 0.05, assuming a TTP of 9.4 months in the LET population[8,9] and 11.75 months in the ATA and TOR arm, and requiring 842 patients (421 per treatment group) accrued during 24 months, an assumed dropout rate of 3% per year, and that the last patient would be observed for at least 12 months.

Baseline patient characteristics were summarized using descriptive statistics. For the primary end point, TTP, a Kaplan-Meier curve was generated and the comparison of distribution of TTP was performed using the log-rank test. For primary and secondary time-related event end points (time to treatment failure and survival), the Cox proportional hazards ratio for the two treatment groups was reported with the 95% CI for the ratio. Differences between treatment groups in response rates were analyzed using logistic regression. All data were analyzed on an intent-to-treat basis. Analyses were performed using JMP statistical software, version 6.0.2 (SAS Institute; Cary, NC).

RESULTS

A total of 865 patients were enrolled in 60 centers in the United States, Canada, Ukraine, and Russia between July 2002 and February 2005. Of these 865 patients, 26 were enrolled in the United States, 18 were enrolled in Canada, 406 were enrolled in Ukraine, and 415 were enrolled in Russia, using the identical study protocol, case report forms, and study conduct guidelines, and applying the same rules for assessment of activity and safety. The last tumor assessment was performed in January 2006. The baseline characteristics of the patients enrolled were well-balanced between the groups (Table 1). The median age was 64 years, typical of postmenopausal women with receptor-positive breast cancer, with approximately 70% of patients having soft tissue and/or bony metastases (26% of patients had bone metastasis only). A large majority of participants, approximately 80%, were treatment naïve, having had neither prior chemotherapy nor hormonal therapy.

Four hundred thirty-four women were randomly assigned to receive ATA and TOR and 431 women were randomly assigned to receive LET. There was no difference in the primary end point of TTP (Fig 1), 11.2 months, between the two treatment arms (LET *v* ATA + TOR hazard ratio [HR], 1.0; 95% CI, 0.91 to 1.08; $P = .92$). The median time to treatment failure was also similar between the two treatment arms: 9.24 months for ATA + TOR versus 10.44 months for LET (LET *v* ATA + TOR HR, 0.99; 95% CI, 0.92 to 1.06; $P = .70$). Survival was also similar in the two groups, 2.79 *v* 3.01 years, respectively (LET *v* ATA + TOR HR, 0.98; 95% CI, 0.87 to 1.11; $P = .76$; Fig 2). Thirty-six patients in the ATA + TOR arm (8%) and 34 (8%) in the LET arm were not assessable for response. The number of patients responding to treatment (overall response = complete response + partial response) was 132 (30%; 95% CI, 26 to 35) and 154 (36%; 95% CI, 31 to 40; LET *v* ATA + TOR odds ratio, 1.27; 95% CI, 0.96 to 1.69; $P = .10$, likelihood ratio χ^2) in the ATA + TOR and LET arms, respectively. There were 92 women (21%) and 77 women (18%) who had stable disease in the two arms, and 174 women (40%) and 166 women (39%) had PD (Table 2). Overall clinical benefit (overall response + stable disease) occurred in 224 women (52%; 95% CI, 47 to 56 women) and 231 women (54%; 95% CI, 49 to 58 women; LET *v* ATA + TOR odds ratio, 1.08; 95% CI, 0.83 to 1.41; $P = .56$, likelihood

Table 1. Pretreatment Demographic and Clinical Characteristics of Patients

Characteristic	ATA + TOR		Letrozole	
	No. of Patients	%	No. of Patients	%
No. of patients (n = 865)	434		431	
Enrollment by country				
United States	26			
Canada	18			
Russia	415			
Ukraine	406			
Median age, years	65		63	
ECOG performance status				
0	118	27	141	33
1	272	63	243	56
2	42	10	44	10
Site				
Visceral	131	30	130	30
Bone	114	26	107	25
Soft tissue	186	43	193	45
Prior chemotherapy				
Yes	83	19	91	21
No	351	81	340	79
Prior hormonal therapy				
Yes	63	15	55	13
No	371	857	376	67

Abbreviations: ATA, atamestane; TOR, toremifene; ECOG, Eastern Cooperative Oncology Group.

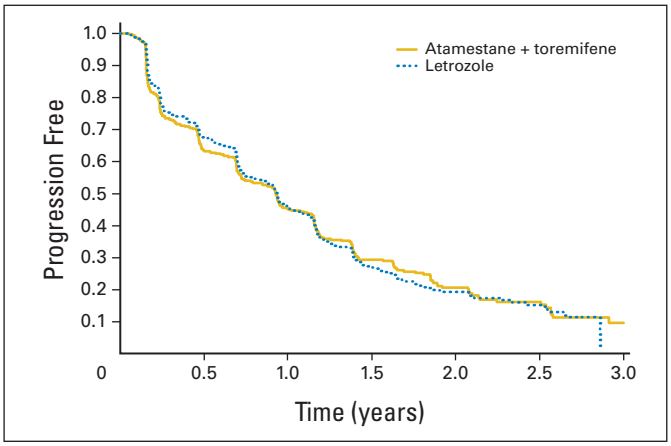

Fig 1. Time to progression. For both atamestane + toremifene and letrozole treatment arms; median time to progression was 0.93 years (11.2 months).

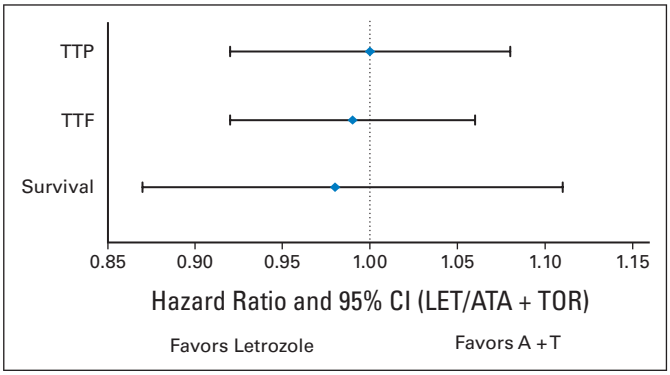

Fig 2. Hazard ratios for letrozole (LET) versus atamestane + toremifene (ATA + TOR) for times to event. Ratios less than 1 favor LET.

ratio χ^2) in the ATA + TOR and LET arms, respectively (Fig 3). There were no significant differences between the two treatment arms in terms of safety. Events that occurred in more than 10% of study participants are listed in Table 3 and included asthenia, weight gain, and hot flushes.

DISCUSSION

Antagonizing estrogen is a mainstay of treating hormone receptor–positive advanced breast cancer. Current therapies include SERMs, exemplified by tamoxifen; AIs including LET, anastrozole, and exemestane; and selective estrogen receptor downregulators, such as fulvestrant. In the past, combination endocrine therapy for advanced disease failed to show superiority to therapy with single agents; hence, sequential use of putatively non–cross-resistant agents has been the standard approach for advanced disease[2] and more recently also in adjuvant therapy.[20] In early-stage disease, several combinations have been investigated. Tamoxifen, aminoglutethimide, and danazol were combined,[21] and more recently, anastrozole and tamoxifen were used together.[15] In both of these studies, no advantage of the combination over monotherapy was observed. One possible explanation for the lack of improved efficacy of these combinations is that tamoxifen acts as an estrogen agonist in a low-estrogen environment, as discussed in the Introduction. In addition, however, aminoglutethimide induced the metabolism of tamoxifen and was poorly tolerated, and anastrozole and tamoxifen induce one another's metabolism as well. Atamestane is metabolized by the 17β-hydroxysteroid dehydrogenase and by hydroxylation of the 1-methyl group, with subsequent attack by 5β-reductase, followed by a hydroxylation at position C-6. ATA would therefore not be expected to induce the cytochrome P450-dependent metabolism of either tamoxifen or TOR.

There are no data in metastatic disease comparing a combination against AI monotherapy. However, on the basis of the combination arm in the Anastrozole, Tamoxifen, and Combined adjuvant trial, it would be anticipated that a combination of an AI and a SERM would be inferior to the AI alone. It is therefore significant that the most relevant and primary end point of our study, TTP, was identical between the two arms. Although one cannot necessarily extrapolate results in the adjuvant setting directly to metastatic disease, our results suggest that our combination regimen might yield superior results compared with anastrozole plus tamoxifen were it tested in the adjuvant setting. Theoretically ATA might be superior to anastrozole but this is unlikely. First, it is not a more potent AI; second, unlike the steroidal AI exemestane, which has a potent androgenic metabolite, the metabolites of ATA are nonandrogenic and only weak AIs. Therefore, it is more likely that in our combination, TOR acted differently from what one would expect with tamoxifen.

Despite two therapies in the combination arm, tolerability seemed similar to that of single-agent LET. Compliance also was

Table 2. Results: Secondary Study End Points

	Atamestane + Toremifene			Letrozole					
Best Response	No. of Patients	%	95% CI	No. of Patients	%	95% CI	Odds Ratio	95% CI	*P*
OR (CR + PR)	132	30	26 to 35	154	36	31 to 40	1.27	0.95 to 1.69	.10
CR	14	3		9	2				
PR	118	27		145	34				
SD	92	21		77	18				
PD	174	40		166	39				
Not available	36	8		34	8				
Clinical benefit (OR + SD)	224	52	47 to 56	231	54	49 to 58	1.08	0.83 to 1.41	.56

Abbreviations: OR, overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

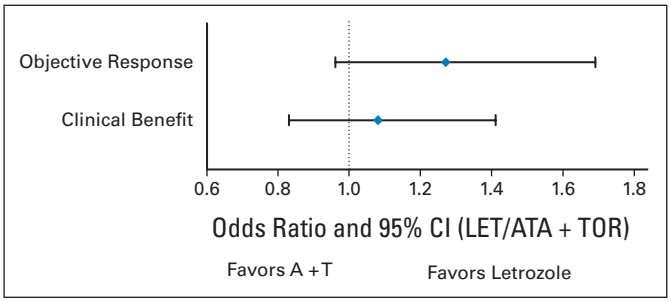

Fig 3. Odds ratios for letrozole (LET) versus atamestane + toremifene (ATA + TOR) for response. Ratios greater than 1 favor LET.

similar in the two arms: 18 patients in the ATA + TOR arm and 13 patients in the LET arm discontinued treatment for reasons of adverse events not associated with disease progression.

Despite the efficacy of AIs as monotherapy, endocrine therapy has not been optimized as yet. The results of this trial do not support the use of combination ATA + TOR in preference to LET, but is of interest in view of the equivalent TTP of 11.2 months. SERMs and selective estrogen receptor downregulators considered more potent and specific than TOR merit testing in combination with AIs in view of our results. In the animal model of Brodie et al,[16] a more complete estrogen blockade with LET plus fulvestrant is significantly superior to LET alone, and the results of a clinical trial of anastrozole combined with fulvestrant versus anastrozole alone are eagerly awaited. In addition to benefiting women with advanced disease, a superior novel therapy for metastatic disease could translate into improved treatment in the adjuvant setting. In summary, our trial results and published preclinical data suggest that attempting more complete estrogen blockade in an effort to improve the outcome of women with hormone receptor–positive breast cancer should be explored further.

Table 3. Results: Safety on Study

	ATA + TOR		Letrozole	
All Events > 10%	No. of Patients	%	No. of Patients	%
Asthenia	49	11	53	12
Weight increased	52	12	43	10
Hot flush	44	10	48	11

Abbreviations: ATA, atamestane; TOR, toremifene.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Data analysis and interpretation: Paul Goss
Manuscript writing: Paul Goss
Final approval of manuscript: Paul Goss, Igor N. Bondarenko, Georgiy N. Manikhas, Kelly B. Pendergrass, Wilson H. Miller Jr, Peter Langecker, Dennis Blanchett

REFERENCES

1. Goss PE, Strasser K: Aromatase inhibitors in the treatment and prevention of breast cancer. J Clin Oncol 19:881-894, 2001

2. Rose C, Mouridsen HT: Endocrine therapy of advanced breast cancer. Acta Oncol 27:721-728, 1988

3. Nabholtz A, Buzdar A, Pollak M, et al: Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multicenter randomized trial. J Clin Oncol 18:3758-3767, 2000

4. Bonneterre J, Thurlimann B, Robertson J, et al: Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability Study. J Clin Oncol 18:3748-3757, 2000

5. Bonneterre J, Buzdar A, Nabholtz JM, et al: Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. Cancer 92:2247-2258, 2001

6. Dirix J, Piccart MJ, Lohrisch C, et al: Efficacy of and tolerance to exemestane versus tamoxifen in first-line hormonal therapy of postmenopausal metastatic breast cancer patients: A European Organization for the Research and Treatment of Cancer Phase II Trial with Pharmacia and Upjohn. Proc Am Soc Clin Oncol 20:29a, 2001 (abstr 114)

7. Buzdar A, Jonat W, Howell A, et al: Significant improved survival with Arimidex (anastrozole) vs megestrol acetate (MA) in postmenopausal advanced breast cancer: Updated results of two randomized trials. Proc Am Soc Clin Oncol 16:156a, 1997 (abstr 545)

8. Mouridsen H, Gershanovich M, Sun Y, et al: Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: Results of a phase III study of the International Letrozole Cancer Group. J Clin Oncol 19:2596-2606, 2001

9. Mouridsen H, Gershanovich M, Sun Y, et al: Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 21:2101-2109, 2003

10. Cole MP, Jones CTA, Todd IDH: A new antiestrogenic agent in late breast cancer: An early appraisal of ICI 46474. Br J Cancer 25:270-275, 1971

11. Brodie AMH, Schwarzel WC, Brodie HJ: Studies on the mechanism of estrogen biosynthesis in the rat ovary: 1. J Steroid Biochem 7:787-793, 1976

12. Lu Q, Yue W, Wang J, et al: The effects of aromatase inhibitors and antiestrogens in the nude mouse model. Breast Cancer Res Treat 50:63-71, 1998

13. Santen RJ, Song RX, Zhang Z, et al: Adaptive hypersensitivity to estrogen: Mechanism for superiority of aromatase inhibitors over selective estrogen receptor modulators for breast cancer treatment and prevention. Endocrine-Related Cancer 10:111-130, 2003

14. Masamura S, Santner Sj, Heitjan DF, et al: Estrogen deprivation causes estradiol hypersensitivity in human breast cancer cells. J Clin Endocrinol Metab 80:2918-2925, 1995

15. Baum M, Budzar AU, Cuzick J, et al: ATAC Trialists' Group: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer—First results of the ATAC randomized trial. Lancet 359:2131-2139, 2002

16. Brodie A, Lu Q, Liu Y, et al: Aromatase inhibitors and their antitumor effects in model systems. Endocr Relat Cancer 6:205-210, 1999

17. di Salle E, Zaccheo T, Ornati G: Antiestrogenic and antitumor properties of the new triphenethylene derivative toremifene in the rat. J Steroid Biochem 36:203-206, 1990

18. Zaccheo T, Giudici D, Ornati G, et al: Comparison of the effects of the irreversible aromatase inhibitor exemestane with atamestane and MDL 18962 in rats with DMBA-induced mammary tumours. Eur J Cancer 27:1145-1150, 1991

19. National Cancer Institute: Common Toxicity Criteria, Version 2.0. Bethesda, MD, DCTD, NCI, NIH, DHHS, 1998

20. 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

21. Powles TJ, Gordon C, Coombes RC: Clinical trial of multiple endocrine therapy for metastatic and locally advanced breast cancer with tamoxifen-aminoglutethimide-danazol compared to tamoxifen used alone. Cancer Res 42:3458s-3460s, 1982

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).