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ORIGINAL REPORT

Comparative Efficacy and Safety of Adjuvant Letrozole Versus Anastrozole in Postmenopausal Patients With Hormone Receptor–Positive, Node-Positive Early Breast Cancer: Final Results of the Randomized Phase III Femara Versus Anastrozole Clinical Evaluation (FACE) Trial

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ABSTRACT

Purpose
The Letrozole (Femara) Versus Anastrozole Clinical Evaluation (FACE) study compared the efficacy and safety of adjuvant letrozole versus anastrozole in postmenopausal patients with hormone receptor (HR) –positive and node-positive early breast cancer (eBC).

Methods
Postmenopausal women with HR-positive and node-positive eBC were randomly assigned to receive adjuvant therapy with either letrozole (2.5 mg) or anastrozole (1 mg) once per day for 5 years or until recurrence of disease. Patients were stratified on the basis of the number of lymph nodes and human epidermal growth factor receptor 2 status. The primary end point was 5-year disease-free survival (DFS), and the key secondary end points were overall survival and safety.

Results
A total of 4,136 patients were randomly assigned to receive either letrozole (n = 2,061) or anastrozole (n = 2,075). The final analysis was done at 709 DFS events (letrozole, 341 [16.5%]; anastrozole, 368 [17.7%]). The 5-year estimated DFS rate was 84.9% for letrozole versus 82.9% for anastrozole arm (hazard ratio, 0.93; 95% CI, 0.80 to 1.07; $P = .3150$). Exploratory analysis showed similar DFS with letrozole and anastrozole in all evaluated subgroups. The 5-year estimated overall survival rate was 89.9% for letrozole versus 89.2% for anastrozole arm (hazard ratio, 0.98; 95% CI, 0.82 to 1.17; $P = .7916$). Most common grade 3 to 4 adverse events (> 5% of patients) reported for letrozole versus anastrozole were arthralgia (3.9% *v* 3.3%, and 48.2% *v* 47.9% for all adverse events), hypertension (1.2% *v* 1.0%), hot flushes (0.8% *v* 0.4%), myalgia (0.8% *v* 0.7%), dyspnea (0.8% *v* 0.5%), and depression (0.8% *v* 0.6%).

Conclusion
Letrozole did not demonstrate significantly superior efficacy or safety compared with anastrozole in postmenopausal patients with HR-positive, node-positive eBC.

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INTRODUCTION

Breast cancer (BC) is the most common cancer affecting women worldwide,[1] with an estimated 1.67 million new cancer cases diagnosed in 2012.[2] Almost 80% of all BCs are hormone receptor (HR) positive (estrogen receptor positive and/or progesterone receptor positive).[3] Aromatase inhibitors (AIs) such as anastrazole, letrozole, and exemestane are the current standard of care as adjuvant therapy for postmenopausal women with estrogen receptor–positive early breast cancer (eBC).[4,5]

Both letrozole and anastrozole have been shown to have superior efficacy compared with tamoxifen.[6,7] In the Breast International Group (BIG) 1-98 trial (median follow-up, 8.7 years), letrozole monotherapy was significantly more effective than tamoxifen, whether by inverse probability of censoring weighting or intention-to-treat analysis (inverse probability of censoring weighting disease-free survival [DFS] hazard ratio, 0.82; 95% CI, 0.74 to 0.92; intention-to-treat DFS hazard

ASSOCIATED CONTENT

Appendix
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ratio, 0.86; 95% CI, 0.7 to 0.96).[6] The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial demonstrated that anastrozole significantly prolonged DFS (hazard ratio, 0.91; 95% CI, 0.83 to 0.99; $P = .04$) and time to recurrence (hazard ratio, 0.84; 95% CI, 0.75 to 0.93; $P = .001$) and significantly reduced distant metastases (hazard ratio, 0.87; 95% CI, 0.77 to 0.99; $P = .03$) versus tamoxifen as adjuvant endocrine therapy in postmenopausal women with HR-positive BC.[7] Pharmacodynamic studies have shown that letrozole more effectively suppresses plasma estradiol levels than anastrozole in patients with advanced BC,[8] but the unanswered question is whether this translates into better efficacy. There were no head-to-head trials comparing the two treatments in the adjuvant setting until now.

Published data have indicated that the relative benefit of both agents varies across patient subgroups,[9,10] and, in particular, an exploratory analysis of the BIG 1-98 trial showed that patients with node-positive disease seemed to derive a greater benefit versus tamoxifen than did patients with node-negative disease.[9] Hence, it was believed that there was an unmet need, first, to assess head to head the relative efficacy of these two nonsteroidal aromatase inhibitors and, second, to evaluate their benefit in higher-risk patients with node-positive disease. The phase III randomized, open-label, multicenter Femara Versus Anastrozole Clinical Evaluation (FACE) trial (NCT00248170) was therefore designed to compare the efficacy and safety of adjuvant letrozole versus anastrozole in postmenopausal patients with HR-positive and node-positive eBC.

METHODS

Patients

The patient population included postmenopausal women with HR-positive and node-positive eBC (stage IIA to IIIC invasive cancer) who were within 12 weeks after breast surgery or completion of adjuvant chemotherapy. Patients who received neoadjuvant chemotherapy or adjuvant treatment with trastuzumab were also eligible. All patients had a WHO performance status of 0 or 1. Patients with metastatic or inflammatory BC (as documented by dermal lymphatic invasion), contralateral BC, or metachronous bilateral BC, including ductal carcinoma in situ, were excluded. Patients who had received neoadjuvant endocrine therapy or adjuvant antiestrogen therapy for $>$ 1 month after surgery, radiotherapy, and/or chemotherapy and patients with Child-Pugh grade C cirrhosis were not eligible for the trial.

Study Design

In this phase IIIb, open-label, multicenter trial conducted across 271 international centers, patients were randomly assigned 1:1 to receive either adjuvant letrozole (2.5 mg) or anastrozole (1 mg) once per day until disease recurrence/relapse or for a maximum of 5 years. There was no predetermined per-patient follow-up period. Two interim analyses were planned for DFS, after approximately one third (320 events) and two thirds (639 events) of the total number of events (959 events). Disease recurrence was assessed as per local practice guidelines by x-ray, computed tomography, ultrasound, or magnetic resonance imaging.

Patients were stratified on the basis of the number of lymph nodes (one to three or four or more) and human epidermal growth factor receptor 2 (HER2) status by locally assessed fluorescence in situ hybridization or immunohistochemistry.

End Points and Analysis Sets

The primary end point was DFS, defined as date from randomization to recurrence of invasive BC (local, regional, or distant), new invasive cancer in the contralateral breast, or death from any cause. The secondary end points were overall survival (OS; time from randomization to death from any cause), time to development of distant metastases (TDM), distant disease-free survival (DDFS), and safety. TDM was defined as the time from the date of randomization to the date of first development of any recurrent or metastatic disease in sites other than the local mastectomy scar, the ipsilateral breast in case of breast conservation, or the contralateral breast. DDFS was the time from the date of randomization to the date of the first development of any recurrence at a distant site or death from any cause.

The intent-to-treat (ITT) population consisted of all randomly assigned patients. The safety cohort included all the patients from the ITT population who received study therapy and had at least one safety assessment after the baseline assessment. The primary efficacy evaluation was based on the ITT set and the safety evaluation on the safety set.

Statistical Analysis

A stratified two-sided log-rank test was used to test the treatment difference in terms of DFS, stratifying for number of lymph nodes (one to three or four or more) and HER2 status (positive or negative). The sample size calculation was based on an expected 5-year DFS of 76.5% for anastrozole versus 80.0% for letrozole, corresponding to a hazard ratio of 0.83 favoring letrozole. These calculations took two interim analyses into account, with adjustment to the significance levels performed via an O'Brien Fleming design. Accounting for 5% loss to follow-up, with 4,000 patients, 2,000 in each arm leading to 959 events would give the study 80% power (two-sided 0.05 significance level) to detect a DFS difference of 3.5% between the treatment arms. On the basis of the observed event rate and also on the availability of patients who could be reconsented for longer follow-up, it was estimated that it could take until 2022 to reach the required 959 events. Hence, after discussion with the steering committee and with notification of the Independent Data Monitoring Committee, the study was terminated early (September 8, 2014). At the time of final analysis, 709 DFS events were included. P value was obtained from the two-sided stratified log-rank test. The hazard ratio and associated 95% CIs were obtained using a stratified Cox model by number of lymph nodes (one to three or four or more) and HER2 status. A sensitivity analysis using a Cox proportional hazards model adjusting for the number of lymph nodes and HER2 status has also been performed. The hazard ratio and associated 95% CI for subgroup analyses were obtained using an unstratified Cox model.

Ethics and Role of Sponsor

The study protocol and informed Consent Form were reviewed by the independent ethics committee or institutional review board for each center, and the study participants were provided with institutional review board/independent ethics committee–approved written informed consent. Patients who did not provide informed consent before randomization were removed from the intent-to-treat (ITT) population and were captured as protocol deviations. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.

The study was sponsored by Novartis Pharmaceuticals and overseen by an independent data monitoring committee with guidance from the study steering committee. The data analysis was performed by an independent statistical group (Michelangelo), and the study sponsor remained blinded until the analysis was complete. The investigators performed the trial-related activities on the basis of the contractual terms of the trial and retained their independence from the sponsor.

RESULTS

Baseline Characteristics

A total of 4,172 patients were randomly assigned between December 2005 and March 2008. Two patients were randomly

assigned in error before they had signed the informed consent, and 34 patients had baseline assessments performed before signing the informed consent. After the exclusion of these 36 patients from the ITT and safety populations, a total of 4,136 patients received either letrozole (n = 2,061) or anastrozole (n = 2,075; Data Supplement). Treatment arms were well balanced with respect to baseline characteristics (Table 1). The median age in both treatment arms was 62 years, and the majority of patients (approximately 86%) were white. The main prior antineoplastic therapies patients had received in the letrozole versus anastrozole arms included adjuvant chemotherapy (62.7% *v* 61.1%) and radiotherapy (31.6% *v* 29.9%).

Patient Disposition

Among the total 4,136 patients, 12 from the letrozole arm and 13 from the anastrozole arm were untreated. The safety population included a total of 4,111 patients who actually took treatment in the letrozole (n = 2,049) and anastrozole arms (n = 2,062; Appendix Table A1, online only). The median duration of exposure was approximately 60 months in both the arms at the final analysis in February 2015. The median duration of follow-up was 65 months in all study patients. Treatment discontinuation was reported in 36.1% and 38.1% of the patients in the letrozole arm and anastrozole arms, respectively. Primary reasons for discontinuation in both the letrozole and anastrozole arms were adverse events (AEs; 15.1% *v* 14.3%) and disease progression (9.5% *v* 10.4%). Patients who were lost to follow-up comprised 1.4% and 1.7% in letrozole and anastrozole arms, respectively.

Efficacy. **DFS.** No statistically significant difference in DFS was observed between the treatment arms (hazard ratio, 0.93; 95% CI, 0.80 to 1.07; stratified log-rank test, $P = .3150$; Fig 1). At the final analysis with 709 DFS events, the 5-year estimated DFS rate was 84.9% (95% CI, 83.2% to 86.4%) for letrozole versus 82.9% (95% CI, 81.2% to 84.5%) for anastrozole, respectively. The median DFS was not reached in either of the treatment arms. Similar 5-year DFS estimates were observed for letrozole versus anastrozole in all evaluated exploratory subgroups, including body mass index, prior adjuvant chemotherapy, tumor stage, HER2 status, and geographic region (Fig 2).

OS. No statistically significant difference in OS was observed between the treatment arms, with a hazard ratio of 0.98 (95% CI, 0.82 to 1.17; $P = .7916$). At the final analysis, 235 (11.4%) deaths were recorded in the letrozole arm versus 242 (11.7%) deaths in the anastrozole arm. The median OS was not reached in either of the treatment arms. The 5-year estimated OS for letrozole and anastrozole arms was 89.9% (95% CI, 88.5% to 91.1%) and 89.2% (95% CI, 87.8% to 90.5%), respectively (Fig 3).

TDM and DDFS. The percentage of patients who developed distant metastases was 10.8% in each arm. Time to distant metastases (TDM) was comparable between the two treatment arms (hazard ratio, 0.99; 95% CI, 0.82 to 1.19; $P = .9391$), and the median TDM was not reached in either arm (Appendix Fig A1, online only). Similarly, the percentage of patients who developed distant disease-free survival (DDFS) was 15.7% and 16.2% in the letrozole and anastrozole arms, respectively. DDFS was comparable between the treatment arms (hazard ratio, 0.96; 95% CI, 0.82 to 1.12; $P = .6204$), and the median DDFS was not reached in either arm (Appendix Fig A2, online only). Distant recurrence occurred in 11% of both the treatment arms, and the sites of metastases were also similar in the two arms. Secondary malignancies occurred in 4.1% and 4.8% of the letrozole- and anastrozole-treated patients, respectively.

Safety. The safety profiles of the two treatment arms were similar (Table 2). The most common AEs (> 10% of patients) reported were arthralgia (48.2% *v* 47.9%), hot flushes (32.5% *v* 32.3%), fatigue (16.8% *v* 16.6%), osteoporosis (10.9% *v* 10.9%), myalgia (11.4% *v* 10.3%), and back pain (10.3% *v* 9.4%). The most common grade 3 or 4 AEs (> 0.8% of patients) reported for

Table 1. Baseline Characteristics and Prior Treatments

Characteristic or Treatment	Letrozole (n = 2,061)	Anastrozole (n = 2,075)
Age, median (range), years	62 (33-96)	62 (33-92)
Age category, years		
< 65	1,236 (60.0)	1,254 (60.4)
≥ 65	825 (40.0)	821 (39.6)
Race, n (%)		
White	1,775 (86.1)	1,799 (86.7)
Black	26 (1.3)	32 (1.5)
Asian	204 (9.9)	196 (9.4)
Native American	3 (0.1)	5 (0.2)
Pacific islander	3 (0.1)	2 (0.1)
Other	50 (2.4)	41 (2.0)
Performance status (WHO)		
0	1,634 (79.3)	1,666 (80.3)
1	404 (19.6)	394 (19.0)
2	2 (0.1)	2 (0.1)
Missing	21 (1.0)	13 (0.6)
Postmenopausal status		
Age ≥ 50 years and amenorrheic for ≥ 6 months in the absence of chemotherapy	1,912 (92.8)	1,920 (92.5)
Age < 50 years and amenorrheic for ≥ 12 months in the absence of chemotherapy	37 (1.8)	39 (1.9)
Prior bilateral oophorectomy	94 (4.6)	100 (4.8)
Missing	18 (0.9)	16 (0.8)
ER status		
Negative	32 (1.6)	22 (1.1)
Positive	2,028 (98.4)	2,053 (98.9)
Unknown	1 (0.0)	0
Progesterone receptor status		
Negative	387 (18.8)	405 (19.5)
Positive	1,645 (79.8)	1,648 (79.4)
Unknown	29 (1.4)	22 (1.1)
HER2 status		
Negative	1,825 (88.5)	1,835 (88.4)
Positive	235 (11.4)	239 (11.5)
Unknown	1 (< 0.1)	1 (< 0.1)
No. of lymph nodes		
1-3	1,477 (71.7)	1,477 (71.2)
≥ 4	584 (28.3)	598 (28.8)
Tumor stage*		
T0 or T1	968 (47.0)	945 (45.5)
T2	908 (44.1)	926 (44.6)
≥ 3	177 (8.6)	196 (9.4)
Prior antineoplastic therapy		
Radiotherapy	652 (31.6)	621 (29.9)
Adjuvant chemotherapy	1,294 (62.7)	1,267 (61.1)

NOTE. Data presented as No. (%) unless otherwise noted.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
*Does not include patients with missing tumor stage (n = 1) or ductal carcinoma in situ (n = 15).

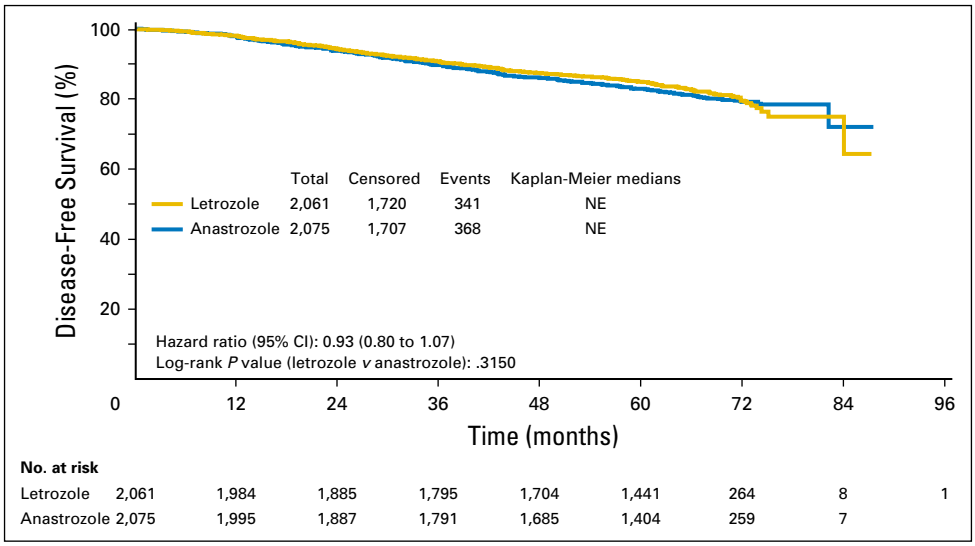

Fig 1. Disease-free survival. NE, non-evaluable.

letrozole versus anastrozole, respectively, were arthralgia (3.9% *v* 3.3%), hypertension (1.2% *v* 1.0%), hot flushes (0.8% *v* 0.4%), myalgia (0.8% *v* 0.7%), dyspnea (0.8% *v* 0.5%), and depression (0.8% *v* 0.6%; Table 3).

Grade 3 or 4 AEs, which were suspected to be treatment related in the letrozole versus anastrozole arms, were 9.5% versus 8.1%, respectively. AEs that were suspected to be treatment related and led to letrozole versus anastrozole discontinuation occurred in 14.0% versus 12.9% of patients, respectively. Serious AEs, which were suspected to be drug related in the letrozole versus anastrozole arms, occurred in 2.6% versus 2.3% of patients, respectively, and AEs leading to dose interruptions/reductions occurred in 8.2% versus 7.7% of patients, respectively. On-treatment deaths occurring in the letrozole- versus anastrozole-treated patients were 42 (2.0%) versus 46 (2.2%; Table 2). The main causes of death during letrozole versus anastrozole treatment were disease progression (147 [7.2%] *v* 142 [6.9%]), cardiac failure (6 [0.3%] *v* 2 [< 0.1%]), pulmonary embolism (2 [0.1%] *v* 4 [0.2%]), and chronic obstructive pulmonary disease (1 [0.05%] *v* 4 [0.2%]), respectively.

DISCUSSION

Anastrozole and letrozole have both been used as front-line adjuvant endocrine therapy for eBC in postmenopausal women for

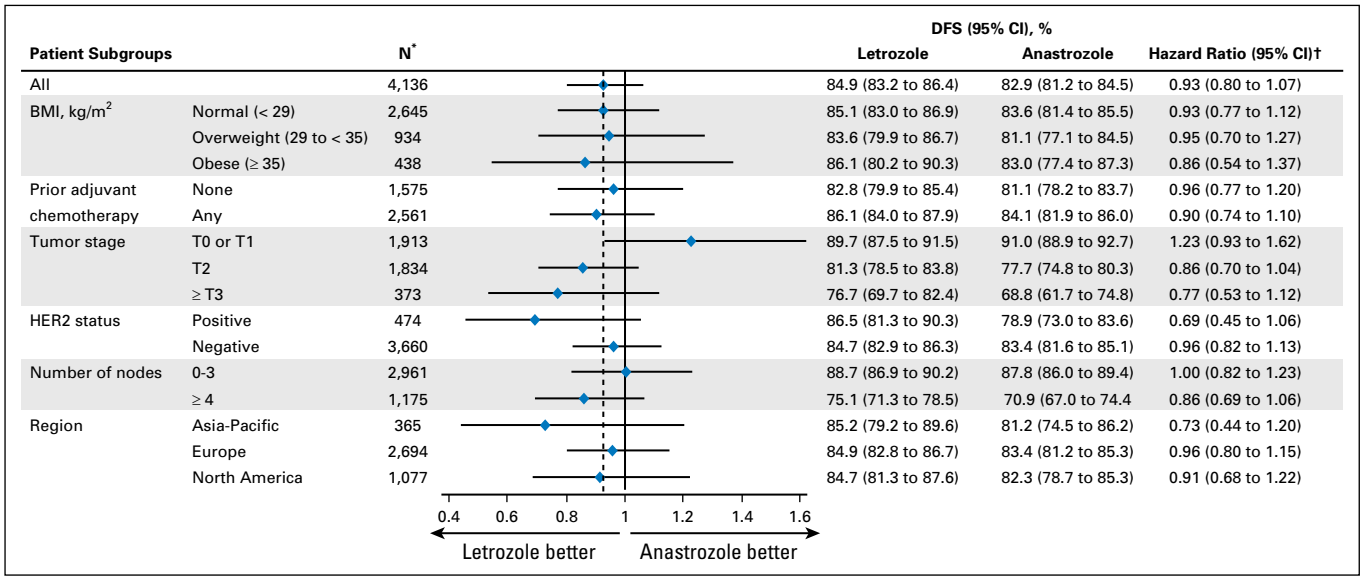

Fig 2. Exploratory subgroup analyses of 5-year disease-free survival (DFS) by baseline characteristics. BMI, body mass index; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2. (*)Sum of N in subgroups is not always 4,136 because of missing data. (†)The hazard ratio was obtained from an unstratified Cox model except for All, which was obtained from the stratified Cox model by number of lymph nodes and HER2 status.

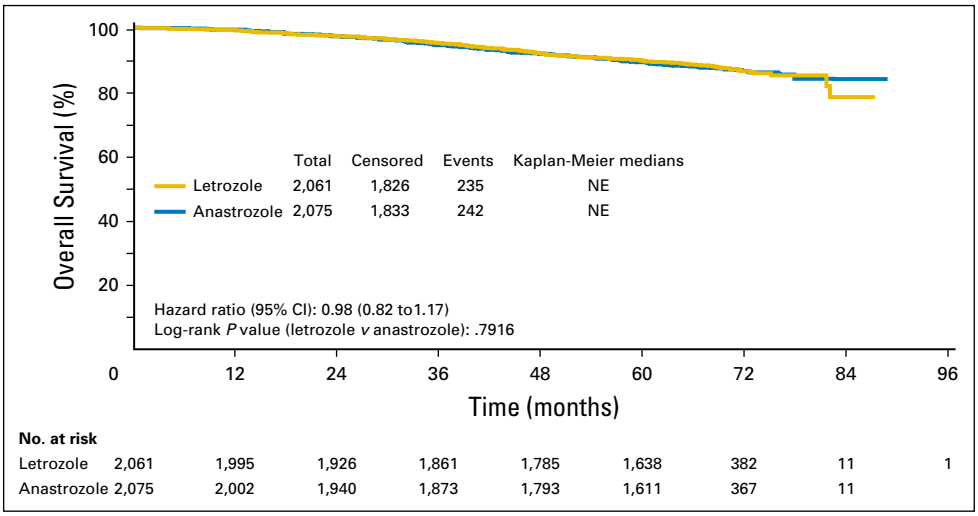

Fig 3. Overall survival. NE, non-evaluable.

more than a decade, and yet there have been no clinical randomized data on their relative efficacies until now. Circumstantial evidence suggested that letrozole might be superior. For example, the BIG 1-98 trial analysis at a median of 8.3 years of follow-up after censoring patients for crossover showed a significant OS benefit with letrozole compared with tamoxifen (hazard ratio, 0.82; $P < .05$).[11] In contrast, in the ATAC trial, no survival benefit with anastrozole compared with tamoxifen was noted even after 10 years of follow-up (hazard ratio, 0.97; $P = .7$).[12] Likewise, letrozole has been shown to be a more potent inhibitor of aromatization and suppressant of circulating levels of serum estrone and estrone sulfate than anastrozole in small studies.[13,14]

Against this background, the present FACE trial involving more than 4,000 patients with node-positive disease failed to confirm the hypothesis that letrozole might be clinically superior to anastrozole as adjuvant endocrine therapy in postmenopausal women. These findings are comparable with results from the phase III trial, NCIC Clinical Trials Group MA.27, which likewise failed to show superior outcomes after 5 years of adjuvant therapy with exemestane versus anastrozole; estimated 4-year DFS rate was 91.0% for exemestane versus 91.2% for anastrozole.[15] They are also in line with the American College of Surgeons Oncology Group (ACOSOG) Z1031, randomized, phase II, neoadjuvant trial, in which no significance difference in clinical responses was observed between letrozole, anastrozole, and exemestane.[16] The observations from the FACE study are also in line with results from an early trial comparing letrozole and anastrozole as second-line treatment of advanced BC in 713 patients; no difference was observed in either time to progression or OS,[17] although letrozole was significantly superior

Table 2. Safety Summary

Event	Letrozole (n = 2,049)	Anastrozole (n = 2,062)
All deaths	235 (11.5)	240 (11.6)
On-treatment deaths*	42 (2.0)	46 (2.2)
Any grade AEs, all/suspected to be drug related	2,049 (100)/1,558 (76.0)	2,062 (100)/1,570 (76.1)
Grade 3 or 4 AEs, all/suspected to be drug related	628 (30.6)/194 (9.5)	591 (28.7)/168 (8.1)
Clinically notable AEs, all/suspected to be drug related	305 (14.9)/50 (2.4)	244 (11.8)/40 (1.9)
Clinical fractures	191 (9.3)	166 (8.0)
Ischemic heart disease	49 (2.4)	31(1.5)
Thromboembolic events	25 (1.2)	24 (1.2)
Cardiac failures/disorders†	31 (1.5)	15 (0.7)
Cerebrovascular accidents	33 (1.6)	30 (1.5)
Serious AEs, all/suspected to be drug related‡	486 (23.7)/54 (2.6)	520 (25.2)/48 (2.3)
AEs leading to discontinuation	357 (17.4)	337 (16.3)
Suspected to be drug related	286 (14.0)	265 (12.9)
Other significant AEs	1,495 (73.0)	1,526 (74.0)
AEs requiring dose interruption/reduction	167 (8.2)	158 (7.7)
AEs requiring additional therapy	1,470 (71.1)	1,493 (72.4)

NOTE. Data presented as No. (%).
Abbreviation: AE, adverse event.
*The main causes of on-treatment deaths (up to 28 days after end of treatment) were breast cancer (0.5% *v* 0.3%), cardiac failure (0.2% *v* 0.0%), and chronic obstructive pulmonary disease (0.0% *v* 0.1%).
†Cardiac failures/disorders include cardiac failure, cardiac failure congestive, cardiac failure acute, cor pulmonale, and diastolic dysfunction.
‡Serious adverse events were indicated as such by the investigators and reported to the sponsor's drug safety department.

Table 3. Most Common Adverse Events (> 5% of patients)

	Letrozole (n = 2,049)		Anastrozole (n = 2,062)	
Preferred Term	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades
Arthralgia	80 (3.9)	987 (48.2)	69 (3.3)	987 (47.9)
Hot flush	17 (0.8)	666 (32.5)	9 (0.4)	666 (32.3)
Fatigue	8 (0.4)	345 (16.8)	10 (0.5)	343 (16.6)
Osteoporosis	5 (0.2)	223 (10.9)	11 (0.5)	225 (10.9)
Myalgia	16 (0.8)	233 (11.4)	15 (0.7)	212 (10.3)
Back pain	11 (0.5)	212 (10.3)	17 (0.8)	193 (9.4)
Osteopenia	4 (0.2)	203 (9.9)	1 (0.0)	173 (8.4)
Pain in extremity	9 (0.4)	168 (8.2)	3 (0.1)	174 (8.4)
Lymphedema	5 (0.2)	159 (7.8)	2 (0.1)	179 (8.7)
Insomnia	7 (0.3)	160 (7.8)	3 (0.1)	149 (7.2)
Hypercholesterolemia	2 (0.1)	155 (7.6)	1 (0.0)	151 (7.3)
Hypertension	25 (1.2)	156 (7.6)	20 (1.0)	149 (7.2)
Depression	16 (0.8)	147 (7.2)	13 (0.6)	137 (6.6)
Bone pain	10 (0.5)	138 (6.7)	9 (0.4)	122 (5.9)
Nausea	6 (0.3)	137 (6.7)	5 (0.2)	152 (7.4)
Headache	3 (0.1)	130 (6.3)	5 (0.2)	168 (8.1)
Alopecia	2 (0.1)	127 (6.2)	0 (0.0)	134 (6.5)
Musculoskeletal pain	6 (0.3)	123 (6.0)	9 (0.4)	147 (7.1)
Radiation skin injury	11 (0.5)	120 (5.9)	6 (0.3)	88 (4.3)
Dyspnea	16 (0.8)	118 (5.8)	10 (0.5)	96 (4.7)
Cough	1 (0.0)	106 (5.2)	1 (0.0)	120 (5.8)
Musculoskeletal stiffness	2 (0.1)	102 (5.0)	2 (0.1)	84 (4.1)
Dizziness	2 (0.1)	94 (4.6)	7 (0.3)	109 (5.3)

NOTE. Data presented as No. (%).

to anastrozole regarding overall response rate (19.1% *v* 12.3%; $P = .013$).

An important secondary finding of the FACE trial was the lack of relationship between obesity and outcome. It has been argued that aromatase inhibitors may be less effective in depleting estradiol in obese women, because of the greater quantity of aromatase in peripheral fatty tissue.[18,19] In the ATAC trial, anastrazole seemed less effective in postmenopausal women who were obese, possibly reflecting its incomplete suppression of estrogen.[20,21] In contrast, in the BIG 1-98 trial, letrozole benefit over tamoxifen did not seem to be influenced by the patient's body mass index,[22] with the hypothesis that this reflected its more complete estrogen suppression. In the FACE trial, however, no significant advantage was seen for letrozole over anastrozole even in patients defined as obese or morbidly obese in an exploratory analysis, despite a nonsignificant trend in favor of letrozole in obese patients, but with wide CIs (hazard ratio, 0.86; 95% CI, 0.54 to 1.37; Fig 2). Our results therefore do not support the hypothesis that obese patients may do better on letrozole than anastrozole.

When the FACE trial was designed, treatment was planned for 5 years or until disease progression, but no set duration of follow-up was determined. Follow-up in the FACE trial was stopped in 2014 by the sponsors because of the lower-than-expected event rate, funding issues, and challenges in restarting and reconsenting patients globally to allow for further follow-up. Nevertheless, the 5-year follow-up results of both the ATAC and the BIG 1-98 trials correctly predicted longer-term outcomes, with the exception that the OS benefit in BIG 1-98 only emerged several years later. The close similarity in the outcome results after 5 years in the FACE trial argues strongly against the likelihood of a clinically significant benefit for either agent emerging later.

A possible small caveat to this was a subgroup analysis showing a nonsignificant trend in favor of letrozole for high-risk patients with four or more nodes involved (hazard ratio for DFS, 0.86; 95% CI, 0.69 to 1.06; Fig 2). A similar trend was reported in the BIG 1-98 trial, in which patients at highest risk had the greatest efficacy advantage of letrozole over tamoxifen.[9] The safety profiles of letrozole and anastrozole in FACE were comparable, and AE-related treatment discontinuations were reported in 15.1% and 14.3% of patients in the letrozole and anastrozole arms, respectively. In contrast, in the NCIC Clinical Trials Group MA.27 trial, the AE-related discontinuation rate for exemestane was slightly higher (33.8%) than for anastrozole (29.4%).[15] In a smaller comparative trial of letrozole and anastrozole in patients with metastatic BC, the rates of AEs, serious AEs, and treatment discontinuations were similar, and no significant safety differences were observed between the two treatment arms.[17]

There is an increasing interest in extending adjuvant endocrine therapy beyond 5 years, in so-called extended adjuvant therapy. In the MA.17R trial, which involved 1,918 women, extending the treatment with letrozole to 10 years resulted in significantly improved DFS. The 5-year DFS was 95% (95% CI, 93% to 96%) in the letrozole group and 91% (95% CI, 89% to 93%) in the placebo group, (hazard ratio, 0.66; 95% CI, 0.48 to 0.91; $P = .01$).[23] It is possible that the lower-than-anticipated event rate (709 *v* 959 planned DFS events), which led to premature termination of the FACE trial, may have been influenced to some extent by the use of extended adjuvant endocrine therapy in some patients, despite this not being prescribed in the protocol. However, data to support or refute this are not available.

In conclusion, Letrozole did not provide statistically superior efficacy over anastrozole in either the primary end point

of DFS or the secondary end point of OS. No new safety concerns were identified, and there were no unexpected short-term or long-term treatment-related toxicities in either of the treatment arms. The study was terminated prematurely because of lower-than-expected DFS events, and the data presented here are based on the final analysis of 709 DFS events. Primary BC tissue, blood, and germline single nucleotide polymorphism biomarker analyses are currently ongoing.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Appendix

Table A1. Patient Disposition

Disposition	Letrozole (n = 2,061)	Anastrozole (n = 2,075)
Patients		
Untreated	12 (0.6)	13 (0.6)
Treated	2,049 (99.4)	2,062 (99.4)
Primary reasons for treatment discontinuation		
Treatment duration completed as per protocol	1,315 (63.8)	1,285 (61.9)
Adverse event(s)	311 (15.1)	296 (14.3)
Disease progression	196 (9.5)	216 (10.4)
Abnormal test procedure result(s)	49 (2.4)	61 (2.9)
Subject withdrew consent	71 (3.4)	79 (3.8)
Protocol violation	35 (1.7)	30 (1.4)
Death	28 (1.4)	47 (2.3)
Lost to follow-up	28 (1.4)	35 (1.7)
Administrative problems	22 (1.1)	25 (1.2)
Abnormal laboratory value(s)	4 (0.2)	0

NOTE. Data presented as No. (%).

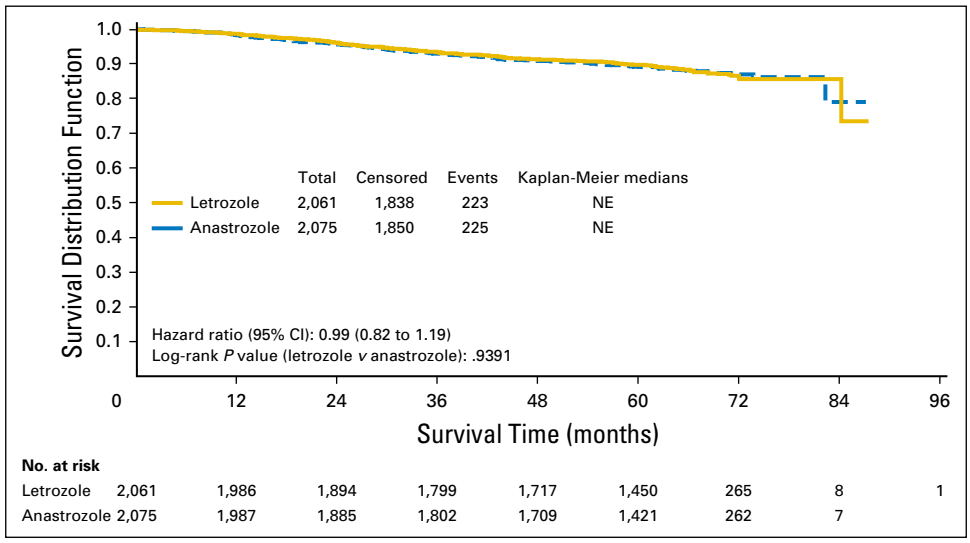

Fig A1. Time to distant metastases. NE, not evaluable.

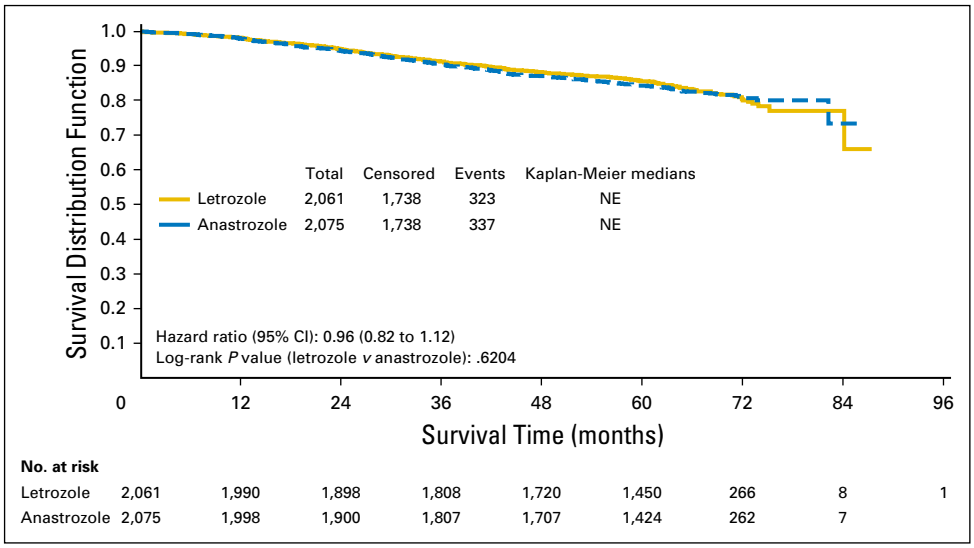

Fig A2. Distant disease-free survival. NE, non-evaluable.