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


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.

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 anastrozole, 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
ratio, 0.86; 95% CI, 0.7 to 0.96). 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. Pharmacodynamic studies have shown that letrozole more effectively suppresses plasma estradiol levels than anastrozole in patients with advanced BC, 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, 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. 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.

**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.
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 antiestrogen 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, respectively, was 84.9% (95% CI, 83.2% to 86.4%) for anastrozole, respectively. The OS 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 10.5%), and back pain (10.3% v 9.4%). The most common grade 3 or 4 AEs (> 0.8% of patients) reported for...
letrozole versus anastrozole, respectively, were arthralgia (3.9% vs 3.3%), hypertension (1.2% vs 1.0%), hot flushes (0.8% vs 0.4%), myalgia (0.8% vs 0.7%), dyspnea (0.8% vs 0.5%), and depression (0.8% vs 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%] vs 142 [6.9%]), cardiac failure (6 [0.3%] vs 2 [0.1%]), pulmonary embolism (2 [0.1%] vs 4 [0.2%]), and chronic obstructive pulmonary disease (1 [0.05%] vs 4 [0.2%]), respectively.

**DISCUSSION**

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Letrozole (n = 2,049)</th>
<th>Anastrozole (n = 2,062)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths</td>
<td>235 (11.5)</td>
<td>240 (11.6)</td>
</tr>
<tr>
<td>On-treatment deaths*</td>
<td>42 (2.0)</td>
<td>46 (2.2)</td>
</tr>
<tr>
<td>Any grade AEs, all/suspected to be drug related</td>
<td>2,049 (100)/1,558 (76.0)</td>
<td>2,062 (100)/1,570 (76.1)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs, all/suspected to be drug related</td>
<td>628 (30.6)/194 (9.5)</td>
<td>591 (28.7)/168 (8.1)</td>
</tr>
<tr>
<td>Clinically notable AEs, all/suspected to be drug related</td>
<td>305 (14.9)/50 (2.4)</td>
<td>244 (11.9)/40 (2.0)</td>
</tr>
<tr>
<td>Clinical fractures</td>
<td>191 (9.3)</td>
<td>166 (8.0)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>49 (2.4)</td>
<td>31 (1.5)</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>25 (1.2)</td>
<td>24 (1.2)</td>
</tr>
<tr>
<td>Cardiac failures/disorders†</td>
<td>31 (1.5)</td>
<td>15 (0.7)</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>33 (1.6)</td>
<td>30 (1.5)</td>
</tr>
<tr>
<td>Serious AEs, all/suspected to be drug related</td>
<td>486 (23.7)/54 (2.6)</td>
<td>520 (25.2)/48 (2.3)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>357 (17.4)</td>
<td>337 (16.3)</td>
</tr>
<tr>
<td>Suspected to be drug related</td>
<td>286 (14.0)</td>
<td>265 (12.9)</td>
</tr>
<tr>
<td>Other significant AEs</td>
<td>1,495 (73.0)</td>
<td>1,526 (74.0)</td>
</tr>
<tr>
<td>AEs requiring dose interruption/reduction</td>
<td>167 (8.2)</td>
<td>158 (7.7)</td>
</tr>
<tr>
<td>AEs requiring additional therapy</td>
<td>1,470 (71.1)</td>
<td>1,495 (72.4)</td>
</tr>
</tbody>
</table>

**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.

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to anastrozole regarding overall response rate (19.1% vs 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 peripheral fatty tissue.22 With the hypothesis that obese patients may do better on letrozole than anastrozole even in patients defined as obese or morbidly obese in an exploratory analysis, despite a nonsignificant trend in favor of letrozole over anastrozole in obese patients, with wide CIs (hazard ratio, 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.23 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%).24 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.25

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.

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Letrozole (n = 2,049)</th>
<th>Anastrozole (n = 2,062)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>80 (3.9)</td>
<td>987 (48.2)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>17 (0.8)</td>
<td>666 (32.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (0.4)</td>
<td>345 (16.8)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>5 (0.2)</td>
<td>223 (10.9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>16 (0.8)</td>
<td>233 (11.4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (0.5)</td>
<td>212 (10.3)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>4 (0.2)</td>
<td>203 (9.9)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>9 (0.4)</td>
<td>168 (8.2)</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>5 (0.2)</td>
<td>159 (7.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 (0.3)</td>
<td>160 (7.8)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2 (0.1)</td>
<td>155 (7.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (1.2)</td>
<td>156 (7.6)</td>
</tr>
<tr>
<td>Depression</td>
<td>16 (0.8)</td>
<td>147 (7.2)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>10 (0.5)</td>
<td>138 (6.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (0.3)</td>
<td>137 (6.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (0.1)</td>
<td>130 (6.3)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2 (0.1)</td>
<td>127 (6.2)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>6 (0.3)</td>
<td>123 (6.0)</td>
</tr>
<tr>
<td>Radiation skin injury</td>
<td>11 (0.5)</td>
<td>120 (5.9)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16 (0.8)</td>
<td>118 (5.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (0.0)</td>
<td>106 (5.2)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>2 (0.1)</td>
<td>102 (5.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (0.1)</td>
<td>94 (4.6)</td>
</tr>
</tbody>
</table>

NOTE. Data presented as No. (%).
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.

**REFERENCES**


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Honoraria: AstraZeneca, Pfizer, Roche, Amgen, Novartis, Eisai
Consulting or Advisory Role: AstraZeneca, Novartis, Pfizer, Roche, Amgen, Eisai
Travel, Accommodations, Expenses: AstraZeneca, Pfizer, Roche, Amgen, Novartis, Eisai

Mitch Dowsett
Honoraria: Pfizer, AstraZeneca, Novartis, Myriad Genetics
Consulting or Advisory Role: Radius, GTx
Research Funding: Pfizer, AstraZeneca, Puma Biotechnology, Radius
Other Relationship: Institute of Cancer Research

Lowell Hart
Honoraria: Genentech, Bristol-Myers Squibb
Speakers’ Bureau: Novartis
Research Funding: Novartis (Inst)

Susan Poggio
Employment: Novartis
Stock or Other Ownership: Novartis

Lisa Comarella
Employment: CROS NT (Contract Research Organization)

Herve Salomon
Employment: Novartis

Barbara Wamil
Employment: Novartis
Stock or Other Ownership: Novartis

Joyce O'Shaughnessy
Honoraria: AstraZeneca, Eli Lilly, AbbVie, Arno Therapeutics, Celgene, Nektar, Eisai, Novartis, Pfizer, Genentech
Consulting or Advisory Role: Novartis, Pfizer, Eli Lilly, Arno Therapeutics, AbbVie, AstraZeneca, Celgene, Nektar, Genentech, Eisai
Travel, Accommodations, Expenses: Celgene, Nektar, Eli Lilly, Novartis, Pfizer, AbbVie
Acknowledgment

Medical editorial assistance for this manuscript was provided by Sai Krishna Arepalli and Avishek Pal (Novartis Healthcare).

Appendix

Table A1. Patient Disposition

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

NOTE. Data presented as No. (%).

Survival Distribution Function

Hazard ratio (95% CI): 0.99 (0.82 to 1.19)
Log-rank P value (letrozole vs anastrozole): .9391

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

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