**Report from the FDA**

**Approval Summary: Letrozole in the Treatment of Postmenopausal Women with Advanced Breast Cancer**

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Abstract

Letrozole (Femara; Novartis Pharmaceuticals Corp., East Hanover, NJ) is a nonsteroidal inhibitor of aromatase enzyme complex. It inhibits the peripheral conversion of circulating androgens to estrogens. In postmenopausal women, letrozole decreases plasma concentrations of estradiol, estrone, and estrone sulfate by 75–95% from baseline with maximal suppression achieved within 2–3 days of treatment initiation. Suppression is dose related, with doses of ≥0.5 mg giving estrone and estrone sulfate values that were often below assay detection limits. At clinically used dosage, letrozole does not impair adrenal synthesis of glucocorticoids or aldosterone.

In 1998, letrozole was approved by the United States Food and Drug Administration (FDA) for the treatment of advanced breast cancer in postmenopausal women, with hormone receptor positive or unknown breast cancer, who had failed one prior antiestrogen treatment (i.e., for “second-line” treatment). Approval was based on two randomized trials comparing tumor RRs of patients receiving 0.5 mg of letrozole, 2.5 mg of letrozole, and either megestrol acetate (MA) or aminoglutethimide. In the megestrol trial, 2.5 mg/day letrozole was superior to 0.5 mg of letrozole and MA (RRs 24, 13, and 16%, respectively), whereas in the aminoglutethimide trial, there was no significant difference in 2.5 mg of letrozole and 0.5 mg of letrozole RRs (20 and 17%). There was a trend toward RR superiority of 2.5 mg of letrozole over aminoglutethimide (P = 0.06). Letrozole (2.5 mg) was the dose chosen for comparison with tamoxifen in the first-line setting.

In July 2000, a marketing application for first-line letrozole treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer was submitted to the FDA. A single double-blind, double dummy, randomized, and multicenter trial compared 2.5 mg of letrozole to 20 mg of tamoxifen (456 patients/arm). Letrozole was superior to tamoxifen with regard to time to progression (TTP) and objective response rate (RR). The median TTP for letrozole treatment was 9.9 months [95% confidence interval (CI) 9.1–12.2] versus 6.2 months (95% CI 5.8–8.5) for tamoxifen, P = 0.0001, hazard ratio 0.713, (95% CI 0.61–0.84). RR was 32% for letrozole versus 21% for tamoxifen (odds ratio 1.74, 95% CI 1.29–2.34, P = 0.0003). Preliminary survival data (survival data are still blinded) indicate that letrozole is unlikely to be worse than tamoxifen. Both treatments were similarly tolerated.

On the basis of these results, the United States FDA approved letrozole tablets, 2.5 mg/day, for first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer. The manufacturer made a commitment to provide updated information on survival.

Introduction

In January 2001, FDA approved letrozole (Femara; Novartis Pharmaceuticals Corp., East Hanover, NJ) for first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer. Letrozole was shown to be more effective (RR and TTP) than tamoxifen in this patient group.

Letrozole is a nonsteroidal aromatase inhibitor. It lowers serum estrogen levels by inhibiting the peripheral conversion of androgens to estrogens. The source of estrogen, a growth promoter for many breast cancers, depends on a woman’s menopausal status. In premenopausal women, estrogens are of ovarian origin predominately; in postmenopausal women, estrogens primarily derive from conversion of circulating androgens to estrogens (Fig. 1).

The aromatase enzyme complex consists of two components: aromatase cytochrome P-450 (P-450arom) and NADH diphosphate-cytochrome P-450 reductase. The cytochrome P-450arom component binds the androgen substrates, which are then reduced, in the presence of molecular oxygen, by the transfer of reducing equivalents from NADPH by cytochrome P-450 reductase (1, 2).

Aromatase inhibitors can be steroidal or nonsteroidal molecules. The former bind to the substrate-binding site of the enzyme, whereas the latter interact with the heme group of the cytochrome P450 component of the enzyme. Steroidal inhibi-
tors, in the absence of substrate, generally attach to the enzyme irreversibly; nonsteroidal inhibitor binding is, in contrast, generally reversible and is dependent on the agent’s continued presence. Steroidal aromatase inactivators include exemestane, formestane, and 4-hydroxy-androstenedione. Nonsteroidal inactivators include letrozole, anastrozole, fadrozole, and vorozole (1, 3, 4).

Aromatase activity can be demonstrated in many peripheral tissues, including adipose tissue, skin fibroblasts, muscle, bone, and brain. Approximately two-thirds of human breast cancers contain measurable aromatase activity (5–8).

Preclinical Pharmacology/Toxicology

Single dose letrozole toxicology studies were performed in mice, rats, and beagle dogs. In the mouse, the LD₅₀ was >2,000 mg/m²; in the rat, it was >12,000 mg/m²; and in the beagle dog, it was ~3,000 mg/m². Acute toxicities included reduced motor activity, hypothermia, recumbency, piloerection, irregular respiration, skin, and mucosal hyperemia with complete recovery of all toxicities in surviving animals and no findings on necropsy. In subacute toxicology studies (14 days to 3 months), females of all species showed signs of estrogen deprivation, including disturbed estrous cycle, cystic and atretic ovarian follicles, decreased uterine weight, and vaginal atrophy. As the letrozole dose and length of drug exposure increased, the severity of these signs increased. In males of each species, signs of testosterone deprivation (presumably secondary to increased luteinizing hormone release inhibiting pituitary gonadotropins) occurred, including decreases in hemoglobin, decreases in testicular weight, spermatic tubular atrophy, epididymal oligospermia, and testicular interstitial cell hyperplasia.

With longer dosing (3 months to 1 year) in the rat and dog, additional changes were noted. In females, ovarian interstitial cell hyperplasia, mammary duct gland hyperplasia with increased secretions, decreased bone density, adenopituitary hyperplasia, hypertrophy of thyroid follicular cells, thymic atrophy, increase in serum cholesterol, elevated liver enzymes, and hepatocellular hypertrophy were observed. In males, prostatic atrophy, decreased mammary gland proliferation, decreased bone density, and adenopituitary hyperplasia also occurred. In both species, higher drug doses were associated with hepatic and renal tubular damage, the latter apparently related to hypercalcemia because of bone resorption.

Two-year murine carcinogenicity studies showed an increased rate of benign ovarian theca cell tumors at doses > 60 mg/kg (180 mg/m²) and a decreased rate of benign and malignant mammary gland tumors. In reproductive toxicology studies, maternal toxicity was reported at all doses, with embryo and fetal toxicity at doses ≥ 0.03 mg/kg (0.09 mg/m²). In the rat study, comparable toxicity was observed at doses of 0.03 mg/kg (0.18 mg/m²). Similar findings were observed in rabbits at doses ≥ 0.066 mg/m². Mutagenicity testing was negative.

In studies with 7,12 dimethylbenz[a]anthracene and methyl nitrosourea-induced estrogen-dependent mammary carcinomas, letrozole caused tumor regression of established tumors and suppressed new tumor development. In a study comparing letrozole to anastrozole in the above tumor models, letrozole slowed tumor growth, whereas comparable doses of anastrozole had little effect (9).

Biopharmaceutics

Letrozole is completely and rapidly absorbed from the gastrointestinal tract. Absorption is not affected by food (10). Once absorbed, it is rapidly and extensively distributed into tissues (volume of distribution at steady state is ~2 liters/kg). Letrozole is eliminated mainly by metabolism. The major metabolite, which does not inhibit aromatase, is 4’-methanobisbenzonitrile. This metabolite is glucuronidated and excreted primarily in the urine. Neither renal impairment (creatinine clearance < 9 ml/min) nor moderate hepatic impairment (Child-Pugh classification A and B) significantly influences letrozole pharmacokinetic parameters. Letrozole pharmacokinetics were not altered by age (range 35 to >80 years); the effects of race have not been studied.

In postmenopausal patients with advanced breast cancer, daily letrozole doses of 0.1–5 mg suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75–95%, with maximal suppression within 2–3 days. Suppression is dose related, with doses of ≥0.5 mg often reducing estrone and estrone sulfate levels to below the limit of detection. Estrogen suppression was maintained throughout treatment in all patients given ≥0.5 mg. At a clinically used dosage, letrozole does not impair adrenal synthesis of glucocorticoids or aldosterone (2).

Clinical Trials

Letrozole was studied initially in six single arm (Phase I/II) trials, including 181 postmenopausal patients with advanced breast cancer. Patients who were hormone receptor positive or unknown and who had been treated previously with hormonal therapy(ies) and possibly chemotherapy received letrozole doses of 0.1–5 mg/day. The studies were intended to: (a) determine the minimally effective dose of letrozole that achieved maximal estrogen suppression; (b) determine the effects of letrozole on other hormones (cortisol, 17-hydroxyprogesterone, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and androstenedione); (c) describe letrozole’s phar-
macokinetics; (d) assess letrozole’s tolerability and toxicity; and (e) obtain preliminary data on antitumor activity.

Significant suppression of serum and urine estrogen levels (>95%) was observed after 2 weeks of therapy at each letrozole dose level. There were no significant changes in adrenal steroid levels nor in thyroid hormone levels. Objective responses were observed, and side effects were tolerable (generally grade 1 and 2, National Cancer Institute Common Toxicity Criteria scale) (11–14).

Two small randomized trials of 0.5 and 2.5 mg/day letrozole have been performed. The first, from Europe (15), included 46 patients, 22 women randomized to 0.5 mg of letrozole and 24 to the higher dose. All patients had progressed on one prior antiestrogen therapy, and all had measurable or evaluable disease. After 2 weeks of letrozole treatment, serum estrogen levels were significantly reduced in both groups. By 4 weeks, 24% of women in the low-dose group and 28% of women in the higher dose group had nondetectable estrogen levels. Neither letrozole dose affected basal or stimulated cortisol or aldosterone plasma levels. Plasma levels of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone were not changed in either group. Sex hormone-binding globulin, follicle-stimulating hormone, and luteinizing hormone levels increased significantly over time. Two complete responses were noted in each treatment group, and an additional 2 women receiving 0.5 mg/day letrozole had partial responses. Median response duration was >170 days, and median TTP was ~100 days.

The second small randomized trial was conducted in the United States (16). Ninety-one women with metastatic breast cancer who had failed two prior hormonal regimens and had measurable or evaluable disease were enrolled, 46 receiving 0.5 mg of letrozole and 45 receiving 2.5 mg of letrozole daily. RRs (documented on two occasions separated by 3 months) were 13 and 18% for the 0.5 and 2.5 mg of letrozole doses, respectively. Median TTP was 97 days for the lower dose and 154 days for the higher dose. Both doses produced acceptable toxicity.

Second-line Trials

Two large randomized trials comparing 0.5 mg and 2.5 mg of letrozole to either aminoglutethimide (17) or MA (18) for the treatment of advanced breast cancer in postmenopausal women with disease progression after antiestrogen therapy (i.e., “second-line” treatment) were submitted.

Both trials included postmenopausal women with advanced breast cancer and positive or unknown hormone receptor status who had failed one prior antiestrogen treatment and had a WHO performance status ≤ 2.

The first study was an open-label multicenter trial that randomized 555 patients to 0.5 (n = 192) and 2.5 mg (n = 185) of letrozole and 250 mg of aminoglutethimide twice daily plus 30 mg of hydrocortisone daily or 37.5 mg of cortisol acetate (n = 178). Objective tumor response (complete or partial), the primary study end point, was seen in 19.5% of patients on 2.5 mg of letrozole, 16.7% of patients on 0.5 mg of letrozole, and 12.4% of patients on aminoglutethimide. These differences were not statistically significant, although there was a trend favoring 2.5 mg of letrozole over aminoglutethimide, *P* = 0.06.

TTP was assessed after ≥80% of patients in each arm had progressed. Cox regression indicated significant superiority of 2.5 mg of letrozole to aminoglutethimide, risk ratio 0.72 (95% CI 0.57–0.92), *P* = 0.008. There was no significant difference between the two letrozole arms. Median TTP was similar for all three treatments (3.2–3.4 months).

Survival analysis was conducted at a time when ~60% of the study population had died. Survival was significantly improved in the 2.5 mg of letrozole group compared with aminoglutethimide (*P* = 0.002) and to 0.5 mg of letrozole (*P* = 0.04). Median survival was 28 months for 2.5 mg of letrozole, 21 months for 0.5 mg of letrozole, and 20 months for aminoglutethimide.

The principle letrozole toxicity was transient nausea. Other letrozole toxicities, occurring in ≥5% of patients, included abdominal pain, asthenia, somnolence, and dyspepsia. One patient on 0.5 mg of letrozole developed deep vein thrombosis.

The second study was a double-blind multicenter trial that randomized 555 patients to 0.5 (n = 188) or 2.5 mg (n = 174) of letrozole or 160 mg of MA (n = 189). Objective tumor response, the primary study end point, was documented in 23.6% of patients on 2.5 mg of letrozole, 12.8% of patients on 0.5 mg of letrozole, and 16.4% of patients on MA. Letrozole (2.5 mg) RR was superior to 0.5 mg of letrozole (*P* = 0.004) and to MA (*P* = 0.04).

TTP was assessed after ≥68% of patients in each arm had progressed. Cox regression analysis indicated significant superiority of 2.5 to 0.5 mg of letrozole, risk ratio 1.35, 95% CI 1.04–1.75 (*P* = 0.02), and a trend favoring 2.5 mg of letrozole over MA. Median TTP was similar for all three treatments (5.1–5.6 months).

 Survival analysis was conducted at a time when ~67% of the study population had died. Survival was significantly improved in the 2.5 mg of letrozole group compared with 0.5 mg of letrozole (*P* = 0.03). There was no significant survival difference between either letrozole dose and MA. Median survival was 25.3 months for 2.5 mg of letrozole, 21.5 months for 0.5 mg of letrozole, and 21.5 months for MA.

The principle letrozole toxicity was transient nausea. Other letrozole toxicities, occurring in ≥5% of patients, included abdominal pain, asthenia, somnolence, and dyspepsia. One patient on 0.5 mg of letrozole developed deep vein thrombosis.

First-line Indication

A single large randomized trial supported the effectiveness of letrozole for first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor-unknown advanced or metastatic breast cancer. This was a double-blind, double-dummy, randomized, multicenter, and two-arm trial comparing 2.5 mg of letrozole daily to 20 mg of tamoxifen (Tamofen) daily. Tamofen, manufactured in Finland, has been shown bioequivalent to Nolvadex. Letrozole and its placebo and tamoxifen and its placebo were of identical outward appearance and taste. A total of 939 patients was randomized in 201 sites in 29 countries.

The primary effectiveness measure was TTP. Secondary measures included objective RR (complete response + PR) and duration, overall survival, and TTF. On progression of disease or any other reason leading to discontinuation of initial treatment, patients, who remained suitable candidates for endocrine anticancer treatment, could be switched to the alternative treatment, still under double-blind conditions.

Initially, there were three treatment arms: (a) 2.5 mg of
letrozole; (b) 20 mg of tamoxifen; and (c) 2.5 mg of letrozole in combination with 20 mg of tamoxifen. It was planned to enroll a minimum of 1371 patients; 457 patients in each treatment arm. The combination treatment arm was eliminated early because of a pharmacokinetic interaction between tamoxifen and letrozole; adding tamoxifen to letrozole lowered mean letrozole blood levels (area under the curve) by ~38% (19).

The study was conducted in postmenopausal women with histological or cytological evidence of breast cancer presenting with locally advanced or locoregionally recurrent disease not amenable to treatment by surgery or by radiotherapy or with metastatic disease. Patients were not to have been treated previously with endocrine anticancer agents for their advanced disease but could have received adjuvant antioestrogen treatment provided they had both a treatment-free interval and disease-free interval of ≥12 months between the end of adjuvant treatment and entry into the study. Patients could have received adjuvant chemotherapy but no more than one regimen of chemotherapy and entry into the study. Patients could have received adjuvant chemotherapy but no more than one regimen of chemotherapy in the advanced disease setting. Patients had to be estrogen-receptor and/or progesterone-receptor positive or have the status of both receptors unknown, with measurable or evaluable disease (patients with blastic bone lesions only could be enrolled) and a Karnofsky performance status of ≥50%.

The primary ITT analysis included all patients randomized to the two monotherapy treatments, excluding only 4 patients from one center that had not complied with good clinical practice regulations and 5 patients proved not to have active cancer. The ITT population includes 2 patients (1 on each treatment arm) who never received any dose of study medication. A total of 907 patients is included in the ITT efficacy population (453 assigned letrozole and 454 assigned tamoxifen).

Tumor evaluations were performed every 3 months. Response criteria had to be met on two consecutive visits at least 1 month apart before an objective response was declared to have occurred.

The letrozole and tamoxifen treatment arms were well balanced with respect to baseline demographic characteristics, extent of disease, and prior therapy (Table 1). Efficacy results are shown in Table 2. Letrozole was superior to tamoxifen with regard to TTP and objective RR. The median TTP for letrozole was 9.9 months (95% CI 9.1–9.8) and for tamoxifen was 6.2 months (95% CI 5.8–6.5; \( P = 0.0001 \), hazard ratio 0.713, 95% CI 0.61–0.84). Objective RR was also greater with letrozole, 32% versus 21% \( P = 0.0003 \), odds ratio 1.74, 95% CI 1.29–2.34), and results were consistent for women with hormone receptor-positive tumors and with unknown receptor status. Data on TTF were not considered in the efficacy analysis. TTF is a composite end point reflecting both efficacy and tolerability and is not considered a useful end point for evaluation of effectiveness.

The FDA, in an exploratory analysis, also examined the effect of therapy on improvement in performance status. The criterion for improvement was ≥10 point increase in Karnofsky performance status maintained for at least two consecutive visits. In this analysis, 110 of 344 letrozole-treated patients (32%) improved during treatment as compared with 65 of 336 (19%) given tamoxifen.

Survival data are not yet mature, and the study remains blinded to treatment. Available survival information indicates that letrozole is unlikely to be worse than tamoxifen.

### Safety

Adverse events (all reported without assessment of causality) were reported for 90% of patients in the letrozole arm and 87% of patients in the tamoxifen arm and were generally similar for the two treatments. Adverse events reported by >10% of patients for letrozole and tamoxifen, respectively, were bone pain (20 and 18%), back pain (21% and 19%), nausea (15 and 16%), dyspnea (14 and 14%), arthralgia (13 and 12%), cough (9 and 10%), and fatigue (11 and 11%). Without a no-treatment group, it is not possible to tel how many of these events were caused by the drug and how many were associated with the underlying disease.

Other less frequent (<2%) adverse experiences, considered clinically important and seen approximately equally in both treatment groups, included peripheral thromboembolic events, cardiovascular events, and cerebrovascular events. Peripheral thromboembolic events included venous thrombosis, thrombophlebitis, portal vein thrombosis, and pulmonary embolism. Cardiovascular events included angina, myocardial infarction, myocardial ischemia, and coronary heart disease. Cerebrovascular events included transient ischemic attacks, thrombotic, or hemorrhagic strokes and development of hemiparesis.

Bone fractures were also approximately equally frequent in the two groups; 21 letrozole-treated patients had a total of 26 fractures compared with 20 fractures in 18 tamoxifen-treated patients. Most of the fractures appeared to be disease related rather than osteoporotic.

### Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Letrozole (n = 456)</th>
<th>Tamoxifen (n = 456)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>65 (31–96)</td>
<td>64 (31–93)</td>
</tr>
<tr>
<td>&lt;50 (no. of pts)</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>&gt;70 (no. of pts)</td>
<td>139</td>
<td>134</td>
</tr>
<tr>
<td>Median BMI (range)</td>
<td>25.9 (14.6–44.5)</td>
<td>25.5 (15.6–52.7)</td>
</tr>
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<td>&gt;30 (no. of pts)</td>
<td>85</td>
<td>78</td>
</tr>
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<td>ER+ and/or PR</td>
<td>296 (65%)</td>
<td>308 (68%)</td>
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<tr>
<td>ER and PR unknown</td>
<td>160 (35%)</td>
<td>148 (32%)</td>
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<tr>
<td>Prior adjuvant therapy</td>
<td>171 (38%)</td>
<td>183 (40%)</td>
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<tr>
<td>Chemotherapy only</td>
<td>74</td>
<td>90</td>
</tr>
<tr>
<td>Hormonal therapy only</td>
<td>68</td>
<td>58</td>
</tr>
<tr>
<td>Both</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td>Prior antiestrogens</td>
<td>86 (19%)</td>
<td>83 (18%)</td>
</tr>
<tr>
<td>Prior advanced disease</td>
<td>27 (6%)</td>
<td>25 (6%)</td>
</tr>
<tr>
<td>chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of antiestrogen Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 years</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>≤2 years</td>
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<td>61</td>
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<tr>
<td>Dominant disease site</td>
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<tr>
<td>Soft tissue</td>
<td>120 (26%)</td>
<td>124 (27%)</td>
</tr>
<tr>
<td>Bone</td>
<td>153 (34%)</td>
<td>136 (30%)</td>
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<tr>
<td>Visceral</td>
<td>183 (40%)</td>
<td>196 (43%)</td>
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<tr>
<td>Liver</td>
<td>61</td>
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<tr>
<td>Performance status</td>
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<tr>
<td>100</td>
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<tr>
<td>90</td>
<td>141 (31%)</td>
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<tr>
<td>80</td>
<td>120 (26%)</td>
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<tr>
<td>70</td>
<td>53 (12%)</td>
<td>40 (9%)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>30 (6%)</td>
<td>39 (8%)</td>
</tr>
</tbody>
</table>

*a BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.*
Regulatory Decision

The criteria for approval by FDA of hormonal agents as compared with cytotoxic agents for initial treatment of advanced, metastatic breast cancer have been different. For cytotoxic drugs, a favorable effect on survival in randomized controlled trials is usually required. When this issue was discussed with the FDA in June 1999, there was consensus that a favorable effect on TTP and/or tumor RR was not adequate for first-line cytotoxic drug approval. The Committee thought that a substantial improvement of TTP in the range of 4–6 months could be adequate for accelerated approval with a Phase IV commitment to demonstrating survival benefit.

In contrast, a favorable effect on tumor response or TTP in randomized controlled trials has been considered adequate evidence of effectiveness for approval of hormonal drugs for initial treatment of metastatic breast cancer. The acceptance of the surrogate end points has been based on the modest toxicity of hormonal agents compared with cytotoxics and because survival benefit for hormonal agents in metastatic breast cancer has not been demonstrated. Whereas demonstration of superior survival to a control or formal assessment of noninferiority to active agent(s) is not required, survival data are examined at the time of approval to see whether survival data are against the new hormonal drug.

Letrozole was superior to tamoxifen for both RR and TTP in the large, double-blind, double-dummy, and randomized trial summarized in this study and was as well tolerated as tamoxifen. On January 10, 2001, letrozole was approved by the United States FDA for first-line hormonal treatment of postmenopausal women with estrogen and/or progesterone receptor-positive or -unknown locally advanced or metastatic breast cancer. Letrozole had been approved previously for the treatment of advanced breast cancer in postmenopausal women with disease progression after antiestrogen therapy.

References

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*Clin Cancer Res* 2002;8:665-669.

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