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# Letrozole

## In Postmenopausal Hormone-Responsive Early-Stage Breast Cancer

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## Abstract

▲ Letrozole is a highly selective, nonsteroidal, third-generation aromatase inhibitor approved for first-line and extended adjuvant therapy in postmenopausal women with hormone-responsive, early-stage breast cancer. Binding of letrozole to the haeme component of the cytochrome P450 subunit of aromatase inhibits estrogen biosynthesis throughout the body.

▲ As first-line adjuvant therapy in ≈8000 postmenopausal women with hormone-responsive, early-stage breast cancer, once-daily letrozole 2.5mg significantly prolonged disease-free survival (DFS; primary endpoint) and reduced the risk of relapse at distant sites relative to once-daily tamoxifen 20mg in the ongoing Breast International Group 1-98, double-blind, multinational trial. The median duration of follow-up for this primary core analysis was 25.8 months.

▲ Extended adjuvant therapy with once-daily letrozole 2.5mg significantly prolonged DFS relative to placebo treatment at a median follow-up of 30 months (primary endpoint) in the MA-17 trial in ≈5000 postmenopausal women who were disease free after 4.5–6 years of tamoxifen therapy for hormone-responsive, early-stage breast cancer.

▲ Letrozole treatment for up to 5 years was generally well tolerated in this clinical setting. As first-line treatment, relative to tamoxifen, letrozole was associated with a significantly lower incidence of venous thromboembolitic events, vaginal bleeding, hot flushes and night sweating, whereas the incidence of cardiac failure, bone fractures and arthralgia was higher in letrozole recipients.

| Features and properties of letrozole (Femara®) | |
|---|---|
| **Featured indication** | |
| Hormone-responsive, early-stage breast cancer in postmenopausal women | |
| **Mechanism of action** | |
| Nonsteroidal aromatase inhibitor | |
| **Dosage and administration** | |
| Usual dose | 2.5mg |
| Route of administration | Oral |
| Frequency of administration | Once daily |
| **Pharmacokinetic profile (oral single 2.5mg dose in postmenopausal women with advanced breast cancer)** | |
| Peak plasma concentration | 107 nmol/L |
| Time to peak plasma concentration | 2h |
| Area under the plasma concentration-time curve | 7387 nmol • h/L |
| Elimination half-life (multiple doses) | 118h |
| **Adverse events (incidence ≥5% as first-line therapy)** | |
| Most frequent | Hot flushes, arthralgia, night sweating, myalgia, bone fractures |

Breast cancer, the most commonly diagnosed cancer in women in Westernised countries, predominantly occurs in postmenopausal women and is associated with a lifetime risk of approximately one in nine.[1] The role of estrogens in the development of breast cancer is well established, with the majority (≈70%) of postmenopausal women having hormone receptor-positive tumours.[1] Hence, agents that reduce circulating estrogen levels and thereby decrease stimulation of estrogen-dependent tumours play a key role in the management of breast cancer.[1-5]

Tamoxifen, a selective estrogen receptor modulator, has been the gold standard for adjuvant care in patients with hormone-responsive early-stage breast cancer for the last 2 decades. However, results from recent large well designed trials mean that aromatase inhibitors, such as letrozole (Femara®)[1] and anastrozole, are challenging this position of tamoxifen as the gold standard for adjuvant treatment in this setting.[1-5]

Letrozole, a third-generation, nonsteroidal aromatase inhibitor, is approved in numerous countries worldwide for first- and second-line treatment of advanced breast cancer in postmenopausal women; these data have been reviewed previously[6-8] and are not discussed further. This article focuses on the clinical use of letrozole as first-line or extended adjuvant therapy in postmenopausal women with hormone-responsive, early-stage breast cancer. All agents were administered orally unless stated otherwise.

## 1. Pharmacodynamic Profile

The pharmacodynamic properties of letrozole are well established[6-11] and are briefly reviewed here.

- Letrozole, a highly specific, nonsteroidal, competitive aromatase inhibitor, binds to the haeme component of the cytochrome P450 (CYP) subunit of the enzyme, thereby inhibiting the conversion of androgens to estrogen and, as a consequence, estrogen biosynthesis in all tissues.[6-11] In preclinical and clinical studies, letrozole potently inhibited plasma levels of estrone, estradiol and estrone sulphate, whilst it had no effect on plasma concentrations of adrenal corticoids, aldosterone or thyroid hormones.[6-11]

- In 12 postmenopausal women with metastatic breast cancer, once-daily letrozole 2.5mg was more effective than once-daily anastrozole 1mg in reducing mean plasma estrone (by 84.3% vs 81.0%, $p = 0.019$) and estrone sulphate levels (98.0% vs 93.5%, $p = 0.0037$) in a crossover study, although there was no between-group difference in reductions in estradiol levels (87.8% vs 84.9%).[12] Moreover, total body aromatisation was suppressed to a significantly greater level in letrozole recipients (>99.1% vs 97.3% with anastrozole, $p = 0.0022$).[12] Whether these small, but significant, differences in inhibition are clinically relevant remains to be determined.

- Letrozole, but not tamoxifen, significantly ($p < 0.0001$) reduced cellular markers of proliferation in human estrogen-dependent tumours that over expressed human epidermal growth factor receptor (HER) 1 and/or HER2.[13] Letrozole also demonstrated antitumour activity in ovariectomised mouse models of postmenopausal estrogen-dependent breast cancer.[6]

- In a companion study (MA-17B) of the MA-17 trial in patients who had previously received ≥5 years of tamoxifen adjuvant therapy (section 3), extended adjuvant therapy with once-daily letrozole 2.5mg ($n = 122$) increased bone resorption relative to placebo ($n = 104$) [abstract presentation].[14] After 2 years of extended adjuvant therapy, letrozole recipients experienced a significant reduction from baseline in total hip (−3.6 at baseline vs −0.71, $p < 0.05$) and lumbar spine (−5.35 at baseline vs −0.7, $p < 0.01$) bone mineral density (BMD; primary endpoint). No patients experienced a reduction in BMD in the hip below the osteoporotic threshold (i.e. T score ≤−2.5 SD below the mean peak bone mass for young normal women) after 2 years, nor was there a significant between-group difference in the percentage of patients who became osteoporotic at the L2-4 spine based on BMD criteria (3.3% vs

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

0% of placebo recipients). Urine levels of the bone resorption marker *N*-telopeptide were significantly increased from baseline at 12 and 24 months (both $p < 0.02$; no further data reported). All patients received calcium 500 mg/day and vitamin D 400 IU/day.[14]

- These data are supported by studies in postmenopausal women with a history of breast disease but without recurrent disease and in healthy postmenopausal women that showed letrozole increased levels of bone resorption markers.[6]
- In another long-term companion study (MA-17L) of the MA-17 trial (section 3), extended-adjuvant therapy with once-daily letrozole 2.5mg (n = 183) did not significantly alter serum lipid parameters relative to placebo (n = 164) after 36 months' treatment.[15] At this timepoint, mean fasting total cholesterol levels were increased by 10.5% versus 8.4% (baseline 5.35 vs 5.51 mmol/L), low-density lipoprotein cholesterol-C levels by 20.7% versus 18.2% (baseline 3.02 vs 3.22 mmol/L) and triglyceride levels by 8.4% versus 3.1% (baseline 2.17 vs 3.01 mmol/L) in the letrozole and placebo groups.[15] Letrozole had minimal effects on serum lipid levels in small short-term studies in healthy women and in postmenopausal women with breast cancer.[6]
- In contrast to tamoxifen, transvaginal ultrasonography indicated that letrozole was not associated with abnormalities in endometrial growth after 3 months' treatment (section 4).[16] There were no changes from baseline in mean double endometrial thickness (DET; 2.54 vs 2.28mm at baseline) and uterine volume (34 vs 34 $cm^3$) in letrozole recipients (n = 9), whereas tamoxifen recipients (n = 20) experienced significant increases in mean DET (6.30 vs 3.82mm at baseline, $p < 0.0001$) and uterine volume (84 vs 61 $cm^3$, $p < 0.01$).[16]

## 2. Pharmacokinetic Profile

The pharmacokinetic properties of letrozole in postmenopausal women with or without breast cancer are well established.[6-8,17] These data are briefly summarised here.

- Letrozole is rapidly and almost completely (99.9% absolute bioavailability) absorbed in the gastrointestinal tract after a single 2.5mg dose, with no influence of food.[6-8,17,18] In 27 postmenopausal women with advanced breast cancer, mean peak plasma concentration ($C_{max}$) and the area under the plasma concentration-time curve extrapolated to infinity ($AUC_\infty$) values were 107 nmol/L and 7387 nmol • h/L after a single 2.5mg dose, with $C_{max}$ attained in a median of 2 hours.[19]
- At steady state, letrozole demonstrates slightly nonlinear pharmacokinetics; steady-state $C_{max}$ values were approximately 1.5–2 times higher than those achieved after a single dose[20] and $AUC_\infty$ values increased by 28%.[19] Steady-state $C_{max}$ values are attained in 2–6 weeks and are maintained for extended periods.[20]
- The large volume of distribution at steady state (1.87 L/kg after a 3-minute intravenous infusion) indicates that letrozole is extensively distributed in tissues.[6,17] The drug is approximately 60% bound to plasma proteins.[6,17]
- Letrozole is converted to the pharmacologically inactive carbinol metabolite 4,4′-methanol-bisbenzonitrile by CYP3A4 and CYP2A6 isoenzymes, with the glucuronide conjugate of this metabolite eliminated primarily in the urine.[6,17,20] After a radiolabelled dose of letrozole, approximately 90% of the dose was eliminated renally, with at least 75% of this being the glucuronide of the carbinol metabolite.[6,20] The mean terminal elimination half-life after multiple 2.5mg doses was 118 hours in postmenopausal women with advanced breast cancer.[19]
- Pharmacokinetic parameters of letrozole are not affected by age (adults aged 35 to >80 years) or renal impairment.[20] Nor were there any clinically relevant affects on these parameters in patients with mild to moderate hepatic impairment (Child Pugh A or B).[20] However, in those with liver cirrhosis and severe hepatic impairment (Child Pugh C), AUC increased 2-fold and systemic clearance was reduced by 47%, with a 50% dosage reduction recommended in these patients.[20]
- Concomitant letrozole had no affect on the pharmacokinetics of warfarin, nor were there any

changes in the pharmacokinetic parameters of letrozole when the drug was coadministered with cimetidine.[20] Concomitant letrozole and tamoxifen reduced plasma levels of letrozole by an average of 38%, although this had no impact on the clinical efficacy of letrozole.[20]

## 3. Therapeutic Efficacy

### First-Line Adjuvant Therapy

The 5-year BIG 1-98 (Breast International Group 1-98) randomised, double-blind, multinational trial compared first-line adjuvant letrozole monotherapy with tamoxifen monotherapy, and also sequential therapy in either order, in postmenopausal women with hormone receptor-positive, early-stage breast cancer.[21] In the sequential therapy arms, patients received once-daily letrozole 2.5mg for 2 years followed by once-daily tamoxifen 20mg for 3 years or vice versa; recipients in the monotherapy arms received the same dosages of letrozole or tamoxifen for 5 years. As per protocol, the primary core analysis of this ongoing trial combined the letrozole or tamoxifen monotherapy arm with the corresponding truncated sequential arm (i.e. excluding events and follow-up occurring >30 days after switching to the other treatment) [letrozole intent-to-treat group = 4003 patients; tamoxifen group n = 4007]. The median follow-up was 25.8 months.[21]

Eligible women (mean age 61 years; range 38–90 years) were postmenopausal (96% prior to chemotherapy, if received, and 2.4% after chemotherapy), had tumours that were estrogen- and/or progesterone-receptor positive, had had primary surgery with clear margins and had adequate haematological, renal and hepatic function.[21] Exclusion criteria included presence of metastatic disease, previous or concurrent malignancy (except adequately-treated non-invasive breast or cervical cancer or basal or squamous cell carcinoma of the skin) within 5 years prior to randomisation, ≥1 months' prior adjuvant anti-estrogen therapy for primary breast cancer and treatment with systemic or topical investigational drugs 30 or 7 days prior to randomisation. There were no between-group differences in baseline characteristics.

The primary endpoint was disease-free survival (DFS), defined as the time from randomisation to the first event of recurrence in local, regional or distant sites, a new invasive breast cancer in the contralateral breast, any secondary non-breast malignancy or death from any cause.[21] Secondary endpoints included overall survival (i.e. the time from randomisation to death from any cause), systemic DFS (excluding local and contralateral breast events), time to recurrence and time to distant recurrence.

- In the per protocol, primary core analysis, DFS was significantly longer in the letrozole than tamoxifen group based on Kaplan Meier estimates (primary endpoint), with letrozole recipients experiencing significantly fewer DFS events (figure 1).[21] Secondary endpoint analyses also generally favoured letrozole (figure 1), including a reduction in the risk of a relapse at distant sites by 27% with letrozole treatment (hazard ratio [HR] 0.73; see time to distant recurrence in figure 1). Numerically fewer women died in the letrozole than tamoxifen group (166 vs 192 patients), although there was no statistical difference in terms of overall survival (figure 1).[21]

- In prospectively planned subgroup analyses, there were significantly (all $p < 0.05$) fewer DFS events in letrozole than tamoxifen recipients who were aged <65 (n = 5143; 187 vs 230 events; HR 0.82; 95% CI 0.67, 0.99) or ≥65 years (n = 2867; 164 vs 198 events; HR 0.79; 95% CI 0.64, 0.97), had a tumour >2cm (n = 2973; 190 vs 251 events; HR 0.76; 95% CI 0.63, 0.92), were node positive (n = 3311; 205 vs 274 events; HR 0.71; 95% CI 0.59, 0.85), had a mastectomy (n = 3452; 223 vs 271 events; HR 0.76; 95% CI 0.64, 0.91), had received (n = 5744; 227 vs 273 events; HR 0.82; 95% CI 0.69, 0.98) or did not receive radiotherapy (n = 2258; 124 vs 155 events; HR 0.77; 95% CI 0.61, 0.98) or had been given chemotherapy (n = 2024; 92 vs 126 events; HR 0.70; 95% CI 0.54, 0.92).[21]

- Moreover, the magnitude of the beneficial reduction in the risk of disease recurrence with letrozole

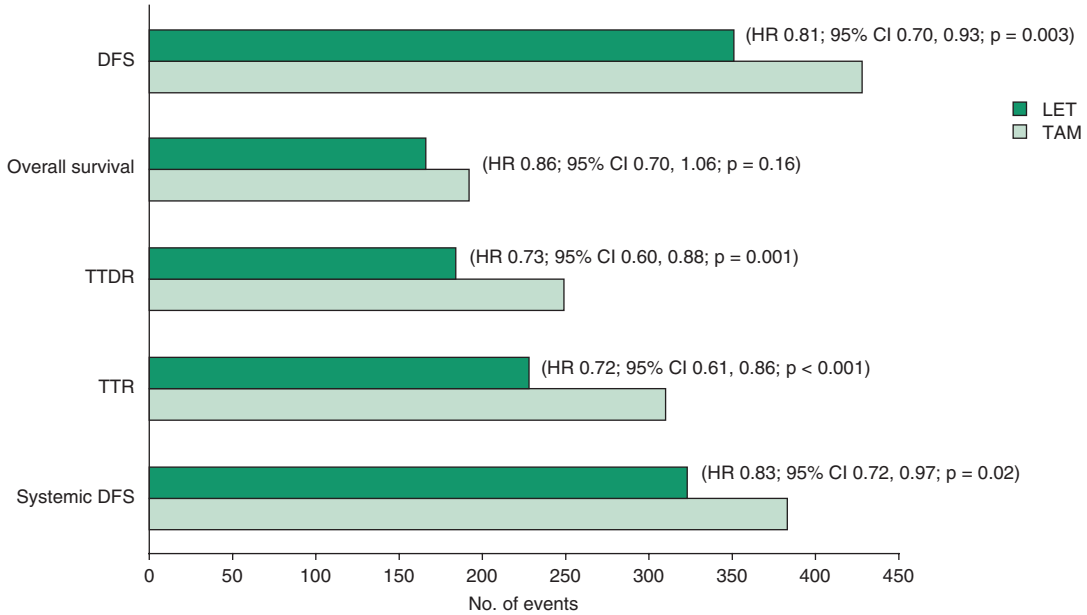


**Fig. 1.** Comparative efficacy of letrozole (LET) in postmenopausal women with hormone-responsive, early-stage breast cancer at a median follow-up of 25.8 months. In this 5-year, randomised, double-blind, multinational trial (Breast International Group 1-98 trial), patients received once-daily LET 2.5mg or tamoxifen (TAM) 20mg for 5 years or sequential therapy with the same dosages of LET for 2 years followed by TAM for 3 years or vice versa.[21] In this per protocol, primary core analysis, the LET or TAM monotherapy arm was combined with the corresponding truncated sequential arm (i.e. excluding events and follow-up occurring more than 30 days after switching to the other treatment) [LET intent-to-treat group = 4003; TAM group = 4007 patients]. DFS, as defined in the text, was the primary endpoint. **DFS** = disease-free survival; **HR** = hazard ratio; **TTDR** = time to distant recurrence; **TTR** = time to recurrence.

treatment was similar in estrogen receptor-positive women, irrespective of whether they were progesterone receptor (PR)-positive (179 vs 208 events with tamoxifen; DFS HR 0.84; 95% CI 0.69, 1.03, p = 0.09), PR-negative (89 vs 107 events; DFS HR 0.83; 95% CI 0.62, 1.10, p = 0.18) or PR status unknown (70 vs 92 events; DFS HR 0.72; 95% CI 0.53, 0.98, p = 0.04).[21] The beneficial effect of letrozole on DFS in estrogen receptor-positive women, irrespective of their PR status, was also shown in a subsequent reanalysis of data conducted after the receptor status of the tumours had been centrally reassessed by the IBCSG (International Breast Cancer Study Group) Central Pathology Laboratory using immunohistochemistry.[22]

### Extended Adjuvant Therapy

Extended adjuvant therapy with letrozole was evaluated in a randomised, double-blind, multicentre trial (MA-17) in postmenopausal women who were disease-free after receiving 4.5–6 years of tamoxifen therapy for hormone receptor-positive, early-stage breast cancer;[23-25] some data are available as oral presentations.[26,27] Women were eligible for enrolment if at the start of tamoxifen therapy they were ≥50 years of age, ≤50 years of age but had undergone bilateral oophorectomy, premenopausal and ≥50 years of age but were amenorrhic during chemotherapy or tamoxifen therapy, or if they had postmenopausal levels of luteinising hormone or follicle-stimulating hormone. Other eligibility criteria included discontinuation of tamoxifen therapy within 3 months of study entry, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a life-expectancy of >5 years. Patients received once-daily letrozole 2.5mg (n = 2575 in the intent-to-treat population) or placebo (n = 2582). The primary endpoint was DFS; per protocol definition was the time from randomisation to the recurrence of primary disease in the breast, chest wall or

nodal or metastatic sites or the development of a new primary breast cancer in the contralateral breast. Secondary endpoints included overall survival (i.e. time to death from any cause) and health-related quality of life (HR-QOL) assessments. See section 1 for discussion of the effects of letrozole on serum lipid profiles (MA-17L)[15] and BMD (MA-17B)[14] in companion studies of the MA-17 trial.

Although the study duration was intended to be 5 years, as per protocol, the beneficial effects of letrozole versus placebo required the study to be unblinded at the interim follow-up period (median 2.4 years, maximum duration of treatment of 4 years).[24] Five-year data, with a median follow-up of 27.4[25] and 30[23] months, have recently been published in full.

- At a median of 2.4 years' follow-up, Kaplan-Meier curves indicated a significant benefit in the letrozole group for DFS ($p < 0.001$) [per protocol definition].[24] At this timepoint, 75 disease recurrences or new contralateral breast tumours had occurred in the letrozole group versus 132 in the placebo group (HR 0.57; 95% CI 0.43, 0.75, $p = 0.00008$); that is, there was a 43% reduction in the risk of recurrence with letrozole treatment. The estimated 4-year DFS rate (93% vs 87%, $p \leq 0.001$) was significantly better in the letrozole than placebo group, with no between-group difference in terms of estimated 4-year overall survival rates (96% vs 94%).[24]

- Using the DFS definition requested by the US FDA (i.e. first event of locoregional recurrence, distant relapse or death from any cause), 315 events had occurred at 27.4 months' follow-up (122 events in the letrozole vs 193 in the placebo group; HR 0.62; 95% CI 0.49, 0.78, $p = 0.00003$),[25] confirming data using the per-protocol definition of DFS as reported by Goss et al.[24] There was also a benefit in terms of distant metastases in the letrozole group (55 vs 92 events in the placebo group; HR 0.61; 95% CI 0.44, 0.84, $p = 0.003$).

- Subsequent follow-up at a median of 30 months (range 1.5–61.4 months) also showed a significant advantage in the letrozole group in terms of DFS using the per protocol definition (HR 0.58; 95% CI 0.45, 0.76, $p < 0.001$) and distant DFS (HR 0.60; 95% CI 0.43, 0.84, $p = 0.002$).[23] There was no between group difference in terms of 4-year overall survival rates (95.4% vs 95.0%); the HR for the risk of death from any cause was 0.82 (95% CI 0.57, 1.19).

- Notably, in a prospectively planned subgroup analysis of lymph node-positive patients, letrozole significantly ($p < 0.05$) reduced the risk of disease recurrence by 39% (DFS HR 0.61; 95% CI 0.45, 0.84), distant recurrence by 47% (distant DFS HR 0.53; 95% CI 0.36, 0.78) and overall survival by 39% (HR 0.61; 95% CI 0.38, 0.98).[26]

- In a separate analysis of these MA-17 data, conducted to evaluate the relationship between the duration of letrozole therapy in the extended adjuvant setting and hazard for recurrence of disease, the benefits of letrozole to placebo treatment increased as the duration of treatment increased.[27] These data were assessed using a nonparametric kernal smoothing method to estimate HR over time and a Cox model with time-dependent covariate. There was a significant ($p < 0.0001$) reduction in the HR for DFS (primary endpoint) from 0.52 (95% CI 0.40, 0.64) at 12 months to 0.19 (95% CI 0.04, 0.34) at 4 years in the placebo/letrozole group. Similarly, the distant DFS HR was reduced from 0.43 to 0.21 ($p = 0.0013$).[27]

- An analysis of the MA-17 trial post-unblinding indicated that women from the placebo group who elected to switch to letrozole (i.e. the placebo/letrozole group) showed an improvement in outcome relative to those who elected to have no treatment (i.e. the placebo group).[26] There were between-group differences in post-unblinding baseline characteristics for these two groups; women switching to letrozole were younger, had more advanced disease, had a worse ECOG performance status and were more likely to have received chemotherapy, whereas the placebo group were older and reasons for remaining off treatment may have included a better prognosis from breast cancer but higher comorbid disease. Data were adjusted for all factors found to be significant in univariate analysis of

baseline characteristics post-unblinding (i.e. age, ECOG performance status, node-negative status and whether patients had prior chemotherapy).[26]

- In this post-unblinding analysis, at up to 80 months follow-up from the initial time of randomisation (median follow-up 54 months), placebo/letrozole recipients experienced a 69% reduction in disease recurrence (adjusted DFS HR 0.31; 95% CI 0.18, 0.55, $p < 0.0001$), a 72% reduction in distant DFS (adjusted HR 0.28; 95% CI 0.13, 0.62, $p = 0.002$), a 47% reduction in the risk of death (adjusted overall survival HR 0.53; 95% CI 0.28, 1.0, $p = 0.05$) and a 77% reduction in the risk of contralateral breast cancer (adjusted HR 0.23; 95% CI 0.07, 0.77, $p = 0.017$) compared with placebo recipients.[26]
- Importantly, relative to placebo recipients, there was no impact on the overall HR-QOL in letrozole recipients after up to 3 years' treatment in a subgroup analysis of 3612 postmenopausal women participating in the MA-17 study.[28] Letrozole recipients experienced relatively minor, but statistically significant, decreases in HR-QOL domains associated with estrogen depletion (e.g. vasomotor and bodily pain), as assessed using the 36 Item Short Form General Health Survey and Menopause Specific QOL questionnaire.[28]

### Pharmacoeconomic Considerations

Extensive discussion of pharmacoeconomic studies relating to the use of letrozole in postmenopausal women with hormone-responsive, early-stage breast cancer is beyond the scope of this review; these data are comprehensively reviewed in a forthcoming article by Dunn and Keam.[29]

- In brief, preliminary results from cost-utility analyses conducted from the UK and US healthpayer perspectives suggest that letrozole may be more cost effective than tamoxifen as first-line adjuvant therapy in postmenopausal women with hormone-responsive, early-stage breast cancer.[29] These pharmacoeconomic analyses used results from the primary core analysis of the BIG 1-98 trial and an adapted decision model (as reviewed by Dunn and Keam[29]).
- In addition, in cost-utility analyses conducted from the healthpayer perspective of various countries (including the US), relative to no further treatment after 5 years' tamoxifen treatment, letrozole (i.e. as extended adjuvant therapy) was shown to be cost-effective in terms of years of life gained after adjustment of results for HR-QOL (reviewed by Dunn and Keam[29]). These analyses used a decision model and data from the MA-17 trial, with results proving robust based on sensitivity analyses.[29]

## 4. Tolerability

Once-daily letrozole 2.5mg was generally well tolerated in postmenopausal women with hormone-responsive, early-stage breast cancer participating in large double-blind trials discussed in section 3, irrespective of whether the drug was given as first-line adjuvant therapy or as extended adjuvant therapy following 5 years' tamoxifen adjuvant therapy.[21,23] These adverse events were typical of those associated with estrogen deprivation.

### First-Line Adjuvant Therapy

- Treatment-emergent adverse events (i.e. those that occurred during or within 28 days of stopping study treatment) that occurred with an incidence of at least 5% (i.e. the most common) in either letrozole or tamoxifen recipients participating in the BIG 1-98 trial are summarised in figure 2.[21] In this trial, 2912 letrozole recipients experienced predefined targeted adverse events of any grade (see figure 2 for criteria used) versus 2554 tamoxifen recipients (no statistical data reported); the majority of adverse events were grade 1 or 2. A similar proportion of patients in both groups experienced a life-threatening or fatal protocol-specified adverse event (67 vs 69 patients).
- Notably, there was a significantly lower incidence of venous thromboembolitic events (1.5% vs 3.5%, $p < 0.001$) and of vaginal bleeding, hot flushes and night sweating (figure 2) in the letrozole than in the tamoxifen group.[21] Conversely, cardiac failure (0.8% vs 0.4%, $p = 0.01$), bone fractures (figure 2) and arthralgia (figure 2) all occurred more frequently in the letrozole group. The time to first fracture reported on or within 4 weeks of discontinu-

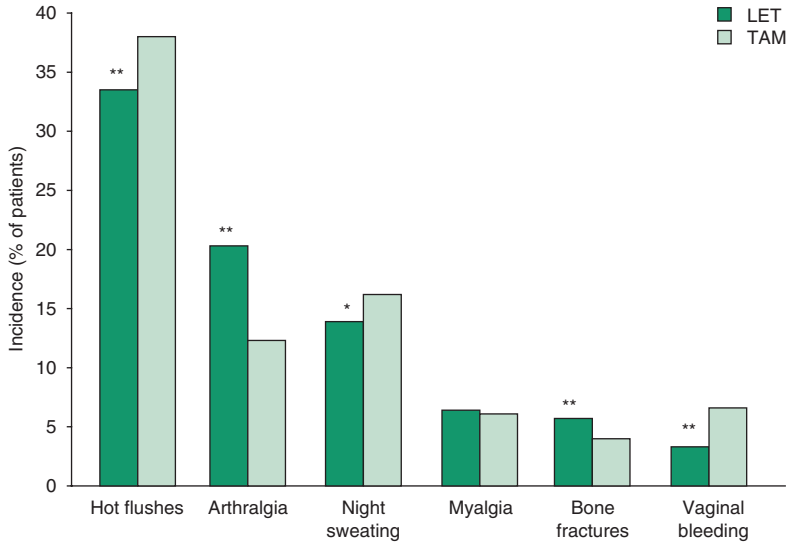


**Fig. 2.** Comparative tolerability of letrozole (LET) in postmenopausal women with hormone-responsive, early-stage breast cancer. Incidence of treatment-emergent adverse events of any grade (based on the Common Toxicity Criteria of the National Cancer Institute, where defined, or the senior oncologist of the International Breast Cancer Study Group) that occurred during or within 28 days of stopping study treatment in ≥5% of patients in either treatment group.[21] In this 5-year, randomised, double-blind, multinational trial (Breast International Group 1-98 trial), patients received once-daily LET 2.5mg or tamoxifen (TAM) 20mg for 5 years or sequential therapy with the same dosages of LET for 2 years followed by TAM for 3 years or vice versa. In the per protocol analysis, the LET or TAM monotherapy arm was combined with the corresponding truncated sequential arm (i.e. excluding events and follow-up occurring more than 30 days after switching to the other treatment) [LET n = 3975 patients; TAM n = 3988]. Median follow-up was 25.8 months. * $p < 0.01$, ** $p < 0.001$ vs TAM.

ing treatment was also significantly ($p < 0.001$) shorter in the letrozole than in the tamoxifen group (no quantitative data reported).[21]

- Forty-four percent of letrozole and 19% of tamoxifen recipients had at least one report of hypercholesterolaemia, of which 35.1% were grade 1 hypercholesterolaemia in letrozole recipients versus 17.3% in tamoxifen recipients.[21] Furthermore, serum cholesterol levels remained stable during 24 months of letrozole treatment (median reduction from baseline of 2%), whereas they appeared to decrease in tamoxifen recipients (reduced by 14% at 24 months) [no baseline or statistical data reported].

### Extended Adjuvant Therapy

- In the MA-17 trial, there was generally no significant difference in the frequency or nature of adverse events that occurred in the letrozole (n = 2572) and placebo groups (n = 2577) [median follow-up of 30 months], although there was a slightly higher incidence of treatment discontinuation because of adverse events in the letrozole group (4.9% vs 3.6%, $p = 0.019$).[23] Approximately 97% of all treatment-emergent adverse events were grade 1 or 2 according to the National Cancer Institute's common toxicity criteria. The frequency of cardiovascular events (5.8% vs 5.6%), hypercholesterolaemia (16% vs 16%) and endometrial cancer (0.2% vs 0.4%) was similar in both groups.

- Hot flushes (58% vs 54%, $p = 0.003$), arthralgia (25% vs 21%, $p < 0.001$), myalgia (15% vs 12%, $p = 0.004$), anorexia (6% vs 4%, $p = 0.039$) and alopecia (5% vs 3%, $p = 0.01$) occurred significantly more frequently in letrozole than placebo recipients, whereas significantly fewer letrozole recipients experienced vaginal bleeding (6% vs 8%, $p = 0.005$).[23] In addition, although the incidence of new self-reported osteoporosis increased in letrozole recipients compared with placebo recipients (8.1% vs 6%, $p = 0.003$), there was no difference between the two treatment groups in the proportion of patients experiencing a clinical fracture during

the study period (5.3% vs 4.6%) or in the incidence of newly diagnosed osteoporosis (no data reported).[23]

## 5. Dosage and Administration

In postmenopausal women with early-stage breast cancer who have received 5 years' prior treatment with tamoxifen, the recommended dosage of oral letrozole for extended adjuvant treatment is 2.5mg once daily.[20] The same dosage of the drug was used as first-line adjuvant therapy in postmenopausal women with hormone-responsive, early-stage breast cancer in the BIG 1-98 trial.[21] The drug may be taken without regard to food.[20]

For comprehensive dosage and administration guidelines, the local manufacturer's prescribing information should be consulted.

## 6. Letrozole: Current Status in Postmenopausal Hormone-Responsive Early-Stage Breast Cancer

The US FDA[30] and UK Medicines and Healthcare Products Regulatory Authority[31] have recently expanded the indications for which the aromatase inhibitor letrozole may be used to include first-line adjuvant treatment of postmenopausal women with early-stage breast cancer. In this clinical setting, letrozole showed better efficacy than tamoxifen at a median of 25.8 months' follow-up, with letrozole treatment significantly prolonging DFS and distant DFS, and associated with fewer DFS events. A 5-year, phase IIIb, randomised, open-label, multinational trial has just started enrolling patients in a head-to-head comparison of the efficacy of letrozole 2.5 mg/day with anastrozole 1 mg/day as adjuvant therapy in approximately 4000 postmenopausal women with hormone-responsive, lymph node-positive breast cancer; results of this trial are awaited with interest.[32]

In several countries worldwide, including the US,[20] Canada[33] and several European countries,[34] letrozole is also approved for extended adjuvant treatment in postmenopausal women with early-stage breast cancer who have received 5 years' prior treatment with tamoxifen therapy; the optimal duration of treatment in this setting remains to be determined. Relative to placebo, extended adjuvant therapy with letrozole showed significant benefits in DFS after a median of 30 months' follow-up, with the benefit of letrozole treatment increasing as the duration of therapy increased. The MA-17 post-unblinding data support the use of letrozole after a prolonged period of no treatment after tamoxifen therapy, offering a significant DFS advantage in women who are hormone receptor-positive. The drug was generally well tolerated in both of the primary and extended adjuvant settings.

## Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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