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REVIEW

Letrozole in advanced breast cancer: the PO25 trial

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Abstract Tamoxifen has been a standard first-line endocrine therapy for post-menopausal women with hormone-responsive advanced breast cancer, but more than half of patients fail to respond and time to progression is less than 12 months in responders. The third-generation aromatase inhibitors were developed to provide more effective alternatives to tamoxifen. In the Femara Study PO25, post-menopausal women with advanced breast cancer were randomized to receive letrozole 2.5 mg ($n = 453$) or tamoxifen 20 mg ($n = 454$) given orally daily until progressive disease occurred. Patients were permitted to cross over to the other treatment at progression. In the primary efficacy analysis, median time to progression (TTP) was significantly longer with letrozole than with tamoxifen (9.4 months vs. 6.0 months, respectively; $P < 0.0001$). The objective response rate (ORR) was significantly higher for letrozole than for tamoxifen (32% vs. 21%; $P = 0.0002$). Prospectively planned analyses of the intent-to-treat population showed that letrozole significantly improved overall survival (OS) compared with tamoxifen over the first 24 months of the trial. An exploratory analysis of patients, who did not cross over, indicated a median OS benefit of 14 months for letrozole compared with tamoxifen. Letrozole is the only third-generation aromatase inhibitor that has demonstrated significant improvements in ORR, TTP, and early OS.

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Introduction and rationale

The treatment goals for advanced or metastatic breast cancer (MBC) are to delay disease progression and to prolong survival [1, 2] and to optimize patient care in terms of ameliorating symptoms, thereby improving or maintaining quality of life [3–5]. Although treatment may include surgery and radiation therapy for the treatment of locally advanced tumors or isolated metastases, systemic therapies (endocrine, cytotoxic, biologic, and palliative) are the foundation of disease management [6, 7]. Systemic therapy for patients with advanced breast cancer should be tailored according to specific tumor biology, particularly with respect to hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status, the growth rate of disease, presence of visceral metastases, history of prior therapy and response, susceptibility to treatment-related toxicity, and individual patient preference [7–14]. Systemic therapy can prolong survival and enhance patient quality of life but is not curative [1]. Consequently, minimally toxic endocrine therapies are generally preferred to cytotoxic therapy as initial therapy for patients with hormone-responsive tumors [6, 15].

Since the 1980s, endocrine therapy with tamoxifen was well established as a standard first-line treatment for post-menopausal women with advanced breast cancer, even though estrogen receptor (ER) expression was not always used routinely to select patients for endocrine therapy [16–18]. The first-generation

aromatase inhibitor aminoglutethimide or a progestin such as megestrol acetate has provided a reasonable second-line alternative [19–22]. The objective response rate (ORR) to tamoxifen was shown to be in the range of 25%–45% [16, 17, 19, 21, 23–32], indicating that more than half of the patients with advanced breast cancer are intrinsically resistant to tamoxifen. Furthermore, the short median time to treatment failure (TTF), in the range 6–8 months, demonstrates a relatively rapid emergence of resistance in patients initially sensitive to tamoxifen [19, 27]. Loss of ER expression appears to be the dominant mechanism of de novo resistance, and most ER/progesterone receptor negative (PgR–) tumors do not respond to tamoxifen [18, 33–36]. However, the majority of patients who develop acquired tamoxifen resistance still express ER at the time of progression [37, 38] and may respond to alternative endocrine therapies [39].

The third-generation aromatase inhibitors letrozole, anastrozole, and exemestane were developed in the search for more effective therapeutic alternatives to tamoxifen. Aromatase inhibitors prevent estrogen synthesis by potently inhibiting the aromatase enzyme, which converts androgens to estrogen [40]. Unlike tamoxifen, the aromatase inhibitors do not have any partial estrogen-agonist activity [41] and are less susceptible to the emergence of resistance associated with long-term estrogen deprivation [42]. The development and mechanism of action of aromatase inhibitors is described in detail in the article by Dr. Bhatnagar in this supplement.

Studies of aromatase inhibitors in the second-line setting

The initial randomized controlled trials of third-generation aromatase inhibitors were conducted in patients with advanced breast cancer in whom tamoxifen had failed (i.e., second-line setting). Letrozole, anastrozole, and exemestane all demonstrated evidence of clinical superiority to megestrol acetate in the second-line setting [43–47]. Thus, the individual trials demonstrate a trend or even a significant difference in favor of the third-generation aromatase inhibitors in one or more efficacy end points; in addition, the aromatase inhibitors were shown to be associated with improved tolerability versus comparator endocrine therapy in these randomized trials.

One trial demonstrated a significantly higher ORR for letrozole (2.5 mg dose) compared with megestrol acetate (24% vs. 16%, respectively; $P = 0.04$) and a trend toward longer time to progression (5.6 vs. 5.1 months, $P = 0.07$) [45]. In this trial, low-dose letrozole (0.5 mg) was associated with similar efficacy outcomes compared with megestrol acetate. However, in another similarly designed trial with letrozole versus megestrol acetate, overall response rates with the two doses of letrozole (0.5 and 2.5 mg) and with the comparator were similar (21%, 16%, and 15%, respectively). In this trial, low-dose letrozole was superior to megestrol acetate in terms of time to progression (TTP) ($P = 0.044$) and survival ($P = 0.053$). Differences in the distribution of baseline variables may explain the different outcomes in the two trials in terms of the superiority of letrozole over megestrol acetate according to dose [48]. Letrozole was significantly better tolerated than megestrol acetate, specifically in terms of serious adverse experiences, discontinuation due to poor tolerability, cardiovascular side effects, and weight gain [45].

Third-generation aromatase inhibitors have demonstrated greater potency and selectivity than the first-generation compound aminoglutethimide [49]. Two doses of the most potent aromatase inhibitor letrozole (2.5 mg and 0.5 mg) [49] were compared with aminoglutethimide in a randomized controlled trial in the second-line setting and demonstrated superior efficacy and improved safety [50]. The higher dose of letrozole showed a trend ($P = 0.06$) toward superior ORR (19.5%) compared with aminoglutethimide (12.4%). Letrozole 2.5 mg was also significantly superior in TTP, TTF, and overall survival (OS). Fewer patients taking letrozole experienced adverse events than those taking aminoglutethimide (33% vs. 46%) [50]. Letrozole has also been compared with anastrozole in a randomized, unblinded trial in the second-line setting in patients with MBC. The trial showed that letrozole was associated with a statistically higher ORR than anastrozole (19.1% vs. 12.3%, respectively; $P = 0.013$), whereas TTP (the major end point), TTF, and clinical benefit and duration of response were similar between the two agents [51]. Both letrozole and anastrozole were well tolerated, and a similar incidence of adverse events was observed in the two groups.

These studies generated the hypothesis that letrozole might have superior efficacy to tamoxifen as first-line therapy for advanced breast cancer. A large clinical trial (Femara Study PO25) was therefore conducted to compare the efficacy and tolerability of letrozole with those of tamoxifen as first-line therapy in post-menopausal women with advanced breast cancer [52]. This review will describe the results of the PO25 trial, highlighting the evidence for the superiority of letrozole over tamoxifen as first-line endocrine therapy in this setting.

Trial design and patients

The Femara Study PO25 was the largest phase 3 trial conducted in the advanced breast cancer setting [52, 53]. This randomized, double-blind, double-dummy trial was powered for superiority and needed to enroll approximately 900 patients to demonstrate a 20% reduction in the risk of progression with the more effective treatment. To achieve the recruitment target, the trial was conducted in 201 centers in 29 countries. Local ethics review boards approved the protocol, and all patients gave written informed consent before study enrollment.

Randomized trial design

Patients were randomized to receive letrozole 2.5 mg or tamoxifen 20 mg given orally daily until progressive disease occurred. Patients were permitted to cross over from 1 treatment arm to the other in a double-blind fashion if their first-line treatment was discontinued because of progressive disease or for any other reason (Fig. 1). Patients in whom endocrine therapy was discontinued were subsequently treated as clinically indicated, using chemotherapy, trastuzumab, and bisphosphonates. The crossover design was an integral part of the study, and it probably affected the assessment of OS.

Patient population

Post-menopausal women with advanced breast cancer, defined as stage IIIB locally advanced disease, locoregionally recurrent disease that was not amenable to surgery or radiotherapy, or metastatic disease, were eligible for inclusion in the trial. All patients presented with measurable or assessable tumors and were candidates for endocrine therapy. Patients had estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PgR+) tumors or unknown HR status. One prior chemotherapy regimen for the treatment of metastatic disease was permitted, but recurrence during or within 12 months of adjuvant antiestrogen therapy and any prior endocrine therapy for advanced breast cancer precluded enrollment.

End points

The primary end point was TTP, defined as the interval between date of randomization and the earliest date of disease progression. Disease progression was determined on the basis of tumor progression (an increase of 25% or more in measurable lesions, an estimated increase of the same magnitude of nonmeasurable lesions, or the appearance of new lesions), treatment discontinuation with evidence of clinical deterioration due to breast cancer, death due to breast cancer, or death of unknown cause (with documented evidence of clinical deterioration due to breast cancer) while receiving treatment or within 6 weeks of discontinuation of treatment.

The secondary end points were ORR, duration of overall response, rate and duration of clinical benefit, TTF, time to response (TTR), time to chemotherapy (TTC), safety, and OS. ORR was defined as the proportion of patients who achieved a complete response (CR) or a partial response (PR), confirmed by a second evaluation 1–3 months later. The duration of overall response was defined for patients with CR or PR, as the interval between date of randomization and the earliest date of disease progression. The rate of clinical benefit was defined as proportion of patients who achieved CR or PR or who stabilized (NC) for at least 24 weeks; the duration of clinical benefit was defined for patients who achieved CR or PR or NC as the interval between date of randomization and the earliest date of disease progression. TTF was defined as the interval between date of randomization and the earliest date of disease progression, withdrawal, lost to follow-up, or death. TTR was defined for CR or PR

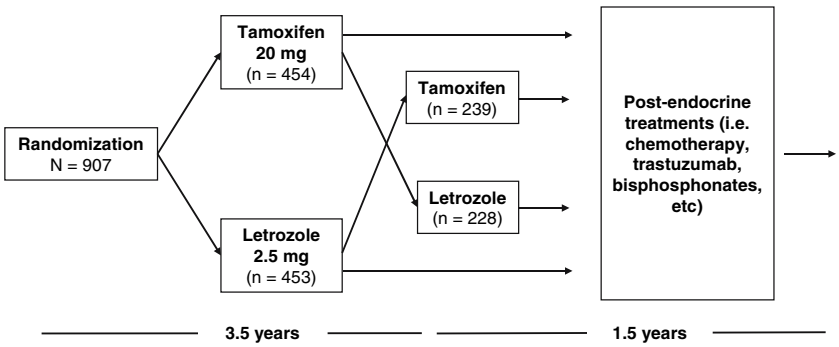


Fig. 1 Study design

patients as the interval between randomization and the earliest documentation of response, and TTC was defined as the total duration of endocrine therapy. The duration of OS was defined as the interval between randomization and death for any reason.

Exploratory analyses of OS were performed. The first analysis included all patients with censoring at crossover, whereas the second included only patients with no crossover. The latter group predominantly comprised of patients with ''nonresponsive'' disease (patients who responded to first-line therapy are more likely to be crossed over later at progression), whereas the former included ''nonresponsive'' as well as ''responsive'' patients.

Efficacy

The characteristics of the 907 patients included in the intent-to-treat (ITT) population were well balanced between the letrozole and tamoxifen arms. The median age of the patients was 65 years (range 31–96 years) in the letrozole arm and 64 years (range 31–93 years) in the tamoxifen arm. Patients were predominantly white (86%), and 92% had Karnofsky performance status (KPS) scores of 80–100. The majority (93%) of the study population had metastatic disease. Soft tissue lesions were the dominant metastatic site in one quarter of patients and were present in 63% and 61% of patients in the letrozole and tamoxifen arms, respectively. Bone metastases were the dominant metastatic site in approximately 30% of patients and were present in 54% and 50%, respectively. Visceral metastases were the dominant site in 43% of patients in the letrozole arm and 46% of the patients in the tamoxifen arm. Most patients (71% in the letrozole arm and 66% in the tamoxifen arm) had not received any prior chemotherapy, and few had received chemotherapy for advanced disease (9% and 11%, respectively). The majority of patients (109 of 167) treated with adjuvant tamoxifen received at least 2 years of therapy, and the treatment-free interval between stopping adjuvant therapy and entering the study was more than 2 years in 126 of 167 patients. Of the 907 patients included in the ITT efficacy population, 467 crossed over to the other treatment arm, 75 continued on first-line therapy without progression, and the remainder terminated first-line treatment without crossover (Fig. 2).

Letrozole was superior to tamoxifen for all primary and secondary efficacy end points, including a prospectively planned survival analysis at 1- and 2-year follow-up [53].

Time to progression

In the primary efficacy analysis, the median TTP was significantly longer with letrozole than with tamoxifen

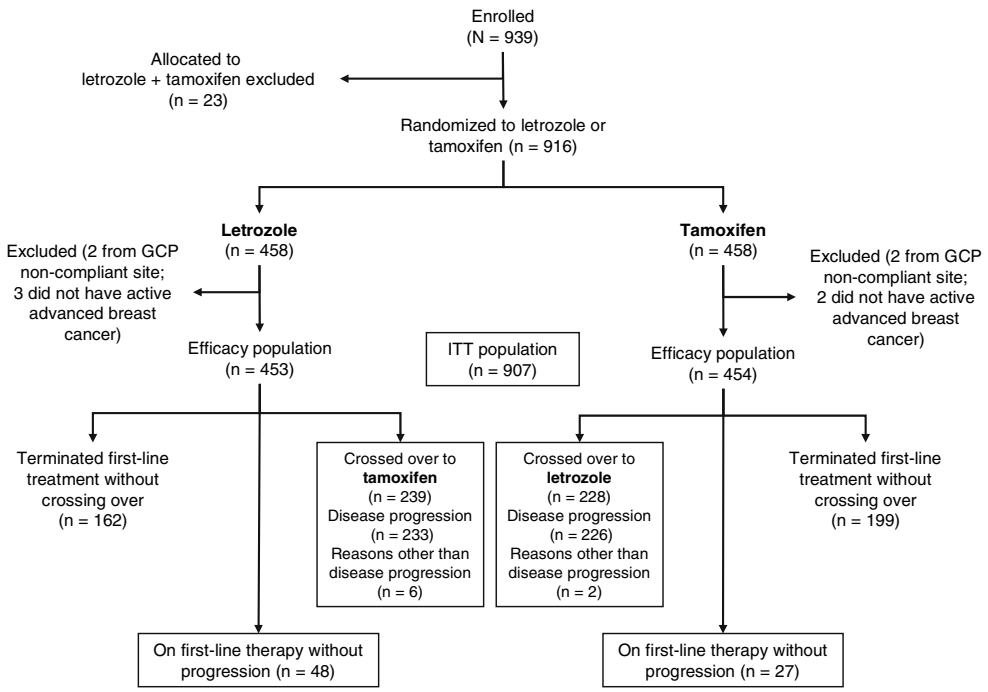


Fig. 2 Patient disposition

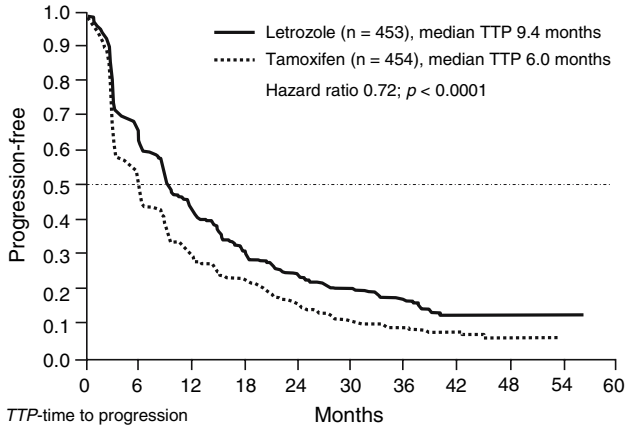


Fig. 3 Time to progression at median follow-up of 32 months for patients on first-line letrozole versus tamoxifen. Reprinted from ref. [53] with permission from the American Society of Clinical Oncology

(9.4 months vs. 6.0 months, respectively; $P < 0.0001$) (Fig. 3) [53]. Of patients in the letrozole arm, 359 (79%) progressed, compared with 387 (85%) in the tamoxifen arm. The hazard ratio of 0.72 represents a 28% reduction in the risk of disease progression with letrozole ($P = 0.0001$).

The significant improvement in TTP with letrozole was confirmed in supportive multivariate analysis of prospectively defined baseline covariates, including receptor status, prior adjuvant tamoxifen therapy, and dominant site of metastatic disease [52, 54]. The analysis showed that the risk of progression was increased by the presence of either visceral or bone metastases as the dominant site of metastatic disease compared with soft tissue as dominant site. In the multivariate analysis, the significant improvement in TTP with letrozole over tamoxifen (hazard ratio 0.70; 95% confidence intervals [CI] 0.60, 0.81; $P = 0.0001$) was similar to the benefit observed in unadjusted analysis and was significant for each individual covariate ($P = 0.0001$) [53]. Median TTP values for letrozole and tamoxifen in the different subgroups are shown in Table 1. In patients with nonvisceral metastases, the risk for progression was 25% lower with letrozole than with tamoxifen, whereas in patients with visceral metastases, excluding the liver, the risk for progression was 34% lower and the median TTP was almost twice as long with letrozole than with tamoxifen [54]. Although TTP was shortest for patients with liver lesions, the risk for progression was still 36% lower with letrozole than with tamoxifen in this subgroup [54].

Patients with prior adjuvant antiestrogen therapy benefited from letrozole in line with the total group, as did patients irrespective of positive or unknown receptor status of the primary tumor.

A prospectively planned analysis by patient age (<70 years and ≥70 years) also demonstrated that median TTP was significantly longer for letrozole than for tamoxifen in both age groups (8.8 months vs. 6.0 months, respectively, in the younger group and 12.2 months vs. 5.8 months in the older group) [55].

Response to therapy

Letrozole was associated with a significantly better response to therapy compared with tamoxifen [52, 53]. ORR was significantly higher for letrozole than for tamoxifen (32% vs. 21%; $P = 0.0002$), and the corresponding rate of CRs was also significantly higher for letrozole (9% vs. 3%; $P = 0.0004$). The rate of treatment failure was lower with letrozole (75%) than with tamoxifen (85%), and median TTF was significantly prolonged (9.0 months vs. 5.7 months, respectively; $P < 0.0001$).

Table 1 Time to progression in different patient subgroups [57]

Subgroup		Letrozole	Tamoxifen
Dominant disease site: soft tissue	*n*	113	115
	Median TTP	12.1 months	6.4 months
Dominant disease site: bone	*n*	145	131
	Median TTP	9.5 months	6.3 months
Dominant disease site: viscera	*n*	195	208
	Median TTP	8.3 months	4.6 months
Patients who had received prior antiestrogen	*n*	94	83
	Median TTP	8.9 months	5.9 months
	Hazard ratio (95% CI)[a]	0.60 (0.43, 0.84)	
HR-positive	*n*	294	305
	Median TTP	9.4 months	6.0 months
	Hazard ratio (95% CI)[a]	0.69 (0.58, 0.83)	
HR-unknown	*n*	159	149
	Median TTP	9.2 months	6.0 months
	Hazard ratio (95% CI)[a]	0.77 (0.60, 0.99)	

TTP, time to progression; CI, confidence interval; HR, hormone receptor

[a] Hazard ratios < 1.0 indicate superiority for letrozole relative to tamoxifen

A supportive multivariate analysis of ORR, adjusted for the same covariates as used for the TTP analysis, showed that prior adjuvant tamoxifen, as well as visceral or bone metastases as the dominant site of metastases, significantly decreased the probability of achieving a response. The analysis also confirmed that letrozole significantly increased the probability of achieving a CR or PR compared with tamoxifen (odds ratio 1.80, 95% CI 1.32–2.47; $P = 0.0002$) and that the superiority of letrozole remained statistically significant for each of covariates ($P = 0.001$) [52]. ORRs achieved with letrozole and tamoxifen in the different subgroups are shown in Table 2.

Overall survival

The median OS was 34 months for the letrozole group and 30 months for the tamoxifen group ($P = 0.53$). Prospectively planned analyses of the ITT population showed that letrozole significantly improved OS compared with tamoxifen over the first 24 months of the trial [53]. A Kolmogorov-Smirnov analysis to compare the survival distributions in the 2 arms [56] demonstrated a significant difference in favor of letrozole between 6 and 20 months ($P = 0.003$) and showed that the maximum difference in survival occurred at 14 months; at this time point, there were 85 deaths (19%) in the letrozole arm compared with 132 deaths (29%) in the tamoxifen arm. In addition, repeated log-rank tests performed at 6-month intervals indicated that survival was significantly greater with letrozole between 6 and 24 months (6 months: $P = 0.0167$; 12 months: $P = 0.0038$; 18 months: $P = 0.0010$; 24 months: $P = 0.0246$) (Fig. 4). The OS curves for the letrozole and tamoxifen groups crossed at around 36 months, at which time point most patients had either crossed over to the other study drug or had switched to different second-line treatments [53].

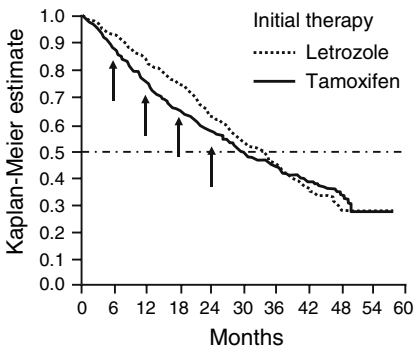
Additional exploratory analyses were therefore performed to determine the influence of crossover on OS. The crossover design was an integral part of the trial and, as with all crossover designs, had a con-

Table 2 Objective response rate in different patient subgroups [57]

Subgroup		Letrozole	Tamoxifen
Dominant disease site: soft tissue	*n*	113	115
	ORR	50%	34%
Dominant disease site: bone	*n*	145	131
	ORR	23%	15%
Dominant disease site: viscera	*n*	195	208
	ORR	28%	17%
Patients who had received prior antiestrogen	*n*	84	83
	ORR	26%	8%
	Odds ratio (95% CI)[a]	3.85 (1.50, 9.60)	
HR-positive	*n*	294	305
	ORR	33%	22%
	Odds ratio (95% CI)[a]	1.78 (1.20, 2.60)	
HR-unknown	*n*	159	149
	ORR	30%	20%
	Odds ratio (95% CI)[a]	1.79 (1.10, 3.00)	

ORR, objective response rate; CI, confidence interval; HR, hormone receptor

[a] Odds ratios >1.0 indicate superiority for letrozole relative to tamoxifen



	Patients alive at 6-month intervals (%)			
	6 mo	12 mo	18 mo	24 mo
Letrozole	93	83	75	64
Tamoxifen	89	75	65	58
p value (log-rank test)	0.02	0.004	0.001	0.02

Fig. 4 Letrozole versus tamoxifen: patients alive at 6-month intervals. Reprinted from ref. [48] with permission from Elsevier

founding influence on the assessment of OS. Second-line endocrine therapy is generally less effective than first-line treatment in patients responsive to first-line therapy [16]; therefore, evaluation of OS may be impaired if the second-line treatment is actually more effective than the original first-line treatment. Furthermore, patients who are responsive to first-line therapy are more likely to cross over than are patients with nonresponsive disease who do not obtain benefit from first-line therapy.

Approximately 50% of patients crossed over to the other treatment arm (Fig. 2), and almost all of the crossovers had occurred by 36 months. The median time to crossover was longer for patients initially randomized to the letrozole arm (17 months for letrozole to tamoxifen vs. 13 months for tamoxifen to letrozole). The median OS from initial randomization, censoring time to death at crossover, was 42 months (95% CI 36 months to not estimable) for letrozole and 30 months (95% CI 27 to <36 months) for tamoxifen [53]. The superior efficacy of letrozole compared with tamoxifen was also indicated by an analysis of mortality rates and OS following crossover to the alternate treatment. The analysis showed that the mortality rate was substantially reduced (47% vs. 63%, respectively), and OS improved in patients who crossed over to second-line letrozole compared with those who crossed over to second-line tamoxifen (31 months; 95% CI 22–40 months vs. 19 months; 95% CI 17–24 months, respectively) [53].

This OS analysis included all patients censored at the time of crossover (i.e., both ''nonresponsive'' and ''responsive'' patients). A second exploratory efficacy analysis of OS included only patients who did not cross over to the other arm and thus predominantly comprised patients with nonresponsive disease. This second analysis, limited to the patients who did not cross over to the alternate drug at progression, indicated a median OS benefit of 14 months for letrozole (35 months; 95% CI 29–43 months) compared with tamoxifen (20 months; 95% CI 16–26 months) [57].

Time to chemotherapy

Hormone therapy is the preferred treatment strategy for patients with hormone-responsive advanced breast cancer, except for those individuals with rapidly progressive disease for whom initial chemotherapy is indicated [15]. Extending the TTC is thus an important goal with hormone therapy and can maintain quality of life without having a detrimental effect on outcome. In the PO25 trial, TTC was significantly longer for patients whose initial treatment was letrozole compared with those initially randomized to receive tamoxifen (16.3 vs. 9.3 months; $P = 0.005$).

Safety

Both letrozole and tamoxifen were well tolerated [52, 53]. The incidence of adverse effects related to study drug during first-line treatment was similar for letrozole (38%) and tamoxifen (37%). Hot flushes (16% and 13%, respectively), nausea (6% and 6%, respectively), and hair thinning (5% and 3%, respectively) were the most common treatment-related adverse events reported. Bone fractures of any etiology occurred in 5.3% of patients in the letrozole group, compared with 4.2% in the tamoxifen arm, resulting in fracture rates per patient-year of treatment of 0.0427 and 0.0451, respectively [52].

A quality-adjusted time without symptoms or toxicity (Q-TWiST) follow-up study assessed the trade-offs between progression-free survival and toxicity in the ITT population from the PO25 trial [58]. The Q-TWiST approach quantitatively adjusts periods in which treatment toxicities or symptoms of disease progression are present to reflect the potentially reduced value for the patient; this methodology divides the survival time of the patient into various health states, assigns utility states to each, and compares treatments based on OS experience [59]. The Q-TWiST analysis of the clinical trial data from the PO25 trial showed that the longer TTP with letrozole compared with tamoxifen is achieved without increased time with adverse events (2.2 vs. 2 months, respectively), resulting in a significantly greater quality-adjusted survival for patients on letrozole (2.5-month advantage; $P < 0.0001$) [58].

Time to worsening of KPS (decrease of ≥20 points) was significantly delayed for first-line letrozole compared with first-line tamoxifen (hazard ratio 0.62; $P = 0.001$) [54]. A subset analysis according to sites of metastases demonstrated that in patients with visceral metastases without liver involvement (mostly lung metastases), significantly fewer letrozole patients (14%) than tamoxifen patients (30%) experienced deteriorations in their KPS scores by ≥20 points [54]. However, KPS was relatively insensitive to change in these first-line patients.

Cost-effectiveness

In addition to its clinical superiority over tamoxifen, economic analyses have also shown that letrozole is highly cost-effective as first-line endocrine therapy in post-menopausal women with advanced breast cancer [60–62]. A follow-up analysis of patient data from the PO25 trial calculated the cost-effectiveness of first-line letrozole and tamoxifen by determining the ratio: difference in costs of breast cancer care to the difference in life years (LYs) between the two treatments [60]. The mean costs of care were $7323 and $5468 for letrozole and tamoxifen, respectively, representing $1855 in incremental costs with first-line letrozole. Mean LYs to death or to the end of first- or second-line hormonal therapy were 1.54 and 1.29 for patients randomized to first-line letrozole or tamoxifen, respectively. Thus, the incremental cost per LY saved with first-line letrozole vs. tamoxifen was $7420 (1855/0.25 = 7420) (2.5–97.5 percentiles $6470–$14,865).

In another economic analysis conducted in the United Kingdom, data from the PO25 trial were used to estimate the effectiveness of treatment [61]. The analysis showed that the mean cost of providing first- and second-line hormonal therapy was GBP4765 for first-line letrozole and GBP3418 for first-line tamoxifen (a difference of GBP1347). Since patients receiving first-line letrozole gain an additional 0.228 LYs, or 0.158 quality-adjusted life years (QALYs), the cost-effectiveness analysis showed that first-line hormonal therapy with letrozole gains additional LYs at a cost of GBP5917, whereas the cost per additional QALY gained is GBP8514, which is well within the accepted cost range.

The PO25 trial data were also used in a Canadian analysis that compared the cost-effectiveness of letrozole, anastrozole, and tamoxifen [62]. The analysis showed an incremental cost per quality-adjusted progression-free year of CAN$12,500 and CAN$19,600 for letrozole and anastrozole, respectively, relative to tamoxifen. The authors concluded that both letrozole and anastrozole are economically acceptable alternatives to tamoxifen.

Conclusions

The Femara Study PO25 has provided evidence from a well-powered, randomized, controlled trial to show that letrozole provides a significant advantage in OS compared with tamoxifen as first-line treatment of patients with advanced breast cancer [53]. Letrozole is the only aromatase inhibitor to demonstrate consistent superiority over tamoxifen in this setting [53, 54].

Randomized first-line therapy trials of anastrozole, as part of the TARGET study [63–66], and exemestane in the EORTC study [67, 68] have provided evidence of clinical equivalence or superiority to tamoxifen in post-menopausal women with advanced breast cancer. However, none of these trials demonstrated statistically significant improvements in all three end points (ORR, TTP, and OS) for the aromatase inhibitor compared with tamoxifen. The PO25 study was the largest of these randomized trials in the first-line setting and demonstrated extremely strong clinical benefits, evidenced by significant superiority in TTP and ORR, with letrozole compared with tamoxifen as first-line hormone therapy. The benefits of letrozole were observed in all patient subgroups, defined by prior antiestrogen therapy, dominant site of metastatic disease, HR status (positive or unknown), and age [52–55]. Furthermore, letrozole is the only aromatase inhibitor associated with an OS advantage for the first-line setting indication at 1-year and 2-year follow-up [53]. As demonstrated in the exploratory analysis of patients who did not cross over to the alternative treatment arm, letrozole prolonged OS by 14 months compared with tamoxifen. Thus, for every 100 patients treated with hormone therapy, eight more will be alive at 1 year if they receive letrozole instead of tamoxifen.

In conclusion, third-generation aromatase inhibitors are effective and well tolerated. Letrozole should be considered as the first-line endocrine treatment in post-menopausal women with hormone-sensitive advanced or MBC. Of the available agents, only letrozole has demonstrated significant improvements in ORR, TTP, and early OS.

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