Femara® (letrozole tablets)

ONCOLOGIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

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First-Line Breast Cancer Indication

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LIST OF STUDIES

Study	Objective	Patients	Treatment duration	Treatments
025	Randomized, phase III, double-blind, crossover; first-line treatment (completed)	939[1]	Until progression or withdrawal	Letrozole 2.5 mg/day Tamoxifen 20 mg/day*
024	Randomized, phase III, double-blind, 2 parallel groups; preoperative treatment (completed)	337[3]	4 months	Letrozole 2.5 mg/day Tamoxifen 20 mg/day*
012	Randomized, double-blind, 3 parallel groups; first-line treatment (completed)	32[2]	Until progression or withdrawal	Letrozole 0.5 mg/day Letrozole 2.5 mg/day Tamoxifen 30 mg/day
026	Randomized, open-label; first-line treatment (discontinued)	18[4]	Until disease progression or withdrawal from study	Letrozole 2.5 mg/day Letrozole 2.5 mg plus Tamoxifen 20 mg/day*
0102	Bioequivalence, double-blind, intrapatient crossover; single-dose study	36	Single-dose in healthy post-menopausal women	Tamoxifen (Nolvadex®) versus Tamofen® (generic tamoxifen)

*Tamofen (generic tamoxifen) was used.

[1]Letrozole: n = 458; tamoxifen: n = 458; combination: n = 23.

[2] Letrozole 0.5 mg: n = 10; Letrozole: n = 12; tamoxifen 30 mg: n = 10.

[3] Letrozole: n = 162; tamoxifen: n = 175.

[4] Letrozole: n = 9; Letrozole + tamoxifen: n = 9.

EXECUTIVE SUMMARY

Development History of Femara[®] in Second-Line Therapy of Breast Cancer

Femara (letrozole, Novartis Pharmaceuticals Corporation, East Hanover, NJ) is a potent, selective aromatase inhibitor that specifically blocks estrogen biosynthesis. Femara is registered worldwide for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.[1-4]

Two large, randomized, controlled, multinational clinical trials were the basis of approval of Femara by the US FDA in 1997. In one trial, patients were randomized to Femara (0.5 or 2.5 mg daily) or a comparator (megestrol acetate [160 mg daily]), and aminoglutethimide (250 mg BID) with corticosteroid supplementation in the other trial. In these trials, Femara (2.5 mg) significantly reduced the relative risk of progression compared with either megestrol acetate or aminoglutethimide. Femara was also better tolerated with a superior safety profile than either comparator. The results of an additional phase III trial (Study 02) that compared the same 2 doses of Femara with megestrol acetate (160 mg daily) demonstrated that both doses of Femara were at least as efficacious as megestrol acetate and that the 0.5 mg dose improved time to progression (TTP). A meta-analysis of these three trials support that Femara 2.5 mg is effective and likely to produce good objective response rates and longer disease control when used as second-line hormonal therapy (data on file).

Development History of Femara[®] in First-Line Therapy of Breast Cancer

The efficacy and safety of Femara in the second-line treatment of advanced breast cancer in postmenopausal women, supported its development in first-line treatment. In November 1996, one large, double-blind, double-dummy, well-controlled, randomized, multinational, phase III study (Study 025) was initiated comparing Femara as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer against the current standard of care, tamoxifen.

In addition, 2 small, pilot studies (Studies 012 and 026) in first-line treatment of advanced breast cancer in postmenopausal women were also conducted. Study 012 was initiated prior to the pivotal trial, Study 025. Study 012 used the same comparator, tamoxifen, as Study 025 and randomized patients to 0.5 and 2.5 mg daily doses of Femara and 30 mg of tamoxifen. This trial was initiated before the second-line studies were completed and was discontinued early, after 32 patients were enrolled, when the 2.5 mg dose was approved as second-line treatment. Study 026 was initiated in November 1996 and was a phase II, open-label study that compared Femara at 2.5 mg daily doses to Femara at 2.5 mg in combination with 20 mg tamoxifen. This study was discontinued after 18 patients were enrolled when the results of a pharmacokinetic interaction study indicated that adding tamoxifen to Femara reduced mean Femara blood levels (AUC) by 38%.[5]

Study 024, initiated in March 1998, was a double-blind, double-dummy, well-controlled, randomized, multinational phase II/III study comparing Femara or tamoxifen for 4 months prior to surgery in postmenopausal patients with ER and/or PgR positive, stage II/III primary breast cancer. Study 024 was supportive of the pivotal Study 025 in that it preselected a group of breast cancer patients who would most likely respond to endocrine therapy (postmenopausal

women with ER and/or PgR positive tumors) and who were more importantly never exposed to either endocrine or other forms of therapy. Therefore, these truly therapy-naive patients represented an appropriate group of patients in whom to evaluate differences between two endocrine therapies.

Pivotal Study 025

Study Design

Study 025 was a double-blind, double-dummy, randomized, multinational, phase III trial comparing Femara versus tamoxifen as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. The original protocol was designed as a comparison of 3 arms: 2.5 mg Femara, 20 mg tamoxifen, and the combination of 2.5 mg Femara plus 20 mg tamoxifen; however, preliminary data from a pharmacokinetic study indicated that adding tamoxifen to Femara reduced Femara blood levels (AUC) by 38% on average.[5] Therefore, the combination therapy arm was dropped. The protocol was amended to demonstrate superiority of Femara over tamoxifen using time to progression as the primary endpoint. Patients were randomized to initial double-blind therapy with Femara (2.5 mg daily) or tamoxifen (20 mg) until progression or discontinuation of initial treatment. At such time patients were allowed to cross over to the alternative therapy still under double-blind conditions if they still qualified for further endocrine therapy. All patients were followed for survival. Secondary endpoints included rate and duration of overall tumor response (CR + PR), rate and duration of clinical benefit (CR + PR + SD $\geq$ 6 months), time to treatment failure (TTF), overall survival, and safety.

A total of 916 patients were randomly assigned treatment on the monotherapy arms in 29 countries from 201 centers. The intent-to-treat (ITT) population included a total of 907 patients, 453 on Femara and 454 on tamoxifen. The results presented here on the ITT population represent the primary analysis of all efficacy endpoints (excluding survival and safety) from the initial treatment phase (ie, first-line therapy). Data are current until March 8, 2000. The efficacy results of the "ITT" and "all randomized patients" populations are nearly identical. A subsequent supplementary analysis that will report the results of the crossover treatment and also include the final analysis of survival for the ITT population, is anticipated in the fourth quarter of 2001. This study represents the largest randomized phase III study of endocrine therapy in postmenopausal women with advanced breast cancer.

Patient Demographic and Efficacy Results

Important patient characteristics and major efficacy results are shown in Table 1.

Femara was superior to tamoxifen in prolonging time to progression and time to treatment failure, and in the rates of overall objective response and clinical benefit. There were no significant differences between treatments in duration of overall tumor response or in duration of clinical benefit.

Table 1. Study 025 Summary of Demographic Characteristics and Efficacy Results

	Femara® (N = 453), n (%)	Tamoxifen (N = 454), n (%)
Patient Demographics		
Median Age, years (range)	65 (31 – 96)	64 (31 – 93)
WHO Performance Status		
0	253 (56)	264 (58)
1	170 (38)	150 (33)
2	30 (7)	39 (9)
Receptor Status		
ER and/or PgR positive	294 (64)	305 (67)
Both Unknown	156 (35)	149 (33)
Disease Stage		
III B	25 (6)	32 (7)
Metastatic disease	422 (93)	419 (92)
Efficacy results		
Median time to progression*, months	9.4	6.0
	$P = .0001$	
Median time to treatment failure*, months	9.1	5.7
	$P = .0001$	
Confirmed response rate (CR + PR), %**	137 (30)	92 (20)
	$P = .0006$	
Clinical benefit rate (CR + PR + SD $\geq$ 6 months), %**	221 (49)	173 (38)
	$P = .001$	

CI = Confidence interval; CR = Complete response; PR = Partial response; SD = Stable disease.

WHO = World Health Organization, ER = Estrogen receptor, PgR = Progesterone receptor

* Cox regression analysis, ** Logistic regression analysis

A full survival analysis was initially planned to be conducted at the end of year 2001 at the time of completion of the supplementary analysis. The protocol was subsequently amended to include two interim analyses. The primary analysis indicated that Femara was superior to tamoxifen in all main endpoints (ie, TTP, TTF, and rates of objective response and clinical benefit). As became obvious, the protocol-specified evaluation of the number of deaths in each treatment arm differed from expectation, and it might be advisable to constitute a group of experts to consider whether there were any issues that would warrant a modification of the trial or analysis plan. In order to maintain the integrity of the survival analysis, Novartis convened an independent, external Data Monitoring Committee (DMC) under the chairmanship of Dr. Thomas Fleming, University of Washington, Seattle. The DMC recommended that a formal group sequential analysis plan be implemented for overall survival with O'Brien-Fleming type boundaries and Lan-DeMets alpha spending function to maintain an overall two-sided significance level of $P = .05$ with a maximum of 3 looks at the data. The results of the survival data at the time of the primary analysis constitute the first interim look. The second look would be 6-9 months later. These decisions were made prior to the DMC's learning the results of the formal survival analysis. The recommendation of the DMC with regard to the first interim analysis was that no results be disclosed. The results of the second interim analysis may or may not be presented at the ODAC meeting pending the recommendations of the DMC.

Safety

Discontinuations due to adverse events were reported in 2% of Femara-treated patients and in 3% of tamoxifen-treated patients. The nature and frequency of adverse events irrespective of study drug relationship were similar for Femara-treated patients and tamoxifen-treated patients. The most frequently reported adverse events were bone pain, hot flashes, back pain, and nausea. Thromboembolic events were reported in 6 (1%) patients in the Femara group and in 11 (2%) patients in the tamoxifen group. Pulmonary embolus was reported in 2 patients, 1 in each treatment group.

Overall, Femara was safe and very well tolerated.

Supportive Study 024

Study Design

Study 024 was a double-blind, double-dummy, randomized, multinational, Phase II/III study comparing once-daily doses of Femara (2.5 mg) or tamoxifen (20 mg) for 4 months prior to surgery in postmenopausal patients with ER and/or PgR positive, stage II/III primary breast cancer. Response rate (CR + PR) was the primary endpoint as assessed by clinical palpation (the primary endpoint) and by ultrasound and mammography. In addition, the rate of breast conserving surgery was to be compared. In total, 337 patients were enrolled at 55 centers in 16 countries. The intent-to-treat population included 154 patients on Femara and 170 on tamoxifen.

Efficacy and Safety Results

The important demographic characteristics and efficacy results of Study 024 are shown in Table 2.

Table 2. Study 024 Summary of Demographic Characteristics and Efficacy

	Patients, no. (%)	
	Femara® (2.5 mg) (N =154)	Tamoxifen (20 mg) (N =170)
Demographics		
Age, years		
Median (range)	68 (44 - 91)	67 (48 - 89)
Receptor status		
ER+ and PgR+	90 (58)	91 (54)
ER+ or PgR+	64 (42)	76 (45)
Tumor stage		
T2	77 (50)	91 (54)
T3	42 (27)	31 (18)
T4	35 (23)	48 (28)
Efficacy results*		
Clinical response	85 (55)	61 (36)
	($P < .001$)	
Ultrasound response	54 (35)	43 (25)
	($P = .042$)	
Mammographic response	53 (34)	28 (17)
	($P < .001$)	
Breast-conserving surgery	69 (45)	59 (35)
	($P = .022$)	

ER = Estrogen receptor; PgR = Progesterone receptor.

* Stratified Mantel Haenszel test

      Both treatment groups were well-balanced with regard to demographic and baseline disease characteristics. The median age of the study population was 67 years (range, 44-91 years). All but 3 patients were ER and/or PgR receptor positive. Regardless of the method of evaluation, the response rate was significantly higher in the Femara group compared with the tamoxifen group. In addition, a significantly greater proportion of patients treated with Femara were able to undergo breast-conserving surgery. In Study 024, Femara was equally safe and well tolerated compared with tamoxifen.

Overall Conclusions

The results of the pivotal Study 025 demonstrate that Femara is superior to tamoxifen in time to progression, objective tumor response rate, clinical benefit rate and time to treatment failure in first-line therapy of postmenopausal women with advanced breast cancer. Study 024 confirmed the superiority of Femara compared with tamoxifen in overall response rate as assessed by clinical palpation, ultrasound, mammography, and rate of breast-conserving surgery in a selected group of postmenopausal patients with primary hormone-sensitive breast cancer in whom potential bias due to previous treatment with tamoxifen or other therapies was eliminated. The safety results of both studies demonstrate that Femara is equally well tolerated compared with tamoxifen and is safe.

These data support our first-line study 025 results comparing Femara to tamoxifen and further demonstrate that treatment with Femara is associated with:

- Significantly longer time to progression

- Significantly higher objective tumor response rate

- Significantly higher clinical benefit rate

- Significantly longer time to treatment failure

- Consistently superior results in all subgroup analyses

Given the consistently superior results demonstrated in these trials, Novartis is seeking expanded label indication *for first-line therapy in postmenopausal women with advanced breast cancer*.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AUC	Area under the curve
BID	Twice daily
CI	Confidence interval
CNS	Central nervous system
COSTART	Coding symbols for a thesaurus of adverse reaction terms
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ER	Estrogen receptor
FDA	US Food and Drug Administration
FPFV	First patient, first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IU	International Units
ITT	Intent to treat
K_i	Inhibitory constant
KPS	Karnofsky performance status
LH	Luteinizing hormone
NA	Not applicable
NA/NE	Not assessable/not evaluable
NCI	National Cancer Institute
NDA	New Drug Application
NOS	Not otherwise specified
NSAIDs	Nonsteroidal anti-inflammatory drugs
ODAC	Oncologic Drugs Advisory Committee
ORR	Objective response rate
PD	Progression of disease
PK	Pharmacokinetics
PgR	Progesterone receptor
PR	Partial response
SAE	Serious adverse events
SAERS	Serious Adverse Event Reporting System
SD	Stable disease
TTF	Time to treatment failure
TTP	Time to tumor progression
TTR	Time to response
TSH	Thyroid-stimulating hormone
UICC	International Union Against Cancer
US	United States
WHO	World Health Organization

1.0   BACKGROUND

1.1   Existing Therapies for Postmenopausal Women With Advanced Breast Cancer

Breast cancer is an estrogen-dependent tumor and, therefore, inhibition of estrogen action or production provides an effective therapy for patients with hormone-dependent breast cancer.[6,7] In postmenopausal women, the major source of estrogens is from the conversion of adrenal androgens to estrogens by the aromatase enzyme present in peripheral tissues (eg, adipose tissue). Selective aromatase inhibition results in suppression of estrogen production without influencing adrenal steroidogenesis. This deprives the tumor cells of their growth stimulus. Another approach that deprives tumor cells of their growth stimulus is to block the ER with an antiestrogen (eg, tamoxifen). The goals of hormonal therapy are to induce tumor regression or stabilization, delay progression, and prolong survival, with minimal impact on the patient's quality of life.

Approximately 60 - 75% of postmenopausal women with breast cancer will be ER positive, with ER status highly dependent on age.[7,8] It has been hypothesized that similar percentages of postmenopausal women with unknown hormone receptor status would be ER and/or PgR positive. Currently, tamoxifen is the standard of care as first-line therapy in postmenopausal women with endocrine sensitive advanced breast cancer. Although this agent is generally well tolerated, its adverse effects (eg, increased incidence of endometrial cancer) are related to its estrogenic effects in certain tissues. The use of tamoxifen has also been reported to increase the incidence of uterine carcinoma and thromboembolic events. Although these events occur infrequently, they are of important clinical consequence to the patient. Thus, there is a need for more well-tolerated alternative hormonal therapies for postmenopausal women with advanced breast cancer.

1.2   Overview of Femara®

Femara tablets for oral administration contain 2.5 mg of letrozole, a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). It is chemically described as 4,4'-(1H-1,2,4-Triazol-1-ylmethylene) dibenzonitrile, and its structural formula is shown in Figure 1.
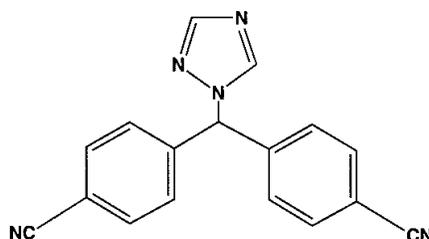

Figure 1.—Molecular structure of Femara.

1.2.1 Pharmacology

Letrozole is a potent and selective inhibitor of estrogen biosynthesis. It is a nonsteroidal inhibitor of the aromatase enzyme system that inhibits the conversion of androgens to estrogens by competitively binding to the heme of the cytochrome P450 subunit of the enzyme.

Pharmacodynamic in vitro studies demonstrated that letrozole competitively inhibits the human placental microsomal aromatase enzyme and is about 150- to 250-fold more potent than aminoglutethimide.[9,10] Similarly, letrozole was approximately 650 times more potent than aminoglutethimide in inhibiting estrogen production and, unlike aminoglutethimide, letrozole did not inhibit adrenal steroidogenesis in vitro.[11,12] In vivo studies have also demonstrated that letrozole is > 10,000-fold more potent than aminoglutethimide with respect to inhibition of aromatase enzyme activity.[9-11] In adult female animals, letrozole is as effective as ovariectomy in reducing uterine weight, elevating serum luteinizing hormone (LH) level, and causing the regression of estrogen-dependent tumors. In contrast with ovariectomy, treatment with letrozole does not lead to an increase in serum follicle-stimulating hormone (FSH) level. letrozole selectively inhibits gonadal steroidogenesis but has no significant effect on adrenal mineralocorticoid or glucocorticoid synthesis. In a model that is more appropriate to human breast cancer, the effects of long-term administration of letrozole on spontaneously occurring rat mammary tumors was examined. In this long-term study, 2 years of letrozole treatment completely blocked the spontaneous appearance of both benign and malignant mammary tumors. Furthermore, treatment of aromatase transgenic mice with letrozole (5 µg/day) resulted in complete reduction or disappearance of breast hyperplasia and other preneoplastic and neoplastic changes that were induced as a consequence of the overexpression of aromatase in the mammary gland.

In humans, the activity of letrozole has been demonstrated by measuring the suppression of circulating estrogen (estrone and estradiol) levels in healthy volunteers and patients with breast cancer, as well as by assessing the inhibition of in vivo aromatization of radiolabeled androstenedione into estrone. Other hormones, including cortisol, aldosterone, testosterone, androstenedione, 17-α-OH-progesterone, LH, FSH, TSH, or renin, were not affected to any clinically significant level by treatment with letrozole. In postmenopausal women with metastatic breast cancer, letrozole suppressed estrone and estrone sulfate levels significantly better than anastrozole.[13]

Supply of estrogens to the tumor is, however, not only from the circulation, but also from biosynthesis within the tumor. Letrozole has been shown not only to substantially reduce intratumoral aromatization, but also the total estrogen burden of the tumors through inhibition of peripheral estrogen synthesis.[14]

The results of these pharmacodynamic studies demonstrated that letrozole is a very potent and highly selective inhibitor of aromatase in both in vitro and in vivo experimental models and in humans.

1.2.2 Human Pharmacokinetics and Metabolism

Letrozole is rapidly absorbed and completely bioavailable after oral administration, and food has no effect on the bioavailability.[15,16] The plasma PK profile of letrozole in humans is characterized by a dominant terminal elimination phase, with a half-life of approximately 2 days

in healthy volunteers. The clearance of letrozole is mainly via metabolism to its major carbinol metabolite, CGP44645, which has no pharmacologic activity. Renal clearance of the parent compound represents only approximately 5% of total clearance. The glucuronidated carbinol metabolite is excreted by the kidneys. Approximately 60% of letrozole is bound to plasma proteins, mainly to albumin.[17]

In vitro experiments suggested that the cytochrome P450 isoenzymes 3A4 and 2A6 (CYP3A4, CYP2A6) mediate the metabolic clearance of letrozole.[18] The affinity of CYP3A4 for letrozole appears to be low, and saturation of the enzyme could not be achieved at concentrations far exceeding physiologic levels. The affinity of CYP2A6 for letrozole could not be well defined, but the experiments suggested that it is high, and saturation may occur in the low micromolar range. Letrozole was also shown to be a very strong inhibitor of CYP2A6, with a K_i = 0.12 µM. This suggested that the PK of letrozole might show some nonlinearity due to autoinhibition/saturation of CYP2A6.

In clinical studies, slight deviations from linearity were observed at steady state. Systemic exposure increased proportionally to doses up to 1 mg/day, but steady-state plasma concentrations were higher than predicted at doses $\geq$ 2.5 mg/day, although patients achieved steady state at all doses. At a dose of 10 mg/day plasma levels increased approximately proportionally to those observed at 5 mg/day, indicating no further or only minimal deviation from linearity between these 2 doses. Thus, nonlinearity appears to be observed in the dose range of 2.5 to 5 mg/day. This is consistent with the hypothesis that nonlinearity in the PK of letrozole is a result of partial inhibition of its metabolic clearance due to an autoinhibition/saturation of CYP2A6, whereas clearance may be dose-independent (although lower) at higher doses and at concentrations at which CYP3A4 becomes the dominant metabolizing enzyme.

No dose adjustment is needed in elderly patients or in patients with renal creatine clearance $\geq$ 10 mL/min or moderate hepatic insufficiency, because the PK of letrozole was not markedly changed in these populations. Patients with severe hepatic impairment (Child-Pugh score C) are expected to be exposed to considerably higher levels of letrozole, corresponding to a daily dose of about 5 mg. However, given that normal patients who received daily doses of 5 or 10 mg/day did not show an increased toxicity compared with normal patients who received 2.5 mg/day, no dose adjustment is warranted in patients with severe hepatic dysfunction, although such patients should be kept under close supervision and carefully monitored for adverse events. Prolonged exposure to letrozole in patients with significant liver damage, as indicated by markedly elevated transaminases, bilirubin, or alkaline phosphatase (grade 3 or 4 according to NCI common toxicity criteria), showed mean plasma letrozole levels within the normal range. Thus, no dose adjustment is needed for breast cancer patients with evidence of liver damage.

Letrozole showed no interaction with warfarin or cimetidine, and a review of the data from the phase III trials, as well as in vitro studies of cytochrome P450 enzymes, indicated that letrozole has a low potential for drug interactions. However, concomitant administration of letrozole (2.5 mg/day) and tamoxifen (20 mg/day) resulted in decreased steady-state levels of letrozole; the AUC was reduced by 38% on average.[5] The mechanism of this interaction is not known, but induction of CYP3A4 by tamoxifen was considered to be a likely explanation. The clinical relevance of this finding has not been investigated. Letrozole appears to have no effect on plasma levels of tamoxifen in combination therapy.[19]

1.3 Efficacy and Safety of Femara® in Second-Line Therapy

Two large, randomized, controlled, multinational clinical trials were the basis of approval of Femara by the US FDA in 1997 in the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.[1-3] In the first trial, patients were randomized to Femara (0.5 or 2.5 mg daily) versus megestrol acetate (160 mg daily); in the second trial, patients were randomized to Femara (0.5 or 2.5 mg daily) versus aminoglutethimide (250 mg BID) with corticosteroid supplementation. In each trial > 60% of the patients had received therapeutic antiestrogens, and approximately 20% of patients had an objective tumor response. The megestrol acetate-controlled trial was double-blind; the aminoglutethimide-controlled trial was open-label. Objective tumor response was the primary endpoint of both trials.

1.3.1 Efficacy

In the first trial comparing Femara with megestrol acetate (N = 552), 2.5 mg Femara produced a 24% objective response rate compared with 16% in the megestrol acetate group (odds ratio = 1.58; 95% CI = 0.94 to 2.66; P = .08).[1] With a minimum follow-up of 15 months, the risk of progression was significantly reduced in patients treated with 2.5 mg Femara compared with megestrol acetate (hazard ratio = 0.77, 95% CI = 0.60 to 0.98; P = .03).

In the trial comparing Femara with aminoglutethimide (N = 557), 2.5 mg Femara produced an 18% objective response rate compared with 12% in the aminoglutethimide group (odds ratio = 1.61; 95% CI = 0.90 to 2.87; P =0.11).[3] With a minimum follow-up of 9 months, Femara (2.5 mg) demonstrated a statistically significant reduction in the risk of progression compared with aminoglutethimide (hazard ratio = 0.74; 95% CI = 0.57 to 0.94; P = .02). Overall survival was statistically significantly improved compared with aminoglutethimide, with a reduction of approximately 30% in the risk of death with Femara (hazard ratio = 0.69; 95% CI = 0.53 to 0.91; P < .05).[1]

1.3.2 Safety Profile

Femara was safe and well tolerated in both of these trials and was better tolerated than either megestrol acetate or aminoglutethimide. The most commonly reported adverse events irrespective of study drug relationship in patients treated with 2.5 mg Femara were musculoskeletal pain (includes musculoskeletal pain, skeletal pain, back pain, arm pain, and leg pain) (21%), nausea (13%), headache (9%), arthralgia (8%), fatigue (8%), vomiting (7%), and dyspnea (7%). No adverse event appeared to be dose related. There were fewer thromboembolic events at both Femara doses than on the megestrol acetate arm (<1% vs. 5%). There was also less vaginal bleeding (0.3% vs. 3%) on Femara than on megestrol acetate. In addition, patients treated with megestrol acetate had a higher incidence of weight gain, 9% vs. 2% Femara and dyspnea 16% vs. 7% Femara.

2.0   PHASE II/III TRIALS (FIRST-LINE)

Generic tamoxifen (Tamofen[®], Leiras OY, Finland) was used as the comparator in the international studies 026, 025 and 024. Because this generic tamoxifen is not commercially available in the United States, a bioequivalence study was conducted, to determine if the generic tamoxifen approved and marketed in Europe had equivalent biologic activity to Nolvadex[®] available in the United States. The results confirmed the bioequivalence and equivalent pharmacokinetics of generic tamoxifen and Nolvadex.

2.1   Phase II Trials of Femara[®] in First-Line Therapy

2.1.1   Randomized Phase II Trial (Study 012)

A. Study Design

A phase II, randomized, double-blind, 3-arm study was conducted to determine the antitumor effects of Femara at doses of 0.5 and 2.5 mg daily compared with tamoxifen (30 mg daily) in the first-line treatment of postmenopausal women with advanced breast cancer. This pilot study was initiated before the second-line studies were completed and was discontinued early because of the worldwide approval of Femara at the 2.5 mg dose. A total of 75 patients was planned, but accrual was stopped after 32 patients had been enrolled. Ten patients were randomly assigned Femara (0.5 mg), 12 Femara (2.5 mg), and 10 tamoxifen (30 mg). Patients were treated until disease progression or withdrawal from the study for other reasons. The efficacy data for the Femara groups were pooled for analysis.

B. Results

The overall response rate (CR + PR) was 55% (12/22) for Femara and 20% (2/10) for tamoxifen. Complete response was observed in 3 (14%) patients treated on Femara and in none on tamoxifen; clinical benefit rate (CR + PR + SD $\geq$ 6 months) was 68% (15/22) on Femara and 30% (3/10) on tamoxifen. The median TTP was 17 months (95% CI = 6 to 30 months) on Femara and 3 months on tamoxifen (95% CI = 3 to 18 months). The responses were demonstrated at both 0.5 mg and 2.5 mg. The duration of objective tumor response (CR + PR) ranged from 10 to 37+ months in the Femara group. In the tamoxifen group, the duration of response in the 2 patients with PR was 18 months and 34+ months. Reported adverse events were consistent with the known toxicity profiles associated with Femara and tamoxifen. Although the study was stopped prematurely and the numbers of patients are too small to be conclusive, the efficacy results (time to progression, overall objective tumor response, duration of treatment, and patient population) are consistent with the pivotal Study 025.

2.1.2   Randomized Phase II Trial (Study 026)

A randomized, open-label, phase II trial was conducted to compare the efficacy of 2.5 mg Femara daily with the combination of 2.5 mg Femara plus 20 mg tamoxifen daily. This trial was discontinued after enrolling only 18 patients because preliminary data from a pharmacokinetic study indicated that adding tamoxifen to Femara reduced Femara blood levels (AUC) by 38% on average.[5] The objectives of this study were primarily for safety and no efficacy data were analyzed. Reported adverse events were consistent with the known safety profile associated with Femara.

3.0 PIVOTAL PHASE III STUDY 025

3.1 Study Design

Pivotal Study 025 was a double-blind, double-dummy, randomized, multinational, phase III trial comparing Femara (2.5 mg) versus tamoxifen (20 mg) daily as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. The original protocol was designed as a comparison of 3 groups: 2.5 mg Femara, 20 mg tamoxifen, and the combination of 2.5 mg Femara plus 20 mg tamoxifen; however, preliminary data from a pharmacokinetic study[5] indicated that adding tamoxifen to Femara reduced Femara blood levels (AUC) by 38% on average. Therefore, the study was amended to drop the combination group and the sample size considerations were based on demonstration of superiority of one treatment over the other for time to progression. All efficacy and safety analyses were based on the 2 monotherapy groups and these results are presented.

Initial study treatment was administered until progression of disease or until some other reason necessitated discontinuation from the initial treatment. If at progression the patient remained suitable for further endocrine treatment, she could be switched to the alternative treatment (ie, crossover) still under double-blind conditions or if not suitable, could discontinue treatment. Patients were followed for overall survival at discontinuation of study treatment(s) and every 6 months thereafter.

The dose of 2.5 mg of Femara once daily is the approved dose for treatment of advanced breast cancer in postmenopausal patients with disease progression following antiestrogen therapy. A daily dose of Femara 2.5 mg was therefore selected for the current study as first-line treatment of patients with advanced breast cancer. Manufacturer's recommendations for tamoxifen in the treatment of patients with advanced breast cancer refer to a daily dose of 20 to 40 mg of tamoxifen. The 20 mg dose of tamoxifen is commonly employed in clinical practice in the United States and Europe, and was therefore chosen as the comparator in this study.

3.1.1 Entry Criteria

Postmenopausal women with histologically or cytologically confirmed stage IIIB locally advanced or locoregional recurrence not amenable to treatment by surgery or radiotherapy, or with metastatic breast cancer, met the eligibility criteria for entry into this study. Eligible patients had either ER and/or PgR positive tumors or with both receptors unknown; Karnofsky Performance Status of ≥ 50; and measurable or evaluable disease. However patients with only blastic bone lesions were allowed and these lesions were considered as nonevaluable lesions. Patients previously treated for metastatic disease (only one previous regimen of chemotherapy) were to have objective evidence of progression and no prior systemic endocrine treatment for metastatic disease was allowed. Patients with CNS metastases, or diffuse involvement of the lung and liver or inflammatory breast cancer, were not eligible. Patients with a recurrence of breast cancer on adjuvant tamoxifen therapy or recurrence within 12 months of completing adjuvant tamoxifen therapy were also ineligible. Concomitant bisphosphonate treatment was permitted at randomization for the treatment of bone metastases only.

3.1.2 Randomization Procedures: Treatment Assignment and Blinding

The two treatments were randomly assigned according to a predetermined, computer-generated randomization list using permuted blocks of a fixed size. The double-dummy technique was used to ensure that study treatments were blinded. The treatments were unblinded for the preparation of the Clinical Study Report and regulatory submissions when statistical analysis of the core phase was performed, although investigators and patients remained blinded. Emergency code breaks occurred in 16 patients (11 on Femara, 5 on tamoxifen). These were not due to real emergencies, but to determine further treatment of the patients after termination. No true emergency code breaks occurred in this study. There was no stratification for any demographic variables; however, randomization and packaging were stratified according to linguistic group. Investigators were instructed to take the next lowest number pack available for each subsequent patient enrolled.

3.1.3 Treatment Administration: Study Drug

Study drug was dispensed by center. Femara was provided as 2.5 mg film-coated tablets for daily oral administration. Tamoxifen was provided as 20 mg tablets for daily oral administration. Patients failing first-line treatment with tamoxifen switched to blinded treatment with Femara and vice versa. Supply of either core or crossover study medication was continued as long as a patient was responding (CR, PR, or SD) to treatment. A double-dummy technique was used to ensure blinding.

3.1.4 Types and Timing of Assessments

A. Efficacy Assessments

Tumor measurement and response.—Evaluations of tumor response were performed according to UICC criteria 3 months after the start of treatment and every 3 months thereafter, or when the patient discontinued treatment, with modifications to include liver, lung, or soft tissue lesions of a minimal size and all involved sites rather than a representative indicator lesion. An external peer review on all tumor imaging was to be performed to determine response and the date and site of progression for the core phase of the study. Experience from Novartis' second-line studies showed no important difference in the overall conclusions when external peer review assessments were compared to the assessments by investigators. Therefore, the first-line protocol was amended to replace the external peer review with a blinded internal review of all patients' data by a committee of Novartis personnel. Overall tumor response and in particular, progression of disease, were reviewed internally against the investigator's reported response. Discrepancies were resolved with the investigator.

In each institution all images of all patients were to be reviewed by the same professional ("center-specific radiologist"). Depending on the institution, the "central radiologist" could have been one person or several specialists each assigned to a specific technique (eg, ultrasound, CT scan, nuclear medicine scan). The purpose of the central radiologist's review was to allow uniformity in the assessment of tumor response.

B. Safety Assessments

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events (with their severity classified according to the NCI Common Toxicity Criteria (Version 1.3) and relationship to study drug), the regular monitoring of hematology and blood chemistry, and the performance of physical examinations. Hematologic and blood chemistry tests including hemoglobin, hematocrit, and liver and kidney function were performed.

3.1.5 Statistical Analysis

A. Endpoints

The primary efficacy endpoint was time to progression. Additional efficacy variables included overall objective tumor response rate (CR + PR), duration of overall objective tumor response, clinical benefit rate (CR + PR + SD ≥ 6 months), duration of clinical benefit, time to treatment failure, number of deaths, and overall survival. Safety was characterized in terms of the incidence of adverse events, laboratory abnormalities, discontinuations due to adverse events, and deaths.

B. Core and Extension Phase

The core phase was defined as the interval from first patient randomization until 632 patients had reached the primary endpoint of progressive disease. The crossover (second-line) treatment period of a patient was defined as the time at which a patient was switched to crossover treatment until further progression of disease or until discontinuation for any other reason, whichever occurred earlier. The extension phase was defined as the interval from the end of the core phase until approximately 18 months later, or sooner if all patients discontinued second-line study treatment (ie, crossover treatment) earlier for any reason. It is expected that at this time point the majority of patients on crossover treatment will have progressed and that approximately 72% of patients will have died.

The results of the core phase (ie, first-line treatment, primary analysis) are presented here. A supplementary analysis is planned at the time of analysis of the extension phase to report cross-over data and to conduct the final analysis of overall survival (time to death).

Primary analysis.—Time to progression and time to treatment failure were analyzed by Cox regression (proportional hazards model) estimating the hazard ratio of the risk of progression with Femara compared with the risk of progression with tamoxifen (standard), unadjusted for any baseline covariate. Kaplan-Meier curves were provided.

Overall tumor response (confirmed CR + PR) and rate of clinical benefit (defined as CR + PR + SD ≥ 6 months) were analyzed by a logistic regression procedure, unadjusted for any baseline covariate.

Duration of overall objective tumor response and duration of clinical benefit were calculated by two methods: 1) from date of randomization to earliest date of progression in patients who achieved an objective response or clinical benefit and 2) from onset date of response to earliest date of progression in patients who achieved an objective response or clinical benefit.

Supportive analysis.—A supportive, prospective multivariate analysis (Cox regression for TTP, logistic regression for ORR) was performed adjusting the treatment comparison for the key baseline covariates of receptor status (ER and/or PgR positive/otherwise), prior adjuvant treatment with antiestrogens (yes/no) and dominant site of disease (soft tissue/bone/viscera). The multivariate analysis examined the influence on TTP of each baseline covariate in the presence of all the other baseline covariates. Dominant site was defined as soft tissue if only soft-tissue disease was present (at baseline); as bone if skeletal metastases were present (regardless of coexistent soft-tissue disease) without involvement of visceral sites; and as viscera if visceral metastases were present (irrespective of soft-tissue or bone involvement).

Exploratory analysis.—Two types of prospective exploratory analyses were conducted: multivariate (Cox regression for TTP, logistic regression for ORR) adjusting the treatment comparison for all covariates in the model and stratified analyses (logrank for TTP, Mantel-Haenszel for ORR) examining each baseline covariate ("stratification factors") one covariate at a time, providing a treatment comparison adjusted across the strata of the covariate. These covariates included the 3 key baseline covariates (mentioned previously) as well as other baseline covariates of interest: duration of adjuvant antiestrogen treatment, treatment-free interval, geographic area, age, body mass index, and use of bisphosphonates

C. Survival Analyses

The protocol specified that a comparison of overall survival as assessed by log-rank analysis was to be performed as part of the supplementary analysis at the completion of the extension phase of the study, approximately 18 months following the primary analysis (end of 2001), and that at the time of the primary analysis for TTP the number of deaths during core treatment or within 6 weeks of stopping core treatment would be tabulated by treatment.

The primary analysis indicated that Femara was superior to tamoxifen in all main endpoints (TTP, TTF and rates of objective response and clinical benefit). As became obvious, the number of deaths in each treatment arm was different from expectation and it might be advisable to constitute a group of experts to consider whether there were any issues that would warrant a modification of the trial or analysis. In order to maintain the integrity of the survival analysis, Novartis convened an independent, external Data Monitoring Committee (DMC) under the chairmanship of Dr. Thomas Fleming, University of Washington, Seattle.

The DMC convened on May 9, 2000 to review the survival data, as well as the results of the primary analysis. The DMC recommended that a formal group sequential analysis plan be implemented for overall survival with O'Brien-Fleming type boundaries and Lan-DeMets alpha spending function to maintain an overall two-sided significance level of 0.05 with a maximum of 3 looks at the data. The results of the survival data at the time of the primary analysis constitute the first interim look. The second look would be 6-9 months later. These decisions were made prior to the DMC's learning of the formal survival analysis (for listing of committee members, see Appendix 1).

The recommendation of the DMC with regard to the first-line interim analysis was that no results be disclosed. The results of the second interim analysis are currently under review by the DMC and may or may not be presented at the ODAC meeting, pending the recommendation of the DMC.

D. Populations

All efficacy analyses, inferential or exploratory, were based on patients in the intent-to-treat population, who were randomly assigned study treatment with monotherapy and had advanced breast cancer at study entry, excluding patients at the one GCP-noncompliant center. Novartis took the decision to exclude these 5 patients from all analyses and all tabulations (including demographic characteristics). Efficacy analysis of TTP, rate and duration of overall response, and rate and duration of clinical benefit were performed for all randomized patients (N = 916) and for the protocol-specified ITT population of all randomized patients with active breast cancer at randomization (N = 911) and the results were almost identical to the ITT analysis presented here (N = 907).

The safety population excludes 6 patients from the monotherapy arms, 4 from the one GCP-noncompliant center (2 on each arm) and 2 who never received study medication (1 on each arm). Twenty-two of 23 patients assigned to combination treatment were included in the safety population. One patient was enrolled at the GCP non-compliant center.

3.1.6   *Sample Size and Power Considerations*

In the amended protocol, sample size was calculated on the primary endpoint, time to progression. Sample size was calculated assuming enrollment over 2 years, an exponential distribution, a reduction in the risk of progression under Femara of 20% compared with tamoxifen (i.e. hazard ratio of 0.80), minimum follow-up of around 14 months after enrollment of the last patient, two-sided significance at the 5% level, and 80% power. It was estimated that 632 events of progression should be observed (monotherapy). The calculated sample size was 900 patients. The same sample size allowed the detection of a 10% absolute difference in overall objective tumor response at the 5% significance level with 80% power, assuming an overall response rate of around 35% with tamoxifen.

3.1.7   *Patient Enrollment*

From November, 1996, through January, 1999, a total of 916 patients were randomized, 458 patients on each arm; from 201 centers in 29 participating countries (589 [64%] patients in Europe, 100 [11%] patients in North America and 227 [25%] in the Rest of the World). An additional 23 patients were randomly assigned the combination treatment.

The intent-to-treat population for the monotherapy arm excludes 9 patients: 5 who were randomly assigned study treatment (3 Femara, 2 tamoxifen) but were subsequently found not to have active breast cancer at study entry, and 4 patients from the one GCP-noncompliant center (2 on each arm). Efficacy analyses were based on the ITT population of the core phase of the study.

At the time of this analysis 43% of patients in both monotherapy groups received crossover treatment. In the Femara group, 111 patients remain on core treatment without evidence of progression compared with 67 in the tamoxifen group. All of these patients are in the ITT population. The median follow-up for the ITT population was approximately 18 months. The results that are to be presented here will be for the ITT population unless otherwise specified.

3.1.8 Patient Characteristics

The Femara and tamoxifen treatment groups were well balanced with respect to baseline demographic and disease characteristics (Table 3).

Median age was 65 years (range 31 to 96 years) for the study population. The majority (82%) of patients were WHO performance status 0 or 1 (Karnofsky 70 or better). Two-thirds of the patients were ER and/or PgR positive with the remainder of unknown receptor status. Ninety-three percent of the patients had metastatic disease at the time of randomization. Forty-four percent of the patients had disease in the viscera. Thirty-six percent of patients had only one organ involvement with tumor. The majority of patients had not received prior adjuvant chemotherapy (72%), prior adjuvant antiestrogen therapy (82%), or prior chemotherapy for advanced disease (90%).

Table 3. Patient Characteristics by Treatment Group

Characteristic	Femara® (N = 453), n (%)	Tamoxifen (N = 454), n (%)
Median age, years (range)	65 (31 - 96)	64 (31 - 93)
WHO performance status		
0	253 (56)	264 (58)
1	170 (38)	150 (33)
2	30 (7)	39 (9)
Race, no. patients		
White/Caucasian	385 (85)	393 (87)
Black	12 (3)	13 (3)
Oriental	28 (6)	25 (6)
Other	28 (6)	23 (5)
Disease stage		
IIIB	25 (6)	32 (7)
Metastatic	422 (93)	419 (92)
Disease-free interval*		
< 1 month	145 (32)	146 (32)
≥ 1 month to < 24 months	57 (13)	63 (14)
≥ 24 months	251 (55)	245 (54)
Receptor status		
ER+ and PgR+	174 (38)	186 (41)
ER+ or PgR+	120 (26)	119 (26)
Both unknown	156 (34)	149 (33)
Other	3 (1)	0
Dominant site of disease		
Soft tissue only	113 (25)	116 (25)
Bone ± soft tissue	146 (32)	130 (29)
Visceral ± bone ± soft tissue	194 (43)	208 (46)
Number of organ sites involved		
1	159 (35)	170 (37)
2	156 (34)	158 (35)
≥ 3	138 (30)	126 (28)
Prior therapy*		
Prior adjuvant chemotherapy	93 (21)	105 (23)
Prior adjuvant tamoxifen	84 (19)	83 (18)
Prior chemotherapy for advanced disease	40 (9)	48 (11)

*Includes patients with stage IV or earlier stage of disease at time of study entry.
WHO = World Health Organization; ER = Estrogen receptor; PgR = Progesterone receptor.

A. Baseline and Disease Characteristics in US Patients

Baseline demographic and disease characteristics for the US patients are summarized in Table 4.

Table 4. Baseline and Disease Characteristics (US and Canadian Patients)

Characteristic by geographic area (North America)	Femara® N=49	Tamoxifen N=51
Median age, years	67	70
Race, %		
White/Caucasian	82	84
Black	12	10
Oriental	2	2
Other	4	4
Estrogen receptor status positive, %	98	94
Prior adjuvant tamoxifen, %	33	28
Prior chemotherapy, %		
- adjuvant	27	22
- advanced	6	4

B. Baseline Laboratory Criteria (CTC Grade $\geq$ 1):

There were no baseline entry criteria for hematologic, renal, or liver function tests. The baseline values for a number of important laboratory criteria of CTC grade 1 or greater are summarized in Table 5.

Table 5. Baseline Laboratory Criteria (CTC Grade $\geq$ 1)

Baseline laboratory criterion	Femara®	Tamoxifen
Alkaline phosphatase	167 / 427 (39%)	148 / 423 (35%)
Hemoglobin*	38 / 452 (8%)	27 / 448 (6%)
Creatinine	25 / 452 (6%)	24 / 449 (5%)
Gamma glutamyltransferase	196 / 427 (46%)	201 / 423 (48%)
Aspartate aminotransferase	113 / 452 (25%)	103 / 449 (23%)
Alanine aminotransferase	106 / 452 (23%)	86 / 449 (19%)
Bilirubin	27 / 452 (6%)	22 / 449 (5%)

*CTC grade $\geq$ 2.

3.2 Efficacy

Remarkable consistency across major key efficacy endpoints (TTP, TTF, ORR, and clinical benefit rate) favoring treatment with Femara was demonstrated in this large, double-blind, phase III, randomized, multinational study. In addition, the robustness of the data favoring treatment with Femara was clearly demonstrated in all protocol-specified subgroup analyses of the primary endpoint of TTP and for most subgroup analyses of secondary endpoints.

3.2.1 Time to Progression

Femara was superior to tamoxifen in time to progression (Table 6; Figure 2), reducing the risk of progression by 30% compared with tamoxifen and prolonging median TTP by over 50% (hazard ratio = 0.70, 95% CI = 0.61 to 0.82, *P* = .0001). Fewer patients progressed on Femara (68%) than on tamoxifen (77%) during core treatment.

Because both treatments are relatively safe and TTF is closely correlated with TTP, Femara was significantly superior to tamoxifen in TTF (hazard ratio = 0.71; 95% CI = 0.61 to 0.82, *P* = .0001). Treatment failure occurred in 75% of patients in the Femara group and in 85% of patients in the tamoxifen group. Median TTF was 9.1 months for Femara and 5.7 months for tamoxifen.

Table 6. Study 025 Summary of Efficacy Results

	Femara® (N = 453)		Tamoxifen (N = 454)
Median time to progression, months*	9.4	*P* = .0001	6.0
Median time to treatment failure, months*	9.1	*P* = .0001	5.7
Confirmed response rate (CR + PR), n %**	137 (30)	*P* = .0006	92 (20)
Clinical benefit rate (CR + PR + SD ≥ 6 months), n %**	221 (49)	*P* = .001	173 (38)

CR = Complete response; PR = Partial response; SD = Stable disease.
*Cox regression.
** Logistic regression.
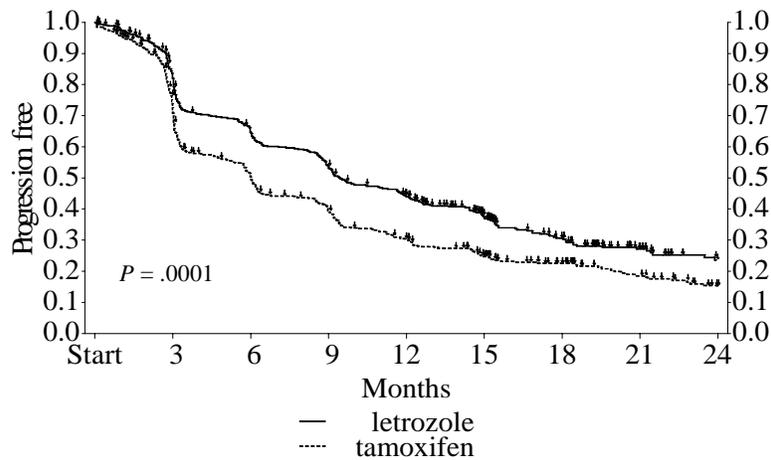
Figure 2.—Kaplan-Meier estimate of time to progression. *P* = .0001 (Cox regression analysis). Marks on curve = censored times.

A. Supportive Analysis

The analysis of TTP, adjusted for the key baseline covariates of receptor status, prior adjuvant antiestrogen treatment, and dominant site of disease, were almost identical to those of the unadjusted analysis, as described below.

The supportive analyses confirmed that

- Treatment with Femara significantly decreased the risk of progression (hazard ratio = 0.70; 95% CI = 0.60 to 0.81, *P* = .0001) and prolonged TTP (median, 9 months versus 6 months) compared with tamoxifen

- The presence of visceral metastases significantly increased the risk of progression (hazard ratio = 1.52; 95% CI = 1.25 to 1.85, *P* = .0001) compared with soft-tissue only disease

- The presence of bone metastases significantly increased risk of progression (hazard ratio = 1.26, 95% CI = 1.02 to 1.56, *P* = .03) compared with soft-tissue only disease

- Neither receptor status nor prior adjuvant treatment with antiestrogens significantly affected TTP

The stratified analyses (Table 7), conducted on the key baseline covariates one at a time, confirmed that the treatment difference adjusted over the strata for each covariate significantly favored Femara.

Table 7. Stratified Analysis of TTP by Baseline Covariates (Supportive Analysis)

| Baseline covariate | Femara® | | Tamoxifen | | Log-rank *P* value |
	No. events of progression (no. patients)	Median TTP, months	No. events of progression (no. patients)	Median TTP, months	
Prior adjuvant treatment					.0001
None	250 (369)	9.7	284 (371)	6.0	
Adjuvant treatment	58 (84)	8.8	66 (83)	5.9	
Receptor status					.0001
ER and/or PgR	199 (294)	9.7	235 (305)	6.0	
Unknown and other	109 (159)	9.2	115 (149)	6.0	
Dominant site					.0001
Soft tissue only	68 (113)	12.9	84 (116)	6.4	
Bone ± soft tissue	100 (146)	9.7	97 (130)	6.2	
Viscera ± bone ± soft tissue	140 (194)	8.3	169 (208)	4.7	

TTP = Time to tumor progression.

The hazard ratios and 95% confidence intervals for TTP by each baseline covariate examined in the supportive analysis are shown in Figure 3. Supportive analysis within strata for each baseline covariate confirmed the superiority of Femara over tamoxifen.
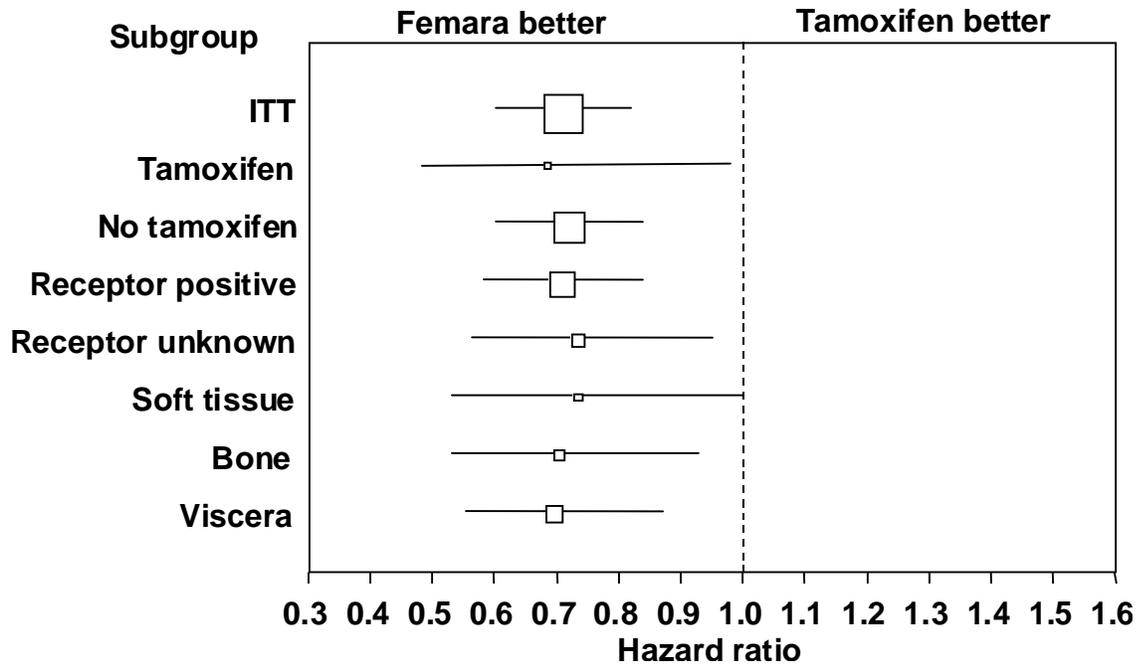
Figure 3.—Hazard ratios and 95% confidence intervals for time to progression within strata for each baseline covariate. Soft tissue = soft tissue only, bone = bone ± soft tissue, viscera = viscera ± bone ± soft tissue, tamoxifen = adjuvant tamoxifen, no tamoxifen = no adjuvant tamoxifen.

Stratified analysis conducted on 9 baseline covariates including 3 key baseline covariates, one at a time, indicated the superiority of Femara over tamoxifen on all covariates examined (Table 8).

Table 8. Stratified Analysis of TTP by Baseline Covariates (Exploratory Analysis)

Baseline covariate	Femara®		Tamoxifen		
	No. events of progression (no. patients)	Median TTP, months	No. events of progression (no. patients)	Median TTP, months	Log-rank *P* value
Duration of prior antiestrogen treatment*					.0001
0 - 2 years	270 (395)	9.4	309 (403)	6.0	
≥ 2 years	38 (58)	9.5	41 (51)	4.1	
Geographic area					.0001
Europe	195 (288)	9.9	225 (292)	6.2	
North America	32 (49)	9.7	35 (51)	6.0	
Rest of World	81 (116)	9.0	90 (111)	3.5	
Age class					.0001
< 70 years	215 (301)	8.8	246 (311)	6.0	
≥ 70 years	93 (152)	12.2	104 (143)	5.8	
Disease-free interval*					.0001
< 2 years	149 (202)	7.4	163 (209)	5.8	
≥ 2 years	159 (251)	12.2	187 (245)	6.2	
Bisphosphonate use**					.0001
No	278 (413)	9.5	312 (405)	6.0	
Yes	30 (40)	3.9	38 (49)	5.8	
Body mass index					.0001
< 30 kg/m^2	230 (337)	9.2	271 (348)	6.0	
≥ 30 kg/m^2	68 (101)	9.9	70 (92)	6.0	

*Includes patients with Stage IV or earlier stage of disease at time of study entry.
**Includes patients irrespective of bone lesions at time of study entry.

An exploratory analysis within strata of the baseline covariate of geographic area confirmed the superiority of Femara over tamoxifen. The hazard ratios and the 95% CI for TTP are shown in Figure 4.
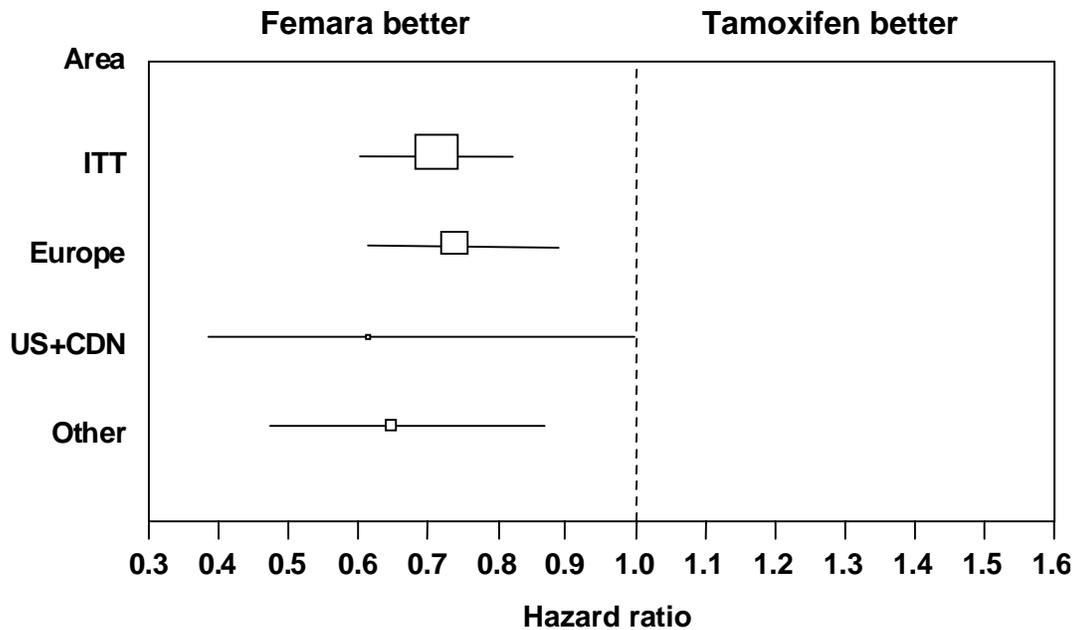
Figure 4.—Exploratory analysis of time to progression by geographic area.

In conclusion, the supportive and exploratory analyses demonstrated that Femara was significantly superior to tamoxifen in TTP for all baseline covariates examined.

3.2.2 Overall Tumor Response

Table 6 demonstrates the distribution of response by treatment. The overall objective tumor response (CR + PR) rate was superior for Femara (30%) compared with tamoxifen (20%) (odds ratio = 1.71, 95% CI = 1.26 to 2.31, P = .0006). Complete response was 8% on Femara and 3% on tamoxifen. Time to response was not significantly different between treatments (median = 3.2 months for both treatment groups). The rate of clinical benefit (CR + PR or SD for $\geq$ 6 months) was significantly higher for Femara (49%) compared with tamoxifen (38%) (odds ratio = 1.55; P = .001).

The adjusted analysis (adjusted for the key covariates of receptor status, prior adjuvant antiestrogen treatment, and dominant site of disease) was similar to the unadjusted analysis (Odds ratio = 1.80, 95% CI = 1.32 to 2.47, P = .0002).

Median duration of response and median duration of clinical benefit were identical in both treatment groups (Figure 5). The duration of overall tumor response calculated from the earliest date of documentation of response (CR or PR) was 17 months for Femara and 16.5 months for tamoxifen (hazard ratio = 0.82; 95% CI = 0.55 to 1.22; P = not significant). Similarly, the duration of clinical benefit calculated from the earliest date of documentation of CR, PR, or SD $\geq$ 6 months was 15.2 months for Femara and 14.8 months for tamoxifen (hazard ratio = 0.81; 95% CI = 0.62 to 1.07; P = not significant).

Duration of Overall Objective Tumor Response (CR + PR)

Calculated from date of randomisation
(ITT Population)
Core phase only

Duration of Clinical Benefit

Calculated from date of randomisation
(ITT Population)
Core phase only
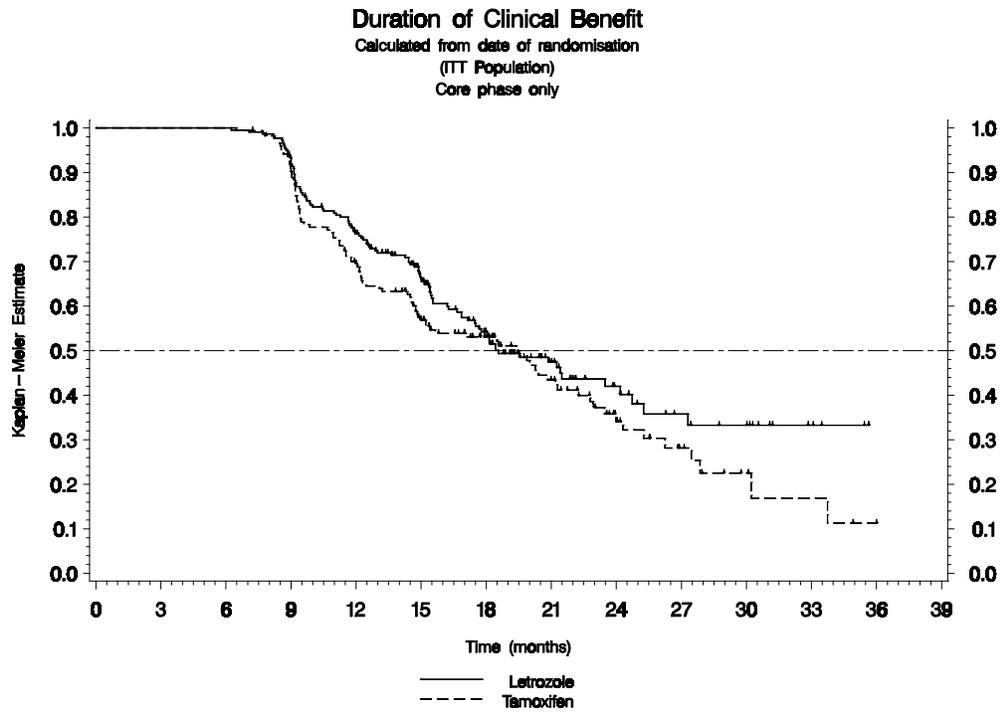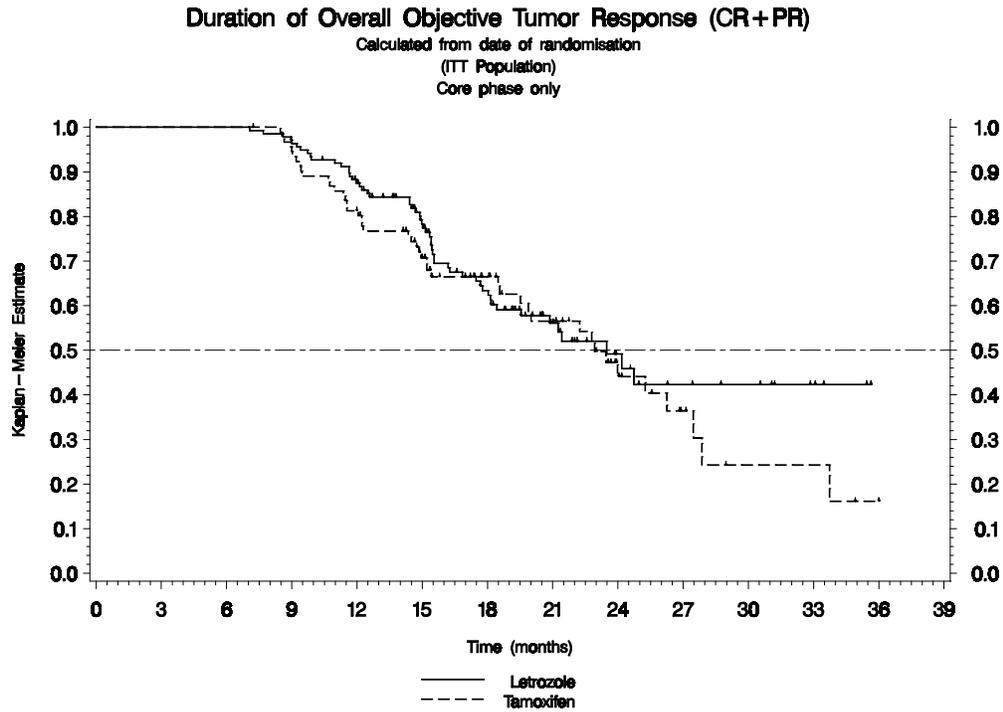
Figure 5.—Kaplan-Meier estimates of duration of overall tumor response (top) and duration of clinical benefit (bottom).

The duration of overall tumor response calculated from the date of randomization was 23 months for both treatments (hazard ratio = 0.84; 95% CI = 0.56 to 1.26, P = NS). Similarly, the duration of clinical benefit calculated from the data randomization was 19 months for both treatments (Hazard ratio = 0.81; 95% CI = 0.62 to 1.07, P = not significant).

A. Supportive Analysis

The analysis for ORR, adjusted for the key baseline covariates of prior adjuvant antiestrogen treatment, receptor status, and dominant site of disease was very similar to the unadjusted analysis as described below. The supportive multivariate analysis indicated that slightly different covariates impact overall response compared with those that were found to impact TTP.

The supportive analysis confirmed that

- Treatment with Femara significantly increased the odds of achieving a CR or PR (odds ratio = 1.80; 95% CI = 1.32 to 2.47, P = .0002)

- The presence of visceral metastases significantly reduced the odds of achieving a CR or PR compared with soft-tissue only disease (odds ratio = 0.37, 95% CI = 0.26 to 0.53, P = .0001)

- The presence of bone metastases significantly reduced the odds of achieving a CR or PR compared with soft-tissue only disease (odds ratio = 0.29, 95% CI = 0.19 to 0.44, P = .0001)

- Prior adjuvant antiestrogen treatment significantly reduced the odds of achieving a CR or PR compared with antiestrogen-naive patients (odds ratio = 0.64; 95% CI = 0.41 to 0.98, P = .04)

- A trend was observed for higher odds of achieving an objective tumor response in receptor-positive patients than in receptor-unknown patients (odds ratio = 1.37; 95% CI = 0.98 to 1.92, P = .07)

The stratified analysis (Table 9) conducted on key baseline covariates one at a time, confirmed that the treatment difference adjusted over the strata for each covariate significantly favored Femara.

Table 9. Stratified Analysis of Objective Overall Tumor Response by Baseline Covariates (Supportive Analysis)

Baseline covariate	Femara® CR + PR, no. patients (%)	Tamoxifen CR + PR, no. patients (%)	P value*
Prior adjuvant treatment			.001
None	113 / 369 (31)	85 / 371 (23)	
Adjuvant treatment	24 / 84 (29)	7 / 83 (8)	
Receptor status			.001
ER+ and/or PgR+	92 / 294 (31)	63 / 305 (21)	
Unknown and other	45 / 159 (28)	29 / 149 (20)	
Dominant site			.001
Soft tissue only	54 / 113 (48)	40 / 116 (35)	
Bone ± soft tissue	32 / 146 (22)	18 /130 (14)	
Visceral ± bone ± soft tissue	51 / 194 (26)	34 / 208 (16)	

*Cochran-Mantel-Haenszel statistic.

CR = Complete response; PR = Partial response; ER = Estrogen receptor; PgR = Progesterone receptor.

Supportive analysis within strata for each baseline covariate confirmed the superiority of Femara over tamoxifen in all stratum except for unknown receptor status and bone ± soft tissue disease. The odds ratios and 95% confidence intervals for objective response are shown in Figure 6.

Figure 6.—Odds ratios and 95% confidence intervals for objective response within strata for each baseline covariate. Upper bound for CI for adjuvant tamoxifen = 10.8. Soft tissue = soft tissue only, bone = bone ± soft tissue, viscera = viscera ± bone ± soft tissue, tamoxifen = adjuvant tamoxifen, no tamoxifen = no adjuvant tamoxifen.

B. Exploratory Analysis

Stratified analysis conducted on 9 baseline covariates (including the 3 key baseline covariates, one at a time) indicated the superiority of Femara over tamoxifen for ORR on all covariates examined (Table 10).
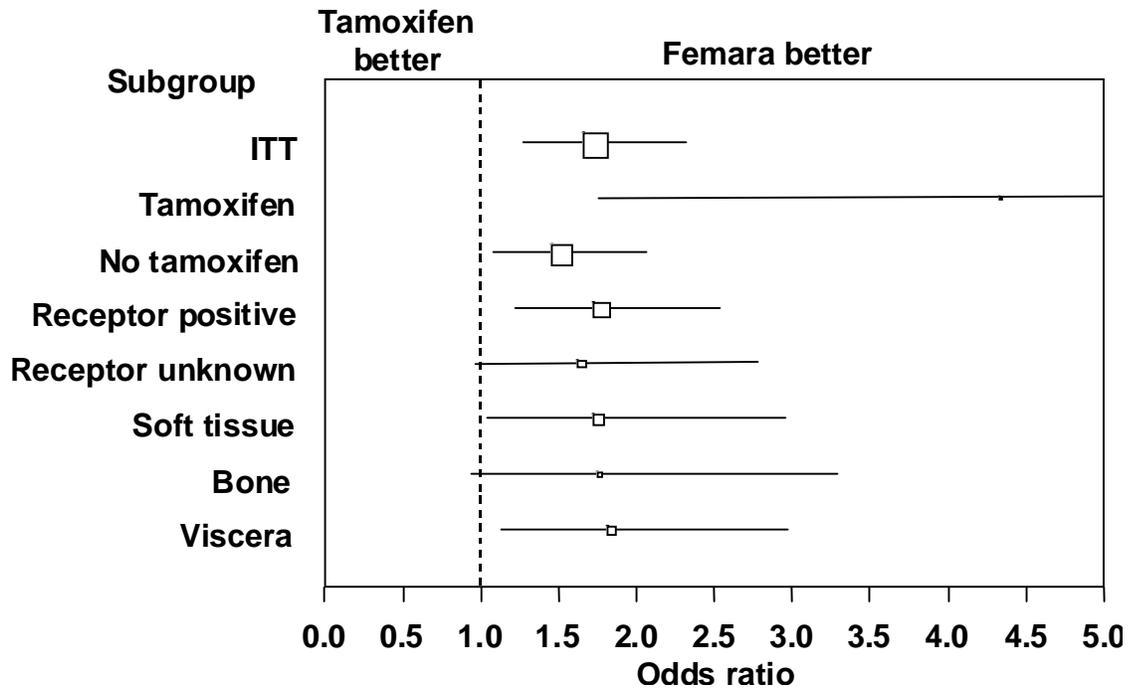
Table 10. Stratified Analysis of Objective Overall Tumor Response by Baseline Covariates (Exploratory Analysis)

Baseline covariate	Femara® CR + PR, no. patients (%)	Tamoxifen CR + PR, no. patients (%)	P value***
Duration of prior antiestrogen therapy*			.001
0 to < 2 years	119 / 395 (30)	89 / 403 (22)	
≥ 2 years	18 / 58 (31)	3 / 51 (6)	
Geographical area			.001
Europe	94 / 288 (33)	65 /292 (22)	
North America	13 / 49 (27)	9 / 51 (18)	
Rest of World	30 / 116 (26)	18 / 111 (16)	
Age class			.001
< 70 years	79 / 301 (26)	67 / 311 (22)	
≥ 70 years	58 / 152 (38)	25 / 143 (18)	
Disease-free interval*			.0001
< 2 years	60 / 202 (30)	44 / 209 (21)	
≥ 2 years	77 / 251(31)	48 / 245 (20)	
Bisphosphonate use**			.0001
No	130 / 413 (32)	85 / 405 (21)	
Yes	7 / 40 (18)	7 / 49 (14)	
Body mass index			.0001
< 30 kg/m^2	100 / 337 (30)	63 / 348 (18)	
≥ 30 kg/m^2	32 / 101(32)	25 / 92 (27)	

*Includes patients with Stage IV or earlier stage of disease at time of study entry.
**Includes patients irrespective of bone lesions at time of study entry.
***Cochran Mantel Haenszel statistic.

3.2.3 Number of Deaths

There were 304 deaths when the primary analysis was conducted (See section 3.1.5 Survival Analyses and Section 5.0 Safety in Phase III studies).

3.2.4 Other Analyses

A. Time to Worsening Performance Status

The median time to worsening of KPS was not reached in the Femara group compared with just under 30 months in the tamoxifen group. The KPS worsened in 77 patients (17%) for Femara, 107 patients (24%) for tamoxifen. There was a significant difference between treatments in the time to worsening of KPS by at least 20 points (hazard ratio 0.62; 95% CI = 0.46 to 0.83; *P* = .002).

3.2.5 Summary

In this, the largest randomized clinical trial in this patient population, Femara demonstrated superior efficacy compared with tamoxifen. Most importantly, Femara significantly reduced the risk of progression (*P* = .0001) and prolonged median time to progression (9.4 months versus 6 months). Further, objective tumor response rate, clinical benefit rate, and time to treatment failure were all significantly improved in the Femara group compared with the tamoxifen group. Objective tumor response rate was 30% in the Femara group versus 20% in the tamoxifen group (*P* = .0006). Supportive and exploratory analyses adjusted for important baseline prognostic factors also demonstrated the statistically significant superiority of Femara. These data support the use of Femara as the endocrine therapy of choice for postmenopausal women with advanced breast cancer, setting a new standard of care in this patient population.

4.0   SUPPORTIVE PHASE IIB/III STUDY 024

4.1   Study Design

Study 024 was an international, multicenter, double-blind, double-dummy, randomized, parallel-group, phase IIb/III trial of once-daily doses of Femara (2.5 mg) or tamoxifen (20 mg) in postmenopausal women with ER and/or PgR positive primary breast cancer (clinical stage T2, T3, T4$_{a-c}$, N0-2, M0). The study was designed to detect a statistically significant and clinically meaningful difference in clinical response rate between Femara and tamoxifen. Study treatment was given for 4 months prior to surgery unless withdrawn due to PD, an adverse event, or at patient/investigator request. Following surgery, treatment with Femara in the adjuvant setting was at the investigator's discretion. During this period, the study blind was not to be broken. Study 024 was supportive of the pivotal Study 025 in that it preselected a group of breast cancer patients who would most likely respond to endocrine therapy (postmenopausal women with ER and/or PgR positive tumors) and who were more importantly never exposed to either endocrine or other forms of therapy. Therefore, these truly therapy-naïve patients represent an appropriate group of patients in whom to evaluate differences between two endocrine therapies.

4.1.1   Entry Criteria

Postmenopausal women with primary invasive and histologically confirmed breast cancer (clinical stage T2, T3, T4$_{a-c}$, N0-2, M0) were eligible for this study. The protocol allowed only patients who were candidates for mastectomy or were inoperable to be enrolled. Patients with clinical stage T2 disease were eligible if the lesion was not considered by the investigator to be eligible for breast-conserving surgery. Eligible patients had measurable tumor by clinical examination, mammography, and ultrasound. Patients with evidence of inflammatory breast cancer or distant metastasis were excluded.

4.1.2   Randomization Procedures

A computer-generated randomization list was created by Novartis so that treatments were balanced within each country. A double-dummy technique was used to ensure that study medication was blinded. The patients, investigators and their staffs, and all Novartis personnel involved in the conduct and monitoring of the trial were blinded to trial drug codes. Treatment codes were unblinded after database lock for Novartis staff only, but patients and investigators and their staffs remained blinded to trial drug codes. Medication was unblinded for 2 patients (1 on Femara, 1 on tamoxifen) during the trial to decide on further treatment.

4.1.3   Treatment Administration

In the Femara treatment group, patients received 1 tablet of Femara (2.5 mg) and 1 placebo tablet for daily oral administration. In the tamoxifen treatment group, patients received 1 tamoxifen tablet (20 mg) and 1 placebo tablet for daily oral administration.

4.1.4 Study Endpoints

A. Efficacy Assessments

The primary efficacy endpoint was tumor response as assessed by clinical examination using WHO criteria. Tumor response was defined as the percentage of patients in each treatment group with a CR or a PR as determined clinically in the breast by palpation at 4 months. Palpable ipsilateral axillary lymph nodal involvement downgraded a clinical CR in tumor. Secondary endpoints included tumor response as assessed by mammography and by ultrasound at 4 months using WHO criteria and the percentage of patients who underwent breast-conserving surgery (quadrantectomy/lumpectomy) instead of mastectomy.

B. Safety Assessments

Safety assessments consisted of monitoring and reporting all adverse events classified by all NCI CTC criteria and all serious adverse events (with their severity and relationship to study drug.

4.1.5 Statistical Analysis

All patients randomly assigned treatment who took at least 1 dose of study medication and with histologic or cytologic confirmation of breast cancer were included in the ITT population, except for patients from two GCP-noncompliant centers. For safety, all patients randomly assigned treatment who took at least 1 dose of study medication were included in the safety population, except for patients from two GCP-noncompliant centers. The data were analyzed by Parexel International (Sheffield, UK) under the supervision of Novartis. All efficacy analyses were performed on the intent-to-treat (ITT) population, and response at 4 months was tabulated. If a patient discontinued study treatment earlier than 4 months (+/- 2 weeks), and had a last assessment of CR, PR, or SD, her final response on all methods was considered not evaluable (NE). If a patient discontinued study treatment earlier than 4 months (+/- 2 weeks) and had a last assessment of PD, the earlier diagnosis of PD was counted.

A. Primary Endpoint

The primary endpoint—the proportion of patients in each treatment group with a CR or PR on clinical assessment—was analyzed by the stratified Mantel-Haenszel chi-square test by tumor size and nodal involvement.

B. Secondary Endpoints

The secondary endpoints—including the proportion of patients in each treatment group with a CR or PR assessed by mammography and ultrasound and the rate of breast conserving surgery—were analyzed similarly, by the stratified Mantel-Haenszel chi-square test.

4.1.6 Sample Size and Power Considerations

It was assumed that the tamoxifen group would have a clinical objective response rate (CR + PR) of 65%, and that a clinically meaningful improvement would be a response rate of

80%. Clinical response was to be based on WHO criteria. A sample size of 302 patients was estimated as sufficient to detect as significant (2-sided test at the 5% level of significance with 80% power) a difference of 15% between treatment groups in clinical objective response. It was expected that 50% of the patients treated with tamoxifen would undergo breast-conserving surgery. It was postulated that 70% of the patients treated with Femara would undergo breast-conserving surgery. The sample size calculated for the primary endpoint was estimated as adequate for detecting as significant this difference (103 patients in each treatment group would be needed for a 2-sided test at the 5% level of significance with 80% power).

4.2   Patient Demographics

4.2.1   Patient Enrollment

From March 1998 until August 1999, a total of 337 patients were enrolled at 55 centers in 16 countries. Countries with > 10% enrollment included Germany (24%), Brazil (15%), and the United Kingdom (11%). The intent-to-treat (ITT) population excludes 13 patients: 4 who were randomly assigned study treatment (Femara) but were subsequently found not to have histologic or cytologic evidence of breast cancer at study entry; and 9 patients from two GCP non-compliant centers (4 Femara, 5 tamoxifen). Efficacy analyses were based on ITT population. The safety population excludes 9 from the GCP non-compliant centers (4 Femara, 5 tamoxifen) and one patient who never took study medication on Femara.

4.2.2   Patient Characteristics

The Femara and tamoxifen treatment groups were well balanced with respect to baseline demographics and disease characteristics (Table 11).

Table 11. Patient Demographic and Disease Characteristics by Treatment Group

	Patients, no. (%)		
	Femara® (2.5 mg) (N =154)	Tamoxifen (20 mg) (N =170)	Total (N = 324)
Median age, years (range)	68 (44 - 91)	67 (48 - 89)	67 (44 - 91)
Receptor status			
ER+ and PgR+	90 (58)	91 (54)	181 (56)
ER+ or PgR+	64 (42)	76 (45)	140 (43)
Both unknown	0 (0)	1 (< 1)	1 (< 1)
ER–, PgR–	0 (0)	2 (1)	2 (< 1)
Clinical stage			
T2	77 (50)	91 (54)	168 (52)
T3	42 (27)	31 (18)	73 (23)
T4	35 (23)	48 (28)	83 (26)
N0	76 (49)	84 (49)	160 (49)
N1	67 (44)	67 (39)	134 (41)
N2	11 (7)	19 (11)	30 (9)
Proposed surgery			
Mastectomy	134 (87)	146 (86)	280 (86)
Not operable	20 (13)	24 (14)	44 (14)

ER = Estrogen receptor; PgR = Progesterone receptor.

4.3   Efficacy

4.3.1 Summary of Results

The response rate, regardless of the efficacy endpoint evaluated, and the rate of breast-conserving surgery were statistically significantly higher for the Femara group compared with the tamoxifen group (Table 12).

Table 12. Summary of Responses

	Patients, no. (%)		
Efficacy endpoint	**Femara® (2.5 mg) (N = 154)**	**Tamoxifen (20 mg) (N = 170)**	**P value**
Clinical response (palpation)	85 (55)	61 (36)	< .001
Ultrasound response	54 (35)	43 (25)	.042
Mammographic response	53 (34)	28 (17)	< .001
Breast-conserving surgery	69 (45)	59 (35)	.022

For the entire ITT population, 15% (50/324) of the patients did not undergo surgical resection following treatment with study drug: 12% (19/154) in the Femara group and 18% (31/170) in the tamoxifen group. Twenty patients did not have surgery because of disease progression, and all of these patients went on to receive other therapies, including chemotherapy and radiotherapy. Six patients were inoperable, and 13 patients refused surgery. Five patients had medical conditions that contraindicated surgery. In the case of 1 patient, there was no available hospital bed. The remaining 5 patients were withdrawn from the study because of ER or PgR negative disease (n = 2), an increase in tumor markers (n = 1), an adverse event (hepatitis; n = 1), and bone metastases (n = 1).

The clinical tumor response rate (CR + PR) was significantly higher with Femara than with tamoxifen (55% versus 36%; P < .001). The response rate was significantly higher for Femara by all methods (clinical, ultrasound, mammography). Significantly more patients underwent breast-conserving therapy after Femara treatment than after tamoxifen treatment (45% versus 35%; P = .022).

5.0   SAFETY IN PHASE III STUDIES

5.1   Study 025 Safety Results

The median duration of core treatment in the Femara group was 11 months compared with a median of 6 months in the tamoxifen group. The median duration of treatments may not necessarily reflect the median duration of progression, as patients may have continued to receive therapy after their date of progression. The nature and frequency of all adverse events irrespective of relationship to study drug were similar in the Femara and tamoxifen treatment groups. The overall incidence of the most frequently reported adverse events is summarized by preferred term in Table 13.

Table 13. Number of Patients With Most Frequent Adverse Events Regardless of Study Drug Relationship ($\geq$ 10% in Either Group) by Preferred Term

	Patients, no. (%)	
Adverse event	Femara® (N =455)	Tamoxifen (N =455)
Bone pain	89 (20)	83 (18)
Hot flashes (NOS)	81 (18)	70 (15)
Pain back	77 (17)	79 (17)
Nausea	66 (15)	72 (16)
Arthralgia	63 (14)	58 (13)
Dyspnea (NOS)	62 (14)	66 (15)
Cough	49 (11)	47 (10)
Fatigue	48 (11)	51 (11)

NOS = Not otherwise specified.

Thromboembolic events irrespective of drug relationship were reported in 6 (1%) patients in the Femara group and in 11 (2%) patients in the tamoxifen group. Pulmonary embolus was reported in 2 patients, 1 in each treatment group. Cardiovascular events (myocardial infarction, angina) occurred in 15 patients (3%) on Femara and in 13 patients (3%) on tamoxifen. Cerebral arterial events occurred in 12 patients (3%) on Femara and 9 patients (2%) on tamoxifen. A total of 53 patients were reported to have bone fractures, including 25 on Femara (6%) and 27 on tamoxifen (6%), and 1 patient on combination therapy. The majority of these events were related to bone metastasis. In addition, 14 patients were reported to have bone fractures during the crossover phase. The numbers of patients with newly occurring or worsening liver enzymes to CTC grade 3 or 4 was low and similar in both treatment arms.

Discontinuations due to adverse events were reported in 2% of Femara-treated patients and in 3% of tamoxifen-treated patients. Discontinuations due to death were reported equally in both groups at 2%. There were no treatment-related deaths.

5.2   Study 024 Safety Results

The nature and frequency of commonly reported adverse events (≥ 5% in either group) irrespective of relationship to study drug, including hot flashes (Femara 20%, tamoxifen 25%), headache (Femara 8%, tamoxifen 5%), nausea (Femara 6%, tamoxifen 8%), fatigue (Femara 5%, tamoxifen 5%), and viral infection (Femara 3%, tamoxifen 7%) were similar for the Femara and tamoxifen groups.

No deaths were reported during the study or within 30 days of any patient receiving the last dose of study drug. In total, 4 patients discontinued medication because of an adverse event (1 patient in the Femara group for pulmonary embolism; 3 patients on tamoxifen for hepatitis C, erythema multiforme, and cholestasis).

6.0   BENEFIT/RISK ASSESSMENT

In patients diagnosed with metastatic breast cancer, therapy is palliative, with the aim of delaying the progress of the underlying disease using treatments that exert a minimum negative effect on the quality of life of the patient. Hormonal therapy, which is known to be well tolerated, is considered to represent a very attractive therapeutic intervention in this indication.

The results of Study 025, a large, randomized, double-blind trial, indicate that the efficacy of Femara is significantly greater than that of tamoxifen in the treatment of advanced breast cancer in postmenopausal women. Femara was significantly superior in the primary endpoint, TTP, and in the secondary endpoints, TTF, ORR, and clinical benefit rate. Overall time to progression was more than 40% longer for Femara than for tamoxifen, which offers a significant clinical advantage to these patients over existing therapies. The robustness of this result is consistently demonstrated within the different patient subgroups, always maintaining statistical significance favoring treatment with Femara. The superior efficacy of Femara over tamoxifen has also been demonstrated in the supportive trial (Study 024) of preoperative therapy in postmenopausal ER and/or PgR positive breast cancer patients comparing Femara with tamoxifen over 4 months of treatment prior to surgical resection of a primary tumor. In this group of patients with *de novo* hormone receptor-positive breast cancer, who were naive to both chemotherapy and hormonal therapy, Femara was superior to tamoxifen in demonstrating a therapeutic effect in tumor regression, allowing patients to undergo breast-conserving surgery.

The safety results obtained with Femara in this indication were entirely consistent with the profile documented thus far, clearly showing that the benefits associated with the use of the drug outweigh any potential risks in this patient population. The most common adverse events in both Femara and tamoxifen were bone pain, hot flashes, back pain, and nausea. Most adverse events were mild to moderate in severity. As expected, only a small percentage of patients discontinued from the studies due to adverse events. The frequency of deaths was also low, and most were considered cancer related. In addition, adverse event data from approximately 3,200 patients in 4 ongoing or recently completed studies showed a similar safety profile.

Overall, the data sufficiently and consistently support a recommendation for Femara as the first choice in the selection of an endocrine treatment for advanced breast cancer in postmenopausal women.

7.0   OVERALL CONCLUSIONS

In Study 025, the largest trial of endocrine treatment for the first-line treatment of postmenopausal women with advanced breast cancer, Femara was superior to tamoxifen as demonstrated by the following:

- Significantly longer time to progression

- Significantly higher objective tumor response rate

- Significantly higher clinical benefit rate

- Significantly longer time to treatment failure

- Consistently superior results in all subgroup analyses

Study 024 demonstrated the superiority of Femara compared with tamoxifen in overall response rate, by clinical parameters and radiologic methods. This results are derived from a selected group of postmenopausal patients with primary hormone-sensitive breast cancer in whom any potential bias due to previous treatment with tamoxifen or other therapies was eliminated. The results of study 024 are, therefore, supportive of the pivotal study 025. Femara was equally well tolerated as tamoxifen in both studies with a lower number of thromboembolic events.

Therefore, results of these adequate and well-controlled studies convincingly demonstrate that Femara is a first-line treatment in postmenopausal women with advanced breast cancer, setting a new standard of care in this patient population.

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