# of Arzoxifene in Patients With Locally Advanced or Metastatic Breast Cancer

By Aman Buzdar, Joyce A. O'Shaughnessy, Daniel J. Booser, John E. Pippen, Jr., Stephen E. Jones, Pamela N. Munster, Patrick Peterson, Allen S. Melemed, Eric Winer, and Clifford Hudis

Purpose: To select a daily dose of arzoxifene (LY353381), a selective estrogen receptor modulator, for use in future studies in women with locally advanced or metastatic breast cancer who are either potentially tamoxifen sensitive (TS) or tamoxifen refractory (TR).

Patients and Methods: This trial was a randomized, double-blind, phase II study of arzoxifene 20 mg (n = 55) and 50 mg (n = 57) in women with advanced or metastatic breast cancer. Patients were randomly assigned to balance for number of metastatic disease sites, prior tamoxifen therapy, and estrogen receptor status. The primary end point was tumor response rate (RR). Secondary end points included clinical benefit rate (CBR), time to progression (TTP), and toxicity.

Results: Forty-nine patients were TS and 63 were TR. According to independent review, among TS patients, RR was higher in the 20-mg arm than the 50-mg arm (26.1% *v* 8.0%), with a longer TTP (8.3 *v* 3.2 months; $P > .05$). Among the TR patients, response rate was the same in the 20-mg and 50-mg arms (10.3%) with similar TTP (2.7 and 2.8 months, respectively; $P > .05$). CBR was higher in the 20-mg arm than in the 50-mg arm among TS patients (39.1% *v* 20.0%) and TR patients (13.8% *v* 10.3%). Arzoxifene was well tolerated. Dose-dependent toxicity was not demonstrated. There were no deaths during study.

Conclusion: Arzoxifene is effective in the treatment of TS and TR patients with advanced or metastatic breast cancer at the 20-mg and 50-mg dose levels. Toxicities are minimal, and the therapy is tolerated. The 20-mg dose seems to be at least as effective as the 50-mg dose. Accordingly, arzoxifene 20 mg/d was selected for further study in patients with breast cancer.

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BREAST CANCER is the most common malignancy among women in the Western hemisphere and the second most common cause of cancer-related mortality. A substantial body of experimental, clinical, and epidemiologic evidence indicates that steroid hormones play a major role in the etiology of breast cancer.[1] The effects of steroid hormones on breast epithelium are mediated through estrogen and progesterone receptors (ER and PgR, respectively).[2] Tamoxifen has been the drug of choice for endocrine manipulation of both early and advanced stages of breast cancer.[3] Its biologic effects are mediated primarily by inhibiting the actions of estrogen through its binding to the ER. Although tamoxifen is generally a well-tolerated drug, it does have significant side effects. These include hot flashes (20% to 80%), thromboembolism (1% to 3%), and a variety of ocular toxicities and endometrial cancer. The risk of developing endometrial cancer with tamoxifen is estimated to increase two- to seven-fold in postmenopausal women receiving long-term treatment.[4-9] Moreover, there are concerns that long-term use (> 5 years) in the treatment of early-stage breast cancer is associated with the development of tamoxifen-dependent breast cancer.[6]

Given the above concerns, considerable attention has been paid to developing more selective antiestrogens. The nonsteroidal benzothiophene selective ER modulator arzoxifene was designed to have potent ER antagonistic activity in the breast and endometrium while maintaining beneficial estrogen agonist activity on bone and lipids. In preclinical studies, both arzoxifene and its desmethyl metabolite bound to the ER with high affinity and inhibited estrogen-dependent growth of MCF-7 cells.[10] Arzoxifene does not stimulate the uterine endometrium in ovariectomized rats; however, it does block estrogen-induced stimulation of the endometrium.[11] It also demonstrated favorable effects on bone and lipids in preclinical studies.[12]

A phase I study of four doses of arzoxifene (10, 20, 50, and 100 mg) was conducted in 32 patients with previously treated breast cancer.[13] The most common side effect was hot flashes (56%). Prospective evaluation of uterine safety, performed at baseline and after 12 weeks of treatment, showed no evidence of endometrial stimulation. Although responses were not seen, six patients had stable disease lasting for 6 months or longer. As no dose-dependent toxicity was identified in that study, this study was conducted to further evaluate the safety and efficacy of arzoxifene 20 mg and 50 mg in patients with advanced or metastatic breast cancer, and to determine the dose of arzoxifene to be used in future phase III trials.

PATIENTS AND METHODS

Study Design

This was a randomized, double-blind, phase II study of arzoxifene. Each participating institutions' independent review board gave approval to the

From the M.D. Anderson Cancer Center and US Oncology Research, Houston, and Baylor-Sammons Cancer Center and Texas Oncology, Dallas, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; Eli Lilly and Company, Indianapolis, IN; and Dana-Farber Cancer Institute, Boston, MA.

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Address reprint requests to Aman Buzdar, MD, M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Box 424, Houston, TX 77030; email: abuzdar@mdanderson.org.

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study design before enrolling patients. After providing informed consent, patients were randomly assigned to receive either 20 or 50 mg of arzoxifene (Eli Lilly and Company, Indianapolis, IN), taken as a single tablet daily with meals. Treatment was continued until disease progression or unacceptable toxicity occurred or informed consent was withdrawn. Patients experiencing disease progression at the 20-mg dose were eligible to receive further open-label arzoxifene treatment at a dose of 50 mg daily, at the investigator's discretion. Treatment was discontinued for any study drug–related grade 4 toxicity. Randomization was performed using the Pocock and Simon method[14] to maximize baseline treatment group balance according to three important prognostic factors: number of metastatic disease sites (< three or ≥ three sites), prior tamoxifen therapy (yes or no), and degree of ER expression (high, low, or unknown). High ER expression was defined as ≥ 50 fmol/mg of ER (biochemical) or ≥ 50% cells positive (immunohistochemistry), and low ER expression was defined as less than 50 fmol/mg of ER (biochemical) or less than 50% cells positive (immunohistochemistry).

Eligibility Criteria

The study population consisted of women who were potentially tamoxifen sensitive (TS), defined as no prior exposure to tamoxifen or patients who experienced relapse more than 12 months after cessation of adjuvant tamoxifen therapy, or tamoxifen refractory (TR), defined as patients who experienced relapse during adjuvant tamoxifen treatment (provided at least 1 year had elapsed between initiation of tamoxifen and development of metastatic disease) or patients treated with tamoxifen as first-line therapy for metastatic disease whose disease was at least stable for ≥ 6 months on tamoxifen and then progressed. All patients were women at least 18 years old with a pathologic diagnosis of locally advanced or metastatic breast cancer. Patients had an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, estimated life expectancy of ≥ 24 weeks, and tumors that were assessable or bidimensionally measurable and were ER- and/or PgR-positive. Patients with inoperable, locally advanced breast cancer were enrolled only if they were not good candidates, in the investigator's judgment, for primary chemotherapy. Patients whose ER/PgR status was unknown were eligible if they were older than 50 years. Prior neoadjuvant or adjuvant chemotherapy was permitted if completed at least 6 months before diagnosis of metastatic disease. Patients who had received prior adjuvant hormonal therapy (including oophorectomy or ovarian irradiation) were enrolled, provided there was an interval of at least 12 months between completion of therapy and diagnosis of metastatic disease. Concomitant medications such as bisphosphonates, hematopoietic growth factors, and palliative radiotherapy were permitted. Patients with child-bearing potential were required to use a barrier contraceptive method during and for 3 months after the trial.

Patients were excluded from the study per investigator's discretion if they had rapidly progressive disease, a serious concomitant systemic disorder, or predisposition to thromboembolic disorder; inadequate end-organ function (eg, serum creatinine ≥ 1.5 times the upper limit of normal [ULN], bilirubin ≥ 1.5 times the ULN, and ALT or AST > 2.5 times the ULN); hypercalcemia; tumor known to be ER- and PgR-negative; or untreated brain metastases or were pregnant, breast-feeding, or had used any investigational agent within 4 weeks before study enrollment.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol and consent process was approved by all relevant ethics boards, and all patients gave written consent before enrollment.

Baseline Evaluations

A complete history and physical examination including PS assessment, blood pressure, pulse, height, and weight were performed at baseline and at each subsequent physician visit. Assessment of tumor markers (eg, carcinoembryonic antigen, CA15–3, and CA-125), urinalysis, and an ECG were also performed at baseline. Measurements of palpable lesions and tumor markers that were elevated at baseline were subsequently obtained monthly for 3 months, then every 2 to 3 months. Additional testing included complete blood cell count, chemistry analysis, serum osteocalcin, sex hormones (luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol, and sex-hormone–binding globulin [SHBG]), and plasma levels of LY353381 and its desmethyl metabolite LY335562, which were obtained monthly for 3 months, then every 2 to 3 months. Radiologic tumor assessments were obtained at day 85 and then every 2 to 3 months while patients were enrolled on the study. All patients who received at least 4 weeks of treatment, had prestudy staging and tumor measurements, and had at least one tumor measurement while receiving treatment were considered assessable for the efficacy analysis. Toxicities were evaluated at each physician visit using the National Cancer Institute Common Toxicity Criteria grading system (version 1.0).[15] All patients who received at least one dose of LY353381 were considered assessable for the safety analysis.

Uterine Evaluations

Uterine safety was prospectively evaluated in this trial for patients with an intact uterus. Transvaginal ultrasounds (TVUs) were performed no more than 4 weeks before initiation of treatment, at day 85 (± 7 days), or sooner for those discontinuing from study for any reason. For patients who continued treatment beyond 12 weeks, a TVU was performed at least every 6 months in the first year and at least yearly thereafter. Endometrial thickness was considered significant, warranting further evaluation if it was more than 8 mm at baseline or at subsequent evaluation or if the increase from baseline was ≥ 5 mm at a subsequent evaluation; follow-up occurred either with saline-infused sonohysterography, hysteroscopy/guided biopsy, or dilatation and curettage (D&C). If inadequate tissue was obtained by blind biopsy or D&C, further attempts to obtain endometrial tissue were required. Slides of endometrial tissue were reviewed centrally by Covance Inc (Princeton, NJ).

Efficacy Assessments

Tumor response rate (RR) was assessed by the investigator and independent review panel using standard World Health Organization response criteria.[16] Clinical benefit rate was prospectively defined as the sum of patients with complete response (CR), partial response (PR), or stable disease (SD) lasting ≥ 6 months during the study. An independent review panel consisting of three independent radiologists reviewed the data for all patients with a response or SD according to the investigator. There was no independent review for patients whose disease was assessed by physical examination alone. Tumor response data collected during the open-label dose-escalation phase were not included in the primary analysis of tumor response.

Time to progression (TTP) was measured from the time of randomization until the time of documented progressive disease (PD), including death by any cause. The duration of response is identical to TTP but is only defined for patients who exhibit tumor response. Survival was defined as the time from randomization until death by any cause. Analyses of secondary end points were based on investigator-determined assessments.

Pharmacokinetics

Concentrations of LY353381 and its desmethyl metabolite LY335562 in plasma were evaluated monthly for the first 3 months, then every 2 to 3 months while patients were enrolled on the study. The desmethyl metabolite, LY335562, is referred to in the protocol as unconjugated dihydroxy metabolite, LY335563. LY335563 is the hydrochloride salt of LY335562. Samples were collected at any time during each visit. Heparinized plasma collected from patients was analyzed for LY353381 and LY335562 using validated high-performance liquid chromatography/mass spectrometry (MS)/MS method.

Statistical Methods

The study was designed to enroll 37 patients per dose cohort, with the primary goal of selecting the better of two doses of arzoxifene.[17] An early stopping rule was included in case one or both doses proved to be inactive. The selection procedure was simply to choose the dose with the higher observed response rate between treatment groups. Assuming the true response rate is at least 15% higher on the better dose, this design has a 90% probability of selecting the better dose. Note that the selection design does not control for type I errors in the comparison of response rates between the dose cohorts, so the question of whether there was a statistically significant difference in response rate was not addressed. Exact 95% binomial confi-

Table 1. Baseline Patient and Disease Characteristics

Characteristic	Arzoxifene 20 mg		Arzoxifene 50 mg	
	No. of Patients	%	No. of Patients	%
Randomized patients	55	100	57	100
Age, years				
Median	58		56	
Range	36 to 84		33 to 84	
Performance status*				
0	17	31	24	42
1	38	69	32	56
ER/PgR status				
ER+, regardless of PgR	46	84	52	91
ER−/PgR+	5	9	2	4
ER unknown/PgR unknown	4	7	3	5
Sites of metastasis				
Bone	40	73	38	67
Lung	16	29	18	32
Liver	11	20	10	18
Skin	11	20	9	16
At least three metastatic sites	12	22	10	18
Tamoxifen sensitivity				
Refractory	31	56	32	56
Sensitive	24	44	25	44

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.
*One patient on the 50-mg arm did not have baseline performance status assessed.

dence intervals (CIs) were computed for response rates, but only for purposes of illustrating the precision of the point estimates.

For end points other than response rate, standard statistical analysis methods were used to summarize and compare cohorts. Kaplan-Meier[18] estimation and the log-rank test were used to evaluate TTP. The Mantel-Haenszel χ^2 test was used to compare incidence of toxicities accounting for severity. Changes from baseline in various end points (eg, hormones, bone-related markers, and physical examinations) were assessed within study arms using the nonparametric sign test to allow for nonsymmetrical distributions, and between study arms using the Wilcoxon rank sum test. All significance tests for secondary end points were performed at the .05 level, whereas all CIs used the 95% level.

RESULTS

Patient Characteristics

Between May 1998 and February 2001, 121 patients were entered onto the study, which was conducted at six study centers in the United States. Nine patients were not assigned to treatment because they either did not meet eligibility criteria (seven patients) or decided not to enter (two patients). One hundred twelve women were enrolled; 55 were randomly assigned to receive 20 mg of arzoxifene, and 57 patients were randomly assigned to receive 50 mg. Table 1 lists the baseline patient and disease characteristics of all randomized patients. Of note, there were more PS 0 patients in the 50-mg arm than in the 20-mg arm (42% v 31%). Also, there were more ER-positive patients in the 50-mg arm than in the 20-mg arm (91% v 84%). Sixty-three patients were defined as TR and 49 were considered TS. Overall, the characteristics were well matched when comparing the 20- and 50-mg cohorts, regardless of tamoxifen sensitivity.

The baseline characteristics of randomized patients are listed in Table 2 by dose and tamoxifen sensitivity. In the comparison of these cohorts, there were some differences in TS patients, with more ER-negative/PgR-positive and premenopausal patients in the 20-mg arm than the 50-mg arm, and more ER-positive/PgR-negative patients in the 50-mg arm than in the 20-mg arm. Also, although the average time from completion of adjuvant tamoxifen to study enrollment was similar between TS patients in the 20-mg and 50-mg arms (2.7 and 2.8 years, respectively), the average length of tamoxifen exposure was longer in the 50-mg arm than the 20-mg arm (5.6 v 3.2 years). Among the TR patients, there were more postmenopausal patients and patients with PS 0 in the 50-mg arm than in the 20-mg arm.

Antitumor Activity

Of the 112 randomized patients, six were not qualified for analysis because of the following reasons: no measurable disease (three patients), treatment with an excluded medication (one patient), unspecified criteria not met (one patient), and wrong medication code (one patient). The overall RR by dose irrespective of tamoxifen sensitivity is shown in Table 3. The investigator-assessed RR and clinical benefit rate (CBR) of the 20-mg cohort were 19.2% and 28.8%, respectively. The investigator-assessed RR and CBR of the 50-mg cohort were 7.4% and 20.4%, respectively. The peer-reviewed RR had one fewer PR on the 20-mg cohort and one more CR on the 50-mg cohort. There was no clear difference in RR between the 20- and 50-mg doses, showing that both are in an effective dose range.

According to the investigators' assessment, in the TS cohort, there were seven responders (RR, 30.4%) and four patients with SD $\geq$ 6 months in the 20-mg arm (CBR, 47.8%) and two responders (RR, 8%) and six patients with SD $\geq$ 6 months (CBR, 32%) in the 50-mg arm (Table 4). The independent review process confirmed all but one PR and one SD in the 20-mg treatment arm, yielding an RR of 26% and a CBR of 39%. In the 50-mg arm, the independent review panel found one additional CR, one fewer PR, and three fewer patients with SD, yielding an RR of 8% and a CBR of 20%. The Kaplan-Meier

Table 2. Baseline Characteristics of All Randomized Patients

Characteristics	Tamoxifen-Sensitive				Tamoxifen-Refractory			
	20 mg (n = 24)		50 mg (n = 25)		20 mg (n = 31)		50 mg (n = 32)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years								
Median	56		56		59		57	
Range	43 to 84		33 to 84		36 to 81		37 to 82	
ER/PgR status								
Positive/positive	17	71	15	60	19	61	22	69
Positive/negative	2	8	6	24	7	23	8	25
Positive/unknown	0	0	1	4	1	3	0	0
Negative/positive	3	13	0	0	2	6	2	6
Unknown/unknown	2	8	3	12	2	6	0	0
Performance status								
0	8	33	9	36	9	29	15	47
1	16	67	16	64	22	71	16	50
Menopausal status								
Premenopausal	6	25	2	8	8	26	3	9
Postmenopausal	18	75	23	92	23	74	29	91
Prior adjuvant chemotherapy	9	38	10	40	19	61	17	53
Prior tamoxifen	8	33	6	24	31	100	32	100
No. of disease sites								
< Three sites	14	58	15	60	21	68	23	72
≥ Three sites	10	42	10	40	10	32	9	28

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.

estimates for TTP were 8.3 months (95% CI, 3.4 to 18.4 months) in the 20-mg arm and 3.2 months (95% CI, 2.8 to 6.2 months) in the 50-mg arm (Fig 1). Thus, regardless of source of efficacy assessment (investigator or independent panel), both dose levels were effective, with the 20-mg dose of arzoxifene showing more responses in TS patients.

According to investigators' assessment, in the TR cohort, there were three responders (RR, 10.3%) and one patient with SD ≥ 6 months (CBR, 13.8%) in the 20-mg arm and two responders (RR, 6.9%) and one patient with SD (CBR, 10.3%) in the 50-mg arm (Table 4). According to the independent review panel, TR patients had the same RR on both the 20-mg and 50-mg dose (10.3%), whereas CBR was higher on the 20-mg dose (13.8% v 10.3%). The Kaplan-Meier estimates for TTP were 2.7 months (95% CI, 2.5 to 2.9 months) in the 20-mg arm and 2.8 months (95% CI, 2.5 to 2.9 months) in the 50-mg arm (Fig 2). Table 5 lists investigator-assessed response durations among qualified patients.

There were six patients (four TR and two TS patients) who crossed over to open-label 50-mg treatment after they experienced PD on the 20-mg arm. During the double-blind 20-mg treatment phase, all six patients experienced PD within 3 months. None of these patients achieved a tumor response during the open-label phase.

A survival analysis was not performed because more than 80% of the enrolled patients were still alive at the time of the final analysis.

Toxicity

One patient with a prior diagnosis of cholelithiasis on the 20-mg arm experienced grade 3 transaminase and grade 3 bilirubin elevations. Overall, grade 2 laboratory aberrations were reported in less than 5% of patients, with only 7% of patients experiencing grade 1 aberrations. There were no investigator-determined grade 4 laboratory abnormalities.

Table 3. Tumor Response and Clinical Benefit Rate by Dose Irrespective of Tamoxifen Sensitivity

	Investigator-Assessed		Peer-Reviewed	
	20 mg (n = 52)	50 mg (n = 54)	20 mg (n = 52)	50 mg (n = 54)
Objective tumor response, CR + PR, n	3 + 7	0 + 4	3 + 6	1 + 4
Response rate, %	19.2	7.4	17.3	9.3
95% CI within group, %*	9.6 to 32.5	2.1 to 17.9	8.2 to 30.3	3.1 to 20.3
95% CI between group, %†	−1.0 to 24.6		−4.8 to 20.9	
Clinical benefit response, CR + PR + SD≥6 months, n	3 + 7 + 5	0 + 4 + 7	3 + 6 + 4	1 + 4 + 3
Clinical benefit rate, %	28.8	20.4	25.0	14.8
95% CI within group, %*	17.1 to 43.1	10.6 to 33.5	14.0 to 38.9	6.6 to 27.1
95% CI between group, %†	−7.9 to 24.8		−4.9 to 25.3	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; CI, confidence interval.
*Within-group confidence interval is exact (based on binomial distribution).
†Between-group confidence interval is based on normal approximation.

Table 4. Investigator-Assessed Tumor Response and Clinical Benefit Rate by Tamoxifen Sensitivity

	Tamoxifen-Sensitive		Tamoxifen-Refractory	
	20 mg (n = 23)	50 mg (n = 25)	20 mg (n = 29)	50 mg (n = 29)
Objective tumor response, CR + PR, n	1 + 6	0 + 2	2 + 1	0 + 2
Response rate, %	30.4	8.0	10.3	6.9
95% CI within group, %*	13.2 to 52.9	1.0 to 26.0	2.2 to 27.4	0.8 to 22.8
95% CI between group, %†	0.8 to 44.0		−11.0 to 17.9	
Clinical benefit response, CR + PR + SD ≥6 months, n	1 + 6 + 4	0 + 2 + 6	2 + 1 + 1	0 + 2 + 1
Clinical benefit rate, %	47.8	32.0	13.8	10.3
95% CI within group, %*	26.8 to 69.4	14.9 to 53.5	3.9 to 31.7	2.2 to 27.4
95% CI between group, %†	−11.6 to 43.2		−13.3 to 20.2	

Abbreviations: CR, complete response; PR, partial response; CI, confidence interval; SD, stable disease.
*Within-group confidence interval is exact (based on binomial distribution).
†Between-group confidence interval is based on normal approximation.

Table 6 presents clinical toxicities reported in at least 2% of patients treated with arzoxifene. There were no statistically significant differences in the toxicities observed between the treatment arms. The most common grade 2 clinical toxicities were hot flashes and nausea. Seven patients (6%) reported with grade 3 toxicities, including nausea/vomiting, rash, neuromotor toxicity (defined as fatigue and asthenia; n = 2), neuromood toxicity (defined as depression), headache, neurocerebellar toxicity (defined as dizziness), and pulmonary toxicity (defined as dyspnea). These events did not result in drug discontinuation. There were no grade 4 clinical toxicities.

Five patients discontinued from the study because of adverse events. One patient experienced deep venous thrombosis, dyspnea, and edema 3 weeks after femoral rod placement for a pathologic fracture. According to the investigator, this serious event was considered possibly related to surgery as well as study drug. One patient was hospitalized for confusion and dyspnea and was subsequently diagnosed with a blockage in her carotid arteries. Another patient was hospitalized and diagnosed with a new primary cancer of the colon. Both of these serious events were considered unrelated to study drug. Two other patients discontinued treatment because of nonserious events: severe temporomandibular joint pain in one patient in the 20-mg arm and severe hot flashes in one patient in the 50-mg arm.

There were five deaths that all occurred within 5 weeks of study discontinuation. Four patients died as a result of PD and

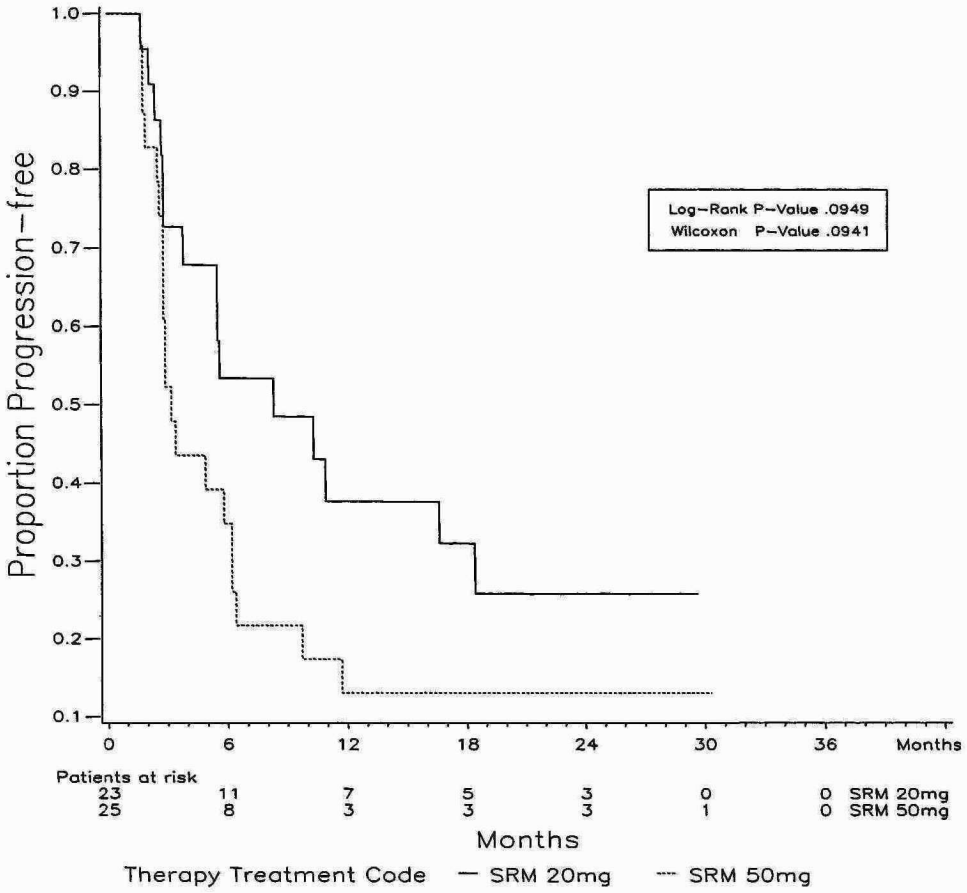

Fig 1. Kaplan-Meier[18] estimate for time to progression (months) in tamoxifen-sensitive patients.

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