Original article

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Randomized, double-blind, multicenter trial comparing two doses of arzoxifene (LY353381) in hormone-sensitive advanced or metastatic breast cancer patients

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Background: This randomized, double-blind, phase II study assessed two doses of the selective estrogen receptor modulator arzoxifene in women with advanced breast cancer. The primary end point was to choose the best of two doses of arzoxifene based on the response rate or the clinical benefit rate (CBR). Pharmacokinetics and toxicities were also assessed.

Patients and methods: Ninety-two patients with advanced breast cancer received arzoxifene 20 or 50 mg/day. Tumor response was assessed using World Health Organization criteria. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) system. Pharmacokinetic data were analyzed using the NONMEM® software program (GloboMax, Hanover, MD, USA).

Results: Response rates in the 20 mg arm were numerically higher than the 50-mg arm according to the investigator (40.5% versus 36.4%) and the independent review panel (42.9% versus 27.3%). CBR was higher in the 20 mg arm according to the investigator (64.3% versus 61.4%) and the independent review panel (59.5% versus 47.7%). Arzoxifene was well tolerated. There were no study drug-related deaths. Mean observed steady-state plasma concentrations of arzoxifene were 3.62 and 7.48 ng/ml for the 20 and 50 mg doses, respectively.

Conclusions: There were no significant differences in efficacy or safety between 20 and 50 mg of arzoxifene. Accordingly, arzoxifene 20 mg/day was selected for further study in patients with breast cancer.

Key words: arzoxifene, breast cancer, LY353381, selective estrogen receptor modulator

Introduction

For many years tamoxifen has been the mainstay of hormonal therapy for patients with breast cancer [1, 2]. As tamoxifen use has increased, so has the importance of its toxicity. Although tamoxifen is generally a well-tolerated drug, it does have significant side-effects, such as thromboembolism, oculopathy and endometrial cancer [1, 3–11]. Tamoxifen has both anti-estrogenic (breast) and estrogenic (uterus, bone, lipids and cardiovascular system) effects, which are mediated predominantly by nuclear estrogen receptors (ERs) [12]. The differential effects of tamoxifen, depending upon target organ and hormonal milieu, and other selective estrogen receptor modulators (SERMs) are thought to be due to subtle differences in the steric binding of these compounds to the ER [12].

Due to the potential side-effects related to the estrogen-agonist effects of tamoxifen, considerable attention has been paid to developing SERMs. The SERM arzoxifene (LY353381) was designed to have potent ER antagonistic activity on the breast and endometrium, while maintaining beneficial estrogen-agonist effects on bone and lipids. Both the parent compound and the active desmethly metabolite bind to the ER with high affinity and inhibit estrogen-dependent growth of MCF-7 breast cancer cells [13]. Arzoxifene is approximately 1200-fold more potent than tamoxifen in inhibiting the growth of MCF-7 cells. Arzoxifene showed dose-dependent inhibition of MCF-7 xenograft growth in nude mice. Moreover, in preclinical studies, arzoxifene blocked estrogen-induced uterine stimulation in ovariectomized rats and did not stimulate the uterine endometrium as indicated by a minimal effect on uterine weight in ovariectomized rats treated [14].

In a phase I study in 32 patients with previously treated advanced breast cancer, four doses of arzoxifene were tested: 10, 20, 50 and 100 mg/day [15]. The most common adverse event (56%) was hot flashes, as expected for this class of agent. Prospective evaluation

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of uterine safety was performed at baseline and on completion of 12 weeks of treatment and showed no evidence of endometrial hyperplasia. There was no evidence of dose-dependent toxicity. Neither complete nor partial responses were seen in this study; however, six patients had stable disease (SD) lasting ≥6 months. In addition, SD lasting ≥3 months was demonstrated in at least one patient from each dose cohort, suggesting possible antitumor activity at all tested doses. This study also established that arzoxifene has a linear pharmacokinetic profile [15].

The current study was conducted to select the best of two doses of arzoxifene (20 and 50 mg) for breast cancer treatment by comparing their efficacy and safety in patients with advanced breast cancer and to assess the compound for evidence of endometrial stimulation. The primary end point of dose selection was chosen on the basis of response rate or clinical benefit rate (CBR). Secondary study end points included response duration, time to progressive disease (TTP), overall survival and toxicity.

Patients and methods

Study design and treatment

A randomized, double-blind phase II study was carried out of arzoxifene 20 or 50 mg (Eli Lilly & Co., Indianapolis, IN) taken orally once daily by patients with advanced breast cancer for 12 weeks or until disease progression. Randomization was performed and balanced with respect to the treatment in each stratum using the Pocock and Simon algorithm [16] for three prognostic factors: number of metastatic disease sites (<3 or ≥3 sites), prior tamoxifen therapy (yes or no) and degree of ER positivity (high, low or unknown).

To preserve the blinding of the study, an assessment committee was appointed. No patients or investigators were inadvertently unblinded. However, patients treated with arzoxifene 20 mg/day, upon disease progression, received further arzoxifene treatment at a dose of 50 mg daily, in an open-label manner, at the investigator's discretion until further disease progression.

In the event of any National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 toxicity, dosing was omitted for a maximum of 2 weeks; upon resolution of the toxicity, treatment was re-initiated with a 50% dose reduction. Patients who had any study drug-related grade 4 toxicity or who progressed after 8 weeks of treatment were discontinued from the study.

Eligibility criteria

Women, at least 18 years of age, with a documented diagnosis of breast cancer (locally advanced or metastatic disease) who had not received any systemic therapy or relapsed >12 months after stopping adjuvant tamoxifen were eligible for this study. Patients with inoperable, locally advanced breast cancer were enrolled only if they were ineligible for primary chemotherapy. Prior neo-adjuvant or adjuvant chemotherapy was permitted if completed ≥6 months prior to the diagnosis of metastatic disease. Patients had to have evaluable or bidimensionally measurable tumors that were ER or progesterone receptor (PgR) positive (>10 fmol/mg by biochemical assay or ≥10% positive cells by immunohistochemistry).

Patients were excluded from the study if they had received prior hormonal therapy or chemotherapy for metastatic breast cancer; had rapidly progressive disease or known central nervous system metastases; inadequate end organ function [bilirubin >1.5 × upper limit of normal (ULN), aspartate aminotransferase/alanine aminotransferase >2.5 × ULN; serum creatinine ≥1.5 × ULN); hypercalcemia (corrected calcium of >11.0 mg/dl or 2.7 mmol/l); were pregnant or breast-feeding; or had used any investigational agent within 4 weeks of study enrollment].

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The protocol and consent process were approved by all relevant ethics review boards and all patients gave written informed consent prior to study enrollment.

Study assessments

All patients were assessed with the following tests: clinical evaluation, hematology, blood chemistry and coagulation profiles, hormone levels, bone markers (osteocalcin and type I collagen fragment) and radiological assessment. All clinical assessments were repeated every 4 weeks for the first 12 weeks of the study. Radiological assessment of involved disease sites was repeated after 12 weeks, or at discontinuation if sooner than 12 weeks, and every 2–3 months thereafter. The same assessment method used to determine the disease status at baseline was used consistently for efficacy evaluation throughout the study.

To prospectively evaluate gynecological safety, patients underwent transvaginal ultrasounds (TVUs) at baseline, 12 weeks and every 6 months thereafter while on arzoxifene treatment. If endometrial thickness >8 mm was noted, or had increased ≥5 mm from baseline, additional evaluation was required. To evaluate the effects of arzoxifene on the hypothalamic–pituitary–gonadal axis, patients also underwent hormonal evaluation [follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol and sex hormone binding globulin (SHBG)] at baseline and every 2 to 3 months during study treatment. To evaluate the effects of arzoxifene on bone metabolism, serum osteocalcin and type 1 collagen fragment were measured at baseline and every 2–3 months during study participation.

Bidimensionally measurable disease was defined as tumor measurements consisting of the diameter of the widest portions of the tumor and the greatest diameter perpendicular to that line. Evaluable disease comprised unidimensionally measurable lesions, masses without clearly defined margins, lesions with both diameters <0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter <2 cm or lytic bone disease. Unmeasurable disease was defined as lesions in previously irradiated fields, ascites, pleural effusions, blastic or mixed bony metastases, or abdominal masses that could be palpated but not measured.

Patients who had baseline staging and tumor measurements, at least one tumor measurement on treatment and had received at least 4 weeks of treatment were eligible for efficacy analyses. Tumor response [complete response (CR) plus partial response (PR)] was assessed by the investigator and the independent review panel using World Health Organization (WHO) criteria [17]. Tumor response data collected during the open-label dose escalation phase were not included in the primary analysis of tumor response. Tumor response had to be confirmed at least 4 weeks after a documented response. An independent review panel, consisting of three radiologists, reviewed the data for all patients with a response or SD according to the investigator. Clinical benefit response was defined as CR plus PR plus SD lasting ≥6 months. TTP was measured from the time of randomization until time of documented progressive disease (PD), including death by any cause. Response duration was identical to TTP but applied only to patients who exhibited a 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.

Patients who received at least one dose of arzoxifene were evaluated for safety and toxicity. Safety was assessed by recording all clinical adverse events at each patient visit, as well as routine hematological and biochemical monitoring. Toxicities were assessed using the NCI-CTC grading system (version 1) [18].

Pharmacokinetic analysis

Heparinized plasma samples were obtained from each patient during each visit for determination of concentrations of unconjugated arzoxifene and its desmethyl metabolite LY335562. Data were pooled and analyzed using a population pharmacokinetic program (NONMEM).

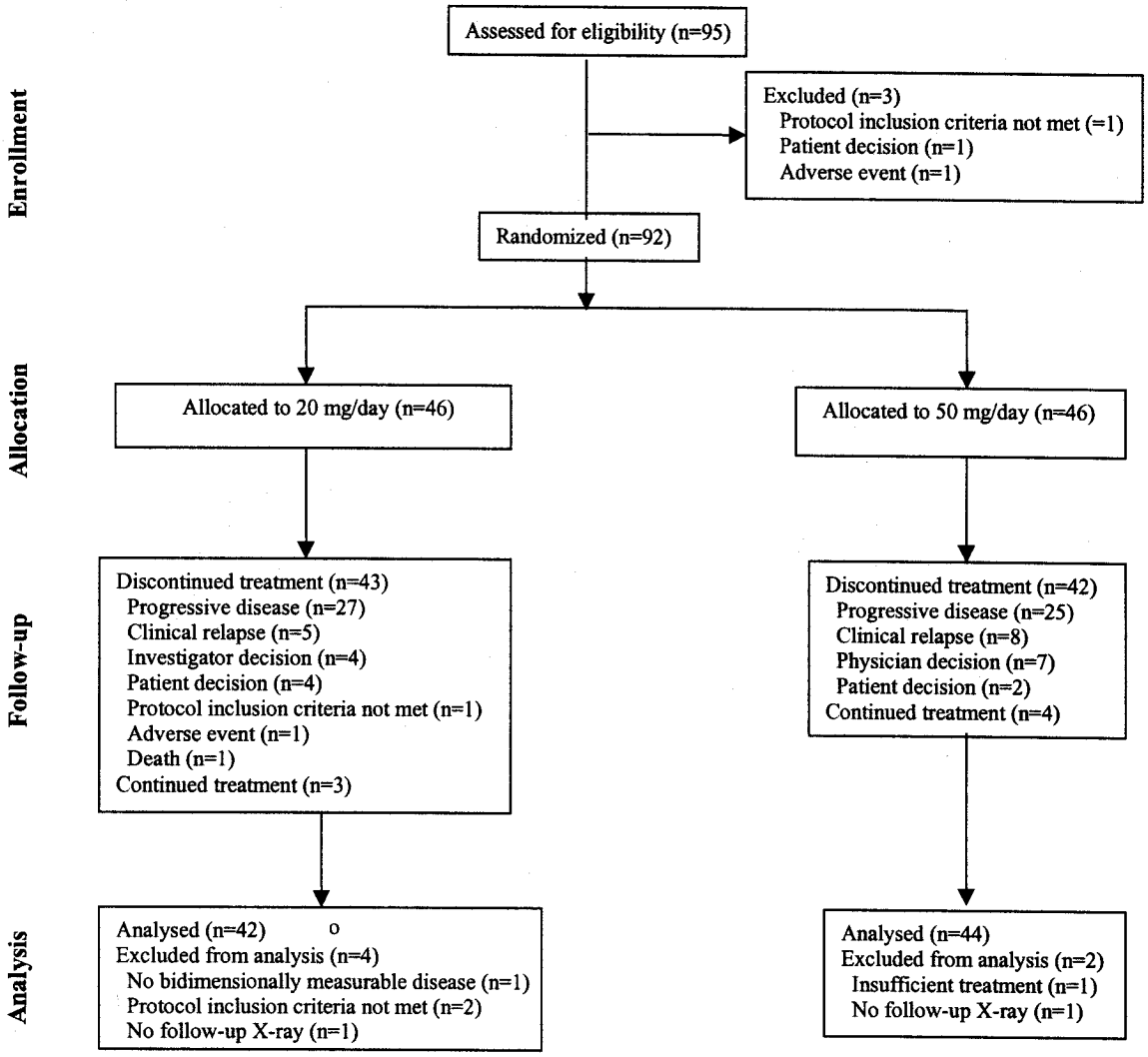

Figure 1. Patient characteristics.

Statistical methods

This study design was based on a ranking and selection methodology [19] in which the treatment arm with the larger observed response rate is selected as the best treatment. This design ensured that if the true response rate for one dose was ≥15% higher than the other dose, there was at least a 90% probability that this more effective dose would be selected. To fulfill this condition, 37 evaluable patients per dose needed to be enrolled.

Time-to-event distributions were estimated using the Kaplan–Meier method [20] and the log-rank test was used to compare treatment groups. The Mantel–Haenszel c^2 test was used to compare the incidence of toxicities accounting for severity. Changes from baseline to study discontinuation at various end points (e.g. hormone levels and bone markers) were assessed within study arms using the nonparametric sign test to allow for non-symmetrical distributions and between study arms using the Wilcoxon rank sum test. Exact binomial confidence intervals were computed for response rates and all confidence intervals and *P* values used a two-sided significance level of 0.05.

Results

Patient characteristics

The study was conducted at 18 European centers and 95 patients with advanced or metastatic breast cancer were entered from July 1998 to March 1999 (Figure 1). Three patients were not randomized: one patient did not meet protocol inclusion criteria, one patient experienced an adverse event and one patient decided not to enroll. Ninety-two patients were randomized: 46 in the 20 mg arm and 46 in the 50 mg arm. All patients were Caucasian. Notably, the median age for the patient population was 69.5 years and 92% were postmenopausal. The percentage of patients who had received adjuvant therapy was low. Baseline patient characteristics were well balanced between the two arms (Table 1).

Response rate and CBR

Forty-two patients in the 20 mg arm and 44 in the 50 mg arm were evaluable for efficacy; no bidimensionally measurable disease, no follow-up radiological assessment, inclusion criteria not fulfilled and insufficient therapy were reasons for non-evaluability.

Table 2 provides a summary of response rates and CBRs as determined by the investigators and the independent review panel. Response rate (40.5% versus 36.4%) and CBR (64.3% versus 61.4%) were numerically higher in the 20 mg arm compared with the 50 mg arm, as determined by the investigator as well as the

Table 1. Baseline patient and disease characteristics

Characteristic	Arzoxifene [*n* (%)]	
	20 mg	50 mg
No. of randomized patients	46 (100)	46 (100)
Age (years)		
Median	70	69
Range	44–86	37–94
Menopausal status[a]		
Postmenopausal	41 (89)	44 (96)
Premenopausal	4 (9)	2 (4)[b]
Disease stage		
Locally advanced (IIIB)	18 (39)	14 (30)
Metastatic (IV)	28 (61)	32 (70)
Site of metastasis		
Liver	5 (11)	4 (9)
Lung (no liver mets)	7 (15)	11 (24)
Bone (no liver or lung mets)	12 (26)	10 (22)
Other	22 (48)	21 (46)
≥3 metastatic sites	15 (33)	15 (33)
Zubrod performance status		
0	26	32
1	20	14
ER/PgR status		
ER+ (regardless of PgR)	34	34
ER–/PgR+	2	0
ER unknown/PgR unknown	10	12
Time since diagnosis (months)		
Median	1.2	1.4
Range	0–232	0–247
Prior adjuvant chemotherapy	7	9
Prior tamoxifen therapy	4	4

[a]One 20 mg patient was excluded from the algorithm since insufficient information was given to classify her status.
[b]One patient had follicle stimulating hormone and estradiol levels compatible with the postmenopausal state; however, she was deemed to still be menstruating in the previous year and was categorized as perimenopausal.
n, number of patients; mets, metastases; ER, estrogen receptor; PgR, progesterone receptor.

independent review panel (Table 2). Thus, the arzoxifene 20 mg dose was chosen for further study. Two patients randomized to arzoxifene 20 mg/day had disease progression and were subsequently administered open-label arzoxifene 50 mg/day. During double-blind therapy with arzoxifene 20 mg, one patient had a best study response of PR prior to progression, while the other patient progressed without response. During open-label therapy with arzoxifene 50 mg, both patients experienced disease progression within 4 months.

Time to event measures

The average follow-up time from study enrollment to last known contact was 22 months. The median response duration was 22.0 months [95% confidence interval (CI) 16.8–24.6 months] for 17 responders in the 20 mg arm and 22.3 months (95% CI, insufficient for calculation) for 16 responders in the 50 mg arm. There was no statistically significant difference between treatment arms. TTP is displayed in Figure 2. In the 20 mg arm, the median TTP was 10.7 months (95% CI 8.6–16.8 months) with 43% of the patients censored; in the 50 mg arm, the median TTP was 8.6 months (95% CI 5.6–14.4 months) with 46% of the patients censored. Based on the log-rank test, the difference between treatment arms was not statistically significant. Median survival analysis was not performed as >80% of the enrolled patients were still alive at the time of the final analysis. However, the average survival time, from study enrollment to last contact or death due to any cause, of patients in the 20 and 50 mg arms, were 21.8 and 22.4 months, respectively.

General safety

Table 3 summarizes the frequency of adverse events. There was a similar frequency of adverse events, irrespective of relationship to study drug, in both arms. Vasodilatation, the most common adverse event assessed as related to study drug, occurred more frequently in the 20 mg arm compared with the 50 mg arm (48% versus 26%), but this difference was not statistically significant. Non-serious adverse events resulting in study discontinuation did not occur.

Serious adverse events (SAEs) were reported in 14% of patients, with a slightly higher frequency in the 20 mg arm compared with the 50 mg arm (17 versus 11%). However, there was only one SAE assessed by the investigator as possibly related to study therapy (uterine perforation complicating surgical removal of an endometrial polyp, occurring in a patient treated with arzoxifene 50 mg/day for approximately 13 months). Dyspnea, the most common SAE, occurred in three patients, all of whom had lung or pleural involvement from their breast cancer at baseline; for all three patients, the event was assessed as disease-related. Two patients discontinued the study due to SAEs: one SAE was unexpected but assessed as possibly related to study therapy and the other SAE was assessed as unrelated to study therapy (cardiac insufficiency in one patient in the 20 mg arm). Although one patient (20 mg arm) died at home from gastrointestinal hemmorrhage after approximately 7 weeks of study therapy, her death was not attributed to study drug or procedure. There were no study drug-related deaths.

NCI-CTC toxicities were mild. There were no statistically significant differences in reported toxicities between the two arms. There were no reported grade 4 laboratory or non-laboratory toxicities during this study. Notably, lymphopenia was the only grade 3 laboratory toxicity, reported in one patient in the 50 mg arm. There were no grade 3 or 4 clinical toxicities. Grade 1 and 2 hot flashes, the most common toxicity, were reported in 27 and 12% of patients in the 20 and 50 mg arms, respectively. Two patients in the 20 mg arm developed deep venous thrombosis

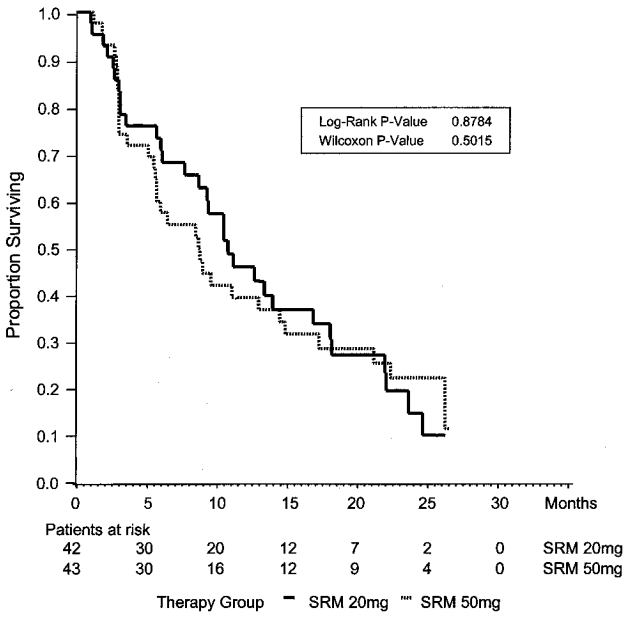

Figure 2. Time to progression.

while on the study drug and one patient in the 20 mg arm, with a pre-study history of phlebitis, developed thrombophlebitis. Approximately 2 months after study discontinuation due to disease progression, one patient in the 20 mg arm developed a pulmonary embolus that was assessed as unrelated to the study drug by the investigator.

Gynecological safety

Table 4 summarizes endometrial data for 52 postmenopausal patients who underwent baseline and at least one follow-up TVU. Overall, the majority of postmenopausal women did not have evidence of endometrial stimulation. In the 50 mg arm, one 70-year-old postmenopausal woman developed an ovarian microcyst, which was unassociated with increased estradiol levels.

Although increased endometrial thickness was observed in three of six premenopausal patients, timing of the TVU with respect to the patients' menstrual cycle was not reported. One 50-year-old premenopausal patient in the 20 mg arm developed ovarian cysts (maximum diameter, 29 mm) associated with a peak estradiol level of 2586 pmol/l.

Endocrinological and bone metabolism evaluation

Among postmenopausal patients in the 20 and 50 mg arms, there was a statistically significant decrease from baseline in FSH (median change, 9.0 and –13.0 IU/l, respectively) and estradiol (median change, 11.5 and –4.0 pmol/l) in both arms, and a statistically significant decrease in LH from baseline in the 50 mg arm (median change, 4.0 U/l). However, there was no statistically significant difference between the two doses of arzoxifene. Similarly, SHBG levels significantly increased from baseline in both arms (median change, +25.0 and +19.0 nmol/l, respectively), with no significant difference between arms.

There were six premenopausal patients. Four of the six premenopausal patients had increases from baseline in estradiol levels without significant changes from baseline in FSH, LH and SHBG levels.

Among postmenopausal patients, there were statistically significant reductions in the 20 and 50 mg arms in serum osteocalcin (median change, –5.4 and –3.5 mg/l, respectively) and type 1 collagen fragment (median change, –1707.0 and –1173.5 pmol/l, respectively), which are consistent with a skeletal anti-resorptive effect of arzoxifene. However, the difference in reductions between treatment groups did not achieve statistical significance.

The small number of premenopausal patients precludes reliable statistical analysis or interpretation.

Pharmacokinetic evaluation

The mean observed steady-state plasma concentrations of arzoxifene were 3.62 and 7.48 ng/ml for the 20 and 50 mg doses, respectively, with <1% of the samples obtained being below the limit of quantitation (<0.05 ng/ml) for both dose groups. However, for desmethyl metabolite LY335562, approximately 46% and 37% of the samples obtained were below the limit of quantitation (<0.05 ng/ml) for the 20 and 50 mg doses, respectively, with resulting mean observed steady-state concentrations ranging from 0.050 to 0.499 ng/ml and from 0.051 to 1.118 ng/ml, respectively.

Discussion

This randomized double-blind phase II trial was designed to compare the efficacy and safety of two doses of arzoxifene in patients with locally advanced or metastatic breast cancer.

The 20 mg arm exhibited a numerically higher response rate, CBR and TTP than the 50 mg arm. Therefore, the 20 mg dose of arzoxifene was recommended for further study. However, the study design did not control for statistical type-1 error; thus, the observed efficacy could also be consistent with no efficacy difference between doses.

Recently, there has been a renewed interest in aromatase inhibitors in the hormonal treatment of breast cancer in postmenopausal women [21, 22]. Their presumed mechanisms of action are inhibition of the aromatase enzyme complex, which is responsible for non-ovarian estrogen synthesis in postmenopausal women, as well as inhibition of intra-tumor aromatase enzymes. Two double-blinded randomized phase III studies [23, 24] have compared the non-steroidal aromatase inhibitor anastrozole with tamoxifen in the treatment of advanced breast cancer in postmenopausal patients. In these studies, anastrozole appeared to be equivalent or superior to tamoxifen in its effects on overall response rate (32.9%/21.0% versus 32.6%/17.0%, respectively) and median TTP (8.2/11.1 months versus 8.3/5.6 months, respectively) [23, 24]. Letrozole, another non-steroidal aromatase inhibitor, appeared to be superior to tamoxifen in its effects upon overall response rate (30% versus 20%, respectively) and median TTP (41 weeks versus 26 weeks, respectively) [25]. The efficacy in terms of response rate demonstrated in this randomized phase II study of arzoxifene is very interesting. Randomized trials against

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