SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: ARIMIDEX™ 1 mg tablet

ACTIVE INGREDIENT: Anastrozole

Trial title (number): A Randomized, Double-blind Trial to Compare the Efficacy and Safety of Anastrozole (ARIMIDEX™ 1 mg Daily) With Tamoxifen Citrate (20 mg Daily) as First-line Therapy for Advanced Breast Cancer in Postmenopausal Women (1033IL/0030)

Clinical phase: IIIB

First patient recruited: 26 February 1996
Last patient recruited: 9 July 1998
Data cutoff: 10 March 1999
Zeneca approval date: 14 July 1999

Principal investigator and location (center number): (Center 0001)

Publications: None at the time of the writing of this report.

OBJECTIVES

The primary objectives of this trial were to compare anastrozole with tamoxifen based on the following measures: time to progression, objective response, and safety. The secondary objectives of this trial were to compare the 2 treatment groups based on the following measures: time to treatment failure, time to death (survival), duration of response, duration of clinical benefit, analgesic use, World Health Organization (WHO) performance score, bone pain, and health economics.

METHODS

Design: This was a randomized, double-blind, double-dummy, multicenter trial to compare the efficacy and safety of anastrozole 1 mg daily with tamoxifen 20 mg daily as first-line therapy for advanced breast cancer in postmenopausal women. Patients were given their randomized treatment until there was sufficient objective evidence of disease progression to stop treatment.

Population: A total of 353 postmenopausal North American women with advanced breast cancer entered this trial.

Key inclusion criteria: Among the key criteria were the inclusion of postmenopausal women who had locally advanced or metastatic breast cancer and were eligible to be given first-line hormonal therapy; hormone receptor status (estrogen or progesterone receptor or both) of positive or unknown status; measurable or evaluable advanced disease; WHO performance status score of 0, 1, or 2; given informed consent to participate in the trial.

Key exclusion criteria: Among the key criteria were the exclusion of women who had previous systemic therapy for advanced breast cancer; who were receiving gonadotropin-releasing hormone (GnRH) analogues; had presence of life-threatening visceral disease; had a history of systemic malignancy other than breast cancer except for (i) adequately treated basal or squamous cell carcinoma of the skin, (ii) cervical cancer that was satisfactorily controlled, or (iii) patients who were treated for malignancy, but were disease-free and off therapy for ≥5 years, and whom the investigator considered "cured"; had an estimated survival of less than 3 months from the start of trial treatment based on clinical judgment; had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 5 times the upper limit of the reference range; had any other significantly abnormal laboratory test result at baseline that would place the patient at unusual risk or confound the results of the trial; had relevant history of any severe concomitant disease that would place the patient at unusual risk or confound the results of the trial; were unlikely to comply with the trial requirements (eg, confusion, infirmity, alcoholism); and had a history of bone marrow transplant or peripheral stem-cell support.

Dosage: Patients were given once-daily oral dosages of either (i) 1 mg of anastrozole and tamoxifen placebo, once daily; or (ii) 20 mg of tamoxifen and anastrozole placebo, once daily. Treatment continued until disease progression or until the patient withdrew from treatment for any reason other than progression. If patients withdrew before progression, they were monitored for time to progression.

Key assessments:

Efficacy: Before randomization, breast cancer history was recorded and the disease state evaluated; this evaluation included identification and measurement of lesions to be monitored during treatment, and assessment of nonmeasurable disease. In addition, the following assessments were performed: quality-of-life assessments (analgesic-use, bone pain, and performance scores) and health economics assessments. Patients were seen every 4 weeks for the first 12 weeks of trial treatment, every 12 weeks thereafter, and at the time of withdrawal from treatment for any reason. The size of measurable lesions and changes in nonmeasurable disease were recorded. On the basis of these assessments, an overall objective response (complete response, partial response, stable disease, or disease progression) was assigned for each visit. Physical findings, quality-of-life assessments, health economics assessments, adverse events, and laboratory measurements were also recorded. Assessments continued until disease

progression was assigned according to the investigator's opinion, irrespective of whether trial treatment was withdrawn before progression.

Safety: Physical examination findings, adverse events, and laboratory measurements were recorded throughout the trial. Assessments continued until disease progression was assigned (according to the investigator's opinion) irrespective of whether trial treatment was withdrawn before progression. Safety assessments were continuous throughout the trial and recorded at the time of patient visits. All adverse events were documented until 14 days after trial treatment was stopped. After withdrawal of trial treatment, patients were monitored at 6-month intervals for survival until death. All adverse events that resulted in withdrawal or death were followed until resolution.

RESULTS

Demography: A total of 353 patients from 97 centers in North America entered the trial; 171 patients were randomized to 1 mg of anastrozole once daily and 182 patients were randomized to 20 mg of tamoxifen once daily. The majority (88.4%) of all patients were Caucasian. The mean age for all patients was 67 years (range 30 through 92 years). The withdrawal rates and reasons for withdrawal were similar between the 2 treatment groups (122 [71.8%] patients who were randomized to anastrozole and 142 [78.0%] patients who were randomized to tamoxifen withdrew). The majority (61.4%) of patients withdrew because of disease progression.

Efficacy: The 2 primary efficacy end points in this trial were time to progression and objective-response. The statistical analyses (intent-to-treat) of time to progression and objective-response rate are shown in Tables A and B, respectively. The results from the per-protocol analyses were consistent with the results of the intent-to-treat analyses.

Table A Statistical analysis of time to disease progression

Comparison (tamoxifen:anastrozole)	Hazard ratio[a]	Lower 95% CL
Time to progression		
Adjusted analysis[b]	1.44	1.16
Unadjusted analysis[c]	1.42	1.15

[a] Hazard ratios greater than 1.00 indicate that anastrozole was associated with a longer time to disease progression than was tamoxifen.

[b] The adjusted analysis was performed using a Cox regression model including factors for treatment, age, previous hormonal therapy, estrogen/progesterone receptor status, and extent of disease at entry.

[c] The unadjusted analysis was performed using a Cox regression model including treatment factor only.

CL Confidence limit.

Table B Statistical analysis of objective-response rate

Comparison (anastrozole:tamoxifen)	Odds ratio[a]	Lower 95% CL	Difference in response rate[b]	Lower 95% CL
Objective-response rate				
Adjusted analysis[c]	1.38	0.87	5.01	–1.90
Unadjusted analysis[d]	1.30	0.83	4.02	–2.47

[a] Odds ratios greater than 1.00 indicate that the anastrozole was associated with a higher response rate than was tamoxifen.
[b] Difference in response rates greater than 0 indicate that anastrozole was associated with a higher response rate than was tamoxifen.
[c] The adjusted analysis was performed using a logistic regression model including factors of treatment, age, previous hormonal therapy, estrogen/progesterone receptor status, and extent of disease at entry.
[d] The unadjusted analysis was performed using a logistic regression model including treatment factor only.
CL Confidence limit.

The analyses of both primary end points found that anastrozole met the prespecified criteria for noninferiority, compared with tamoxifen. Patients who were randomized to anastrozole appeared to have a lower rate of progression and longer median time to progression (66.7% and 338 days, respectively) than did patients who were randomized to tamoxifen (75.8% and 170 days, respectively). Thirty-six (21.1%) patients who were randomized to anastrozole and 31 (17.0%) who were randomized to tamoxifen were considered to be responders (had a best objective response of complete response or partial response).
Supporting results were observed from the secondary end points.
The death rate was similar for the treatment groups (47 [27.5%] patients who were randomized to anastrozole and 53 [29.1%] patients who were randomized to tamoxifen had died at the time of data cutoff). The proportion of patients who were alive longer than 2 years was 57.7% for patients who were randomized to anastrozole and 61.2% for patients who were randomized to tamoxifen. A statistical analysis of survival was not performed because only 100 (28.3%) patients in this trial had died at the time of data cutoff.
Analyses of analgesic use, bone pain scores, and WHO performance scores found no significant differences between the 2 treatments.
Safety: The majority of patients (97.6% of the patients who were given anastrozole and 94.0% of the patients who were given tamoxifen) had 1 or more adverse events during the trial. The most frequently reported adverse event was asthenia, which occurred in 54 (31.8%) patients who were given anastrozole and 65 (35.7%) patients who were given tamoxifen. Other commonly reported adverse events were nausea (52 [30.6%] patients who were given anastrozole and 62 [34.1%] patients who were given tamoxifen), vasodilatation (62 [36.5%] patients who were given anastrozole and 44 [24.2%] patients who were given tamoxifen), and pain (43 [25.3%] patients who were given anastrozole and 48 [26.4%] patients who were given tamoxifen). Nine categories of adverse events were anticipated based upon the pharmacological profiles of anastrozole and tamoxifen. The categories of these prespecified adverse events were depression, tumor flare, thromboembolic disease (includes both venous and arterial events),

gastrointestinal disturbance, hot flushes (includes vasomotor menopause-like symptoms), vaginal dryness, lethargy, vaginal bleeding, and weight gain. Of these 9 anticipated adverse-event categories, the most frequently reported were gastrointestinal disturbance (53.5% of the patients who were given anastrozole and 57.1% of the patients who were given tamoxifen) and hot flushes (38.2% of the patients who were given anastrozole and 27.5% of the patients who were given tamoxifen).

A total of 100 deaths were reported at the time of data cutoff (10 March 1999): 90 deaths from causes related to breast cancer (41 [24.1%] patients who were given anastrozole and 49 [26.9%] patients who were given tamoxifen) and 9 deaths from other causes, including 4 deaths resulting from an adverse event (3 [1.8%] patients who were given anastrozole and 1 [0.5%] patient who was given tamoxifen) and 1 death resulting from an unknown reason. In cases where adverse events led to death, none of the primary causes of death were drug related. Patient 0080/0042 who was given anastrozole had a drug-related event of nausea, which was not the primary cause of death.

A total of 17 (4.8%) patients withdrew from treatment because of adverse events (9 [5.3%] patients who were given anastrozole and 8 [4.4%] patients who were given tamoxifen).

A total of 79 (22.4%) patients had 1 or more serious adverse events (37 [21.8%] patients who were given anastrozole and 42 [23.1%] patients who were given tamoxifen). The most frequently reported serious adverse event was nausea (4 [2.4%]) patients who were given anastrozole and 5 [2.7%] patients who were given tamoxifen). The incidences of the remaining serious adverse events was similar between the 2 treatment groups.

Hematological parameters changed very little during the trial for either treatment group. Mean serum alkaline phosphatase, AST, ALT, GGT, and lactate dehydrogenase levels in both treatment groups tended to decrease for the first year, possibly reflecting efficacy of treatment. Mean serum cholesterol levels tended to increase slightly for patients who were given anastrozole and decreased slightly for patients who were given tamoxifen. More patients who were given anastrozole developed Zeneca-defined laboratory abnormalities in serum alkaline phosphatase and total bilirubin. Review of these cases showed that these abnormalities could be directly related to breast cancer progression.

There was little change in pulse, blood pressure, or weight in either treatment group throughout the trial.