SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: FASLODEX™

ACTIVE INGREDIENT: Fulvestrant

Trial title (number): A Double-blind, Randomized, Multicenter Trial Comparing the Efficacy and Tolerability of 125 and 250 mg of FASLODEX™ (Long-acting ICI 182,780) With 1 mg of ARIMIDEX™ (Anastrozole) in Postmenopausal Women With Advanced Breast Cancer (9238IL/0021)

Clinical phase: III

First patient recruited: 15 May 1997
Last patient recruited: 13 August 1999
AstraZeneca approval date:

Principal investigator(s) and location (center number):

Publications: Osborne CK (On behalf of the North American Faslodex Investigator group). A double-blind randomized trial comparing the efficacy and tolerability of 'Faslodex' (fulvestrant) with 'Arimidex' (anastrozole) in post menopausal (PM) women with advanced breast cancer [abstract 7]. 23rd Annual San Antonio Breast Cancer Symposium: 2000 Dec 6-9; San Antonio, Texas. Breast Cancer Res Treat 2000;64 (1):27.

OBJECTIVES

Primary: Originally, to compare the effect, in terms of time to progression, of 2 doses of long-acting (LA) intramuscular (im) fulvestrant (125 or 250 mg administered every 28±3 days) with oral anastrozole (1 mg daily) in postmenopausal women with advanced breast cancer. Amended (effective 27 April 1998) because a protocol-defined preliminary data summary showed no objective responses in the first 30 patients treated with fulvestrant 125 mg (for this trial and Trial 9238IL/0020; see Design Section below); therefore, this treatment group was discontinued because of insufficient evidence of clinical activity. The primary objective was changed to the following: to compare the effect of 250-mg fulvestrant with 1-mg anastrozole in terms of time to progression in postmenopausal women with advanced breast cancer.

Secondary: (a) to compare objective response rates, duration of response, time to treatment failure, time to death, and quality of life (QOL) of patients treated with fulvestrant 250 mg with those of patients treated with anastrozole, (b) to assess tolerability (local and systemic) and symptomatic response to fulvestrant treatment compared with anastrozole treatment, and (c) to assess the pharmacokinetic profile of fulvestrant over 28 days following administration of a single dose and to assess plasma levels of fulvestrant after multiple monthly administration.

METHODS

Design: This was a multicenter, double-blind, randomized, parallel-group trial.
Trial 9238IL/0020, of similar design, was conducted in Europe, South Africa, and Australia. The efficacy and safety of treatment with the LA im formulation of fulvestrant 250 mg monthly were compared with those of anastrozole 1 mg given orally once daily. Patients continued treatment until objective evidence of disease progression or other events required treatment withdrawal; when these occurred, trial treatment was stopped, and standard therapy was initiated. Thereafter, patients were followed up for survival until death. For the final analysis, efficacy data from the 2 treatment groups were analyzed (or summarized, or both) when at least 340 end-point events (progression or death before progression) had occurred across the 2 groups. A minimum of 392 evaluable patients across both treatment groups (196 per treatment group) had to be recruited to achieve 340 end-point events. Tolerability data were also summarized and compared between treatment groups.

Population: postmenopausal women with advanced breast cancer who relapsed or progressed following previous hormonal therapy

Key inclusion criteria : (1) histologic or cytologic confirmation of breast cancer; (2) objective evidence of recurrence or progression of disease not considered amenable to curative treatment - locally advanced disease was included if considered not amenable to curative therapy;
(3) postmenopausal, defined as any of the following: (i) aged 60 years or older, (ii) aged 45 years or older with amenorrhea for longer than 12 months and an intact uterus, (iii) follicle-stimulating hormone (FSH) levels within the postmenopausal range (defined by the testing laboratory), or (iv) patient had a bilateral oophorectomy; (4) no more than 1 prior hormonal therapy for breast cancer with second-line hormonal treatment required because patient had a relapse after adjuvant endocrine therapy with an antiestrogen or a progesterone, or the patient's disease progressed

after treatment with either an antiestrogen or progesterone as first-line treatment for advanced disease; (5) evidence of hormone sensitivity, defined as (i) at least 12 months of adjuvant hormonal treatment before relapse, or (ii) tumor remission or stabilization resulting from hormonal therapy for at least 3 months before progression in advanced disease, or (iii) estrogen-receptor-positive (ER+) or progesterone receptor-positive (PgR+) status; (6) presence of at least 1 measurable or evaluable (nonmeasurable) lesion; (7) World Health Organization (WHO) performance status of 0, 1, or 2 (Ref WHO 1979); (8) life expectancy longer than 3 months

Key exclusion criteria : (1) presence of life-threatening metastatic visceral disease (defined as extensive hepatic involvement) or any degree of brain or leptomeningeal involvement (past or present) or symptomatic pulmonary lymphangitic spread (Patients with discrete pulmonary parenchymal metastases were eligible provided their respiratory function was not compromised as a result of disease.); (2) previous treatment with fulvestrant or aromatase inhibitors; 2 or more regimens of endocrine therapy for advanced disease (excluding oophorectomy, ovarian radiation, or luteinizing hormone-releasing hormone [LH-RH] analogue therapy), radiation, or chemotherapy within 4 to 6 weeks of baseline tumor assessment; or estrogen replacement therapy or investigational drug therapy within 4 weeks of randomization; (3) previous or current systemic malignancy within 3 years (other than breast cancer or adequately treated in-situ carcinoma of the cervix uteri or basal or squamous cell carcinoma of the skin); (4) evidence of severe or uncontrolled systemic disease

Dosage: Initially, patients were given fulvestrant 125 mg (2.5 ml) im monthly plus anastrozole placebo orally daily; fulvestrant 250 mg (2x2.5 ml) im monthly plus anastrozole placebo orally daily; or anastrozole 1 mg orally daily plus fulvestrant placebo 2.5 ml im monthly or fulvestrant placebo 2x2.5 ml im monthly. Patients randomized to treatment after the 125-mg treatment group was discontinued were given either the fulvestrant 250-mg regimen or the anastrozole regimen as described.

The formulation numbers of drugs and placebos used in this trial are the following: fulvestrant, F6521; fulvestrant placebo, F6522; anastrozole, F11292; and anastrozole placebo, F11314.

Key assessments:

Efficacy: Objective tumor assessments were completed before trial treatment (baseline) and at 3-month intervals during treatment until disease progression. Patients with palpable soft-tissue lesions had lesions assessed monthly for the first 3 months and every 3 months thereafter. Baseline assessment included the designation of lesions as measurable; evaluable but not measurable; or neither measurable nor evaluable. Each patient had to have at least 1 measurable or evaluable lesion to be eligible for the trial. Isotopic bone scan or skeletal survey was performed for screening purposes before treatment. Suspicious lesions identified by isotopic bone scan were confirmed by X-ray (or computed tomography [CT] scan or magnetic resonance imaging [MRI]) within 4 weeks of randomization. X-rays of the chest (or CT scan of the chest) were obtained for all patients within 4 weeks before randomization, and the results were used in the assessment of objective disease, if relevant. Time to disease progression (primary end point); duration of response, time to treatment failure, and time to death; subjective symptomatology (analgesic use score, global pain score, and WHO performance status); quality of life (QOL) (all secondary end points); and health economics variables were determined. Objective tumor assessment was determined according to the Union Internationale Contre Le Cancer (UICC)

criteria (complete response [CR], partial response [PR], stable disease [SD], or disease progression) using a computer algorithm. Certain radiological data were also reviewed by an independent radiologist.

The primary statistical analyses of the efficacy end points were conducted on an intention-to-treat basis, included all randomized patients, and used response data as defined by the computer

algorithm. Secondary (supportive) statistical analyses were conducted on a per-protocol population (according to treatment received) and an intention-to-treat basis with a model that excluded baseline covariates.

A planned preliminary data summary was conducted to assess objective response rates after a total of 30 patients had been treated with fulvestrant 125 mg (across both Trials 9238IL/0020 and 9238IL/0021) and followed up for a minimum of 3 months to assess response at this dose. The preliminary data summary showed that no objective response occurred in these first 30 patients; therefore, the fulvestrant 125-mg group was discontinued from Trials 9238IL/0020 and 9238IL/0021.

An planned interim analysis (including a formal statistical analysis of time to progression) was conducted with combined data from both trials to assess whether fulvestrant treatment was less safe or efficacious than anastrozole treatment. As a result of the interim analysis, the Data Monitoring and Safety Committee (DMC) recommended that Trials 9238IL/0020 and 9238IL/0021 continue.

Pharmacokinetics: The pharmacokinetics of fulvestrant 250 mg were defined over 28 days in a small cohort of patients (N=5) following the first injection. The following parameters were determined; area under the plasma concentration-time curve from 0 to 28 days ($AUC_{0\text{-}28d}$), maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), and the plasma concentration at the end of the dosing interval of 28 days (C_{min}).

"Trough" samples were collected from a large group of patients (N=204) in order to assess the plasma levels of fulvestrant after multiple dosing.

Pharmacokinetic modelling was used to provide fitted profiles for both the single- and multiple-dose data generated in this trial.

Safety: Data for adverse events, deaths, and withdrawals due to adverse events were recorded throughout the trial and follow-up period (ie, 8 weeks after administration of the last injection or 30 days after ingestion of the last tablet, whichever was longer). Health economics data (eg, duration and type of healthcare required because of adverse events) were also collected. Clinical laboratory data were collected at entry and throughout the treatment period to evaluate hematological function; hepatic, renal, lipid, and other biochemistry variables; and endocrine function. Electrocardiographic (ECG) data were collected 3 weeks before randomization, at the time of a cardiac event, and at withdrawal; and blood pressure and pulse and weight data were collected on Day 1 and at every visit including withdrawal.

RESULTS

Demography: A total of 400 patients from 83 centers in North America were randomized to treatment [206 (51.5%) to treatment with fulvestrant 250 mg and 194 (48.5%) to treatment with anastrozole 1 mg]. (Seventy-three patients were randomized to treatment with fulvestrant

125 mg; demographic data from these patients are listed in Appendix G, but were not summarized.)

The mean age for patients randomized to fulvestrant 250 mg was 63 years (range 33 through 89 years), and the mean age for patients randomized to anastrozole 1 mg was 62 years (range 36 through 94). The mean weight and weight range between treatment groups were similar, and the majority of patients (fulvestrant 250 mg: 85.9%; anastrozole 1 mg: 80.9%) were white.

The incidences and types of abnormalities at entry, breast cancer history, baseline characteristics of breast cancer status, baseline data for analgesic use, global pain score, and WHO performance status were all similar between the 2 treatment groups.

Three hundred thirty patients [fulvestrant 250 mg: 170 (83.1%); anastrozole 1 mg 160 (82.9%)] were withdrawn from trial treatment; 76% of patients treated with fulvestrant 250 mg and 77.7% treated with anastrozole 1 mg were withdrawn because of disease progression. Five patients in each treatment group were withdrawn because of adverse events (fulvestrant 250 mg: 2.5%; anastrozole 1 mg: 2.6%), and 2% percent or less of patients in each treatment group were withdrawn because of other reasons (eg, protocol noncompliance, informed consent withdrawn).

Efficacy: The median duration of follow up for time to progression was 140.5 days, and greater than 83% of patients in both treatment groups had disease progression at the data cutoff date.

The primary statistical analysis of time to progression (confirmed by the 2 secondary analyses) did not show a statistically significant difference (p=0.4295; hazard ratio for fulvestrant to anastrozole of 0.92 and confidence interval of 0.74 to 1.14) between the 2 treatments, ie, showed similar efficacy for fulvestrant 250-mg and anastrozole 1-mg treatment. Similar proportions of patients had disease progression at the time of the data cutoff, but the median time to progression was longer for patients randomized to fulvestrant 250 mg (165 days) compared with patients randomized to anastrozole 1 mg (103 days).

The primary statistical analysis of objective response rate (confirmed by the 2 secondary analyses) showed no statistically significant difference (p=0.9647; odds ratio 1.01, 95.14% confidence interval 0.59 to 1.73) between the 2 treatment groups, ie,, fulvestrant 250 mg and anastrozole 1 mg resulted in similar proportions of patients who responded to treatment (ie, achieved a best response of CR or PR; 17.5% for both treatment groups).

The proportion of patients who received clinical benefit (ie, CR+PR+SD for ≥24 weeks) was somewhat higher in the fulvestrant 250-mg treatment group (fulvestrant 250 mg: 46.3%; anastrozole 1 mg: 41.4%).

The median duration of objective response measured from the date of randomization was 588 days for the 36 patients in the fulvestrant 250-mg group and 318 days for the 34 patients in the anastrozole 1-mg group who responded to treatment (ie, had a best objective CR or PR to treatment). For the 87 (42.2%) patients who received clinical benefit in the fulvestrant 250-mg group, the median duration was 391 days, and for the 70 (36.1%) patients in the anastrozole 1-mg group, the median duration was 329 days.

At the time of data cutoff, 178 (86.4%) patients in the fulvestrant 250-mg group and 170 (87.6%) patients in the anastrozole 1-mg group had failed treatment. The difference in median time to treatment failure between the 2 groups was 39.5 days in favor of patients randomized to fulvestrant 250 mg.

The primary analysis of time to treatment failure (confirmed by the secondary analyses) showed fulvestrant 250 mg was similar to anastrozole 1 mg (p=0.6947; hazard ratio 0.96;

95% confidence interval 0.77 to 1.19). The majority of patients in both treatment groups were considered to have failed treatment because of disease progression (164 of 178 patients randomized to fulvestrant 250 mg and 163 of 170 patients randomized to anastrozole 1 mg).
As of the data cutoff, 73 (35.4%) patients randomized to fulvestrant 250-mg group and 65 (33.5%) randomized to anastrozole 1-mg group had died. The median duration of follow up for time to death was 510 days. Because half of the patients across both treatment groups had not died at the time of data cutoff, in accordance with the statistical analysis plan, a formal statistical analysis was not performed.
Symptomatic response (analgesic use, global pain score, WHO performance status) data were generally similar between treatment groups, for Visits 1 through 12 (from randomization), more patients randomized to fulvestrant 250 mg reported a global pain score of no pain and required no analgesics during the 7 days before the visit compared with patients randomized to anastrozole 1 mg.
Insufficient QOL data were collected after disease progression to allow the data after progression to be used in the statistical analysis; therefore, only QOL data collected up to the date of the patient's last visit within the previous 12 months or the visit at which it was determined the patient had disease progression (whichever occurred earlier) were included in the statistical analyses and summaries of QOL data (ie, TOI, VAS, and time to deterioration in QOL). Most patients reported no change in overall QOL at each visit. The pattern of change in overall QOL was similar between the fulvestrant 250-mg and anastrozole 1-mg groups.
There was no evidence of a difference between treatment groups for either TOI (p=0.8062) or VAS (p=0.0937). The difference between treatment groups in median time to deterioration in QOL was 51 days in favor of fulvestrant; however, results from the analysis of deterioration in QOL showed no statistically significantly difference (p=0.1641) between treatment groups.
Pharmacokinetics: Following a single dose of fulvestrant 250 mg, pharmacokinetic assessments were made in 4 patients only; release from the injection site was prolonged, and the time taken to achieve peak plasma concentrations (t_{max}) was approximately 9 days. The gmean C_{max} was 4.76 ng/ml, and the gmean $AUC_{(0\text{-}28d)}$ was 88.4 ng.d/ml fulvestrant. Following C_{max}, plasma levels declined slowly, falling to a gmean plasma concentration of 1.89 ng/ml after 28 days.
Following repeated dosing of fulvestrant 250 mg, trough samples were collected from a large number of patients (N=193); gmean trough concentrations increased steadily from 2.38 ng/ml after the first injection to 8.90 ng/ml after 21 injections. A modeled profile of this data suggested that steady-state kinetics were achieved after approximately 6 injections. $AUC_{0\text{-}28d}$ values generated from the model indicated there was a 2- to 3-fold increase in exposure due to accumulation of fulvestrant. There was no evidence, however, of a change in the pharmacokinetic behavior of fulvestrant on repeated dosing.
Safety: The median duration of trial treatment was 170.5 days (range 28 to 1119 days) for the fulvestrant 250-mg group and 168 days (range 28 to 957 days) for the anastrozole 1-mg group. Similar proportions of patients in both treatment groups had a wide variety of concomitant drug and nondrug treatments during the trial.
The majority of patients (>90% in each group) had 1 or more adverse events during the trial; approximately 50% of patients in each treatment group had events that were considered drug related. The most frequently reported adverse events (>15% in either group in decreasing order of incidence) included asthenia, nausea, pain – location not specified, headache, vasodilatation,

pharyngitis, dyspnea, back pain, diarrhea, bone pain, abdominal pain, injection-site pain, pelvic pain, vomiting, peripheral edema, cough increased, and rash. The incidence of events was generally similar between treatment groups; however, a lower percentage of patients treated with fulvestrant 250 mg compared with patients treated with anastrozole 1 mg had asthenia (30.9% and 36.8%, respectively), nausea (30.4% and 33.7%, respectively), diarrhea (15.7% and 20.7%, respectively), insomnia (8.8% and 12.4%, respectively), and fever (5.9% and 10.4%, respectively); and a higher percentage of patients treated with fulvestrant 250 mg compared with anastrozole 1 mg had dyspnea (22.5% and 16.6%, respectively), dizziness (11.8% and 8.3%, respectively), urinary tract infection (9.3% and 5.2%, respectively), and hypertension (6.4% and 2.6%, respectively).

The highest percentage of patients had mild events, and the lowest percentage had severe events. The number of deaths due to adverse events was small [fulvestrant 250 mg: 4 (2.0%); anastrozole 1 mg: 3 (1.6%)], no patient died of an adverse event considered related to trial treatment, and few patients were withdrawn from treatment because of adverse events [fulvestrant 250 mg: 5 (2.5%); anastrozole 1 mg: 5 (2.6%)]. Although a higher percentage of patients treated with fulvestrant 250 mg (18.6%) had serious adverse events compared with patients treated with anastrozole 1 mg, similar proportions were considered drug related (1.5% and 1.0%, respectively) or led to death (2.0%, and 1.6%, respectively).

Joint disorders occurred in fewer patients given fulvestrant, and urinary tract infections occurred in more patients. Gastrointestinal disturbances and hot flashes occurred at similar frequencies in both treatment groups. The incidences of thromboembolic disease, vaginitis, and weight gain were similar (ie, low, and few were considered drug related) in both treatment groups.

Patients in this trial had a variety of concomitant medical illnesses and previous treatments for breast cancer; therefore, laboratory values for hematology and biochemistry variables were commonly outside the reference range. No trends were seen across time (including for patients with abnormal baseline values), clinical laboratory testing results were generally similar between treatment groups, and few abnormalities were considered causally related to trial treatment.

Hormone levels (FSH, LH, and estradiol) demonstrated a slight rise within the first 3 to 6 months of trial entry. Lipid biochemistry values did not appear to be affected by treatment with fulvestrant 250 mg. Values outside the normal range for cholesterol and triglyceride levels during treatment were similar between treatment groups.

Similar proportions of patients given fulvestrant or placebo had injection-site events, most of which were mild; 1 (0.5%) patient in the fulvestrant 250-mg group had severe reaction-site pain and was withdrawn from treatment (at her request); however, the investigator did not consider the event related to drug. Two patients with moderate events related to placebo injections were also withdrawn from treatment. Fifty-five (27.0%) patients given fulvestrant 250 mg and 45 (23.3%) patients given injections of fulvestrant placebo reported injection-site events, and similar percentages of courses of injections with fulvestrant (4.6%) and placebo (4.4%) resulted in injection-site events.

Safety data from patients treated with fulvestrant 125 mg were broadly consistent with those from patients treated with fulvestrant 250 mg and did not show a dose to toxicity relationship.