Abbreviated Clinical Study Report Synopsis	
Drug Substance	Gefitinib (IRESSA; ZD1839)
Study Code	D7917L00002 (1839US/0713)
Edition Number	1
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Phase II Multicenter, Double-Blind, Randomized Trial Comparing Anastrozole (ZD1033, Arimidex™)-Placebo to the Combination Anastrozole–ZD1839 (gefitinib, IRESSA™) in Postmenopausal Patients with Estrogen Receptor (ER) and/or Progesterone Receptor (PgR) Metastatic Breast Cancer

Study dates: First patient enrolled: 27 January 2004
Last patient enrolled: 10 August 2006
Data cut-off date: 31 January 2007

Phase of development: Phase II

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

This study was conducted at 50 centers in four countries (United States, Mexico, Venezuela, and Colombia). The first patient entered the study on 27 January 2004. Enrollment was stopped after 94 patients had entered because initiatives to achieve the full complement of 174 evaluable patients within a reasonable time period were not successful. The last patient was enrolled on 10 August 2006.

Publications

At the time of writing, data from this study had been presented at the 2008 Annual Meeting of the American Society of Clinical Oncology:

Cristofanilli M, Valero V, Mangalik A, Rabinowitz I, Arena FP, Kroener JF, Curcio E, Watkins C, Magill P. A phase II multicenter, double-blind, randomized trial to compare anastrozole plus gefinitib with anastrozole plus placebo in postmenopausal women with hormone receptor-positive (HR+) metastatic breast cancer (MBC). J Clin Oncol 2008; 26 (Suppl): Abstract 1012.

Objectives

To reflect the incomplete enrollment, Protocol Amendment 3 (dated 31 January 2007) revised the study objectives from formal comparisons between the treatment groups to estimation of treatment effects; in addition, patients were no longer to be followed-up for survival. The amended objectives and variables are presented in Table S1.

Table S1 Study objectives and variables

Objective	Variable
Primary	
To estimate time to tumor progression for each of the two treatment groups (anastrozole/placebo and anastrozole/gefitinib) in postmenopausal patients with newly diagnosed metastatic breast cancer. (Hereafter, time to progression is referred to as progression-free survival [PFS] for consistency with other gefitinib study reports.)	PFS, calculated from the date of randomization to the date of first documented disease progression or death[a]
Secondary	
To estimate the objective response rate (ORR) for each of the two treatment groups	ORR, defined as complete response (CR) + partial response (PR; as per RECIST), in patients with measurable disease[a]
To estimate the clinical benefit rate (CBR) for each of the two treatment groups	CBR, defined as CR + PR + stable disease ≥24 weeks (as per RECIST) after the start of study treatment, in patients with measurable disease[a]
To estimate overall survival (OS) for each of the two treatment groups	OS, calculated from the date of the start of study treatment to the date of patient death due to any cause, or to the last date the patient was known to be alive[a]
To compare the tolerability of anastrozole/placebo to that of anastrozole/gefitinib	The frequency and severity of adverse events (AEs); clinical laboratory parameters were also assessed[b]

Table S1 Study objectives and variables

Objective	Variable
To determine steady-state trough plasma concentrations of anastrozole in all patients; and to determine steady-state trough plasma concentrations of gefitinib, and to relate values to historical data.	Anastrozole and gefitinib steady-state trough plasma concentrations (C_{min})[a]
Exploratory	
To obtain tumor tissue and blood samples for biologic studies in the limited patient population available, and measure expression of markers that might potentially correlate with response to treatment in this patient population	Biomarker data will be reported separately.

[a] Data were collected up to the data cut-off date of 31 January 2007 (date of Protocol Amendment 3).
[b] Safety data were collected from all patients taking study medication and for 30 days after stopping study medication.
ER Estrogen receptor.
PgR Progesterone receptor.

Study design

This was a Phase-II, multicenter, randomized, double-blind, placebo-controlled study. Eligible patients were randomized to one of two treatment groups on a 1:1 basis: anastrozole 1 mg/day concurrent with placebo, or anastrozole 1 mg/day and gefitinib 250 mg/day.

Target patient population and sample size

The target patient population was female postmenopausal patients aged 18 years or older with newly diagnosed metastatic estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive breast cancer. Patients who developed metastatic disease during or after adjuvant tamoxifen, or patients who were hormone therapy-naïve were eligible for this study.

The original sample size was 174 patients, and the sample size goal was to have a 90% probability of observing a 5% improvement in PFS for gefitinib if the true improvement was 33% (118 patients with disease progression were required). However, enrollment was stopped after 94 patients had been enrolled (and 54 patients had progressed) and no formal statistical comparisons (p-values) between the treatment groups were performed.

Investigational product and comparator(s): dosage, mode of administration and batch numbers´

Patients received anastrozole given orally at 1 mg/day concurrent with placebo given orally (one tablet per day), or anastrozole given orally at 1 mg/day and gefitinib given orally at 250 mg/day. Formulation numbers were: anastrozole 1-mg tablet, F011292; gefitinib 250-mg tablet, F012653; and gefitinib-matched placebo, F012647. Batch numbers are included in the study report.

Duration of treatment

Even though enrollment was stopped, patients could continue to receive study medication until progression of disease (as per RECIST), in the absence of unacceptable toxicity and provided the patient wanted to continue receiving treatment.

Statistical methods

As enrollment was stopped after 94 patients had been enrolled (and 54 patients had progressed), no formal statistical comparisons (p-values) between the treatment groups were performed. PFS, ORR, and CBR have been presented in summary form; hazard ratios (HRs) and 95% confidence intervals (CIs) have been provided for illustrative purposes only.

Subject population

Ninety-four patients were randomized to treatment: 50 to anastrozole/placebo and 44 to anastrozole/gefitinib. However, one of the anastrozole/gefitinib patients had a cardiac arrest and died before being treated; thus, 93 patients were analyzed for efficacy and safety.

Twenty-eight patients (30%) were 'withdrawn prematurely from study'. This category was used when a patient was withdrawn completely from the study (i.e. the patient was not followed for survival status); it was not necessarily used when a patient discontinued therapy (see below), although a patient could have been counted in both categories. The most common reasons for discontinuing the study were withdrawal of informed consent, disease progression and death. (Disease progression and death were captured in the 'withdrawn prematurely from study' category, but by definition these are not reasons for premature discontinuations; they were categorized as 'other' on the Case Report Form.) The most common reasons for discontinuing investigational therapy were objective disease progression and AE. (Note: the reason for discontinuation of investigational therapy was not always required to be collected, e.g. if a patient died between visits.)

Patients were representative of a population with histologically-confirmed metastatic ER-positive and/or PgR-positive adenocarcinoma of the breast, who were candidates for hormonal treatment. The treatment groups were generally well balanced in terms of demography and baseline characteristics, although fewer patients in the anastrozole/gefitinib group vs. the anastrozole/placebo group had good WHO performance status (40% vs. 62%, respectively) and poorly differentiated tumors (21% vs. 34%, respectively). The anastrozole/placebo and anastrozole/gefitinib groups also differed slightly in terms of ER status (85% vs. 95% ER-positive, respectively) and PgR status (63% vs. 90% PgR-positive, respectively) according to the central laboratory. Small imbalances in patient characteristics due to chance are not unusual in a study of this size.

Summary of efficacy results

PFS showed an advantage in favor of anastrozole/gefitinib compared with anastrozole/placebo (median PFS of 441 days [14.7 months] vs. 251 days [8.4 months]; HR of placebo:gefitinib 1.83 [95% CI 1.06 to 3.15]; HR of gefitinib:placebo 0.55 [95% CI 0.32 to 0.94]). ORR was

numerically lower in the anastrozole/gefitinib group compared with the anastrozole/placebo group (2% vs. 12%), but – due to a greater number of patients who had stable disease in the anastrozole/gefitinib group vs. the anastrozole/placebo group – CBR showed a numerical advantage in favor of anastrozole/gefitinib (49% vs. 34% in the anastrozole/placebo group). The number of patients who died before the data cut-off date (six gefitinib and seven placebo patients, 14% in each treatment group) was too small to allow any conclusions to be drawn regarding patient survival.

Summary of pharmacokinetic results

In the anastrozole/gefitinib group, the geometric mean concentrations of gefitinib were generally consistent at Visits 3, 4 and 5 (245 ng/mL, 281 ng/mL and 246 ng/mL, respectively). At Visit 6, the number of patients was small (n=18) and the geometric mean concentration of gefitinib was slightly lower (213 ng/mL), which was possibly due to a patient having stopped taking gefitinib some days before the Visit-6 blood sample was taken (the concentration range was 18 ng/mL to 852 ng/mL). The values were broadly similar to the mean trough concentrations seen in previous studies where gefitinib was administered alone (216 ng/mL in patients with non-small cell lung cancer [Studies D7913C00016 and D7913C00039]; 305 ng/mL in patients with squamous cell carcinoma of the head and neck [Study D7919C00704]).

In the anastrozole/placebo and anastrozole/gefitinib groups, the geometric mean concentrations of anastrozole were generally consistent at Visits 3, 4, 5 and 6 (34 ng/mL, 35 ng/mL, 38 ng/mL and 39 ng/mL, respectively). These values were slightly lower than historical values (41.3 ng/mL in Study D7917C00223), which could imply interruption to anastrozole dosing.

The mean anastrozole concentrations were not different between the anastrozole/placebo and anastrozole/gefitinib treatment groups (details of this post-hoc supplementary analysis are provided in the study report). Taken together with the observation of expected concentrations of gefitinib, this suggests an absence of pharmacokinetic interactions between anastrozole and gefitinib.

Summary of safety results

The proportions of patients with any AE, any SAE, or any CTC grade 3 to 5 AE were similar between the treatment groups (Table S2). However, greater incidences of treatment-related AEs and AEs leading to discontinuation of treatment were reported by patients treated with anastrozole/gefitinib compared with anastrozole/placebo. The types of AEs reported were consistent with the known safety profiles of gefitinib and anastrozole. Two SAEs with an outcome of death occurred in patients taking anastrozole/gefitinib and one occurred in a patient taking anastrozole/placebo; none was considered treatment-related. No unexpected clinical laboratory test results, and no clinically relevant trends in vital signs were observed.

Table S2 Number (%) of patients who had at least one adverse event in any category: safety population

Category	n (%) of patients[a]	
	Anastrozole/placebo n=50	**Anastrozole/gefitinib n=43**
Patients with any AE	43 (86.0)	39 (90.7)
Patients with any AE considered related to study drug	19 (38.0)	34 (79.1)
Patients with any SAE	8 (16.0)	6 (14.0)
Patient deaths	7 (14.0)	6 (14.0)
Patients with any SAE with an outcome of death	1	2
Deaths related to cancer	6	4
Patients with any SAE with a non-fatal outcome	7 (14.0)	4 (9.3%)
Patients with any AE that led to discontinuation of study treatment	2 (4.0)	9 (20.9)
Patients with any CTC grade 3 to 5 AE	12 (24.0)	10 (23.3)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

AE, Adverse event; CTC, Common Toxicity Criteria; SAE, Serious adverse event; n, Number of patients.