Drug product:	IRESSA™ 250 mg	**SYNOPSIS**	
Drug substance(s):	Gefitinib/fulvestran		
Document No.:	<<>>		
Edition No.:	Final		
Study code:	1839IL/0141		
Date:	9 April 2009		

A PHASE II TRIAL TO EVALUATE THE COMBINATION OF ZD1839 (IRESSA™) AND FULVESTRANT (FASLODEX®) IN PATIENTS WITH ADVANCED OR METASTATIC BREAST CANCER

Study dates		**Phase of development**
First patient enrolled	10 June 2004	II
Last patient enrolled	22 December 2005	
Date of data cut-off	23 June 2007	

Objectives

The primary objective of the study was to evaluate the time to progression (TTP) of the combination of ZD1839 (gefitinib, Iressa™) and fulvestrant in patients with advanced or metastatic breast cancer.

The secondary objectives of the study were:

Efficacy:

1. To estimate the objective response rate (complete response [CR] and partial response [PR]) at trial closure
2. To estimate the disease control rate at trial closure
3. To estimate overall survival

Safety:

To evaluate the safety and tolerability of the combination of Gefitinib and fulvestrant.

Exploratory:

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To evaluate the effect of the combination Gefitinib and fulvestrant on serum and tissue biomarkers that can help to define agent efficacy and appropriate dose.

Study design

This was a multi-centre, open-label, non-comparative, phase II trial.

Recruitment was planned to be by strata, requiring that all patients were positive for oestrogen receptor (ER) or progesterone receptor (PgR), at least 30 of the 60 patients were both ER and PgR positive and at least 30 of patients had measurable disease following RECIST criteria. Patients were assigned to the single treatment group.

The primary outcome variable was TTP.

One ZD1839 tablet (250 mg) was to be taken daily, continuously through the study. The ER down-regulator fulvestrant (Faslodex®) was administered as a 250 mg intramuscular (i.m.) injection once a month.

The combination therapy was administered until disease progression, unacceptable toxicity or withdrawal of consent. There was screening period of up to 28 days. Treatment commenced on Day 1, and trial visits were made on Day 1, Day 31 and monthly (every 30+/-3 days) thereafter.

Target patient population and sample size

The target trial population comprised postmenopausal female patients with histologically confirmed advanced or metastatic, ER and/or PgR +/- breast cancer. Previous adjuvant hormone therapy and/or previous adjuvant chemotherapy were allowed. Patients enrolled into the trial could have measurable disease according to RECIST (Response Evaluation Criteria in Solid Tumours) criteria and/or non-measurable bone disease.

A total of 49 eligible patients were recruited.

Key inclusion criteria: Histologically confirmed advanced or metastatic breast adenocarcinoma; postmenopausal females with measurable disease (RECIST) and/or non-measurable bone disease.

Sample size: With 60 patients the study was calculated to have 80% power to demonstrate that the median TTP was greater than 7 months when the true median TTP was 11 months (one-sided alpha of 5%).

The sample size was assessed by simulation based on a model with exponential TTP. It was assumed that patients would be censored at 18 months follow-up and that 10% of patients would discontinue for reasons other than progression/death.

Sub-group analyses were planned, thus balanced samples were necessary for the following two factors:

- Patients with both receptors (ER and PgR) positives versus patients with only one of the receptors positive

- Patients with measurable disease versus patients with non-measurable disease

In order to achieve approximately 50 % of the trial population in each of the subgroups, the recruitment in any of the respective strata was to be stopped when 30 patients was reached. This was to be done independently for both factors. The same procedure was to be used for the factor measurable disease or non-measurable disease, respectively.

The study was terminated after 49 eligible patients had been recruited, i.e., the sample size did not meet the planned criteria for analysis.

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

ZD1839 (Iressa™, gefitinib) was supplied by AstraZeneca as brown, plain-faced film-coated tablets of 250 mg, formulation number F12653.

Fulvestrant (Faslodex® [LA ICI 182,780]) was supplied by AstraZeneca as a 50 mg/mL single-dose oily solution designated as Faslodex 5% w/v injection, formulation number F6521. AstraZeneca Farmaceutica Spain S.A. provided the sites with this material as a pre-filled syringe.

Duration of treatment

The combination therapy was administered until disease progression, unacceptable toxicity or withdrawal of consent.

Criteria for evaluation (main variables)

Patient-reported outcomes (PRO)

Not applicable.

Efficacy

- Primary endpoint: TTP

Patients were classified at closure as

- Alive and progression-free at trial closure
- Having disease progression by trial closure
- Dead without prior documented disease progression by trial closure
- Progression status unknown at trial closure

TTP was calculated as the number of days from the first dose of ZD1839 or fulvestrant (whichever was earlier) to the earlier of a) death (from any cause) or progression or b) the last

on-study tumour assessment. If TTP did not correspond to the patient's death or disease progression then TTP was treated as censored (with censoring at the date of trial closure if the patient was known to be alive and progression-free after trial closure).

- Secondary efficacy endpoints
    - Objective tumour response (CR and PR) based on RECIST
    - Incidence of controlled disease (CR + PR + stable disease (SD)) at trial closure
    - Overall survival

Safety

- The safety endpoints were:
    - Nature, incidence and severity of adverse events (AEs)
    - Incidence of and reasons for trial drug dose interruptions and withdrawals
    - Trial drug exposure, laboratory assessments, physical examinations

AEs were coded using MedDRA v 5.1. "Drug-related" AEs were those for which the investigator considered there was a reasonable possibility that the event may have been caused by the 'investigational product' (ZD1839) or by 'other trial therapies' (fulvestrant).

Statistical methods

All patients who were enrolled and received at least one dose of gefitinib or fulvestrant were considered the intention to treat (ITT) population. This was the analysis population for both efficacy and safety.

The standard summary statistics for continuous variables were the mean, standard deviation, median, quartiles, minimum and maximum. The standard summary statistics for discrete variables were counts and proportions. Unless stated otherwise, changes in continuous variables were calculated as later value minus earlier value.

Progression status at trial closure was presented. An exact 95% confidence interval was presented for the proportion alive and progression-free at trial closure.

Median TTP was calculated by Kaplan-Meier methods and the 90% and 95% confidence intervals for the median were calculated by the Brookmeyer-Crowley method. The 95% CI provided a range of median TTP times consistent with the observed data. The trial drug was considered to have shown clinically relevant activity if the hypothesis that the median TTP time is 7 months was rejected in favour of a higher median. This would occur if the lower limit of the 90% CI was greater than 7 months.

The proportion of patients alive and progression-free at 18 months (from start of study medication) and a 95% confidence for the proportion were calculated by Kaplan-Meier methods. Results of the Kaplan-Meier analysis were also presented for patients who were both ER and PgR positive and, separately, for patients who were not both ER and PgR positive.

The objective tumour response was calculated as a proportion (percentage) of patients responding together with an exact 95% confidence interval. The confidence interval provided a range of objective response rates consistent with the observed data.

Overall best response and objective tumour response were listed and tabulated. The confidence intervals were tabulated and were also presented for patients who were both ER and PgR positive and, separately, for patients who were not both ER and PgR positive.

The proportion of patients with controlled disease was calculated together with the exact 95% confidence interval. Confidence intervals were also presented for patients who were both ER and PgR positive and, separately, for patients who were not both ER and PgR positive.

Survival status at trial closure was presented. An exact 95% confidence interval was presented for the proportion of patients alive at trial closure.

Median survival time was calculated by Kaplan-Meier methods and the 95% confidence interval for the median was calculated by the Brookmeyer-Crowley method.

The proportions of patients alive at 6 months and at 18 months (from start of study medication) and 95% confidence intervals for the proportions were calculated by Kaplan-Meier methods. Results of the Kaplan-Meier analysis for survival were also presented for patients who were both ER and PgR positive and, separately, for patients who were not both ER and PgR positive.

Analyses using sub-groups with measurable or non-measurable disease was not performed.

Patient population

A total of 49 patients from 5 centres in Spain were registered in this study. The median age of the patients was 74 years (ranging from 43 to 85 years). Forty one patients (83,7%) had received previous treatment for their disease: surgery, 40 patients; radiotherapy 22 patients; chemotherapy 22 patients. Twenty patients were both ER and PgR positive. Twenty four patients were not both ER and PgR positive. All 49 patients were analysed in the ITT population.

Efficacy results

The analyses based on a data cut-off of 23 June 2007 indicate:

Median TTP for the ITT population was 287 days, 90% CI 147 – 439 days. In the sub-group analysis, median TTP for patients who were both ER and PgR positive was 214 days, 90% CI 95 – 371 days. For patients who were not both ER and PgR positive the median TTP was 331

days, 90% CI 182 – 497 days. The proportion of patients alive and progression-free, as estimated by Kaplan-Meier analysis at 18 months was 28.2%, 95% CI 15.5% - 40.9%.

Seven (14.3%) patients of the ITT population were classified as responders (CR or PR). The 95% CI for the proportion of responders was 5.9% - 27.2%. Of the 42 (85.7%) non-responders, 28 (57.1%) had SD, 13 (26.5%) had PD and 1 (2.0%) was not evaluable (NE). Amongst the 20 patients who were both ER and PgR positive, there were 4 (20.0%) responders; amongst the 21 patients who were not both ER and PgR positive there were 2 responders (9.5%).

Thirty-five (71.4%) patients (95% CI 56.7% - 83.4%) in the ITT population had controlled disease (CR/PR/SD). Of the 20 patients who were both ER and PgR positive, 13 (65.0%) had controlled disease. Amongst the 21 patients who were not both ER and PgR positive, 17 (81.0%) had controlled disease.

At trial closure 24 (49.0%, 95% CI 34.4% - 63.7%) patients in the ITT population were alive, 24 (49.0%) were dead, and the fate of one (2.0%) was unknown. Median survival time was 916 days (no CI could be estimated). The estimated (Kaplan-Meier analysis) proportion of patients alive at 6 months was 87.8% (95% CI 78.6 – 96.9%) and at 18 months was 63.3% (95% CI 49.8% - 76.8%).

Safety results

- Fourteen patients (28.6%) had one or more dose interruptions. Eleven (22.4%) had one or more dose reductions because of toxicity. The median time on trial was 312 days (limits 6 – 970 days).

- The majority of patients experienced one or more Aes. A full listing of all AEs may be found in the data listings, whilst Table S1 presents an overview of AEs reported in this study:

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Table S1 Categories of adverse events: number (%) of patients who had at least one adverse event in any category (ITT population)

Category[a]	ZD1839 250 mg N = 49
All adverse events (AEs)	37 (75.5)
Treatment-related[b] AEs	26 (53.1)
ZD1839-related AEs	25 (51.0)
Fulvestrant-related[c] AEs	3 (6.1)
All serious adverse events (SAEs)	10 (20.4)
Treatment-related[b] SAEs	2 (4.1)
ZD1839-related SAEs	1 (2.0)
Fulvestrant-related SAEs	1 (2.0)
Non-fatal SAEs	9 (18.4)
Deaths due to SAEs	1 (2.0)
Deaths due to treatment-related[b] SAEs	0 (0.0)
Discontinuations from study treatment due to AEs	2 (4.1)
Due to treatment-related[b] AEs	0 (0.0)
Due to SAEs	1 (2.0)
Due to treatment-related[b] SAEs	0 (0.0)
CTC[c] Grade 3 or 4 AEs	10 (20.4)
Treatment-related[b] CTC[d] grade 3 or 4 AEs	4 (8.2)
ZD1839-related AEs	3 (6.1)
Fulvestrant-related AEs	1 (2.0)

[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.

[b] Treatment-related adverse events were those events that the investigator considered to be possibly related to ZD1839 or fulvestrant.

[c] For one patient, the investigator indicated that the AE was related to other trial treatments (i.e., fulvestrant), but specified zometa on the CRF. The data tabulated in Table T4.3 thus over-estimate by 1 the number of patients with fulvestrant-related AEs as 4 (8.2%).

[d] CTC Grade NCI version 2.0.

N Number of patients.

- ZD1839 was generally well tolerated. Twenty-five patients (51.0%) had AES that were considered by the investigator to be related to ZD1839. The most commonly reported of these were gastrointestinal disorders in 18 (36.7%) patients (most commonly diarrhoea in 9 [18.4%]) and skin and subcutaneous tissue disorders in 16

(32.7%) patients (most commonly pruritus in 6 [12.2%]). The majority of these events were CTC grades 1 or 2.

- Three (6.1%) patients experienced AEs that were considered by the investigator to be related to fulvestrant (for one other patient the investigator had noted that causality was related to "other trial treatments", i.e., fulvestrant, but had, elsewhere, specified the responsible treatment as zometa).

- There were 2 (4.1 %) patients who withdrew because of an AE. Neither of these was a treatment-related AE with ZD1839 or with fulvestrant. One patient (2.0%) died because of an AE; neither ZD1839 nor fulvestrant were considered by the investigator to be associated with this AE.

- Interstitial lung disease (ILD) was not observed in this study.

- The clinical chemistry and haematology results for patients receiving ZD1839 were similar to those seen in previous studies.