AstraZeneca

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Drug substance(s):	Gefitinib		
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Phase II, Placebo Controlled, Parallel Group, Double Blind, Randomised, Multicentre Trial Comparing the Anastrozole (Arimidex®)-Placebo Combination to the Anastrozole –ZD1839 (Iressa™) Combination as Neoadjuvant Treatment in Postmenopausal Women with Stage I-IIIB (tumour ≥2cm) Non Inflammatory Breast Cancer and Oestrogen Receptor (ER) and /or Progesterone Receptor (PgR) Positive Tumours

Study centre(s)

This multi-centre study was conducted at 33 research sites in Europe. Seven countries participated in the study; there were 5 research sites in the Czech Republic, 3 research sites in France, 5 research sites in Hungary, 3 research sites in Portugal, 4 research sites in Spain, 3 research sites in Sweden and 10 research sites in the United Kingdom.

Publications

An abstract has been selected to be presented as part of the Scientific Program in the Breast Cancer I Oral Presentation by the American Society of Clinical Oncology (ASCO), 2006. Abstract ID: 515

Study dates		Phase of development
First patient enrolled	12 January 2004	Therapeutic exploratory (II)
Last patient completed	3 November 2005	

Objectives

Primary objectives

1. To compare Ki67 changes after 16 weeks between anastrozole and placebo (arm C) versus anastrozole and gefitinib (arm A) and anastrozole and gefitinib added after 2 weeks (arm B) (ie, comparison of arm C versus the combination of arms A+B). The percentage change in Ki67 from baseline to 16 weeks was the primary analysis for this study.

2. To compare Ki67 changes after 2 weeks of treatment with anastrozole and placebo (arms B +C) versus anastrozole and gefitinib (arm A)

3. After 2 weeks of anastrozole alone, to compare further Ki67 changes following 14 additional weeks of gefitinib (arm B) versus placebo (arm C) both overall and by initial sensitivity to anastrozole

Secondary objectives

1. To compare clinical response between anastrozole and placebo (arm C) versus the average of anastrozole and gefitinib (arm A) and anastrozole and gefitinib added after 2 weeks (arm B) (ie, comparison of arm C versus the combination of arms A+B)

2. To compare clinical response between anastrozole and placebo (arm C) versus anastrozole and gefitinib added after 2 weeks (arm B) by initial sensitivity to anastrozole

3. To compare the tolerability of gefitinib/anastrozole to that of placebo/ anastrozole

4. To assess whether the steady state exposure of gefitinib is altered by the addition of anastrozole comparison of C_{min} to historical data

5. To assess whether the steady state exposure of anastrozole is altered when given with gefitinib by determination of C_{min} in arm A and B compared to anastrozole alone (arm C)

6. To evaluate relationships between gefitinib C_{min} and biomarker changes

7. To assess whether gefitinib affects the suppression of the mean plasma level of oestradiol compared to that obtained with anastrozole alone.

8. To further characterise adverse events previously associated with gefitinib treatment

9. To compare the mastectomy rate between arm A+B versus arm C overall and among patients deemed by surgeon to require mastectomy at start of study

10. Comparison of clinical response between World Health Organisation (WHO) and Response Evaluation Criteria In Solid Tumours (RECIST) criteria

Exploratory objectives

1. To obtain tumour tissue for further biologic studies in this patient population to attempt to identify gene or protein expression within the tumour, or identify specific metabolic profile in patient's blood and/or urine that correlate with resistance/response to gefitinib and/or anastrozole.

2. To study proteomic and metabonomic patterns of expression in plasma and urine.

Study design

This was a phase II, randomised, parallel group, double blind and placebo-controlled multicentre study comparing the efficacy and safety of anastrozole (1 mg daily) and placebo versus anastrozole (1 mg daily) and gefitinib (250 mg daily) when given to postmenopausal women with breast cancer for up to 16 weeks. Patients received anastrozole 1 mg once daily for the 16-week treatment period. Each patient was randomised in an approximate 2:5:5 ratio to also receive one of the following:

- Arm A: gefitinib 250 mg daily for 16 weeks
- Arm B: gefitinib placebo 1 tablet daily for 2 weeks followed by gefitinib 250 mg daily for 14 weeks
- Arm C: gefitinib placebo 1 tablet daily for 16 weeks.

Target patient population and sample size

Postmenopausal women, with oestrogen receptor (ER) and/or progesterone receptor (PgR) positive newly diagnosed stage I-IIIB (tumour ≥2 cm) non inflammatory invasive adenocarcinoma of the breast according to the revised American Joint Committee on Cancer Staging system for breast cancer (Singletary et al 2002).

The sample size calculations were based on the primary variables. For each of these comparisons, the goal was to have ≥90% power to detect a 1 standard deviation difference at a 2-sided 5% significance level, using the Mann-Whitney rank sum test. This required ≥26 fully evaluable patients in arm A and ≥26 fully evaluable patients in the sensitive and less sensitive subgroups within arms B and C. Based on the assumed sensitive rate of 60%, arms B and C each required 26 less sensitive and 39 sensitive fully evaluable patients. Thus, a total of 156 fully evaluable patients were required for this study (26 arm A, 65 arm B and 65 arm C). To be fully evaluable, patients had to have adequate tumour sample for Ki67 analysis at baseline, 2 weeks and 16 weeks (surgery/biopsy) and no other major protocol deviations.

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

Anastrozole 1 mg tablet, orally once daily, formulation number F011292, Analytical Department Macclesfield (ADM) numbers: 82954C01, 93034I02 and 22683I04.

Gefitinib 250 mg tablet, orally once daily, formulation number: F012653, ADM numbers: 91087E02 and 10828G03

Placebo tablet matching gefitinib, orally once daily, formulation number: F012647, ADM numbers: 12417I03, 12520J03 and 22034A04

Duration of treatment

Sixteen weeks.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variables:
  - Changes in proliferation marker Ki67 at 16 weeks. This was the primary analysis.
  - Changes in proliferation marker Ki67 at 2 weeks
  - Changes in proliferation marker Ki67 between arm B and C at 16 weeks overall and initial sensitivity to anastrozole. Patients in arms B and C were retrospectively categorized as sensitive and less sensitive to anastrozole if Ki67 decreased by at least 65% at 2 weeks or not, respectively.
- Secondary variables:
  - Objective tumour response: complete response (CR) and partial response (PR) rate based on the modified Union Internationale Contre le Cancer/World Health Organisation (UICC/ WHO) criteria
  - Objective tumour response: CR and PR rate based on modified UICC/ WHO criteria according to the initial sensitivity to anastrozole
  - C_{min} for gefitinib
  - C_{min} for anastrozole
  - Gefitinib C_{min} and changes in Ki67 and exploratory biomarkers from baseline
  - Oestradiol levels at baseline, 2 weeks after starting treatment and the day before surgery at week 16
  - Frequency of mastectomy and alternative procedures at surgery
  - Comparison of response rates using the different assessment criteria (UICC/WHO and RECIST)

- Exploratory variables
  - Biomarkers related to the epidermal growth factor receptor (EGFR) transduction pathway (pERK1/2, pAKT) by immunohistochemistry performed on tumour samples
  - Gene expression profiles using microarray of tumour mRNA extracts
  - Proteomics and metabonomics of blood and urine samples

Safety

- Safety variables
  - Frequency, severity, time of onset, resolution, treatment interruption and medication given for selected adverse events (AEs) eg, alopecia, rash and diarrhoea
  - Frequency and severity of AEs

Statistical methods

The intention to treat (ITT) analysis set included all randomised patients who received at least 1 dose of study treatment. The per protocol (PP) biomarker analysis set and PP clinical analysis set included all patients in the ITT analysis set without major protocol deviations relevant to the type of outcome (biomarker or clinical). The primary analysis set for all efficacy outcome variables was the PP analysis set (biomarker or clinical). The analysis of the primary variable, change in Ki67 and the analysis of objective tumour response were repeated for the ITT analysis set to assess sensitivity of the analysis.

Primary variables: Analysis of covariance (ANCOVA) was used to compare Ki67 changes between the treatment arms, using log transformed data. All comparisons were made at a 2-sided 5% significance level (unadjusted). The percentage change in Ki67 from baseline to 16 weeks was the primary analysis.

Secondary variables: Objective tumour response was assessed by comparison of the objective response rate (CR+PR) between treatment groups, based on the tumour evaluation performed using the modified UICC/WHO criteria at 16 weeks. The following treatment comparisons were performed using the chi-square test:

- Objective response between anastrozole and placebo (arm C) versus the average of anastrozole and gefitinib (arm A) and anastrozole and gefitinib added after 2 weeks (arm B). This was the primary comparison of objective tumour response.
- Objective response between anastrozole and placebo (arm C) versus anastrozole and gefitinib added after 2 weeks (arm B). Additional comparisons were performed within the subgroups of sensitive and less sensitive patients.

Oestradiol plasma concentrations were compared between treatments. Plasma concentration data were analysed using a two-sided 2-sample t-test following log transformation. Simultaneous pharmacokinetic-pharmacodynamic (PK-PD) analysis of the trough plasma concentrations of gefitinib and the Ki67 data was conducted in WinBUGs version 1.4.1 employing Markov chain Monte Carlo simulation. Correlations between Ki67 and objective tumour response were examined. Descriptive statistics were used to describe the safety variables.

Patient population

In total, 270 patients were enrolled in the study and 206 were randomised to treatment. The patient demographics and baseline characteristics for all randomised patients are given in Table S1. The patients who participated in this study were broadly representative of a newly diagnosed breast cancer population. The demographic characteristics of the 3 treatment groups were well balanced at baseline.

Table S1 Patient population and characteristics

	Anastrozole + gefitinib (AG)		**Anastrozole to AG**		**Anastrozole alone**	
	Arm A		**Arm B**		**Arm C**	
Population						
N randomised (N planned)	31	(31)	90	(77)	85	(77)
Demographic characteristics						
Sex (n and % of patients)						
Female	31	(100)	90	(100)	85	(100)
Age (years)						
Mean (SD)	69.8	(10.1)	70.2	(8.9)	70.3	(9.8)
Range	51 to 86		49 to 89		50 to 92	
Race (n and % of patients)						
Caucasian	31	(100)	89	(98.9)	83	(97.6)
Black	0	(0)	1	(1.1)	2	(2.4)
Baseline breast tumour characteristics						
Oestrogen receptor (ER) status: n (%)						
Negative	1	(3.2)	0	(0)	2	(2.4)
Positive	30	(96.8)	90	(100)	83	(97.6)
Progesterone receptor (PgR) status: n (%)						
Negative	12	(38.7)	21	(23.3)	16	(18.8)
Positive	19	(61.3)	66	(73.3)	67	(78.8)

Table S1 Patient population and characteristics

	Anastrozole + gefitinib (AG) Arm A		Anastrozole to AG Arm B		Anastrozole alone Arm C	
Population						
Not recorded	0	(0)	3	(3.3)	2	(2.4)
Tumour grade: n (%)						
Well differentiated	7	(22.6)	16	(17.8)	18	(21.2)
Moderately differentiated	10	(32.3)	45	(50.0)	33	(38.8)
Poorly differentiated	7	(22.6)	7	(7.8)	16	(18.8)
Unassessable	7	(22.6)	15	(16.7)	10	(11.8)
Not recorded	0	(0)	7	(7.8)	8	(9.4)
Operative procedure planned: n (%)						
Lumpectomy	5	(16.1)	16	(17.8)	14	(16.5)
Mastectomy	24	(77.4)	63	(70.0)	68	(80.0)
Other	2	(6.5)	10	(11.1)	2	(2.4)
Not recorded	0	(0)	1	(1.1)	1	(1.2)

The patient disposition and populations analysed are given in Table S2.

Table S2 Patient disposition and populations

		Anastrozole + gefitinib (AG) Arm A		Anastrozole to AG Arm B		Anastrozole alone Arm C	
N (%) of patients who	completed	23	(74.2)	72	(80.0)	74	(87.1)
	discontinued	8	(25.8)	18	(20.0)	11	(12.9)
N (%) of patients analysed for:							
Safety [a] and efficacy (ITT)		31	(100)	90	(100)	85	(100)
Biomarker (ITT) [b]		22	(71.0)	64	(71.1)	67	(78.8)
Biomarker (PP biomarker) [b]		16	(51.6)	43	(47.8)	50	(58.8)
Efficacy (PP clinical)		29	(93.5)	80	(88.9)	79	(92.9)

[a] Number of patients randomised who received at least 1 dose of study treatment
[b] Number of patients with evaluable Ki67 samples at baseline and 16 weeks (primary analysis)
ITT Intention to treat
PP Per protocol
N Number

Efficacy and pharmacokinetic results

Primary variable: Changes in proliferation marker Ki67

Changes in Ki67 from baseline to 16 weeks

The changes in Ki67 levels from baseline to 16 weeks were not significantly different in those patients who received anastrozole and gefitinib (arms A+B 77% geometric mean reduction) compared with those who received anastrozole alone (arm C 84% geometric mean reduction, p=0.257, see Table S3).

Table S3 Changes in Ki67 levels from baseline to 16 weeks (geometric mean %, 95% confidence intervals) , PP biomarker analysis set

	Anastrozole + gefitinib Arm A + B (n=59)	**Anastrozole alone Arm C (n=50)**
Baseline Ki67	13.4 (10.8, 16.6)	14.6 (11.1, 19.1)
Reduction in Ki67 at 16 weeks	77.4 (67.1, 84.5)	83.6 (75.3, 89.1)
Geometric mean ratio % (95% CI)	1.37 (0.79, 2.39)	
p-value	0.257	

Changes in Ki67 from baseline to 2 weeks

The changes in Ki67 levels from baseline to 2 weeks were also not significantly different in those patients who received anastrozole and gefitinib (arm A 80% geometric mean reduction) compared with those who received anastrozole alone (arms B+C 71% geometric mean reduction, p=0.223).

Changes in Ki67 from 2 to 16 weeks

The Ki67 geometric mean values at 2 weeks for sensitive (to anastrozole) patients were 1.5% and 2.1% and for less sensitive (to anastrozole) patients were 15.2% and 11.2% for anastrozole to combined treatment (arm B) and anastrozole alone (arm C) respectively. There was no significant difference in the change in Ki67 (geometric mean reductions) from 2 to 16 weeks between combination and anastrozole alone treatment (arm B vs arm C) in less sensitive (-40% vs -42%, geometric mean ratio 1.04, p=0.927) or sensitive patients -11% vs -41%, geometric mean ratio 1.51, p=0.223).

Secondary variables

Objective tumour response

An objective tumour response (UICC/WHO) was observed in 48% (52/109) patients who received anastrozole and gefitinib (arms A+B) and in 61% (48/79) patients treated with

anastrozole alone (arm C), but this difference was not statistically significant (-13.1%, 95% CI -27.3 to 1.2, p=0.077).

The objective tumour responders (CR +PR) in each treatment group obtained using both the UICC/WHO and RECIST criteria are shown in Table S4.

Table S4 Objective tumour responders using UICC/WHO and RECIST criteria (best response), PP clinical analysis set

	Number (%) of patients		
	Anastrozole + gefitinib Arm A (n=29)	**Anastrozole to AG Arm B (n=80)**	**Anastrozole alone Arm C (n=79)**
UICC/WHO criteria			
Responders (CR + PR)	16 (55.2)	36 (45.0)	48 (60.8)
RECIST criteria			
Responders (CR + PR)	15 (51.7)	36 (45.0)	45 (57.0)

Oestradiol concentrations

Large reductions in mean oestradiol concentrations were observed in all treatment groups from baseline to 2 weeks and were maintained at 16 weeks. The mean oestradiol concentration in patients treated with gefitinib (arm A) was significantly lower than in patients receiving only anastrozole (arms B+C) at 2 weeks (arm A geometric mean 3.22, baseline 29.76, arms B+C geometric mean 4.26, baseline 34.21; arm A vs arms B+C geometric mean ratio 0.76, 95% CI 0.57 to 1.00, p=0.049). There was no significant difference between these treatment groups at 16 weeks (arms A+B geometric mean 4.49, baseline 30.57, arm C geometric mean 4.08, baseline 38.19; arms A+B vs arm C geometric mean ratio 1.10, 95% CI 0.85 to 1.42, p=0.470). The results of the comparative analysis at 2 weeks should be treated with caution due to the high proportion of patients with oestradiol concentrations below the limit of sensitivity of the assay and the lack of confirmation at 16 weeks compared to 2 weeks.

Frequency of mastectomy and other procedures

The number of patients undergoing mastectomy was significantly smaller in patients treated with anastrozole and gefitinib than with anastrozole alone, both for all patients and the subgroup of patients with planned mastectomy at baseline using all data (Table S5). A disproportionate number of data were missing from the combined anastrozole gefitinib treatment group (arms A+B), mainly due to withdrawals following adverse events; these may have led, inappropriately, to a reduction in the proportion of patients recorded as having mastectomy.

When discontinued patients were excluded from the analysis, the mastectomy rate for patients with planned mastectomy at baseline was no longer statistically significant. However, this analysis assumes that patients with missing data behave in the same way as those with data,

which may not be the case. Therefore the mastectomy results should be interpreted with caution.

Table S5 Number (percentage) of patients with mastectomy or other surgical procedure on primary breast tumour, ITT analysis set

Mastectomy rate	Anastrozole + gefitinib Arms A + B	Anastrozole alone Arm C
All patients	n=121	n=85
Number (%) of patients with mastectomy	36 (29.8)	41 (48.2)
Treatment difference (95% CI)	-18.5% (-31.9, -5.1)	
Excluding patients discontinued prior to surgery [a]	n=94	n=74
Number (%) of patients with mastectomy	36 (38.3)	41 (55.4)
Treatment difference (95% CI)	-17.1% (-32.1, -2.1)	
Patients with mastectomy planned at baseline	n=87	n=68
Number (%) of patients with mastectomy	34 (39.1)	38 (55.9)
Treatment difference (95% CI)	-16.8% (-32.4, -1.2)	
Excluding patients discontinued prior to surgery [a]	n=69	n=61
Number (%) of patients with mastectomy	34 (49.3)	38 (62.3)
Treatment difference (95% CI)	-13.0% (-30.0, 3.9)	

[a] All patients except one in arm B were discontinued from the study prior to the 16-week surgery visit. This was an additional analysis planned after unblinding of study data.

Pharmacokinetics of gefitinib and anastrozole

There was no apparent pharmacokinetic interaction between gefitinib and anastrozole, as the steady state pharmacokinetics were not affected by the co-administration of the other drug.

- Gefitinib
  - The mean $C_{ss, min}$ for gefitinib was 299 ng/mL (coefficient of variation [CV] 66.0%). This is 14% higher than the equivalent value from historical data (1839IL/0016 and 1839IL/0039, IDEAL studies) of 261 ng/mL (CV 66.4%), but this difference was not significant (p=0.19).
- Anastrozole
  - The mean $C_{ss, min}$ values for anastrozole in the anastrozole alone groups were 41.3 ng/mL (CV 39.9%) and 40.4 ng/mL (CV 38.9%). In the presence of gefitinib the mean values of 41.3 ng/mL (CV 52.9%) and 42.2 ng/mL (CV 56.9%) were zero and 4% higher. These differences were not significant (p=0.99, p=0.78).

Relationships between plasma concentrations of gefitinib and Ki67

In the simultaneous PK-PD analysis of gefitinib plasma concentrations and the Ki67 data, no statistically significant effect of gefitinib concentration on Ki67 could be characterised.

Exploratory biomarker

All exploratory biomarker data were to be reported in a separate addendum to this clinical study report. Proteomic, metabonomic and genomic data may be reported later in an addendum.

Safety results

A summary of adverse events (AEs) in each category is given in Table S6.

Table S6 Number (%) of patients who had a least 1 treatment-emergent adverse event in any category, safety analysis set

AE category	Number (%) of patients [a]			
	Anastrozole + gefitinib Arms A + B (n=121)		Anastrozole alone Arm C (n=85)	
Any adverse events (AE)	106	(87.6)	60	(70.6)
Serious adverse events (SAE)				
Serious adverse events leading to death	3	(2.5)	1	(1.2)
Serious adverse events not leading to death	19	(15.7)	7	(8.2)
Discontinuations of study treatment due to AEs	16	(13.2)	2	(2.4)
Other significant adverse events [b]	1	(0.8)	1	(1.2)
CTC grade 3 or 4 AEs	26	(21.5)	10	(11.8)
Drug-related adverse events: gefitinib/placebo				
Drug-related AEs	99	(81.8)	36	(42.4)
Serious drug-related AEs	6	(5.0)	1	(1.2)
CTC grade 3 or 4 drug-related AEs	12	(9.9)	2	(2.4)
Drug-related adverse events: anastrozole				
Drug-related AEs	58	(47.9)	30	(35.3)
Serious drug-related AEs	5	(4.1)	0	
CTC grade 3 or 4 drug-related AEs	8	(6.6)	0	

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Any AE deemed by the sponsor to be significant, excluding AEs reported as SAEs or led to the discontinuation of treatment

The safety profiles of gefitinib 250 mg daily and anastrozole 1 mg daily in this study were consistent with previous studies and no new safety issues were identified. The main findings were as follows:

- The majority of patients experienced one or more AEs, which were generally mild (grade 1) or moderate (grade 2).

- The study treatments were generally well tolerated, although AEs, discontinuations of study treatment due to AEs, SAEs, common toxicity criteria (CTC) grade 3/4 AEs, drug–related AEs and dose interruptions due to AE were reported more frequently for patients treated with anastrozole and gefitinib than for patients treated only with anastrozole.

- Overall, 5 patients had SAEs resulting in death during the study, including one patient excluded from the safety analysis set who died during the screening period. One death due to pulmonary embolism was assessed as related to anastrozole and gefitinib treatment.

- Diarrhoea, rash, alopecia, dry skin and nausea were the most frequently reported (>10% patients) AEs in patients treated with anastrozole and gefitinib. Diarrhoea, nausea and hot flush were the most frequently reported (>10% patients) in patients treated with anastrozole alone.

- The most common AEs related to gefitinib/placebo (>10% patients) were diarrhoea, rash, alopecia and dry skin. These AEs are consistent with the known side effect profile of gefitinib. In patients receiving anastrozole alone, hot flush, nausea, diarrhoea, fatigue and headache were the most common AEs (>4% patients) related to anastrozole treatment.

- The AE characterisation questionnaire showed the following:

  - The incidence of alopecia was generally low in all treatment groups.

  - The majority of patients treated with the anastrozole gefitinib combination who experienced new or worsening diarrhoea since the last visit, were either not bothered at all or only somewhat bothered by it (eg, of the 26% of patients reporting diarrhoea at 8 weeks who were treated with the anastrozole gefitinib combination, 59% were not at all bothered, 28% were somewhat bothered and 13% were very much bothered by it).

  - The majority of patients treated with the anastrozole gefitinib combination who experienced skin rash, which was predominantly on the face rather than the body were at least somewhat bothered by it (eg, of the 29% patients reporting skin rash at 8 weeks, 54% were somewhat bothered and 17% were very much bothered by it).

- All drug-related CTC grade 3 or 4 AEs reported by more than one patient occurred in patients treated with anastrozole and gefitinib. They included rash, hepatic enzyme increased (including preferred terms of liver function abnormal, alanine aminotransferase [ALT] increased and aspartate aminotransferase [AST] increased), deep vein thrombosis and diarrhoea.

- The majority of transaminase changes were CTC grade 1 or 2. A higher proportion of gefitinib treated patients had CTC grade 3 or 4 increases in AST, ALT or both transaminases than patients treated with anastrozole alone (4.1% vs 1.2%).

Date of the report

6 June 2006