Drug product:	Gefitinib	SYNOPSIS	
Drug substance(s):	ZD1839		
Edition No.:	1		
Study code:	1839IL/0225		
Date:	2 October 2007		

A Phase II randomised, double-blind, stratified, multi-centre trial comparing the Nolvadex 20 mg and placebo combination to the Nolvadex 20 mg and ZD1839 (IRESSA™) 250 mg combination in patients with metastatic breast cancer and estrogen receptor (ER) and/or progesterone (PgR) positive tumours

Study centre(s)

This study was conducted in Argentina (9 centres), Australia (4 centres), Belgium (3 centres), Brazil (6 centres), Canada (5 centres), Denmark (1 centre), France (3 centres), Germany (5 centres), South Africa (3 centres), Spain (6 centres), the United Kingdom (4 centres) and the United States (5 centres).

Publications

None at the time of writing this report

Study dates		Phase of development
First patient enrolled	14 October 2003	Therapeutic exploratory (II)
Date of data cut-off	29 December 2006	

Objectives

Patients were stratified into 2 categories based on their prior hormonal therapy. The 2 strata were as follows: 1) Stratum 1- patients with newly diagnosed disease or patients who had completed adjuvant therapy with tamoxifen (Nolvadex) at least 1 year prior to starting this study and 2) Stratum 2 - patients with recurrent disease during, or after adjuvant aromatase

inhibitor (AI), or failing first line treatment with an AI for metastatic disease. The objectives of the study were:

Primary Efficacy

- **Stratum 1:** To compare the time to progression (TTP) between 2 treatment arms (tamoxifen + gefitinib [IRESSA™] versus tamoxifen + placebo).

- **Stratum 2:** To compare the clinical benefit rate (CBR) between 2 treatment arms (tamoxifen + gefitinib versus tamoxifen + placebo).

Secondary Efficacy

- To compare the CBR between 2 treatment arms (tamoxifen + gefitinib versus tamoxifen + placebo) in Stratum 1 and overall.

- To compare TTP between 2 treatment arms (tamoxifen + gefitinib versus tamoxifen + placebo) in Stratum 2 and overall.

- To compare the objective response rate between tamoxifen + gefitinib and tamoxifen + placebo in each stratum and overall.

- To estimate duration of response for the tamoxifen + gefitinib and tamoxifen + placebo treatments in each stratum and overall.

- To compare overall survival between the tamoxifen + gefitinib and tamoxifen + placebo in each stratum and overall. Note, no further survival data were collected following the implementation of Protocol Amendment 1 (17 July 2007) in each country.

- To assess whether patients with high tumour levels of HER2 and/or AIB1 demonstrate de novo resistance to tamoxifen therapy or have shorter TTP or response duration when compared with tamoxifen + gefitinib treatment. At the time of writing this report, this analysis was not complete.

- To compare the objective response rate between the tamoxifen + gefitinib and tamoxifen + placebo treatment arms in the subset of all patients with ER+ tumours staining 2+/3+ for Her2neu by immunohistochemistry. As Her2neu status was not characterised as 0-1, 2+ or 3+, this objective was assessed using the Allred scoring method, which was a close equivalent.

Safety

- To compare the safety and tolerability of tamoxifen + gefitinib versus tamoxifen + placebo

Pharmacokinetics

- To determine steady-state plasma trough concentrations of tamoxifen in all patients and to compare between the tamoxifen + gefitinib and tamoxifen + placebo treatment arms
- To determine steady-state plasma trough concentrations of gefitinib and relate values to historical data
- To relate steady-state plasma trough concentrations of gefitinib to demographic, response and safety variables. At the time of writing this report, this analysis was not complete.

Quality of Life

- To assess the quality of life (QoL) and symptom relief based on the Functional Assessment of Cancer Therapy - Breast (FACT-B) in both treatment arms

Exploratory

- To investigate patient hospital resource use and health status (Health Economics)
- To characterise specific adverse events (AEs) (Safety)
- To obtain tumour tissue for biologic studies in this patient population (Biomarkers)

Study design

This was a randomised, parallel-group, double-blind, stratified, multi-centre study comparing the tamoxifen 20 mg and placebo combination to the tamoxifen 20 mg and gefitinib 250 mg combination in patients with metastatic breast cancer and estrogen receptor (ER) and/or progesterone receptor (PgR) positive tumours, treated until progression of disease as per the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.

Target patient population and sample size

Female patients aged 18 years or older, pre- or post-menopausal presenting with ER and/or PgR positive metastatic adenocarcinoma of the breast determined by the local laboratory in each centre. Estrogen receptor and/or PgR positive disease was confirmed by a central laboratory. Patients were stratified into 2 groups based on prior hormonal therapy:

- Patients with newly diagnosed metastatic disease or who completed adjuvant therapy with tamoxifen at least 1 year prior to starting this protocol (Stratum 1)
- Patients with recurrent disease during, or after adjuvant AI or failing first line treatment with AI for metastatic disease (Stratum 2)

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

Gefitinib (ZD1839; IRESSA™) 250 mg orally once daily and tamoxifen (Nolvadex™) 20 mg orally once daily, or placebo and tamoxifen 20 mg orally once daily. Batch numbers were: gefitinib (250 mg tablet): 10166J03, 10257F03, 10782F03, 10828G03, 10909G03, 11837J03, 12049K03, 12328G03, 13005J03, 21063J04, 21510C04, 22121I04, 33116F05, 90539A02, 92819B02, 92882F02, 93511A02, 94367J02; tamoxifen (20 mg tablet): 10356D03,10357A03, 10358I03, 32546C05, 7502J, 7503K, 91729J02, 94704A02, LC4624, LM4606; placebo to match gefitinib: 12417I03, 12520J03, 22034A04, 22626B04, 31281B05, 40935H06, 75365A00, 8018H, 8020H, 9025H, 91542K02, 92984F02, 92994B02. Study drug administration started within 72 hours of randomisation.

Duration of treatment

Patients continued to receive therapy until progression of disease as per RECIST criteria, in the absence of unacceptable toxicity and provided the patient was willing to continue on study. It was intended that patients would be followed-up for survival to a 75% mortality rate of all randomised patients in order to characterise long-term survival adequately. The change in practice with adjuvant therapy combined with the small numbers of patients available for survival analysis in this study imply that follow-up for survival will no longer provide interpretable results. Therefore, the follow-up for survival was no longer appropriate and the secondary survival endpoint of the study was removed from the protocol by Protocol Amendment 1, dated 17 July 2007. No further survival data were collected after the implementation of this amendment in each country.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: Stratum 1 - TTP (progressive disease or death; equivalent to progression-free survival); Stratum 2 - overall clinical benefit rate (CBR) defined as complete response (CR), partial response (PR) or stable disease (SD) >24 weeks using the RECIST criteria.

- Secondary variables: Overall CBR after >24 weeks in each treatment arm, defined according to RECIST criteria in Stratum 1 and overall; Time to progression (progressive disease or death) in Stratum 2 and overall; objective tumour response defined according to RECIST criteria in each stratum and overall; duration of response (CR and PR) in each stratum and overall; overall survival in each stratum and overall. Time to progression (progressive disease or death) and duration of response (CR and PR) were planned to be assessed in patients with high tumour levels of HER2 and /or AIB1 and objective tumour response was planned to be assessed in the subset of all patients with ER+ tumours staining 2+/3+ for Her2neu by immunohistochemistry. As AIB1 biomarker data were not available at the time of reporting, objectives related to this variable are not addressed in this report. Her2neu status was assessed using the Allred scoring system.

- Pharmacokinetics: tamoxifen (C_{min}) steady-state plasma concentration; gefitinib (C_{min}) steady-state plasma concentration.
- Quality of Life: FACT-B questionnaire and FACT-B Symptom Index (FBSI)

Safety

- Frequency and severity of AEs.

Exploratory

- Health Economics – hospitalisations and EuroQol EQ-5D questionnaire
- Safety - characterisation of AEs such as alopecia, rash and diarrhoea
- Biomarkers –ER, PgR and HER2.

Statistical methods

Primary efficacy analyses were performed in the intent-to-treat (ITT) population and sensitivity analyses were performed in the per protocol (PP) population. The TTP hazard ratio for placebo relative to gefitinib was estimated using the Cox proportional hazards model and presented with its 95% confidence interval (CI) and p-value. The proportions of patients who experienced clinical benefit were compared between the tamoxifen + gefitinib and tamoxifen + placebo arms using logistic regression. The odds ratio for comparison of treatment arms was summarised with its associated 95% CI and p-value. The primary variable for each stratum was adjusted for the following baseline factors: HER2 status (positive versus negative), PgR status (positive versus negative), World Health Organization (WHO) performance status (0-1 versus 2), and visceral metastases (yes versus no).

For the purposes of interpreting the primary efficacy results, for Stratum 1, a TTP hazard ratio point estimate for tamoxifen + placebo relative to tamoxifen + gefitinib of >1.05 was defined in the protocol as providing an affirmative indication for the further evaluation of treatment with gefitinib in combination with tamoxifen. For Stratum 2, if the CBR was at least 5% greater in the tamoxifen + gefitinib group than in the tamoxifen + placebo group, this was considered an affirmative indication for further evaluation of this treatment combination.

Patient population

In the overall patient population (ie, Strata 1 and 2 combined), the 2 treatment arms were generally comparable for the demographic characteristics assessed. These patients were typical of the broad population of patients with metastatic breast cancer (mean age 62.3 years). Breast cancer history was representative of that typically seen among patients with metastatic breast cancer; in general, approximately 70% of patients in each treatment arm had bone metastases and 30% had lung metastases. Most patients had moderately or poorly differentiated tumours and approximately 80% of patients were PgR positive.

The treatment arms were well balanced within Stratum 1 for the prognostic factors HER2 status and for the proportion of patients with visceral disease. However, a slightly higher proportion of patients in the tamoxifen + gefitinib group were PgR positive than in the tamoxifen + placebo group (84.8% versus 76.2%), and a slightly higher proportion of patients in the tamoxifen + gefitinib group had a WHO performance status of 2 (9.5% versus 3.0%, respectively). Within Stratum 2, HER2 status and WHO performance status were similar in each treatment arm, but a higher proportion of patients in the tamoxifen + gefitinib group were PgR positive than in the tamoxifen + placebo group (83.3% versus 71.4%) and a higher proportion of patients in the tamoxifen + placebo group had visceral disease than in the tamoxifen + gefitinib group (62.9% versus 52.1%).

Table S1 Patient population and disposition

		Tamoxifen + gefitinib		Tamoxifen + placebo	
N randomised (N planned)		153	(137)	137[a]	(137)
Stratum 1		105	(98)	101	(98)
Stratum 2		48	(39)	36	(39)
Demographic characteristics (ITT population):	N	153		136	
Age (years)	Mean (SD)	61.6	(10.95)	63.1	(11.09)
	Range	40 to 89		40 to 86	
Race (n and % of patients)	Caucasian	143	(93.5%)	128	(94.1%)
	Black	1	(0.7%)	3	(2.2%)
	Oriental	2	(1.3%)	0	
	Other	7	(4.6%)	5	(3.7%)
Baseline characteristics (ITT population):					
HER2 status[b]	Positive	26	(17.0%)	17	(12.5%)
	Negative	127	(83.0%)	119	(87.5%)
PgR status[b]	Positive	129	(84.3%)	102	(75.0%)
	Negative	24	(15.7%)	34	(25.0%)
WHO performance status	0 to 1	141	(92.2%)	131	(96.3%)
	2	12	(7.8%)	5	(3.7%)
Visceral disease	No	73	(47.7%)	68	(50.0%)
	Yes	80	(52.3%)	68	(50.0%)
Disposition:					
N (%) of patients with	Premature discontinuation	14	(9.2%)	13	(9.5%)
	Discontinuing therapy	122	(79.7%)	103	(75.2%)
N (%) in ITT population[a]		153	(100.0%)	136	(99.3%)
N (%) in PP population[a]		110	(71.9%)	105	(76.6%)
N (%) evaluable for QoL[a]		132	(86.3%)	115	(83.9%)
N (%) evaluable for response[a]		93	(60.8%)	88	(64.2%)

ITT=Intention to treat; N=Number; PP=Per protocol; PgR= progesterone receptor; SD=standard deviation; QoL=quality of life

[a] One patient was randomised to tamoxifen + placebo but did not start treatment.

[b] As determined by Baylor Laboratory.

Efficacy and pharmacokinetic results

Key efficacy results are summarised in the following table.

Table S2 Summary of key efficacy results comparing tamoxifen + gefitinib and tamoxifen + placebo: intent-to-treat population

Variable	Tamoxifen + gefitinib (n=153) S1: n=105 S2: n=48		Tamoxifen + placebo (n=136) S1: n=101 S2: n=35		Hazard[a] or Odds[b] ratio	95% CI	p-value[c]
Primary variables							
Stratum 1 – No. progressed or died (%)	69	(65.7)	66	(65.3)	–	–	–
Stratum 1 – Median TTP[a] (days)	331		267		1.20	0.84, 1.69	0.3141
Stratum 2 – CBR[b], n (%)	14	(29.2)	11	(31.4)	0.72	0.26, 1.95	0.5167
Secondary variables - Stratum 1:							
CBR[b], n (%)	53	(50.5)	46	(45.5)	1.10	0.62, 1.95	0.7480
No. progressed or died - HER2+ subset[d]	17		14		–	–	–
Median TTP[a] (days) - HER2+ subset	205		178		1.86	0.87, 3.98	0.1113
Objective response rate[b], n (%)	13	(12.4)	15	(14.9)	0.76	0.33, 1.75	0.5178
Median duration of response (days)[e]	502		380		–	–	–
Overall survival (no. alive)	79	(75.2)	75	(74.3)	–	–	–
Secondary variables - Stratum 2:							
No. progressed or died (%)	40	(83.3)	26	(74.3)	–	–	–
Median TTP[a] (days)	174		214		0.86	0.52, 1.44	0.5773
Objective response rate[b], n (%)	0		0		–	–	–
Median duration of response (days)[c]	–		–		–	–	–
Overall survival (no. alive)	35	(72.9)	26	(74.3)	–	–	–
Secondary variables - Overall:							
No. progressed or died (%)	109	(71.2)	92	(67.6)	–	–	–
Median TTP [a] (days)	252		260		1.07	0.81, 1.43	0.6164
CBR[b], n (%)	67	(43.8)	57	(41.9)	0.98	0.60, 1.59	0.9246
Objective response rate[b], n (%)	13	(8.5)	15	(11.0)	0.69	0.31, 1.54	0.3630
Median duration of response (days)[c]	502		380		–	–	–
Overall survival (no. alive)	114	(74.5)	101	(74.3)	–	–	–

CBR=clinical benefit rate; CI=confidence interval; TTP=time to progression)

[a] For TTP, a hazard ratio (placebo:gefitinib) >1 implies risk of progression is lower on the tamoxifen + gefitinib arm than the tamoxifen + placebo arm. For TTP, it was pre-defined that a hazard ratio point estimate of >1.05 is an affirmative indication for potential further evaluation in this population.

[b] For CBR and objective response rate, an odds ratio (gefitinib:placebo) of >1 indicates higher odds of a clinical benefit or objective response in the tamoxifen + gefitinib combination than the tamoxifen + placebo arm. For CBR, it was pre-defined that a 5% increase in CBR on the gefitinib arm compared to the placebo arm is an affirmative indication for potential further evaluation in this population

[c] p-values are presented for illustrative purposes only.

[d] The HER2+ subset comprised 26 patients in the tamoxifen + gefitinib group (22 patients in Stratum 1 and 4 patients in Stratum 2) and 17 patients in the tamoxifen + placebo group (15 in patients in Stratum 1 and 2 patients in Stratum 2).

[e] Duration of response is calculated only in the small non-randomised subgroup of patients with an objective tumour response and so should be interpreted with great caution. Median event time is defined as the time from the initial response to when half of the responding patients have progressive disease

For the primary endpoint of Stratum 1, TTP, there was a 20% numerical improvement on the tamoxifen + gefitinib arm. The TTP hazard ratio for tamoxifen + placebo relative to tamoxifen + gefitinib was greater than the pre-defined criteria of 1.05, indicating that the combination of tamoxifen and gefitinib could be suitable for potential further evaluation in patients with either newly diagnosed metastatic breast cancer or patients who completed adjuvant tamoxifen 1 year before starting treatment.

For the primary endpoint of Stratum 2, CBR, patients had a slightly lower CBR when treated with tamoxifen + gefitinib (29.2%) compared with those treated with tamoxifen + placebo (31.4%). Hence the pre-defined criteria for potential further evaluation of tamoxifen + gefitinib in these patients (ie, a 5% increase in CBR) was not met.

The result for the Stratum 1 secondary endpoint, CBR, was supportive of the positive results observed for the primary variable for Stratum 1. The slight advantage for patients treated with tamoxifen + gefitinib in terms of CBR was driven by the greater number of patients who experienced SD (>24 weeks).

Consistent with the primary variable for Stratum 2, the Stratum 2 secondary variable of TTP showed no advantage for the tamoxifen + gefitinib arm over the tamoxifen + placebo arm.

In the overall population, the interpretation of CBR results was confounded by differences in the 2 strata. Patients in the overall population receiving tamoxifen + gefitinib combination therapy had a very slight numerical advantage in terms of median TTP relative to patients receiving tamoxifen + placebo.

Fewer than 25% of patients had died at the time of data cut-off, and there were no clear differences in survival between the treatment arms in either stratum.

In the sub-set of 37 patients within Stratum 1 who were HER2+, the TTP hazard ratio for tamoxifen + placebo relative to tamoxifen + gefitinib was greater than the pre-defined criteria of 1.05, indicating a numerical advantage for HER2+ patients receiving tamoxifen + gefitinib relative to patients receiving tamoxifen + placebo. Too few patients were HER2+ in Stratum 2 for conclusions to be drawn concerning TTP in this sub-set of patients.

Quality of life data (FACT-B score) did not indicate any detriment to QoL in Stratum 1 for patients receiving tamoxifen + gefitinib compared with patients receiving tamoxifen + placebo. Similar results were seen in Stratum 2, although the small number of patients in Stratum 2 makes results more difficult to interpret.

Pharmacokinetic (PK) analysis of tamoxifen concentrations showed no difference in the tamoxifen C_{min} in the absence or presence of gefitinib. In the overall population, C_{min} was estimated to be 126 ng/mL for Months 3 to 9 and 109 ng/mL for Month 1, varying between individuals by 37% (coefficient of variation [CV%]). The tamoxifen C_{min} obtained in this

study was similar to previously published data. Pharmacokinetic analysis of gefitinib concentrations indicated that the gefitinib C_{min}, estimated to be 228 ng/mL, was similar to that seen in previous studies. C_{min} for gefitinib varied between individuals by 56% (CV%).

Safety results

An evaluable-for-safety population was not defined; therefore, all safety tables are presented for the ITT population. However, no patients were misrandomised in this study. One patient was randomised but never received study treatment.

A summary of AEs is provided in the following table:

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events: intent-to-treat population

AE category	Number (%) of patients [a]			
	Tamoxifen + gefitinib (n=153)		Tamoxifen + placebo (n=136)	
Any AE	150	(98.0)	118	(86.8)
Tamoxifen related	83	(54.2)	62	(45.6)
Gefitinib/placebo related	125	(81.7)	69	(50.7)
Any SAE (including events with an outcome of death)	40	(26.1)	21	(15.4)
Tamoxifen related	10	(6.5)	3	(2.2)
Gefitinib/placebo related	8	(5.2)	1	(0.7)
Any non-fatal SAE	39	(25.5)	20	(14.7)
Tamoxifen related	10	(6.5)	2	(1.5)
Gefitinib/placebo related	8	(5.2)	1	(0.7)
Any AE leading to discontinuation of treatment	25	(16.3)	5	(3.7)
Tamoxifen related	6	(3.9)	3	(2.2)
Gefitinib/placebo related	16	(10.5)	2	(1.5)
Any AE with an outcome of death	4	(2.6)	1	(0.7)
Tamoxifen related	0	(0)	1	(0.7)
Gefitinib/placebo related	0	(0)	0	(0)
Any CTC grade 3 or 4 AE	63	(41.2)	21	(15.4)
Tamoxifen related	9	(5.9)	1	(0.7)
Gefitinib/placebo related	19	(12.4)	0	(0)

AE=adverse event; CTC=Common Toxicity Criteria; SAE=serious adverse event

[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.

The observation of higher frequencies of AEs in patients receiving tamoxifen + gefitinib group compared with patients receiving tamoxifen alone is consistent with the known safety profile of gefitinib. The tamoxifen + gefitinib combination was associated with a greater incidence of SAEs, grade 3 and 4 AEs, treatment-related AEs and AEs leading to discontinuation of therapy than the tamoxifen + placebo combination.

Four patients in the tamoxifen + gefitinib group had AEs with an outcome of death (none were considered related to treatment) compared with one patient in the tamoxifen + placebo group who had a fatal pulmonary embolism considered related to tamoxifen treatment.

The most commonly reported AEs are summarised in the following table:

Table S4 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency in the tamoxifen + gefitinib group: intent-to-treat population

Preferred term	Number (%) of patients [a, b]			
	Tamoxifen + gefitinib (n=153)		Tamoxifen + placebo (n=136)	
Diarrhoea	93	(60.8)	31	(22.8)
Alopecia	76	(49.7)	28	(20.6)
Rash	67	(43.8)	19	(14.0)
Nausea	48	(31.4)	36	(26.5)
Vomiting	34	(22.2)	18	(13.2)
Dry skin	34	(22.2)	7	(5.1)
Fatigue	23	(15.0)	24	(17.6)
Headache	19	(12.4)	12	(8.8)
Muscle spasms	18	(11.8)	4	(2.9)
Pruritis	18	(11.8)	13	(9.6)
Dyspnoea	15	(9.8)	17	(12.5)
Hot flush	15	(9.8)	25	(18.4)
Arthralgia	13	(8.5)	14	(10.3)
Bone pain	12	(7.8)	17	(12.5)

[a] Number (%) of patients with AEs, presented in decreasing order of frequency (sorted by total number on tamoxifen + gefitinib).
[b] This table uses a cut-off of 10% in either group.

Diarrhoea, alopecia, rash, and nausea were the most common AEs reported with tamoxifen + gefitinib therapy. These events are consistent with the known safety profile of these 2 drugs derived from earlier studies. The incidences of fatigue, arthralgia, bone pain, headache and dyspnoea were comparable across both treatment arms. Many of the commonly reported

events (eg, bone pain, dyspnoea, headaches, and fatigue) are frequently seen in patients with metastatic breast cancer and are related both to the disease process and co-morbid conditions that are typically experienced by this patient population. Muscle spasms were also reported at a higher incidence in the tamoxifen + gefitinib arm than in the tamoxifen + placebo arm (11.8% versus 2.9%, respectively), however, the incidence of muscle spasms in the tamoxifen + gefitinib arm assessed by investigators as related to gefitinib was low (2.0%). Muscle spasms were reviewed in detail, and no additional safety concerns were identified in relation to these events.

Apart from slight increases in mean ALT and AST in the tamoxifen + gefitinib group, no clinically relevant changes in haematology or clinical chemistry parameters were apparent between the 2 treatment arms and the majority of patients experienced no change in Common Toxicity Criteria (CTC) grade from baseline for any laboratory parameter. No new safety concerns have been identified from the clinical laboratory results.

No clinically relevant changes in vital signs (pulse rate, blood pressure and weight) were apparent between the 2 treatment arms and no new safety concerns were identified from the vital sign data.