Drug Product	IRESSA™ 250 mg	**SYNOPSIS**	
Drug Substance	Gefitinib (ZD1839)		
Study Code	D7913C00711		
Edition Number	1		
Date	17 September 2007		

A Phase II Multicentre Randomised, Parallel Group, Double-Blind, Placebo Controlled Study of ZD1839 (Iressa™) (250mg Tablet) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Chemotherapy Naïve Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) and Poor Performance Status

INSTEP (Iressa NSCLC Trial Evaluating Poor Performance Patients)

Study centres

This study was conducted at 37 centres in Australia (7 centres), Canada (19 centres) the Czech Republic (2 centres) the Netherlands (4 centres) and the UK (5 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	27 September 2004	Therapeutic exploratory (II)
Last patient enrolled	22 December 2006	
Data cut-off date:	22 February 2007	

Objectives

The primary objective was to compare ZD1839 (IRESSA™, gefitinib) + best supportive care (BSC) versus placebo + BSC in terms of progression-free survival (PFS).

Secondary objectives were to compare gefitinib + BSC versus placebo + BSC in terms of:

- overall objective tumour response rate (complete response [CR] and partial response [PR])
- overall survival
- pulmonary symptom improvement
- quality of life
- tolerability

Exploratory objectives of the study were:

- To investigate the correlation of gefitinib efficacy and toxicity with expression of EGFR and other related biomarker status, and to determine a set of biomarkers to be evaluated in tumoural tissue or surrogate tissues prior to gefitinib therapy to enable patient selection for therapy.
- To compare gefitinib + BSC versus Placebo + BSC in terms of Health Resource Utilisation
- To compare gefitinib + BSC versus Placebo + BSC in terms of changes in pain and fatigue

Note that the wording of the first exploratory objective was clarified in protocol amendment 1 (17 October 2005) as follows:

- To investigate the correlation of the expression of biomarkers in tumour tissue obtained prior to gefitinib therapy with gefitinib clinical efficacy and to determine a set of biomarkers to enable patient selection for therapy.

The following exploratory objective was also added by protocol amendment 1 (17 October 2005):

- To obtain blood samples for DNA extraction for possible future pharmacogenetic analysis and other potential correlative markers of the activity of gefitinib

Study design

This was a randomised double blind, placebo controlled, parallel group, multicentre, Phase II study to assess whether the addition of gefitinib (250 mg tablet once daily) to BSC confers an improvement in PFS in chemotherapy-naïve patients with advanced (stage IIIB or IV) non-small cell lung cancer (NSCLC) and poor performance status (2 or 3). Patients received the BSC available as judged by the treating investigator and were randomised to receive either gefitinib or placebo in a 1:1 ratio. The primary variable was PFS and tumour assessments were performed every 6 weeks until objective disease progression was documented.

Target patient population and sample size

Male or female patients aged 18 years or older with histologically or cytologically confirmed advanced (stage IIIB or IV) NSCLC who were chemotherapy-naïve, had a poor performance status (PS = 2 or 3) and were considered unfit for chemotherapy treatment.

Sample size calculations were based on PFS (the primary endpoint). While median PFS for patients on BSC is expected to be in the region of 4 weeks, there are no data in this setting from which the effectiveness of gefitinib can be accurately anticipated. A total of 134 progression events was estimated to be sufficient to detect a 75% improvement in PFS with gefitinib, with 90% power, assuming the 2-sided alpha level was 5% (see Section 5.2); this number of events would also suffice to detect a 50% improvement with gefitinib with 81% power. Two-hundred randomised patients (100 per treatment group) recruited over an 11-12-month accrual period and followed for a minimum of 2 months was estimated to be sufficient to observe 134 progression events. Note that due to slow recruitment the accrual period was increased to 27 months by protocol amendment 1 (17 October 2005). Patients were to be followed up until at least 134 progression events had occurred, or all patients had been followed up for at least 2 months, which ever occurred later. Hence, the actual number of progression events in the analysis could be greater than 134.

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

Gefitinib 250 mg (one tablet) orally once daily with matching placebo tablets used for the comparator. The formulation (batch) numbers were F12653, (10782F03, 10909G03, 10828G03, 11837J03, 12328G03, 13005J03, 22121I04, 33116F05, 21063J04, 21510C04) and F12647 (12417I03, 40935H06, 22626B04, 31281B05, 22034A04) for the gefitinib 250 mg and placebo tablets, respectively.

Duration of treatment

Patients received daily gefitinib or placebo until unacceptable toxicity, patient refusal or the investigator considered the patient to have clear evidence of radiological and/or clinical progression. Following protocol amendment 1 (17 October 2005), patients who had confirmed objective progression, but in the opinion of both the investigator and patient continued to derive clinical benefit, could continue treatment with study medication following discussion with the AstraZeneca CST Physician.

At the point of disease progression, further therapy was at the discretion of the investigator and the patient. All patients were followed for a minimum of 2 months and the study was closed after the last patient had been followed for 2 months.

Criteria for evaluation (main variables)

Efficacy and patient-reported outcomes (PROs)

- Primary variable: PFS (defined as the interval between the date of randomisation and the earliest date of objective disease progression according to The Response

Evaluation Criteria in Solid Tumours [RECIST] or death due to any cause in the absence of progression)

- Secondary efficacy variables:
  - Overall objective tumour response (CR and PR) according to the RECIST criteria
  - Overall Survival (OS; time to death - defined as the interval between the date of randomisation and the date of patient death due to any cause)
- Secondary PRO variables:
  - Pulmonary Symptom Improvement (PSI) as measured by the 4 pulmonary items of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) Lung Cancer Subscale (LCS); the 4 pulmonary items are shortness of breath, ease of breathing, tightness in chest, and cough
  - Improvement in patient-reported functionality (PRF) as measured by the Trial Outcome Index (TOI; the TOI comprises the physical and functional well-being sections and LCS domain of the FACT-L) and QoL as measured by the FACT-L total score

Safety

- Secondary variable: the adverse event (AE) profile based on the type, frequency, and severity of AEs, laboratory parameters, and vital signs

Exploratory

- The biomarker assessed in this study (described in the Statistical Analysis Plan; Appendix 12.1.9) was:
  - Epidermal growth factor receptor (EGFR) gene copy number status (measured by fluorescence in situ hybridisation [FISH] and categorised as EGFR FISH+ [a high EGFR gene copy number], EGFR FISH- [a low EGFR gene copy number], or EGFR FISH unknown [no evaluable tumour sample])

EGFR gene copy number was investigated in relation to clinical efficacy (PFS, objective tumour response rate, and OS).

- Changes in pain and fatigue as measured by the single items from the physical well-being section of the FACT-L

Statistical methods

The primary analysis compared PFS between gefitinib and placebo using a proportional hazards model, which included various factors (gender, WHO performance status, histology, smoking history, disease stage). The hazard ratio (gefitinib:placebo) was estimated, together with its associated 95% confidence interval (CI) and p-value. The analysis was performed on the intent-to-treat population (ITT).

Objective response rate (ORR) was analysed using a logistic regression model (which allowed for the effect of treatment and included the same covariates as used in the primary analysis of PFS); the odds ratio and its associated 95% CI were estimated from the model. OS was analysed using a proportional hazards model (which allowed for the effect of treatment and included the same covariates as used in the primary analysis of PFS); the hazard ratio was estimated, together with its associated 95% CI. These efficacy analyses were performed on the ITT population.

Pulmonary symptom and QoL improvement rates were analysed in a similar way to ORR using the evaluable-for-pulmonary-symptom-improvement and evaluable-for-QoL populations (sub-sets of the ITT population), respectively.

If there were at least 20 events in either the EGFR FISH+ or FISH- sub-groups, hazard ratios and 95% CIs were to be produced for that subgroup for both PFS and OS in the same way as for the primary analysis. Hazard ratios and 95% confidence intervals were also to be produced comparing EGFR FISH status within each treatment separately.

There was no formal statistical analysis of the exploratory variable of changes in pain and fatigue or any of the safety variables.

Patient population

The patients who participated in this study were representative of a chemotherapy naïve population with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC, and poor performance status. A total of 201 patients were randomised to treatment (100 patients to receive gefitinib 250 mg and 101 patients to receive placebo); these patients were recruited from 37 centres in 5 countries. Approximately 39% of patients were female, 9.5% were never smokers, 37% had adenocarcinoma histology and 3.5% were of Asian racial origin. The median age of the patients was 74 years (ranging from 42 to 90 years).

The two treatment groups were well balanced at baseline with respect to all important factors, thus enabling valid conclusions to be drawn from the efficacy, QoL, and safety analyses.

The number of major protocol deviations was similar between the two treatment groups (12 patients [12.0%] in the gefitinib treatment arm, 11 patients [10.9%] in the placebo treatment arm).

Efficacy results

The analyses were based on a data cut-off date of 22 February 2007. The results are as follows (note: hazard ratios of <1.00 and odds ratios of >1.00 indicate a favourable outcome for gefitinib compared with placebo):

- In the overall population, gefitinib showed some improvement compared to placebo in terms of PFS (primary outcome variable), objective response rate, and OS (ITT population), although this did not reach statistical significance:
  - The hazard ratio for the comparison of PFS between gefitinib and placebo was 0.821 (95% CI 0.600 to 1.123; p=0.2165)
  - The odds ratio for the comparison of objective response rate between gefitinib and placebo was 6.566 (95% CI 0.741 to 58.173); objective tumour responses were achieved for 6 patients (6.0%) and 1 patient (1.0%) in the gefitinib and placebo groups, respectively
  - The hazard ratio for the comparison of OS between gefitinib and placebo was 0.840 (95% CI 0.615 to 1.147, p=0.2722)

Exploratory efficacy results

- EGFR FISH positivity (high EGFR gene copy number; EGFR FISH+) appeared predictive for a gefitinib effect over placebo (ITT population):
  - The subgroup of 32 (38.1%) EGFR FISH+ patients had superior PFS (HR 0.288, 95% CI 0.114 to 0.725) and numerically improved OS (HR 0.437, 95% CI 0.170 to 1.121) when treated with gefitinib as opposed to placebo.
- For the sub-group of 52 (61.9%) patients with a low EGFR gene copy number (EGFR FISH-) there was no strong evidence of a difference in efficacy between gefitinib and placebo
  - The HR for the comparison of PFS between gefitinib and placebo was 0.740 (95% CI 0.379 to 1.447), HR for OS was 1.022 (95% CI 0.557 to 1.878)
- Furthermore, the sub-group of EGFR FISH+ patients appeared to achieve better clinical outcomes than the sub-group of EGFR FISH-patients when treated with gefitinib (ITT population), although these data should be interpreted with caution as this is a non-randomised comparison. For gefitinib-treated patients:
  - The hazard ratio for the comparison of PFS between EGFR FISH+ patients and EGFR FISH- patients was 0.262 (95% CI 0.112 to 0.612)

- The hazard ratio for the comparison of OS between EGFR FISH+ patients and EGFR FISH- patients was 0.468 (95% CI 0.209 to 1.047)

PRO results

- Symptom improvement (PSI and LCS) rates were similar for gefitinib and placebo-treated patients:
  - The odds ratio for the comparison of PSI between gefitinib (28.3% improved) and placebo (28.3% improved) was 0.986 (95% CI 0.395 to 2.460).
  - The odds ratio for the comparison of LCS between gefitinib (32.9% improved) and placebo (30.8% improved) was 1.108 (95% CI 0.525 to 2.338).
- Overall PRF and QoL improvement (TOI and FACT-L) rates were similar in gefitinib and placebo-treated patients:
  - The odds ratio for the comparison of TOI between gefitinib (15.8% improved) and placebo (13.8% improved) was 1.033 (95% CI 0.381 to 2.800).
  - The odds ratio for the comparison of FACT-L total score between gefitinib (21.1% improved) and placebo (20.0% improved) was 1.007 (95% CI 0.421 to 2.408).

Exploratory PRO results

- Overall changes in pain and fatigue appeared similar for gefitinib and placebo-treated patients.

Safety results

The tolerability profile of gefitinib was generally consistent with that seen in previously conducted gefitinib monotherapy studies.

- The majority of patients experienced one or more AEs. No clinically relevant differences between the treatment groups in the frequency of SAEs or Common Terminology Criteria (CTC) grade 3 or 4 AEs were evident. The frequencies of AEs leading to discontinuation and AEs with an outcome of death were slightly higher in gefitinib-treated patients compared to placebo-treated patients (Table S1). There were no unusual clinical features and no new safety signals were identified. None of the AEs with an outcome of death for either group were considered by the investigator to be causally related to treatment.

Table S1 Number (%) of patients who had an AE in any category: EFS population

Category	Number (%) of patients[a]			
	Gefitinib 250 mg N=100		Placebo N=101	
Any AE	93	(93.0)	94	(93.1)
Any SAE	25	(25.0)	25	(24.8)
SAE leading to death	10	(10.0)	3	(3.0)
Any AE leading to discontinuation of treatment	14	(14.0)	7	(6.9)
Any CTC[b] grade 3 or 4 AE	36	(36.0)	43	(42.6)
Any CTC[b] grade 3, 4, or 5 AE	41	(41.0)	46	(45.5)

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 National Cancer Institute (NCI) Common Terminology Criteria (CTC) for Adverse Events, Version 3.0
AE, Adverse event; EFS, Evaluable for safety; N, Number of patients; SAE, Serious AE.

- Consistent with the known safety profile for gefitinib, the most frequently reported adverse events for gefitinib 250 mg were diarrhoea, and skin disorders (rashes/acnes, pruritus, dry skin) (Table S2). The majority of these events were CTC grade 1 (mild) or 2 (moderate).

Table S2 Most common adverse events[a]: EFS population

	Number (%) of patients							
	Gefitinib 250 mg (N=100)				Placebo (N=101)			
	All CTC grades		CTC grade 3/4/5		All CTC grades		CTC grade 3/4/5	
Diarrhoea	51	(51.0)	3	(3.0)	20	(19.8)	3	(3.0)
Rash[b]	34	(34.0)	0	(0)	10	(9.9)	0	(0)
Nausea	30	(30.0)	0	(0)	33	(32.7)	4	(4.0)
Vomiting	21	(21.0)	0	(0)	14	(13.9)	0	(0)
Anorexia	20	(20.0)	2	(2.0)	17	(16.8)	0	(0)
Dry skin	19	(19.0)	0	(0)	1	(1.0)	0	(0)
Dyspnoea	19	(19.0)	11	(11.0)	13	(12.9)	6	(5.9)
Constipation	17	(17.0)	1	(1.0)	19	(18.8)	1	(1.0)
Fatigue	15	(15.0)	6	(6.0)	22	(21.8)	8	(7.9)
Oedema peripheral	13	(13.0)	1	(1.0)	13	(12.9)	2	(2.0)
Abdominal Pain	11	(11.0)	1	(1.0)	9	(8.9)	2	(2.0)
Insomnia	11	(11.0)	0	(0)	4	(4.0)	0	(0)
Lower respiratory tract infection	11	(11.0)	0	(0)	8	(7.9)	4	(4.0)
Anxiety	9	(9.0)	0	(0)	5	(5.0)	0	(0)
Asthenia	9	(9.0)	4	(4.0)	8	(7.9)	5	(5.0)
Pruritus	9	(9.0)	0	(0)	2	(2.0)	0	(0)
Stomatitis	9	(9.0)	0	(0)	5	(5.0)	0	(0)
Epistaxis	8	(8.0)	0	(0)	2	(2.0)	0	(0)
Muscular Weakness	8	(8.0)	3	(3.0)	5	(5.0)	1	(1.0)
Urinary Tract Infection	8	(8.0)	0	(0)	8	(7.9)	1	(1.0)
Anaemia	7	(7.0)	3	(3.0)	1	(1.0)	0	(0)
Back pain	7	(7.0)	0	(0)	8	(7.9)	2	(2.0)
Musculoskeletal pain	7	(7.0)	0	(0)	5	(5.0)	0	(0)
Confusional State	6	(6.0)	3	(3.0)	9	(8.9)	4	(4.0)
Cough	6	(6.0)	0	(0)	11	(10.9)	1	(1.0)
Dry eye	5	(5.0)	0	(0)	0	(0)	0	(0)

a This table includes those adverse events occurring in at least 7% of the study population, in either treatment group, or with a ≥5% difference between treatment groups

b The frequency of rash is based solely on adverse events with the MedDRA preferred term of rash. This is likely to provide an underestimate of the true incidence of skin toxicity associated with gefitinib therapy. When the MedDRA high level term (HLT) acnes is combined with HLT rashes, eruptions and exanthems and preferred term rash pustular, the incidence of skin toxicity is increased to 40 [40.0%] in gefitinib-treated patients and 11 [10.9%] in placebo-treated patients. There were no Grade 3, 4 or 5 events of rashes/acnes reported for either treatment group.

EFS, Evaluable for safety

- There was one interstitial lung disease (ILD) type event in the placebo group, and none in the gefitinib treatment group

- The clinical laboratory results were similar to those seen in previous gefitinib monotherapy studies:
  - No clinically relevant changes in haematology or clinical chemistry parameters between treatment groups were evident; gefitinib 250 mg was comparable to placebo
  - Consistent with previous gefitinib monotherapy studies, proteinuria and haematuria (as observed by urinalysis) were reported for a small number of gefitinib-treated patients.
- No clinically relevant changes in vital signs and physical findings were evident with either gefitinib or placebo

Date of the report

17 September 2007