Drug product:	IRESSA™	**SYNOPSIS**	
Drug substance(s):	Gefitinib (ZD1839)		
Document No.:	CSR D7913C00120		
Edition No.:	1.0		
Study code:	D7913C00120		
Date:	26 June 2007		

An open, phase II study of ZD1839 (IRESSA™) plus best supportive care (BSC) in chemotherapy-naïve patients ineligible for chemotherapy with advanced (stage IIIB or IV) non-small cell lung cancer

Study centre(s)

Patients were screened and enrolled in this study at 2 oncology research sites at hospitals in the United Kingdom: New Cross Hospital, Wolverhampton and the Queen Elizabeth University Hospital, Birmingham.

Additional skin toxicity assessments were undertaken by Dr Irshad Zaki at Solihull Hospital, Solihull, B91 2JL, United Kingdom.

Publications

There were no publications at the time of this report.

Study dates		**Phase of development**
First patient enrolled	22 November 2002	Therapeutic exploratory (II)
Last patient enrolled	28 July 2004	
Data cut off date	10 October 2006	

Objectives

Primary objective

The primary objective of the study was to assess objective tumour response rate (complete + partial response) to gefitinib (AstraZeneca ZD1839, IRESSA™) using the RECIST criteria

Secondary objectives

Secondary objectives of the study were:

1. To measure the disease control rate (complete + partial response + stable disease)

2. To measure duration of response (complete + partial)

3. To measure overall survival and progression-free survival

4. To assess the safety and tolerability of the gefitinib by analysis of overall and drug-related adverse events

5. To measure the quality of life (QoL) compared to baseline using the Functional Assessment of Cancer Therapy-Lung (FACT-L)

6. To measure the change in disease related symptoms compared to baseline using the lung cancer subscale (LCS) from FACT-L

Tertiary objectives

Tertiary objectives of the study were:

1. To characterise the skin toxicity observed in patients who were taking gefitinib monotherapy

2. To ascertain the appropriate management of the skin toxicity by validating a predetermined treatment protocol.

3. To create a valid visual grading scale of the skin toxicity for use as a guide in treatment, according to severity.

Study design

This was an open, phase II, multi-centre study in chemotherapy-naïve patients with advanced (stage IIIB or IV), non-small cell lung cancer (NSCLC), who would receive best supportive care (BSC) and gefitinib 250 mg daily.

Target patient population and sample size

The target patient population was male and female patients aged 18 years or older who were performance status 0-2, chemotherapy-naïve with advanced (stage IIIB or IV) NSCLC. Patients were unwilling to receive or were considered unsuitable for chemotherapy.

Recruitment was to be discontinued early if there was no objective response among the first 18 evaluable patients receiving gefitinib, which would provide 98% certainty that the response rate was <20%. With 1 or more responses, 22 patients were to be added. Five or more responses would indicate an active regimen. This provided an overall one-sided significance

level less than 5% and a power of at least 90% given a null 5% and alternative 20% response rates.

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

Gefitinib (ZD1839, IRESSA™) 250 mg brown, film-coated tablet, 1 tablet once a day, taken orally. Formulation Number: F12653, batch numbers P/1607/32, P/1427/49, and P/4005/37.

Patients who participated in the separate skin toxicity assessments could receive different dermatology treatments depending upon the type and severity of rash. Three patients with seborrhoeic dermatitis participated in this assessment and received the following treatment:

Daktacort™ ointment (Janssen-Cilag Ltd), hydrocortisone 1%, miconazole nitrate 2%, twice daily topically

Duration of treatment

Patients were treated with 250 mg gefitinib until evidence of disease progression or until withdrawal. If the patient was deemed to be benefiting from the treatment at the end of the study the patient could continue to receive gefitinib at the discretion of the investigator.

Dermatological treatment continued concomitantly with gefitinib and continued for a minimum of 3 months once dermal symptomatic response had been achieved. If the symptoms reappeared then the treatment schedule was resumed depending on the severity of the symptoms.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Objective tumour response (complete response, [CR] and partial response [PR] rate) based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria
- Secondary variables:
  - Overall survival
  - Progression-free survival
  - Duration of response
  - Disease control rate (CR+PR+stable disease)
  - Change in NSCLC symptoms

Patient reported outcomes (PROs)

- Secondary variables:
  - Change in FACT-L questionnaire scores from baseline
  - Change in LCS scores from the FACT-L questionnaire from baseline

Safety

- Secondary variables:
  - Incidence of adverse events (AEs), discontinuations of study treatment due to adverse event (DAEs) and serious adverse events (SAEs)
  - Incidence and severity of treatment related adverse events AEs, DAEs and SAEs
- Tertiary variables:
  - Clinical and/or histopathological diagnosis of skin toxicity
  - Validated treatment schedule for skin toxicity
  - Pictorial grading system for skin toxicity

Statistical methods

The primary and secondary efficacy and PRO variables were analysed using an intention-to-treat analysis set, which included all patients enrolled into the study who received at least 1 dose of study drug. A per protocol analysis was also undertaken on the primary efficacy variable.

Primary variable: The objective tumour response rate was calculated with 95% confidence intervals with a type I error of 5%.

Secondary efficacy variables: Overall and progression-free survival were determined using the Kaplan-Meier method of survival analysis.

Patient population

Forty-six patients from 2 research sites in the United Kingdom were screened and 45 patients were enrolled into the study. Forty-one patients received study treatment. All 41 treated patients discontinued treatment during the study. The main reason for discontinuation among all enrolled patients was objective progression of the disease (32/45, 71.1%). All 41 patients who received study treatment were included in the ITT and safety analysis sets and 26 patients were included in a PP analysis.

The patient demographic and baseline characteristics are shown in Table S1. The patients were elderly with a mean age of 76 years (range 59 to 86 years) and were mainly of Caucasian origin (95%). Most patients had restricted activity or stayed in bed ≤50% of the time (WHO performance status 1 and 2). Patients included in this study were representative of a population with advanced NSCLC, which was not amenable to curative surgery or radiotherapy.

Table S1 Patient demographic and baseline characteristics

Demographic or baseline characteristic	Intention to treat (n=41)
Demographic characteristics	
Sex (n and %)	
Male	24 (58.5)
Female	17 (41.5)
Age (years)	
Mean (SD)	76.2 (5.0)
Median	76.0
Range	59 to 86
Race (n and %)	
Caucasian	39 (95.1)
Black	2 (4.9)
Baseline characteristics	
Time from diagnosis of NSCLC to start of treatment (days)	
Mean (SD)	90.0 (155.9)
Median	44.0
Range	15 to 989
Previous therapy/surgery for NSCLC (n and %)	
Radiotherapy for NSCLC	4 (9.8)
Surgery for NSCLC	3 (7.3)
WHO Performance status (n and %)	
0 = normal activity	4 (9.8)
1 = restricted activity	17 (41.5)
2 = in bed ≤ 50% of the time	16 (39.0)
Missing	4 (9.8)

Efficacy results

Primary variable: Objective tumour response

Three (7.3%) of the 41 patients treated with gefitinib in this study were objective tumour responders using the RECIST criteria (Table S2). There were 2 partial responders and one complete responder. The overall aim of the study to obtain 5 responders from 40 treated patients was not reached and hence the response rate was not significant (p=0.403).

Table S2 Objective tumour response, ITT analysis set

	Intention To Treat (n=41)
Responders: CR + PR (Number (%) of patients)	3 (7.32)
95% confidence interval	(1.54, 19.92)
Exact p, true response rate>10%	0.403

Secondary efficacy variables

The median duration of response, for the 3 responders was 464 days. The individual duration of response times were 108, 464 and 567 days. Three patients met the RECIST criteria for stable disease. Hence, disease control was achieved by 6 (15%) patients.

Overall and progression free survival analyses using the Kaplan-Meier method were based on all enrolled patients and used a data cut-off of 10 October 2006. By this time, 41 of the 45 enrolled patients had died and 42 had disease progression. One of the treated patients was still alive and 3 of the enrolled patients were alive at the last contact (date of discontinuation from the study as untreated patients were not followed up for survival). The survival estimate for the percentage of enrolled patients who were alive at 6 months was 36%. The median overall survival time was 124 days. The survival estimate for the percentage of enrolled patients who were progression free at 6 months was 13%. The median progression free survival time was 31 days.

PRO results

Limited data were available for all the quality of life (FACT-L) and disease related quality of life (LCS) assessments and only 5 patients had any 16 week (visit 8) data. The changes from baseline were all not significant.

Three patients in the study had a best overall response of improved for FACT-L and LCS, but only a few patients had sufficient data to allow categorisation into improved, no change or worsened. The median time to improvement for FACT-L and LCS was 27 days. The duration of improvement was over 100 days for all 3 patients with FACT-L or LCS improvement.

Safety results

The median actual days of gefitinib treatment was 38 days. A summary of AEs in each category is given in Table S3. All treated patients in the study except one (40, 97.6%) experienced at least 1 AE, and nearly half of the patients (20/41, 48.8%) experienced at least one CTC grade 3 or 4 AE. However, the majority of AEs were mild or moderate (328/366, CTC grade 1 or 2).

One patient had a SAE of bronchopneumonia leading to death and 4 patients had a treatment emergent SAE other than death. None of the SAEs were assessed as related to study treatment. One patient also experienced a SAE during the screening period. Four (9.8%) patients discontinued from study treatment due to AEs, one patient due to interstitial lung disease. Two patients had AEs of transient ischaemic attack classed as other significant AEs. There were no unexpected deaths, SAEs, discontinuations due to AEs or other significant AEs.

Table S3 Number (%) of patients who had a treatment emergent adverse event in any category, safety analysis set

Category of adverse event	Number (%) of patients [a] (n=41)
Any adverse events	40 (97.6)
Serious adverse events	
Serious adverse events leading to death	1 (2.4)
Serious adverse events not leading to death	4 (9.8)
Discontinuations of study treatment due to adverse events	4 (9.8)
Other significant adverse events	2 (4.9)
CTC grade 3 adverse events	19 (46.3)
CTC grade 4 adverse events	3 (7.3)
CTC grade 3/4 adverse events	20 (48.8)

[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.

Rash, diarrhoea and dry skin were the most common AEs (>20% patients) related to gefitinib treatment, but were CTC grade 1 or 2 except for 2 patients.

Three patients had clinically important increases in alanine aminotransferase after entry to the study. One patient had a CTC grade 3 AE of increased alkaline phosphatase and one patient had a clinically important increase in creatinine after entry to the study.

Skin toxicity assessment

Only 3 patients participated in the skin toxicity part of the study. All 3 patients were diagnosed with seborrhoeic dermatitis. The overall clinical and patients' evaluation of their skin toxicity improved following treatment with Daktacort in all 3 patients.

Date of the report

26 June 2007