Drug Product	IRESSA™	**SYNOPSIS**	
Drug Substance	Gefitinib		
Study Code	D7913L00012		
Edition Number	1.0		
Date	22 January 2008		

Phase II study of Iressa in relapsed and refractory SCLC

Study centre(s)

Patients were enrolled in this study at 3 oncology research sites at hospitals in Denmark and the United Kingdom: Rigshospitalet Hospital, Copenhagen, Denmark; Herlev Hospital, Copenhagen, Denmark and Christie Hospital, Manchester, UK.

Publications

Langer SW, Pedersen BS, Ranson M, Loft A, Pappot H, Thatcher N. Phase II study of Iressa (gefitinib) in relapsed and refractory small cell lung cancer (SCLC). Abstract submitted for publication at the 1st European Lung Cancer Conference in April 2008, Geneva, Switzerland.

Study dates		**Phase of development**
First patient enrolled	15 September 2004	Therapeutic exploratory (II)
Last patient completed	23 March 2007	

Objectives

The primary objective of the study was to determine the disease control rate [complete response (CR) plus partial response (PR) plus stable disease (≥90 days)] at trial closure and after the first stage of the study based on Response Evaluation Criteria in Solid Tumours (RECIST) criteria in patients with relapsed or refractory small cell lung cancer (SCLC) treated with gefitinib.

The secondary objectives were:

- To determine the objective response rate (CR + PR) at trial closure in patients with relapsed or refractory SCLC and measurable disease treated with gefitinib

- To determine the time to progression-or-death in patients with relapsed or refractory SCLC and measurable disease treated with gefitinib
- To determine overall survival in patients with relapsed or refractory SCLC and measurable disease treated with gefitinib
- To determine symptom improvement and quality of life after the start of gefitinib treatment according to Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and its 7-item disease-specific Lung Cancer Subscale (LCS)
- To characterise the safety profile of gefitinib at a daily dose of 250 mg in patients with SCLC.

The explorative objectives were:

- To correlate the change in tumour FDG-uptake measured by repeated FDG-PET scanning during gefitinib treatment with clinical outcome
- To correlate the change in plasma levels of uPAR and its cleavage products during gefitinib treatment with clinical outcome
- To correlate the clinical outcome with demographic variables.

Study design

This was designed as an open-label, non-randomised, two-stage explorative phase II study in consecutive patients with relapsed or refractory SCLC (stage IIIB or IV).

Target patient population and sample size

The target patient population was patients with histologically confirmed relapsed or refractory SCLC after previous chemotherapy. Relapsed SCLC describes patients with SCLC responding to first-line treatment and progressing later than 3 months after chemotherapy discontinuation (also called 'sensitive'). Refractory SCLC describes patients with SCLC where first-line treatment failed with progression ≤3 months from chemotherapy discontinuation (also called 'resistant'). Male and female patients aged 18 years or older, WHO performance status ≤2, measurable disease by CT scanning of chest and/or abdomen and a life expectancy of over 2 months were eligible for the study.

The sample size for evaluating disease control rate was based on a 2-stage design incorporating the ad hoc rule of Green and Dahlberg (Green and Dahlberg 1992), based on an overall 80% power, a one-sided type 1 error of 5% and a 2% false negative rate for the first stage. Assuming a baseline disease control rate of 20% and a clinically relevant increase of 15%, 27 patients were to be recruited to the first stage. Recruitment was to stop if 4 or fewer patients exhibited disease control. If 5 or more patients exhibited disease control in the first stage, then it was planned to recruit a further 29 patients into the second stage, giving 56 patients in total.

After recruitment to the first stage had been completed, a decision was taken by the Study Team to close recruitment and not to proceed into the second stage. This decision was taken based on new clinical data. In the timeframe since the study was initiated, sufficient clinical data with topotecan had been published to support its use as a new standard second line treatment of relapsed SCLC (O'Brien et al 2006). In this clinical setting, it was no longer considered feasible or ethically acceptable to include SCLC patients in a second line protocol.

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.

Patients received oral gefitinib 250 mg once daily. Treatment continued in the absence of disease progression-or-death as long as the patient was included in the study. There was to be no dose modification of gefitinib.

Duration of treatment

Patients were treated with gefitinib until disease progression, death or until withdrawal.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: Number (%) of patients exhibiting disease control [complete response (CR) + partial response (PR) + stable disease (≥90 days)] according to RECIST criteria
- Secondary variables:
  - Number (%) of patients with an objective tumour response (CR + PR) according to RECIST criteria. Objective tumour responders were those patients with 2 consecutive visits of CR or PR, a minimum of 4 weeks apart.
  - Median progression-free survival time (ie, time to progression or death) and the estimated proportion of patients progression-free at 6 months (Kaplan Meier method)
  - Median survival time (ie, time to death) and the estimated proportion of patients alive at 6 months and trial closure (Kaplan Meier method)
- Exploratory variables:
  - Maximum 18F-FDG uptake value recorded across all lesions at baseline, after 2 weeks of treatment, and at time of progression and percentage changes from baseline

- Area under the plasma concentration curve (AUC) for uPAR and its cleavage products at baseline, every 4 weeks and at time of progression / discontinuation.

Patient reported outcomes (PROs)

- Secondary variables:
  - Changes in the FACT-L, treatment outcome index (TOI), LCS and the FACT-L domain scores from baseline
  - Best overall response for FACT-L, TOI and LCS scores

Safety

- Secondary variables:
  - Nature, incidence and severity of adverse events (AEs), and serious adverse events (SAEs)
  - Incidence of and reasons for study drug dose interruptions and withdrawals

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.

Primary variable: The disease control rate according to RECIST criteria was calculated with 95% confidence intervals. The null hypothesis was that the disease control rate was less than or equal to the baseline rate of 20%.

Secondary efficacy variables: The objective response (CR + PR) according to RECIST criteria was calculated with 95% confidence intervals. Progression-free and overall survival were determined using the Kaplan Meier method of survival analysis.

Patient population

The patient population and disposition are shown in Table S1. Thirty-two patients were screened and 29 patients were enrolled into the study and received study treatment. Twenty-two patients were known to have dies before study closure. Seven patients discontinued the study prior to known death. All 29 patients who received study treatment were included in the ITT and safety analysis sets.

The study was closed after the first stage of the study had been completed.

Table S1 Patient population and disposition

		Number (%) of patients	
Population			
Number enrolled		29	
Number entered in treatment phase		29	(100)
Disposition			
Number (%) of patients who discontinued		7	(24.1)
Eligibility criteria not fulfilled		1	(3.4)
Lost to follow up		3	(10.3)
Other [a]		3	(10.3)
Analysis sets			
Number (%) of patients:	analysed for safety [b]	29	(100)
	analysed for efficacy (ITT) [b]	29	(100)
	analysed for response (subset of ITT) [c]	26	(89.7)

[a] Two patients in the survival follow up and one patient receiving treatment were discontinued when the study was closed.
[b] Number of patients enrolled in the study who received at least 1 dose of study medication
[c] Subset of the ITT analysis set including who had received at least 4 weeks of study treatment and patients who had withdrawn earlier for progression or death due to progression ie, patients discontinued prior to the 4-week assessment without having progressed or died were excluded
ITT=Intention to treat

The patient demographic and baseline characteristics are shown in Table S2. The population was Caucasian with a mean age of 65 years (range 44 to 84 years). Seventeen (59%) patients had refractory SCLC and 12 (41%) patients had relapsed SCLC. The majority of patients (19, 66%) had restricted activity (WHO performance status 1). Patients included in this study were considered representative of a population with relapsed or refractory SCLC.

Table S2 Patient demographic and baseline characteristics

Demographic or baseline characteristic	Intention to treat (n=29)
Demographic characteristics	
Sex (n and %)	
Male	13 (44.8%)
Female	16 (55.2%)
Age (years)	
Mean (SD)	64.6 (9.0)
Median	64.0
Range	44 to 84
Race (n and %)	
Caucasian	29 (100.0%)
Baseline characteristics	
Previous Chemotherapy for SCLC (n and %)	29 (100.0%)
Previous Radiotherapy for SCLC (n and %)	17 (58.6%)
Classification of SCLC progression	
Relapsed	12 (41.4%)
Refractory	17 (58.6%)
WHO performance status	
0 Normal activity	6 (20.7)
1 Restricted activity	19 (65.5)
2 In bed ≤50% of the time	4 (13.8)

Efficacy and patient reported outcome results

Primary variable

Disease control was achieved in 6 (21%) patients in the ITT analysis set (Table S3).

Table S3 Disease control rate, ITT analysis set

	Intention To Treat (n=29)
Disease control (CR+PR+stable disease): n (%)	6 (20.69)
Complete response	0
Partial response	1 (3.4)
Stable disease	5 (17.2)
95% Confidence Interval for disease control	(7.99, 39.72)
Exact p, true disease control rate >20%	0.537

Disease control was also achieved in 6 (23%) patients in the evaluable for response analysis set. This analysis set was a subset of the ITT analysis set including patients who had received at least 4 weeks of study treatment and patients who had withdrawn earlier for progression or death due to progression and was used to test the sensitivity of the main analysis.

Secondary variables

One patient (3%, ITT analysis set) treated with gefitinib had an objective tumour response (RECIST). This patient had a best overall response of PR, which was ongoing after 605 days (days from first visit response of PR to last visit of PR).

The Kaplan Meier survival estimate for the percentage of patients who were progression free at 6 months was 10%. The median progression free survival time was 59 days. One patient was progression free at the time of last follow up with a progression free survival time of 709 days.

The Kaplan Meier survival estimate for the percentage of enrolled patients who were alive at 6 months was 41%. The median overall survival time was 140 days.

The patient reported quality of life and disease related symptoms, as assessed by FACT-L and LCS questionnaires remained relatively unchanged during the study, although only limited data were available after 4 weeks. There were no statistically significant changes in FACT-L, LCS, TOI or any domain scores to any assessed visit. Eight (29%) patients in the study had a clinically important improvement in quality of life relating to lung symptoms (LCS) and 7 (25%) patients had a clinically important worsening.

Exploratory variables

The maximum FDG uptake value (18-F FDG SUV_{max}) increased from baseline to 2 weeks (mean + 5.1%) and to progression / discontinuation (+16.4%), although only 4 patients had

progression / discontinuation data. The changes in FDG SUV_{max} from baseline to 2 weeks ranged from –4.1 to +4.3 in the 6 patients who had a best response of disease control during the study.

The mean uPAR (I-III) at baseline was 59.85 (SD 23.54) for patients with disease control and 43.96 (SD 13.2) for uncontrolled patients.

Safety results

The median exposure to gefitinib was 59 days (range 15 to 767 days). Five of the 29 patients had dose interruptions to their gefitinib therapy, 2 patients due to AE.

A summary of AEs in each category is given in Table S4. All but one patient (28, 97%) experienced at least 1 AE and 23 patients (79%) experienced an AE related to gefitinib treatment, as judged by the investigator. Eleven (38%) patients had a CTC grade 3 or 4 AE and 3 (10%) patients had a gefitinib related CTC grade 3 or 4 AE.

Twenty-two patients died during the study. Twenty-one patients died due to progression of the disease, SCLC or lung cancer and one patient died due to an SAE of CTC grade 4 haemoptysis, 31 days after discontinuing treatment with gefitinib.

Eight patients experienced 11 SAEs other than death after receiving the first dose of study drug. One SAE, dehydration was assessed as related to gefitinib treatment and other reasons (patient not eating or drinking for several days), as judged by the investigator. Four (14%) patients were discontinued from study treatment due to 7 AEs.

One patient discontinued during the screening period (due to eligibility criteria not fulfilled) and hence excluded from the safety analysis set had an SAE of CTC grade 3 anaemia.

Table S4 Number (%) of patients who had an adverse event in any category, safety analysis set

Category of adverse event	Number (%) of patients [a] (n=29)
Any adverse event	28 (96.6)
Serious adverse events:	
Serious Adverse Events leading to death	1 (3.4)
Serious adverse events not leading to death	8 (27.6)
Discontinuation of study treatment due to adverse events	4 (13.8)
Other significant adverse events	0
CTC grade 3/4 adverse events	11 (37.9)
Gefitinib related AE	23 (79.3)
Gefitinib related SAE not leading to death	1 (3.4)

Category of adverse event	Number (%) of patients [a] (n=29)
Gefitinib related CTC grade 3/4 AE	3 (10.3)

[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.

Gastrointestinal disorders, skin and subcutaneous tissue disorders were the most commonly reported system organ classes (≥50%; Table S5).

Table S5 Number (%) of patients with the most commonly reported adverse events by system organ class, safety analysis set

System organ class	Number (%) of patients [a] (n= 29)
Gastrointestinal disorders	23 (79.3)
Skin and subcutaneous tissue disorders	16 (55.2)
General disorders and administration site conditions	13 (44.8)
Infections and infestations	12 (41.4)
Metabolism and nutrition disorders	11 (37.9)
Respiratory, thoracic and mediastinal disorders	7 (24.1)
Eye disorders	5 (17.2)
Nervous system disorders	5 (17.2)
Psychiatric disorders	5 (17.2)
Musculoskeletal and connective tissue disorders	4 (13.8)
Investigations	3 (10.3)

Diarrhoea, fatigue, acne, nausea, dry skin and pneumonia were the most commonly reported preferred terms (≥15%; Table S6). Diarrhoea, acne and dry skin were the most common AEs (≥15%) related to gefitinib treatment.

Table S6 Number (%) of patients with the most commonly reported adverse events by preferred term, safety analysis set

Preferred Term	Number (%) of patients (n=29)
Diarrhoea	16 (55.2)
Fatigue	9 (31.0)
Acne	8 (27.6)
Nausea	8 (27.6)
Dry skin	7 (24.1)
Pneumonia	5 (17.2)
Decreased appetite	4 (13.8)
Dyspnoea	4 (13.8)
Rash	4 (13.8)
Stomatitis	4 (13.8)
Anorexia	3 (10.3)
Constipation	3 (10.3)
Dehydration	3 (10.3)
Gastritis	3 (10.3)
Nasopharyngitis	3 (10.3)
Pyrexia	3 (10.3)
Vomiting	3 (10.3)

[a] Adverse events with an occurrence of ≥10% are included in this table, which is ordered by decreasing frequency

Three patients had asymptomatic, clinically important abnormal values of increased AST or ALT. Bilirubin remained in the normal range for these patients. There was a shift to worsening performance status from baseline to final visit, which was expected given the patient population under investigation. By the final visit, 7 (24%) patients had a performance status >2 and remained in bed for more than 50% of the time. Slight decreases in mean sitting blood pressure (systolic –11 mmHg, diastolic –5.3 mmHg) and weight (-1.4 kg) from baseline to withdrawal/completion were observed.