Drug product:	IRESSA™	**SYNOPSIS**	
Drug substance(s):	Gefitinib		
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A phase I study of ZD1839 (IRESSA ™) and palliative thoracic radiotherapy in patients with non-small lung cancer

Study centre(s)

This study was performed in 20 patients at 2 oncology research sites at hospitals in the United Kingdom: Western General Hospital, Edinburgh and Cookridge Hospital, Cookridge.

Publications

There were no publications at the time of this report.

Study dates		**Phase of development**
First patient enrolled	10 May 2004	Clinical pharmacology (I)
Last patient completed	8 June 2006	

Objectives

Primary objective

The primary objective of this study was to characterise the safety profile of ZD1839, 250 mg administered once daily in combination with palliative thoracic radiotherapy in patients with Stage IIIB/ IV non-small cell lung cancer (NSCLC). The primary outcome variable was the number of patients with an individual drug-related Dose Limiting Toxicity (DLT) event. The

safety related secondary outcome measures were to provide further support to the primary objective of assessing the safety profile of ZD1839.

Secondary objectives

Secondary objectives of the study were:

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

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

Study design

This was a 2-centre, open-label, non-comparative phase I study in patients with advanced NCSLC (stage IIIB or IV). Patients received gefitinib 250 mg daily from 7-10 days prior to administration of palliative thoracic radiotherapy at one of the 3 different dose levels (10 Gy in 1 fraction, 20 Gy in 5 fractions or 39 Gy in 13 fractions).

The number of patients treated with gefitinib in combination with each of the 3 radiotherapy regimens increased from an initial 3 patients to a maximum of 12, depending upon the incidence of DLT. Assessment of DLT was based upon the acute toxicities observed during the first 3 months of therapy. Based on the anticipated toxicities of palliative thoracic radiotherapy, gefitinib monotherapy and conventionally used criteria, an individual drug-related DLT event was defined using National Institutes of Health and National Institute of Cancer (NCI) Common Toxicity Criteria (CTC) version 2.0.

It was planned to close the study after the last patient had completed 12 months from their first dose of radiotherapy.

Target patient population and sample size

The target patient population was male and female patients aged 18 years or older with histologically confirmed NSCLC, which was locally advanced (stage IIIB), not curable with surgery or radiotherapy, or metastatic (stage IV).

The maximum number of patients planned for inclusion in this study was 36, with a group of 12 patients treated at each of the 3 different palliative thoracic radiotherapy dose levels.

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

Gefitinib (ZD1839, Iressa) 250 mg tablets, formulation number: F12653, batch numbers P/1607/45, P/1427/49, and P/4026/10. One tablet was taken orally in the morning at approximately the same time each day. The gefitinib dose level for this study was 250 mg.

Palliative thoracic radiotherapy was delivered to each patient at one of 3 dose levels:

For patients requiring low dose palliative thoracic radiotherapy:

- If the portal size was less than or equal to 150 cm^2 (excluding areas of blocking) a total dose of 10 Grays (Gy) delivered in a single fraction was given.
- If the portal size was greater than 150 cm^2 (excluding areas of blocking), a total dose of 20 Gy delivered in 5 fractions of 4 Gy administered 5 days per week for one week, was given.

For patients requiring high dose palliative thoracic radiotherapy:

- A total dose of 39 Gy delivered in 13 fractions of 3 Gy administered 5 days per week for 2.5 weeks. The portal size was to be less than 192 cm^2 (excluding areas of blocking).

Radiotherapy was to be delivered at approximately the same time each day after the gefitinib dose had been taken.

Duration of treatment

Treatment with gefitinib 250 mg daily commenced 7 to 10 days prior to administration of palliative thoracic radiotherapy, and continued daily thereafter until disease progression, withdrawal due to adverse events or withdrawal as a result of patient/clinician choice.

Criteria for evaluation (main variables)

Safety

- Primary variable: Number of patients with an individual drug-related DLT event (as per DLT definition).
- Secondary variables:
  - The incidence (number of patients) with a chronic late occurring toxicity (RTOG) event
  - Nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
  - Incidence of and reasons for study drug dose interruptions and withdrawals
  - Study drug exposure, laboratory assessments, physical examinations

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

Statistical methods

The primary safety variable and PRO variables were analysed using an intention-to treat analysis set, which included all patients enrolled into the study.

The secondary safety variables were analysed using the safety analysis set, which consisted of all enrolled patients who received at least 1 dose of gefitinib. The safety data was summarised descriptively.

Patient population

The patient population and disposition are given in Table S1. Twenty patients were enrolled in the study and were treated with gefitinib. All 20 patients discontinued treatment during the study. The main reasons for discontinuation were death (7 patients), objective progression of the disease (6 patients) and adverse event (6 patients). The patient demographic and baseline characteristics are shown in Table S2.

Recruitment into the study was stopped with the agreement of the chief investigator before the target number of planned patients had been achieved.

Table S1 Patient population and disposition

		Number (%) of patients		
		Gefitinib + 10 Gy (n=1)	**Gefitinib + 20 Gy (n=12)**	**Gefitinib + 39 Gy (n=7)**
Population				
N randomised (N planned)		1 (12)	12 (12)	7 (12)
Disposition				
N (%) of patients who	completed	0	0	0
	discontinued	1	12	7
N analysed for primary variable (ITT)		1	12	7
N analysed for safety[a]		1	12	7

[a] Number of enrolled patients who took at least 1 dose of gefitinib
ITT=Intention to treat; N=Number

Table S2 Patient demographic and baseline characteristics

Demographic or baseline characteristic	Number (%) of patients		
	Gefitinib + 10 Gy (n=1)	**Gefitinib + 20 Gy (n=12)**	**Gefitinib + 39 Gy (n=7)**
Demographic characteristics			
Sex (n and %)			
Male		6 (50.0)	4 (57.1)
Female	1 (100)	6 (50.0)	3 (42.9)
Age (years)			
Mean (SD)	80	68.4 (14.6)	75.6 (5.2)
Range		36 to 84	65 to 82
Race (n and %)			
Caucasian	1 (100.0)	12 (100.0)	7 (100.0)
Previous therapy for NSCLC			
Chemotherapy	0	3 (25.0)	1 (14.3)
Radiotherapy	0	3 (25.0)	0
WHO performance status			
0: Normal activity (0)	0	0	2 (28.6)
1: Restricted activity	1	8 (66.7)	5 (71.4)
2: In bed ≤50% of the time	0	4 (33.3)	0

PRO results

Overall, the FACT-L scores in response to questions about their quality of life indicated that there was little or no change from baseline. Only one patient in the study (gefitinib + 20 Gy) had a clinically important improvement in quality of life.

The changes in disease related symptoms, as assessed by the LCS from FACT-L were also minimal.

Safety results

Primary variable

No patients in the study experienced a DLT event. It was planned to assess DLTs based upon acute toxicities observed during the first 3 months of therapy. However, only 2 patients remained in the study for 3 months or longer.

One patient in the study experienced a RTOG toxicity event. This patient who was treated with 39 Gy radiotherapy, experienced gastroesophageal reflux (RTOG grade 1) and dizziness due to anaemia (RTOG grade 2) after 120 and 127 days in the study respectively.

Adverse events

A summary of AEs in each category is given in Table S3. The majority of patients (18, 90.0%) in the study experienced at least 1 AE, which were generally mild or moderate (CTC grade 1 or 2). Overall, 7 (35.0%) patients had a CTC grade 3 or 4 AE.

Table S3 Number (%) of patients who had at least 1 adverse event in any category, safety analysis set

Category of adverse event	Number (%) of patients [a]	
	Gefitinib + 20 Gy (n=12)	Gefitinib + 39 Gy (n=7)
Any adverse event (AE)	11 (91.7)	7 (100.0)
Serious adverse events (SAEs):		
Serious adverse events leading to death	0	1 (14.3)
Serious adverse events not leading to death	3 (25.0)	5 (71.4)
Discontinuation of study treatment due to AEs	4 (33.3)	3 (42.9)
Other significant AEs	0	0
CTC grade 3 or 4 adverse events	3 (25.0)	4 (57.1)
Drug related adverse events		
Gefitinib	8 (66.7)	5 (71.4)
Palliative thoracic radiotherapy	4 (33.3)	3 (42.9)
Other	1 (8.3)	0
Drug related serious adverse events		
Gefitinib	1 (8.3)	1 (14.3)
Palliative thoracic radiotherapy	1 (8.3)	1 (14.3)
Drug related CTC grade 3/4 AEs		
Gefitinib	0	1 (14.3)
Palliative thoracic radiotherapy	1 (8.3)	1 (14.3)

[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.

Diarrhoea, lower respiratory infection, nausea, acne, rash and vomiting were the most frequently reported AEs (Table S4).

Table S4 Number (%) of patients with the most commonly reported adverse events by preferred term, safety analysis set

	Number (%) of patients [a]	
Preferred Term	**Gefitinib + 20 Gy (n=12)**	**Gefitinib + 39 Gy (n=7)**
Diarrhoea	3 (25.0)	4 (57.1)
Lower respiratory infection	3 (25.0)	2 (28.6)
Nausea	3 (25.0)	1 (14.3)
Acne	2 (16.7)	1 (14.3)
Rash	2 (16.7)	1 (14.3)
Vomiting	2 (16.7)	1 (14.3)

[a] Events with a total frequency of ≥15% across all treatment groups are included in this table.

No patients had a dose interruption of their gefitinib therapy. Nine (45%) patients discontinued study drug early for reasons other than because of the natural endpoints of the study (disease progression/death).

The median exposures to gefitinib were 39 days for the 20 Gy treatment group and 55 days for the 39 Gy treatment group. One patient (gefitinib and 20 Gy radiotherapy) had clinically important abnormalities in clinical chemistry, increases in ALT (124 IU/L) and AST (120 IU/L), which were greater than 2.5 times the ULRR if no demonstrable liver metastases. No clinically relevant trends in vital signs or weight were observed that were related to study treatment.