AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: ZD1839
ACTIVE INGREDIENT: IRESSA

Study No: 1839IL/0073

A PHASE I TRIAL TO EVALUATE ZD1839 (IRESSA™) AND CONCURRENT CHEMO-RADIATION IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Developmental Phase: I
Study Completion Date: 17 November 2005
Date of Report: 8 April 2011

OBJECTIVES:

Primary

The primary objective of the trial was to determine the maximum tolerated dose (MTD), if any, of the combination of daily ZD1839 250 mg with carboplatin area under the time concentration curve (AUC) 2 and 60 Gray (Gy) irradiation and up to 45 mg/m^2 paclitaxel.

Secondary

Secondary objectives of the trial were:

1. To evaluate the activity potential of the combination of ZD1839, carboplatin, paclitaxel, and radiation therapy by estimating the objective response rate (complete response [CR] and partial response [PR]) as assessed by positron emission tomography with (^{18}F)-labelled fluorodeoxyglucose (PET-FDG)

2. To estimate the objective response rate (CR and PR) as assessed by computerised tomography (CT) scan

3. To estimate the complete response rate (CR) as assessed by PET-FDG

4. To estimate time to progression (TTP) as assessed by CT scan ± PET-FDG

5. To estimate overall survival

6. To characterise the safety and tolerability of ZD1839 combined with concurrent carboplatin, paclitaxel and radiation

7. To determine the site of first failure (characterised as local-regional, distant or both)

Exploratory

The exploratory objective was to document the presence of hypoxia at baseline and 8 weeks post radiotherapy by assessment with PET-FAZA and to relate this to objective tumour response assessed by PET-FDG. For those patients that were PET-FAZA negative at baseline, PET-FAZA was not to be repeated at 8 weeks post chemoradiation. This was only performed at the Peter MacCallum Cancer Institute.

METHODS:

Trial design

A multicentre, open-label, non-comparative, phase I trial. ZD1839 at a dose of 250 mg daily with 60 Gy radiotherapy, carboplatin at a dose of AUC 2 and ascending doses of paclitaxel (0, 25, 35, and 45 mg/m^2).

Once the MTD had been established further patients were to be enrolled so that a maximum of 26 patients received the MTD to further assess safety and provide an estimate of potential efficacy.

Target patient population

Male and female patients aged 18 years or older with histologically or cytologically confirmed locally advanced stage IIIA or IIIB (without pleural effusion) non-small cell lung cancer (NSCLC) (the key population).

Investigational product, dosage and mode of administration

ZD1839 (Iressa^{TM}) tablets 250 mg (1 tablet) orally once daily from Day 1 of radiotherapy until Day 5, Week 6 of radiotherapy. In the original protocol, against which the study was initiated, it had been planned that patients would subsequently continue to receive ZD1839 in a monotherapy phase until disease progression, unacceptable toxicity, or withdrawal of consent, and a number of patients in Dose Groups 1 and 2 entered such a monotherapy phase after having completed the combination radiotherapy phase of the study.

Combination therapy, dosage and mode of administration

Radiation therapy 60 Gy; 30 fractions of 2 Gy (5 days a week, for 6 weeks) administered until a total dose of 60 Gy had been reached. All patients enrolled received the same dose of radiotherapy.

Carboplatin intravenous (iv) infusion; the dose was calculated to target an area under the concentration-time curve (AUC) of 2 (as calculated by the Calvert formula [Calvert AH et al, J Clin Oncol 1989;7:1748-56]) once a week for 6 weeks starting on Day 1 of the trial.

Paclitaxel iv infusion; 0 mg/m^2, 25 mg/m^2, 35 mg/m^2 or 45 mg/m^2 (depending on the dose level) once a week for 6 weeks starting on Day 1.

Premedication was dexamethasone 20 mg iv, promethazine 12.5-25 mg iv and ranitidine 50 mg iv (all administered before paclitaxel).

Dose levels used in the study

Dose Levels	Carboplatin (AUC), weekly	Paclitaxel (mg/m^2), weekly	ZD1839 (mg) daily	RT (Gy), 30 fr, 5/week
1	2	0	250	60
2	2	25	250	60
3	2	35	250	60
4	2	45	250	60

Duration of treatment

ZD1839 was administered once daily from Day 1 of radiotherapy until Day 5, Week 6 of radiotherapy. A small number of patients in Dose Groups 1 and 2 who had been enrolled against the original protocol continued receiving ZD1839 during a subsequent monotherapy phase.

The minimum follow up for patients not progressing in the study was 18 months. Database lock was planned to occur 18 months after the last patient had been enrolled into the trial.

Criteria for evaluation (main variables)

Safety (primary)

- Tolerability (National Cancer Institute Common Toxicity Criteria [NCI CTC] version 2.0)
- Safety (secondary)
- Nature, incidence and severity of adverse events (AEs)
- Incidence of and reasons for trial drug dose interruptions, trial drug dose reductions and withdrawals
- Trial drug exposure, laboratory assessments, physical examinations

Efficacy (secondary)

- Objective tumour response (CR and PR) as assessed by PET-FDG
- Objective tumour response (CR and PR) as assessed by CT scan
- Complete response rate (CR) as assessed by PET-FDG
- Complete response rate (CR) as assessed by CT scan
- TTP as assessed by clinical examination, chest x-ray, CT scan ± PET-FDG
- Site of first failure
- Overall survival

STATISTICAL METHODS:

Sample sizes for the study were based on practical considerations of safety, tolerability, and the exploratory nature of the trial.

For all efficacy and safety endpoints, the analysis population was the intention to treat

(ITT) population, comprising all patients who received at least 1 dose of trial drug.

The standard summary statistics for continuous variables were: mean, standard deviation, median, quartiles, minimum and maximum. The standard summary statistics for discrete variables were count and proportion. Objective response rates were summarised by proportions. Proportions and durations (of TTP, overall survival and duration of response) were summarised by Kaplan-Meier methods. Tolerability was summarised by the appropriate standard summary statistics.

RESULTS:

Patient Population:

Twenty-nine patients were screened, 27 were recorded as eligible for the trial, and 28 were registered, received at least 1 dose of ZD1839 and comprised the ITT population. All registered patients satisfied the selection criteria except patient 0111-5001 who failed inclusion criterion 2. This patient was recorded as ineligible but was registered and treated. Three patients (Dose Group 1) received ZD1839, carboplatin, and radiotherapy; 6 patients (Dose Group 2) additionally received paclitaxel at 25 mg/m^2 weekly, 3 (Dose Group 3) additionally received paclitaxel at 35 mg/m^2 weekly, and 16 (Dose Group 4 – patients in the dose escalation phase were identified as Group 4.1 and those in the expanded cohort as Group 4.2) additionally received paclitaxel at 45 mg/m^2 weekly. The population of trial patients was an acceptable representative group for this Phase I trial.

Table S1 Patient population and disposition

Demographic characteristics (N = 28)			
All patients			
Age (years)	Median	64.5	
	Range	50 to 75	
Sex (n and % of patients)	Male	17	(60.7)
	Female	11	(39.3)
Race (n and % of patients)	Caucasian	25	(89.3)
	Asian	2	(7.1)
	Other	1	(3.6)
Height (cm)	Mean (SD)	168.7	(8.71)
	Range	150 to 185	
Baseline characteristics			
Weight (kg)	Mean (SD)	80.8	(19.02)
	Range	57.0 to 131.8	
Systolic blood pressure (mm Hg)	Mean (SD)	139.5	(22.85)
	Range	104 to 208	
Diastolic blood pressure (mm Hg)	Mean (SD)	75.8	(14.20)
	Range	54 to 110	
Heart rate (BPM)	Mean (SD)	79.8	(10.79)
	Range	53 to 103	
WHO performance status (n and % of patients)	0 1	11 17	(39.3) (60.7)
Disposition (number (%) of patients in group)			
Dose Group 1 (n = 3)			
Completed combination therapy		3	(100.0)
Entered monotherapy, not continuing at trial end		2	(66.7)
Continuing monotherapy at trial end		1	(33.3)
Dose Group 2 (n = 6)			
Completed combination therapy		6	(100.0)
Entered monotherapy, not continuing at trial end		4	(66.7)
Completed combination therapy, did not enter monotherapy		2	(33.3)

Demographic characteristics (N = 28)		
Dose Group 3 (n = 3)		
Completed combination therapy, did not enter monotherapy	3	(100.0)
Dose Group 4.1 (n = 3)		
Completed combination therapy, did not enter monotherapy	3	(100.0)
Dose Group 4.2 (n = 13)		
Completed combination therapy, did not enter monotherapy	13	(100.0)
N analysed for safety[a] and efficacy (ITT)	28	(100.0)

[a] Number of patients who took at least one dose of trial treatment and had at least one data point after dosing

Primary objective

The MTD was not reached in this study.

Efficacy results

Based on PET-FDG, there were 17 (60.7%) responders (exact 95% confidence interval [CI] for proportion of responders, 40.6% - 78.5%) at Visit 10 or Visit 16; 12 (42.9%) with CR and 5 (17.9%) with PR. There were 11 (39.3%) non-responders.

Based on CT scan, there were 13 (46.4%) responders (exact 95% CI for proportion of responders, 27.5% to 66.1%); 6 (21.4%) with CR, and 7 (25.0%) with PR. Among the 15 (53.6%) non-responders, stable disease (SD) was recorded for 11 (39.3%) patients and progressive disease (PD) was recorded for 4 (14.3%).

CR was recorded at Visit 10 or Visit 16 for 12 (42.9%) patients (exact 95% CI for proportion with CR by PET-FDG, 24.5% - 62.8%). Sixteen (57.1%) patients did not have CR. CR by CT scan was recorded for 6 (21.4%) patients (exact 95% CI for proportion with CR, 8.3% - 41.0%). Twenty-two (78.6%) patients did not have CR by CT scan.

Median time to progression was 422 days (95% CI 163 to 660 days). The proportion of patients alive and progression-free at 12 months was 59.3% (95% CI 40.7% to 77.9%). Censored observations were recorded for 11 (39.3%) patients). At trial closure 10 (35.7%, 95% CI 18.6% to 55.9%) patients were alive and progression-free, 16 (57.1%) were recorded with disease progression, 1 (3.6%) had died without prior documented disease progression, and the status of the remaining patient was unknown. The proportion of patients alive and progression-free at 24 months was 28.2% (95% CI 8.7% to 47.8%).

Of 16 patients for whom a site of first failure was recorded, this was locoregional for 11 (68.8%), distant for 4 (25.0%), and both for 1 (6.3%).

Nineteen (67.9%, exact 95% CI 47.6% – 84.1%) patients were alive at trial closure and 9 (32.1%) were dead. At 12 months, 72.3% (95% CI 54.7% - 89.9%) of patients were alive and at 24 months, 60.4% (95% CI 39.2% - 81.6%) of patients were alive. Median survival time could not be estimated. Nineteen (67.9%) patients had censored observations.

Safety results

Median time on trial was 43.0 days (range 33 to 1205 days), with median time on ZD1839 treatment being 42.5 days (33 to 1196 days). Seven (25.0%) patients had interruptions in ZD1839 dose; for 4 (14.3%) of these it was because of toxicity. All 28 (100.0%) patients completed combination therapy. Six (21.4%) discontinued later - 5 (17.9%) because of AEs and the sixth (3.6%) for other reasons.

Five (38.5%) of 13 patients in the expansion cohort (Dose Group 4.2) experienced grade 3 or 4 lower respiratory tract infection, with or without neutropenia, that met the protocol-defined criteria for dose-limiting toxicity (DLT) although only febrile neutropenia in one of these patients was reported as a DLT. The MTD was not established.

AEs were recorded for all 28 (100.0%) trial patients while receiving combination therapy. Most commonly affected system organ classes were gastrointestinal disorders (28 [100.0%] patients), skin and subcutaneous tissue disorders (24 [85.7%] patients), general disorders and administration site conditions (21 [75.0%] patients), respiratory, thoracic and mediastinal disorders (17 [60.7%] patients), nervous system disorders (15 [53.6%] patients), and blood and lymphatic system disorders, infections and infestations, and metabolism and nutrition disorders (each 14 [50.0%] patients).

Oesophagitis was the most commonly reported AE, affecting 18 (64.3%) patients. Rash was reported for 17 (60.7%) patients, and diarrhoea and nausea were reported for 16 (57.1%) patients each.

In general, the profile of AEs judged by the investigator as related to study drug was as expected for ZD1839, with rash and diarrhoea being most commonly recorded (16 [57.1%] and 12 [42.9%] patients, respectively). Most commonly reported AEs related to other trial therapy were oesophagitis affecting 18 (64.3%) patients, nausea affecting 15 (53.6%) and fatigue affecting 10 (35.7%).

There were no AEs leading to death during combination therapy. Nine patients had died by trial closure. All of the deaths were recorded as being related to cancer.

SAEs were recorded for 15 (53.6%) patients. The most frequently affected system organ classes were gastrointestinal disorders (6 [21.4%] patients), infections and infestations (5 [17.9%]) patients, and metabolism and nutrition disorders and blood and lymphatic system disorders (each 3 [10.7%] patients).

Individual SAEs judged by the investigator to be related to ZD1839 treatment were reported for 4 (14.3%) patients; oesophagitis was reported in 2 (7.1%) patients, and anaemia, dehydration, pneumonitis, and skin toxicity were each reported in 1 (3.6%) patient. SAEs considered to be related to other trial therapy in 8 (28.6%) patients comprised oesophagitis, febrile neutropenia, lower respiratory tract infection, anaemia, vomiting, chest discomfort, pyrexia, hypersensitivity, infection, pneumonia, dehydration, pneumonitis, skin toxicity, and flushing.

One patient was withdrawn during the combination phase because of radiation pneumonitis. This was considered possibly related to both ZD1839 treatment and other trial therapy (radiation).

Some values for individual haematology parameters above or below project specific ranges were recorded as AEs. Three were reported as serious: 2 instances of febrile neutropenia in Dose Group 4.2 (1 recorded as a DLT) attributed to chemotherapy and 1 instance of anaemia in Dose Group 3, considered to be possibly related to both ZD1839 and radiation treatment.

Some values for individual blood chemistry parameters above or below project specific ranges were recorded as AEs.

Table S2 Number (%) of patients who had an AE in any category during combination therapy (ITT analysis set)

Category of AE	**Number (%) of patients who had an AE in each category[a]**	
Any AE	28	(100.0)
Drug-related AE	26	(92.9)
SAE	15	(53.6)
Serious drug-related AE	4	(14.3)
AE leading to death	0	(0.0)
CTC grade 3 or 4 AE	21	(75.0)
CTC grade 3 or 4 drug-related AE	5	(17.9)
Withdrawal due to AE	1	(3.6)
Withdrawal due to SAE	0	(0.0)
Withdrawal due to drug-related AE	1	(3.6)

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.

Table S3 **Number (%) of patients with the most commonly reported drug-related AEs[a] during combination therapy, sorted by decreasing order of frequency and by relationship to ZD1839 or other trial therapy**

Preferred term	Number (%) of patients who had an AE in each category	
AEs related to ZD1839	**26**	**(92.9)**
Rash	16	(57.1)
Diarrhoea	12	(42.9)
Oesophagitis	7	(25.0)
Nausea	5	(17.9)
Fatigue	4	(14.3)
Dysphagia	3	(10.7)
Pneumonitis	3	(10.7)
Lethargy	2	(7.1)
Mucosal inflammation	2	(7.1)
Dehydration	2	(7.1)
Dermatitis acneiform	2	(7.1)
AEs related to other trial therapy	**28**	**(100.0)**
Oesophagitis	18	(64.3)
Nausea	15	(53.6)
Fatigue	10	(35.7)
Dysphagia	8	(28.6)
Dyspepsia	7	(25.0)
Diarrhoea	6	(21.4)
Lethargy	6	(21.4)
Dermatitis radiation	6	(21.4)
Radiation skin sensitivity	6	(21.4)
Neutropenia	6	(21.4)
Cough	6	(21.4)
Vomiting	5	(17.9)
Lymphopenia	4	(14.3)
Dehydration	4	(14.3)
Constipation	4	(14.3)
Odynophagia	4	(14.3)
Anaemia	3	(10.7)
Mucosal inflammation	3	(10.7)
Pneumonitis	3	(10.7)
Dysgeusia	3	(10.7)
Paraesthesia	3	(10.7)
Pyrexia	3	(10.7)

Preferred term	Number (%) of patients who had an AE in each category	
Hypomagnesaemia	3	(10.7)
Alopecia	2	(7.1)
Anorexia	2	(7.1)
Febrile neutropenia	2	(7.1)
Thrombocytopenia	2	(7.1)
Rash	2	(7.1)
Oral pain	2	(7.1)
Hypersensitivity	2	(7.1)
Lower respiratory tract infection	2	(7.1)
Weight decreased	2	(7.1)
Decreased appetite	2	(7.1)
Hypokalaemia	2	(7.1)
Muscle twitching	2	(7.1)
Dyspnoea	2	(7.1)
Haemoptysis	2	(7.1)

[a] This table uses a cut-off of 5%

Exploratory objective

Two of six patients had grade 4 hypoxia at baseline as estimated by PET-FAZA (one patient with a hypoxic primary tumour and node, the other with a hypoxic primary). One patient had missing data. All sites found to be hypoxic had a complete response as measured by PET-FDG.