AstraZeneca

Drug Product	IRESSA™	**SYNOPSIS**	
Drug Substance	Gefitinib (ZD1839)		
Study Code	D7913L00544/1839IL0544		
Edition Number	1.0		
Date	26 February 2008		

A randomized phase II study to investigate the feasibility and benefits of combining ZD1839 (Iressa™) and cisplatin/ 5FU, as induction therapy, in patients with locally advanced squamous cell carcinoma of the head and neck

Publications

There were no publications at the time of this report.

Study dates

First patient enrolled 26 February 2004

Last patient completed 28 June 2007

Phase of development

Therapeutic exploratory (II)

Objectives

The primary objective of the study was:

To compare the response rate (complete + partial response) between the cisplatin/5FU, and cisplatin/5FU + ZD1839 (IRESSA™) combination using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria

Secondary objectives of the study were:

- To assess the safety and tolerability of cisplatin day1 q21 days, and 5FU d1-4 q21 days + ZD1839 (IRESSA) d1-21 combination by analysis of overall and drug related adverse events
- To compare safety of radiotherapy post treatment
- To compare the changes in signal transduction by estimating tumour transcriptional and protein changes in EGFR signalling pathways in biopsies from primary tumour and metastases in response to ZD1839 (IRESSA) therapy – using standard laboratory methods of analysis
- To compare progression free survival and overall survival
- To compare duration of response (complete + partial)
- To compare disease control rate (complete + partial + stable disease)
- To assess quality of life (QoL) and symptom relief, based on FACT-H&N, of subjects treated with cisplatin/5FU + ZD1839 (IRESSA) versus cisplatin/5FU

Study design

This was an open, randomised, single centre study comparing standard therapy of cisplatin/5FU with cisplatin/5FU and gefitinib 250 mg daily in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Target patient population and sample size

The target population of patients had a histological diagnosis of inoperable SCCHN (stages 3 and 4), and were considered suitable for induction chemotherapy (rapid tumour growth – doubling of tumour size in 30 days, large (>6cm) tumour mass, or potential airway obstruction) followed by radical radiotherapy or chemoradiotherapy.

The planned sample size was a total of 64 patients to receive standard therapy of either cisplatin/5FU (32 patients) or cisplatin/5FU + gefitinib (32 patients). Sample size calculations were based on the assumption that the clinical response rate for cisplatin/5FU alone was 55% and that the addition of gefitinib could increase the clinical response rate by up to 20% over cisplatin/5FU. The sample size provided a power of 80% to detect an observed difference in clinical response rate between the 2 treatment groups of ≥10%. Cisplatin/5FU + gefitinib would be considered for further evaluation if the observed clinical response rate for the cisplatin/5FU + gefitinib was at least 10% greater than the observed rate for cisplatin/5FU alone.

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

Gefitinib (ZD1839, IRESSA™) tablets (250 mg) were given orally once per day at approximately the same time each day.

Cisplatin was given at a dose of 100 mg/m^2 day1 q21 days as an intravenous infusion given over 4 hours in 1000 mL bag of saline. The frequency of dosing was every 21 days for 2 cycles.

5-Fluorouracil was given at a dose of 1000 mg/m^2 on days 1, 2, 3 and 4 as an intravenous infusion given in 1000 mL bag of saline over 96 hours on a continuous basis. The frequency of dosing was every 21 days for 2 cycles.

Duration of treatment

Cisplatin/5FU: Patients received two, 21-day cycles of cisplatin/5FU as induction chemotherapy treatment.

Gefitinib: 42 days. Gefitinib was given continuously from day 1 until commencement of radical treatment (radiotherapy or chemoradiotherapy) commenced at the end of cycle 2 (Day 42), withdrawal due to adverse events or withdrawal as a result of patient/clinician choice.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: - Objective tumour response (CR and PR) rate based on the RECIST criteria. CT scans were performed at baseline, just before commencement of radical treatment (day 42) and at the follow-up visit (day 70).

- Secondary variables:

  – Changes in signal transduction by estimating tumour transcriptional and protein changes in EGFR signalling pathways in biopsies from primary tumour and metastases in response to gefitinib therapy. Histological specimens were compared between pre treatment biopsies and biopsies taken on day 14.

  – Progression free survival and overall survival

  – Duration of response

  – Disease control rate

Patient reported outcomes (PROs)

- Secondary variables: ·

- Global quality of life (FACT-H&N total score, Trial Outcome Index [TOI])
- Change in Head and Neck symptoms (FACT-H&N symptom index) compared to baseline

Safety

- Secondary variables:
  - Adverse event and serious adverse event data
  - Incidence and severity of treatment related adverse events

Statistical methods

The efficacy and PRO variables were analysed using an intention to treat analysis set, which included all randomised patients.

Overall survival was determined using the Kaplan Meier method of survival analysis. PRO data were summarised descriptively.

Analyses of safety variables were performed on patients from the safety analysis set, which included all randomised patients who had received at least 1 dose of study medication.

Patient population

The patient population and disposition are shown in Table S1. Thirty-eight patients were screened and randomised to receive study treatment (19 patients to cisplatin/5FU and gefitinib; 19 patients to cisplatin/5FU). Eighteen patients received treatment with cisplatin/5FU and gefitinib and 19 patients with treatment with cisplatin/5FU. All 38 patients who were randomised to study treatment were included in the ITT analysis set and the 37 patients who received study treatment were included in the safety analysis set.

The study was closed for further recruitment into the study in August 2006 before the planned number of 64 patients had been reached. Survival follow up was also curtailed and the last patient completed the study on 28 June 2007. The decision to stop recruitment and not to continue to follow up patients to death was taken with the agreement of the principal investigator. Three patients randomised to cisplatin/5FU and gefitinib discontinued the study prior to death or the day 70 follow up visit.

Table S1 Patient population and disposition

	Cisplatin/5FU + Gefitinib	Cisplatin/5FU
Population and disposition		
Number enrolled	19	19
Number randomised (N planned)	19 (32)	19 (32)
Number (%) discontinued due to:		
Eligibility criteria not fulfilled	1 (5.3)	0
Number received study treatment	18 (94.7)	19 (100)
Number (%) discontinued due to:		
Adverse event	1 (5.3)	0
Development of study specific discontinuation criteria	1 (5.3)	0
Analysis sets		
Number (%) analysed for ITT [a]	19 (100)	19 (100)
Number (%) analysed for safety	18 (94.7)	19 (100)

ITT Intention to treat

The patient demographic and baseline characteristics are shown in Table S2. The treatment groups were reasonably balanced in terms of sex and age. The mean age of patients was 53.8 years (range 23 to 68 years) in the cisplatin/5FU and gefitinib group and 59.4 years (range 37 to 76 years) in the cisplatin/5FU group. The patients who participated in this study were broadly representative of the population of patients with previously untreated, locally advanced SCCHN. Concomitant treatments were consistent with those expected to be prescribed to patients with SCCHN.

Table S2 Patient characteristics, ITT analysis set

Characteristic	Cisplatin/5FU + Gefitinib (N=19)	Cisplatin/5FU (N=19)
Sex: n (%)		
Male	18 (94.7%)	16 (84.2%)
Female	1 (5.3%)	3 (15.8%)
Age (years)		
N	19	19
Mean (SD)	53.8 (10.5)	59.4 (9.4)
Median	55.0	61.0
Range	23 to 68	37 to 76
Race: n (%)		
Caucasian	18 (94.7%)	17 (89.5%)
Black	1 (5.3%)	2 (10.5%)
WHO performance status: n (%)		
0 (normal activity)	15 (83.3%)	15 (78.9%)
1 (restricted activity)	3 (16.7%)	4 (21.1%)

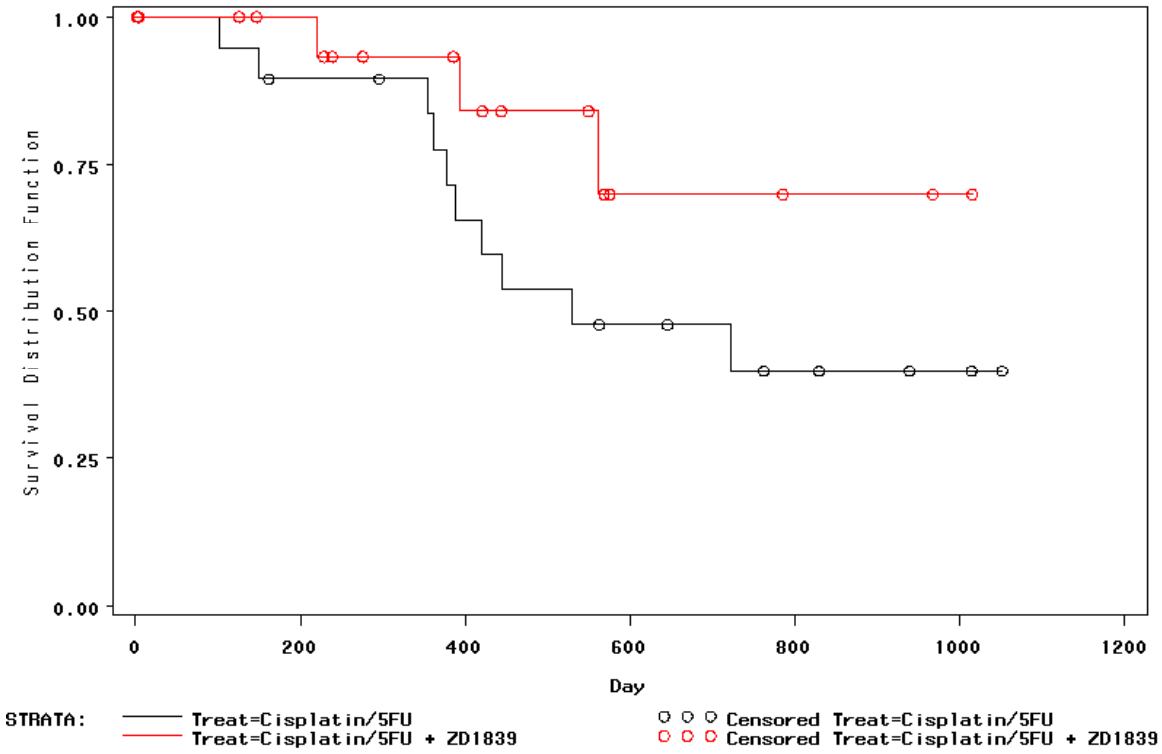
Efficacy and pharmacokinetic results

The analyses were based on a data cut-off of 28 June 2007, by which time 13 deaths (cisplatin/5FU + gefitinib 3 deaths, 15.8%; cisplatin/5FU 10 deaths, 52.6%) had accrued. Total mortality was 34.2%.

Secondary efficacy variable: Overall survival

The 6-month survival rate was 100% (CI 100.0, 100.0) for the cisplatin/5FU and gefitinib group and 89.5% (CI 75.7, 100.0) for the cisplatin/5FU group. The Kaplan Meier survival plot is shown in Figure S1.

Figure S1 Kaplan Meier plot of overall survival, ITT analysis set



Secondary patient reported outcome variables: Quality of Life (FACT-H&N) and symptoms

The quality of life and head and neck symptoms worsened slightly from baseline to the end of the treatment period (42 days, visit 5) in patients treated with cisplatin/5FU and gefitinib but remained relatively unchanged in patients treated with cisplatin/5FU, as assessed by the overall FACT-H&N (-7.7 vs 1.13), TOI (-9.15 vs –2.2), additional concerns (-3.6 vs 0.4) and head and neck symptom scores (-2.23 vs 1.56; Table S3).

Table S3 Changes from baseline to visit 5 (42 days) and visit 6 (70 days), ITT analysis set

Score [a]	Baseline			Change from baseline to visit 5 (42 days)			Change from baseline to visit 6 (70 days)		
	n	Mean (SD)		n	Mean (SD)		n	Mean (SD)	
Cisplatin/5FU + Gefitinib									
Overall FACT-H&N	15	104.90	(17.72)	10	-7.67	(23.89)	5	-20.12	(20.59)
TOI	16	65.04	(15.71)	11	-9.15	(22.12)	6	-20.92	(15.68)
Additional concerns	16	23.69	(6.89)	11	-3.55	(9.96)	6	-10.17	(8.04)
H & N symptom relief	16	28.75	(6.41)	11	-2.23	(9.42)	6	-7.41	(5.99)
Cisplatin/5FU									
Overall FACT-H&N	19	109.08	(13.63)	15	1.13	(21.87)	14	-22.79	(16.65)
TOI	19	67.15	(11.54)	15	-2.21	(20.75)	14	-22.77	(15.01)
Additional concerns	19	23.93	(6.76)	15	0.36	(10.83)	14	-9.19	(7.67)
H & N symptom relief	19	28.65	(5.30)	15	1.56	(8.11)	14	-7.32	(5.26)

[a] A reduction in the scores indicates a worsening in the patient's quality of life, treatment outcome index, symptom relief or additional concerns. The maximum overall FACT-H&N score is 144, maximum TOI is 92, maximum additional concerns is 36 and maximum H&N symptom relief is 40.

Safety results

The median overall exposure to gefitinib was 43 days (mean 40.1, range 3 to 54 days), which corresponded well with the planned duration of treatment (42 days).

A summary of AEs in each category is shown in Table S4. All patients in the study experienced at least 1 AE. Four patients in the cisplatin/5FU + gefitinib treatment group and 10 patients in the cisplatin/5FU treatment group experienced had a CTC grade 3 or 4 AE.

There were no SAEs leading to death during the study. Four patients in the cisplatin/5FU + gefitinib treatment group and 7 patients in the cisplatin/5FU treatment group experienced an SAE. One patient in the cisplatin/5FU + gefitinib treatment group discontinued study treatment with gefitinib due to an AE. This was an SAE of myocardial infarction experienced after treatment with 2 days of study drug.

Ten patients (10/18, 56%) experienced an AE related to gefitinib treatment and in one patient (6%), this was a CTC grade 3 or 4 AE (CTC grade 3 papular rash). An SAE of diarrhoea (patient 202) was assessed as related to gefitinib treatment by the investigator. The majority of patients experienced an AE related to cisplatin, 5FU or other (mainly radiotherapy) during the study.

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

Category of adverse event	Number (%) of patients [a] Cisplatin/5FU + Gefitinib (N=18)	Cisplatin/5FU (N=19)
Any Adverse Event	18 (100.0)	19 (100.0)
Serious adverse events:		
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	4 (22.2)	7 (36.8)
Discontinuation due to adverse event	1 (5.6)	0
Other significant adverse events	0	0
CTC grade 3/4 adverse events	4 (22.2)	10 (52.6)
Gefitinib related AE	10 (55.6)	
Gefitinib related SAE	1 (5.6)	
Gefitinib related CTC grade 3/4 AE	1 (5.6)	

[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.

General disorders and administration site conditions; gastrointestinal disorders; injury, poisoning and procedural complications; skin and subcutaneous tissue disorders; and blood and lymphatic system disorders and were the most commonly reported system organ classes (≥50%) in patients in the gefitinib treatment group (Table S5).

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

System Organ Class	Number(%) of patients Cisplatin/5FU + gefitinib (N=18)	Cisplatin/5FU (N=19)
General disorders and administration site conditions	13 (72.2)	16 (84.2)
Gastrointestinal disorders	11 (61.1)	18 (94.7)
Injury, poisoning and procedural complications	11 (61.1)	14 (73.7)
Skin and subcutaneous tissue disorders	10 (55.6)	6 (31.6)
Blood and lymphatic system disorders	9 (50.0)	11 (57.9)
Metabolism and nutrition disorders	5 (27.8)	4 (21.1)
Ear and labyrinth disorders	5 (27.8)	2 (10.5)

System Organ Class	Number(%) of patients	
	Cisplatin/5FU + gefitinib (N=18)	Cisplatin/5FU (N=19)
Respiratory, thoracic and mediastinal disorders	5 (27.8)	2 (10.5)

[a] Adverse events by system organ class with an occurrence of ≥25% in the cisplatin/5FU + gefitinib treatment group are included in this table, which is ordered by overall decreasing frequency in this treatment group.

Mucosal inflammation, radiation skin injury, nausea and anaemia were the most commonly reported preferred terms (≥38%) in both treatment groups (Table S6). Rash was more prevalent in the treatment group receiving gefitinib, with no patients in the cisplatin/5FU group reporting rash.

During the treatment phase, rash, nausea, diarrhoea, anaemia and constipation were the most commonly reported AEs (≥20%) in the cisplatin/5FU + gefitinib treatment group. Nausea, constipation, fatigue, vomiting and neutropenia were the most commonly reported AEs (≥20%) in the cisplatin/5FU treatment group in this period. The most common adverse events experienced during radiotherapy phase of the study were mucosal inflammation, radiation skin injury and anaemia (≥20%) in both treatment groups.

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

Preferred Term	Number (%) of patients [a]	
	Cisplatin/5FU + gefitinib (N=18)	Cisplatin/5FU (N=19)
Mucosal inflammation	11 (61.1)	13 (68.4)
Radiation skin injury	10 (55.6)	13 (68.4)
Nausea	7 (38.9)	11 (57.9)
Anaemia	7 (38.9)	8 (42.1)
Rash	6 (33.3)	0
Constipation	5 (27.8)	7 (36.8)
Diarrhoea	5 (27.8)	3 (15.8)
Tinnitus	4 (22.2)	2 (10.5)
Neutropenia	3 (16.7)	4 (21.1)
Stomatitis	3 (16.7)	2 (10.5)
Anorexia	3 (16.7)	1 (5.3)
Dysgeusia	3 (16.7)	1 (5.3)

[a] Adverse events with an occurrence of ≥15% in the cisplatin/5FU + gefitinib treatment group are included in this table, which is ordered by overall decreasing frequency in this treatment group.

Three patients in the cisplatin/5-FU + gefitinib group and 2 patients in the cisplatin/5FU group had a clinically important low neutrophil count. One patient in the cisplatin/5FU group also had clinically important low WBC count and one patient had clinically important low platelet count. Two patients, one in each treatment group had a clinically important raised serum bilirubin concentration.