AstraZeneca

**STUDY REPORT SUMMARY**

**ASTRAZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:** IRESSA™
**ACTIVE INGREDIENT:** Gefitinib

| **Study No:** 1839IL/0151, NCT00239304 |
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| A PHASE I/II TRIAL OF ZD1839 (GEFITINIB, IRESSA™) GIVEN CONCURRENTLY WITH CISPLATIN AND RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED HEAD AND NECK CANCER |

**Developmental phase:** Phase I/II
**Study Completion Date:** 9 March 2006
**Date of Report:** 11 March 2009

**OBJECTIVES:**

**Primary objectives**

***Part 1***

To determine the safety of 250 mg gefitinib in combination with three-dimensional conformal radiotherapy (3D-CRT) in patients with locally advanced head and neck cancer.

***Part 2***

To determine the safety of 250 mg gefitinib in combination with concurrent cisplatin and 3D-CRT or IMRT (Intensity Modulated Radiotherapy) in patients with locally advanced head and neck cancer.

***Part 3 (not undertaken)***

To characterise the safety and tolerability of an optimal dose of gefitinib in combination with concurrent cisplatin and 3D-CRT or intensity modulated radiotherapy (IMRT) in patients with locally advanced head and neck cancer.

**Secondary objectives**

***Parts 1 and 2***

To characterise the safety and tolerability of 250 mg gefitinib in combination with concurrent 3D-CRT (Part 1) or in combination with concurrent cisplatin and 3D-CRT or IMRT (Part 2) in patients with locally advanced head and neck cancer.

***Part 2 and 3 (Part 3 was not undertaken)***

To estimate the (preliminary) efficacy of 250 mg gefitinib given concurrently with cisplatin-3D-CRT or IMRT.

**Exploratory objectives**

***Parts 1, 2 and 3 (Part 3 was not undertaken)***

To investigate the correlation of Epidermal Growth Factor Receptor (EGF-R1) expression, amplification and activation status (autophosphorylation; p-EGF-R1) with the efficacy of the combined gefitinib and cisplatin-3D-CRT or IMRT.

To investigate the correlation of serum Vascular Endothelial Growth Factor (sVEGF) levels with the efficacy of the combined gefitinib and cisplatin-3D-CRT or IMRT.

## METHODS:

### Trial design

A single-centre, non-randomised, non-comparative, open-label safety (Parts 1 and 2) and safety and tolerability (Part 3, not undertaken) and preliminary efficacy (Parts 2 and 3, Part 3 not undertaken) of 250 mg gefitinib given in combination with 3D-CRT (Part 1) and with concurrent cisplatin and 3D-CRT or IMRT (Parts 2 and 3, Part 3 not undertaken) in patients with locally advanced head and neck cancer.

### Target patient population

Patients with histologically confirmed squamous cell carcinoma of the head and neck (SCCHN). In particular, patients with locally advanced stage III or IV (T3/T4) SCCHN of the oral cavity, oropharynx, and hypopharynx cancers who were chemo- and radiotherapy naive. Lymph node negative or positive (N0-N3), but metastasis negative (M0) patients with WHO performance status 0-2.

### Investigational product, dosage and mode of administration

Investigational product: ZD1839, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoline-4-amine (IRESSA$^{TM}$, gefitinib) tablets 250 mg.
Dosages: 250 mg gefitinib given in combination with 3D-CRT (Part 1) or with concurrent cisplatin and 3D-CRT or IMRT (Parts 2 and 3).
Administration: 250 mg tablet(s) of gefitinib orally, once daily and continuously. On Days 1 to 7, gefitinib was taken on a neoadjuvant basis. From Day 8 to Day 54, gefitinib, was taken first in combination with 3D-CRT (Part 1), and if no severe trial drug-related toxicity occurred thereafter in combination with concurrent cisplatin and 3D-CRT or IMRT (Parts 2 and 3).
The first six patients in Part 1 of the trial were to receive 250 mg gefitinib from Day 1. If three or more patients at the 250 mg gefitinib experienced dose limiting toxicity (DLT), the maximum-tolerated dose (MTD) had been exceeded and no more patients were to be recruited into the study. If two or fewer of these patients developed a DLT in combination with concurrent 3D-CRT, a further nine patients were to be recruited to receive 250 mg gefitinib in combination with concurrent cisplatin and 3D-CRT or IMRT in Part 2. If four or more patients at the 250 mg gefitinib combined with cisplatin and 3D-CRT or IMRT experienced DLT, the MTD had been exceeded and no more patients were to be recruited into the study. If three or fewer of these patients developed a DLT in combination with concurrent cisplatin and 3D-CRT or IMRT, the recruitment of the expanded cohort of the study, Part 3, was to start. This Part of the study was not undertaken.

DLT was defined as: any trial drug-related grade 4 haematological toxicity or trial drug-related grade 3 or higher non-haematological toxicity (National Cancer Institute Common Toxicity Criteria [NCI CTC] version 2.0); gefitinib dose delay for over 14 days; more than three interruptions in treatment; or death from any cause.

**Combined chemo radiotherapy, dosage and mode of administration**

Cisplatin (20 mg/$m^2$ – originally 40 mg/$m^2$ – only one patient received 20 mg/$m^2$) was to be administrated intravenously in an infusion of 500 ml 0.9% NaCl along with a programme of hydration. The infusion programme was to contain at least 1.5 litres of fluids over a minimum of 3 hours. Cisplatin administration was to be every week (on Days 9, 16, 23, etc). 3D-CRT was to be administered as follows; 50 Grays (Gy) (2 Gy per day) was to be given to the gross tumour and to the microscopic disease area in 25 fractions (25 radiation therapy days, 5 days a week). Second, 20 Gy (2 Gy per day) was to be given to the CT (Computerized Tomography) registered tumour area with about 2 cm margin in 10 fractions (10 radiation therapy days, 5 days a week). 3D-CRT of the tumour was thereby to consist of 70 Gy given in 35 fractions, and overall total treatment time of 3D-CRT about 47 days. IMRT was to be provided as an alternative option for 3D-CRT when it was considered to be necessary to produce more homogenous tumour dose or when it was necessary to lower radiotherapy doses of vital normal structures. The IMRT radiotherapy doses to macroscopic tumour and to the microscopic disease were to be the same as with conventional 3D-CRT.

**Comparator, dosage and mode of administration**

Not applicable.

**Duration of treatment**

A dose of gefitinib was to be taken for 7 days alone (neoadjuvant) and then in combination with 3D-CRT (Part 1) or with concurrent cisplatin and 3D-CRT or IMRT (Parts 2 and 3; Part 3 was not undertaken) for 7 weeks, altogether for 54 days. Patients were to be followed-up to 3 months for acute treatment-related toxicities.

**Endpoints**

**Efficacy**

**Secondary endpoint**

***Parts 2 and 3 (Part 3 not undertaken)***

Incidence of complete response (CR) at 3 months after the end of trial treatment based on Response Evaluation in Solid Tumours (RECIST) criteria.

**Safety**

**Primary endpoints**

***Parts 1 and 2*** (safety parts of trial; phase I)

- Incidence of DLTs (NCI CTC v2.0)

***Part 3*** (safety and tolerability part of trial; phase II – not undertaken)

- *Nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs)*
- Incidence of and reasons for trial dose interruptions and withdrawals
- Trial drug exposure, laboratory assessments, physical examinations

**Exploratory endpoints**

***Parts 1, 2 and 3 (Part 3 not undertaken)***

- EGF-R1 expression, amplification and activation (autophosphorylation, p-EGF-R) status (immunohistochemistry)
- serum VEGF levels (enzyme-linked immunosorbent ELISA assay)

**Statistical methods**

Fleming's method was used to calculate the number of patients required. A sample size of 34 patients at the MTD from Parts 2 and 3 was sufficient to give an 80% probability of rejecting a baseline DLT rate of 33% with an exact 5% one-sided significance test when the true DLT rate is 56%. The hypothesis that the actual DLT was equal to or less than the baseline, was rejected if 17 or more DLTs were observed in the 34 patients. The exact size and power of this test were 3.0% and 81.0% respectively.

The safety population was to consist of all patients who were enrolled and received study drug. The intent-to-treat (ITT) population was to consist of all patients who were randomised to receive the MTD (as defined by Part 2 of the study) in both Parts 2 and 3 of the study. For all efficacy endpoints, the analysis population was to be the ITT population. For calculation of the MTD, the analysis population was to be the ITT population. For all other safety presentations, the analysis population was to be the safety population.

Standard survival techniques were to be used to estimate the incidence of complete response (CR) at 3 months after the end of trial treatment. The analysis of all other endpoints was to be descriptive in nature.

**Patient population**

The population of trial patients was an acceptable representative group for this Phase I/II trial. Fifteen patients were enrolled and received at least one dose of gefitinib; six received gefitinib plus radiation treatment (i.e., Part 1 of the study) and nine received gefitinib plus radiation treatment and cisplatin (i.e., Part 2 of the study). Part 3 of the study was not undertaken. These fifteen patients were considered the safety/ITT population. This was the analysis population for both efficacy and safety.

**Table S1 Patient population and disposition**

| **Demographic or baseline characteristic** | | **Treatment group** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Part 1, Gefitinib + radiation (N=6)** | | **Part 2, Gefitinib + radiation + cisplatin (N=9)** | | **Total (N=15)** | |
| **Demographic characteristics** | | | | | | | |
| Sex (n and % of patients) | Male | 5 | (83.3) | 8 | (88.9) | 13 | (86.7) |
| | Female | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Age (years) Mean (SD) | | 54.67 | (4.68) | 60.67 | (9.91) | 58.27 | (8.56) |
| | Range | 49.0 to 62.0 | | 46.0 to 76.0 | | 46.0 to 76.0 | |
| Race (n and % of patients) | Caucasian | 6 | (100.0) | 9 | (100.0) | 15 | (100.0) |
| **Baseline characteristics** | | | | | | | |
| Previous cancer | Yes | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |

| Demographic or baseline characteristic | | Treatment group | | | | | |
|---|---|---|---|---|---|---|---|
| | | Part 1, Gefitinib + radiation (N=6) | | Part 2, Gefitinib + radiation + cisplatin (N=9) | | Total (N=15) | |
| treatment (n and % of patients) | No | 5 | (83.3) | 9 | (100.0) | 14 | (93.3) |
| Previous surgery cancer treatment (n and % of patients) | Yes | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| | No | 5 | (83.3) | 9 | (100.0) | 14 | (93.3) |
| Previous radiotherapy cancer treatment (n and % of patients) | Yes | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | No | 6 | (100.0) | 9 | (100.0) | 15 | (100.0) |
| Previous chemotherapy cancer treatment (n and % of patients) | Yes | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| | No | 6 | (100.0) | 9 | (100.0) | 15 | (100.0) |
| Histology type | SCC | 6 | (100.0) | 9 | (100.0) | 15 | (100.0) |
| | Other | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

Data from Summary Tables 3 to 6

**RESULTS:**

**Efficacy results**

Twelve patients had a best overall response recorded. One (16.7%) in Part 1 and four (44.4%) in Part 2 had a best response of CR, and four (66.7%) in Part 1 and three (33.3%) in Part 2 had a best response of partial response (PR).

***Exploratory results***

All 12 patients with a response recorded had either CR or PR, and of these 9 (66.7%) had VEGF levels of $\geq$ 150 ng/mL both pre-treatment and at termination. Four of five patients (80.0%) with CR had VEGF of $\geq$ 150 ng/mL, as did five of seven patients (71.4%) with PR. Five patients who had a response (41.7%) had EGFR amplification; of these two had CR and three had PR.

**Safety results**

For Parts 1 and 2, respectively, median time on gefitinib treatment was 50.5 days (range 27 to 63 days) and 56.0 days (range 14 to 66 days) excluding interruptions or, including interruptions, 54.0 days (range 28 to 63 days) and 56.0 days (range 28 to 74 days). Three (50.0%) patients in Part 1 and five (55.6%) in Part 2 had one ZD1839 dose interruption because of toxicity.

During radiotherapy, median numbers of Gy received by patients in the respective treatment groups were 70.0 (range 56.0 to 70.0) and 68.0 (range 36.0 to 70.0). Two (33.3%) and eight (88.9%) patients had at least one interruption in treatment; this was because of toxicity for five (55.6%) Part 2 patients who each had more than four interruptions.

Median cumulative cisplatin dose for Part 2 patients was 320.0 ($mg/m^2$) (range 170.0 to 470.0) and median dose intensity was 16.2 (range 11.1 to 21.5). Seven (77.8%) patients

had at least one dose interruption because of toxicity; two (22.2%) had one interruption, four (44.4%) had two and one (11.1%) had more than four. Six (66.7%) patients had at least one dose delay – because of toxicity for five (55.6%); four (44.4%) had one delay because of toxicity and one (11.1%) had three. Four (44.4%) patients had two dose adjustments because of toxicity.
Eleven (73.3%) patients completed the trial; five (83.3%) in Part 1 and six (66.7%) in Part 2.

All 15 (100.0%) patients in the trial experienced AEs; these were considered to be trial drug-related in six (100.0%) in Part 1 and seven (77.8%) in Part 2. Four (66.7%) patients in Part 1 and five (55.6%) in Part 2 had CTC grade 3 or 4 AE(s). Two (33.3%) Part 1 patients and three (33.3%) in Part 2 had DLTs.

The most commonly reported AEs in both treatment groups were general disorders and administration site conditions (15 [100.0%] patients), gastrointestinal disorders (six [100.0%] patients in Part 1 and seven [77.8%] in Part 2), skin and subcutaneous tissue disorders (five [83.3%] patients in Part 1 and six [66.7%] in Part 2) and infections and infestations (four [66.7%] and six [66.7%] in the respective treatment groups. Respiratory, thoracic and mediastinal disorders were recorded for Part 2 only (five [55.6%] patients). Mucosal inflammation and dermatitis were the most commonly reported individual AEs in both treatment groups, respectively affecting five (83.3%) and four (66.7%) patients in Part 1 and seven (77.8%) and three (33.3%) patients in Part 2.

The profile of AEs recorded as gefitinib related only was similar for both treatments, with acne, AST increased, ALT increased and erythema each reported for at least one patient in each Part of the trial. Most commonly reported as related to both gefitinib and other trial treatment was dermatitis, recorded for four (66.7%) patients in Part 1 and two (22.2%) patients in Part 2. Mucosal inflammation, the most commonly recorded trial drug-related AE overall, was reported as both gefitinib and other trial treatments-related for five (83.3%) patients in Part 1 and as related to other trial treatments only for seven (77.8%) patients in Part 2. A wide range of other individual AEs was each recorded as other trial treatments-related only for up to four (26.7%) patients.

Death was recorded for a single Part 2 patient with pneumonia with onset approximately 6 weeks before death. This was not reported as treatment-related.
In Part 1, a single patient suffered SAEs comprising gastrointestinal disorders that were not considered to be treatment-related. In Part 2, a range of individual SAEs was each recorded for one or two patients. These were considered to be related to gefitinib treatment and other trial therapies in one instance of stomatitis; all other SAEs were recorded as either related to other trial therapy, or not treatment-related.
AEs leading to discontinuation were recorded for one Part 1 patient with alanine aminotransferase (ALT) increased, considered to be gefitinib treatment-related but not serious, and three Part 2 patients, comprising one with ALT and aspartate aminotransferase (AST) increased and one each with nausea (attributed to other trial therapy but not serious) and pneumonia (serious but not treatment-related).
Clinically important abnormalities in haematology were recorded as AEs for three patients in Part 2 - one (11.1%) with anaemia and neutropenic infection, one with anaemia alone and one with neutropenic infection alone. Both instances of neutropenic infection, one of CTC grade2 and one of grade 3, were reported as SAEs. All of the abnormalities were considered to be related to other trial therapy.

Three patients in Part 1 and two in Part 2 were recorded with AEs comprising clinical chemistry abnormalities. In Part 1, two patients had AST increased and one had ALT increased. The three CTC grade 3 abnormalities, which were not considered to be serious, were reported to be related to gefitinib treatment. One patient had CTC grade 2 blood creatinine increased and CTC grade 3 C-reactive protein increased, both reported as SAEs and related to other trial therapy. A second patient had CTC grade 3 ALT increased and grade 2 AST increased. These abnormalities were reported as gefitinib treatment-related but not serious. She also had grade 1 blood creatinine increased, not serious and related to other trial therapy.
There were no individual clinically important abnormalities in the vital signs and ECG data.

**Table S2 Number (%) of patients who had an adverse event in any category (safety/ITT population)**

| Category of adverse event | Number (%) of patients who had an adverse event in each category[a] | | | | | |
|---|---|---|---|---|---|---|
| | Part 1 Gefitinib + radiation (N=6) | | Part 2 Gefitinib + radiation + cisplatin (N=9) | | Total (N=15) | |
| Any adverse events | 6 | (100.0) | 9 | (100.0) | 15 | (100.0) |
| Gefitinib-related* adverse events | 6 | (100.0) | 7 | (77.8) | 13 | (86.7) |
| Serious adverse events | 1 | (16.7) | 7 | (77.8) | 8 | (53.3) |
| Discontinuations of trial treatment due to adverse events | 1 | (16.7) | 3 | (33.3) | 4 | (26.7) |
| NCI-CTC grade 3 or 4 adverse events | 4 | (66.7) | 5 | (55.6) | 9 | (60.0) |
| DLT | 2 | (33.3) | 3 | (33.3) | 5 | (33.3) |
| Death | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |

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.

* AEs related to gefitinib or to gefitinib and other trial treatments.

**Table S3 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over both treatment groups (safety/ITT population)**

| Preferred term | Part 1 Gefitinib + radiation (N=6) | | Part 2 Gefitinib + radiation + cisplatin (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Mucosal inflammation | 5 | (83.3) | 7 | (77.8) | 12 | (80.0) |
| Dermatitis | 4 | (66.7) | 3 | (33.3) | 7 | (46.7) |
| Diarrhoea | 4 | (66.7) | 2 | (22.2) | 6 | (40.0) |
| Stomatitis | 2 | (33.3) | 4 | (44.4) | 6 | (40.0) |

| Preferred term | Part 1 Gefitinib + radiation (N=6) | | Part 2 Gefitinib + radiation + cisplatin (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Fatigue | 3 | (50.0) | 2 | (22.2) | 5 | (33.3) |
| Nausea | 2 | (33.3) | 3 | (33.3) | 5 | (33.3) |
| Acne | 3 | (50.0) | 2 | (22.2) | 5 | (33.3) |
| Dysgeusia | 2 | (33.3) | 2 | (22.2) | 4 | (26.7) |
| Pyrexia | 3 | (50.0) | 0 | (0.0) | 3 | (20.0) |
| Dry mouth | 0 | (0.0) | 3 | (33.3) | 3 | (20.0) |
| Postoperative wound infection | 1 | (16.7) | 2 | (22.2) | 3 | (20.0) |
| Influenza | 1 | (16.7) | 2 | (22.2) | 3 | (20.0) |
| AST increased | 2 | (33.3) | 1 | (11.1) | 3 | (20.0) |
| Constipation | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Dysphagia | 2 | (33.3) | 0 | (0.0) | 2 | (13.3) |
| Haematemesis | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Vomiting | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Erythema | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Pruritus | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Neutropenic infection | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| ALT increased | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Blood creatinine increased | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Anaemia | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |

[a] This table uses a cut-off of 10%
Data from Summary Table 12.1

**Table S4 Number (%) of patients with adverse events of CTC grade 3 or 4 in any system organ class, in decreasing order of frequency within system organ class (safety/ITT population)**

| System organ class and preferred term | Part 1 Gefitinib + radiation (N=6) | | Part 2 Gefitinib + radiation + cisplatin (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Gastrointestinal disorders | 3 | (50.0) | 2 | (22.2) | 5 | (33.3) |
| Stomatitis | 1 | (16.7) | 2 | (22.2) | 3 | (20.0) |
| Dysphagia | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Gastric ulcer | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Haematemesis | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |

| System organ class and preferred term | Part 1 Gefitinib + radiation (N=6) | | Part 2 Gefitinib + radiation + cisplatin (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Melaena | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Investigations | 3 | (50.0) | 2 | (22.2) | 5 | (33.3) |
| AST increased | 2 | (33.3) | 0 | (0.0) | 2 | (13.3) |
| ALT increased | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| C-reactive protein increased | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Infections and infestations | 1 | (16.7) | 3 | (33.3) | 4 | (26.7) |
| Abdominal abscess | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Neutropenic infection | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Otitis media | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Pneumonia | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| General disorders and administration site conditions | 2 | (33.3) | 1 | (11.1) | 3 | (20.0) |
| Mucosal inflammation | 2 | (33.3) | 1 | (11.1) | 3 | (20.0) |
| Injury, poisoning and procedural complications | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Radiation dysphagia | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Metabolism and nutrition disorders | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Hyponatraemia | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Respiratory, thoracic and mediastinal disorders | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Cough | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Skin and subcutaneous tissue disorders | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Dermatitis | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |

Data from Summary Table 12.4

**Table S5** **Number (%) of patients with drug-related[a] AEs sorted by decreasing order of frequency and by relationship to gefitinib, to other trial therapy or to both (safety/ITT population)**

| System organ class and preferred term | Part 1 (N=6) | | Part 2 (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| **Gefitinib-related only** | | | | | | |
| Acne | 3 | (50.0) | 2 | (22.2) | 5 | (33.3) |
| AST increased | 2 | (33.3) | 1 | (11.1) | 3 | (20.0) |

| System organ class and preferred term | Part 1 (N=6) | | Part 2 (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| ALT increased | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Erythema | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Diarrhoea | 2 | (33.3) | 0 | (0.0) | 2 | (13.3) |
| Pruritus | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Skin disorder | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| **Related to gefitinib and other trial treatments** | | | | | | |
| Dermatitis | 4 | (66.7) | 2 | (22.2) | 6 | (40.0) |
| Mucosal inflammation | 5 | (83.3) | 0 | (0.0) | 5 | (33.3) |
| Diarrhoea | 2 | (33.3) | 1 | (11.1) | 3 | (20.0) |
| Stomatitis | 1 | (16.7) | 2 | (22.2) | 3 | (20.0) |
| Nausea | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Dysgeusia | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Fatigue | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Alopecia | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Dizziness | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Epistaxis | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| **Other trial treatments-related only** | | | | | | |
| Mucosal inflammation | 0 | (0.0) | 7 | (77.8) | 7 | (46.7) |
| Fatigue | 2 | (33.3) | 2 | (22.2) | 4 | (26.7) |
| Stomatitis | 1 | (16.7) | 2 | (22.2) | 3 | (20.0) |
| Nausea | 1 | (16.7) | 2 | (22.2) | 3 | (20.0) |
| Dry mouth | 0 | (0.0) | 3 | (33.3) | 3 | (20.0) |
| Dysgeusia | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Vomiting | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Neutropenic infection | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Postoperative wound infection | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Blood creatinine increased | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Anaemia | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Dermatitis | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Oedema peripheral | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Soft tissue inflammation | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Constipation | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Dyspepsia | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |

| System organ class and preferred term | Part 1 (N=6) | | Part 2 (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Haematemesis | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Mastoiditis | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Otitis media | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Cough | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Diarrhoea | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Dyspnoea | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Laryngeal oedema | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Pharyngolaryngeal pain | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Headache | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Neuropathy | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Radiation dysphagia | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Radiation skin injury | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| C-reactive protein increased | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Anorexia | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |

[a] Assigned by the investigator as at least possibly related to trial treatment
Data from Summary Table 12.3 and Additional Tables 1 and 3

**Table S6 Number (%) of patients with SAEs in any system organ class, in decreasing order of frequency within system organ class (safety/ITT population)**

| System organ class and preferred term | Part 1 Gefitinib + radiation (N=6) | | Part 2 Gefitinib + radiation + cisplatin (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Gastrointestinal disorders | 1 | (16.7) | 3 | (33.3) | 4 | (26.7) |
| Haematemesis | 1 | (16.7) | 1 | (11.1) | 2 | (13.3) |
| Stomatitis | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Gastric ulcer | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Melaena | 1 | (16.7) | 0 | (0.0) | 1 | (6.7) |
| Infections and infestations | 0 | (0.0) | 4 | (44.4) | 4 | (26.7) |
| Neutropenic infection | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Abdominal abscess | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Pneumonia | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Respiratory, thoracic and mediastinal disorders | 0 | (0.0) | 2 | (22.2) | 2 | (13.3) |
| Dyspnoea | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |

| System organ class and preferred term | Part 1 Gefitinib + radiation (N=6) | | Part 2 Gefitinib + radiation + cisplatin (N=9) | | Total (N=15) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Pharyngolaryngeal pain | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Blood and lymphatic system disorders | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Anaemia | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| General disorders and administration site conditions | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Mucosal inflammation | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Investigations | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Blood creatinine increased | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| C-reactive protein increased | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Metabolism and nutrition disorders | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |
| Hyponatraemia | 0 | (0.0) | 1 | (11.1) | 1 | (6.7) |

Data from Summary Table 12.2