AstraZeneca

Clinical Study Report Synopsis

Drug Substance	IRESSA (gefitinib, ZD1839)
Study Code	D7919C00706; 1839IL/0706
Edition Number	1
Date	9 June 2009

Phase II Randomised, Double Blind, Placebo Controlled, Multicentre Comparative Study of ZD1839 250 mg or 500 mg (Iressa™) Given Either Continuously or Concomitantly with Cisplatin plus Radiotherapy for the Treatment of Patients with Previously Untreated Unresected Late Stage III/IV Non-metastatic Head and Neck Squamous Cell Carcinoma

Study dates: First patient enrolled: 13 November 2004
Last patient completed: 27 June 2008

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

A total of 26 centres from 8 countries participated in the study: Belgium (2 centres), Czech republic (2 centres), Germany (5 centres), India (6 centres), Poland (5 centres), Serbia (3 centres), Taiwan (1 centre), and United States (2 centres).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To assess the additive effect of gefitinib 250 mg and gefitinib 500 mg (given either concomitantly or as maintenance) over cisplatin plus RT in terms of local disease control (progression-free[a]) rate at 2 years.	Local disease control rate (LDCR) at 2 years [Statistical questions P1 and P2][e]
Secondary[b]	**Secondary**
To compare gefitinib 250 mg and gefitinib 500 mg or placebo used continuously[c] (concomitantly and for maintenance) with cisplatin plus RT in terms of local disease control (progression-free[a]) rate at 2 years.	LDCR at 2 years [Statistical questions S1 to S6][e]
To compare gefitinib 250 mg and gefitinib 500 mg or placebo used either concomitantly alone[d] or continuously[c] with cisplatin plus RT in terms of local disease control (progression-free[a]) rate at 1 year.	LDCR at 1 year [Statistical questions P1, P2 and S1 to S6][e]
To compare gefitinib 250 mg and gefitinib 500 mg or placebo used either concomitantly alone[d] or continuously[c] with cisplatin plus RT in terms of CR.	CR by study closure as per RECIST[f] [Statistical questions P1, P2 and S1 to S6][e]
To compare gefitinib 250 mg and gefitinib 500 mg or placebo used either concomitantly alone[d] or continuously[c] with cisplatin plus RT in terms of PFS.	PFS as per RECIST[f] [Statistical questions P1, P2 and S1 to S6][e]
To compare gefitinib 250 mg and gefitinib 500 mg or placebo used either concomitantly alone[d] or continuously[c] with cisplatin plus RT in terms of safety and tolerability.	Nature, incidence and severity of AEs and SAEs; incidence of, and reasons for, study drug dose modifications, delays, interruptions and study drug discontinuations; study drug exposure; laboratory assessments; physical examinations; vital signs; and body weight
To compare gefitinib 250 mg and gefitinib 500 mg or placebo used either concomitantly alone[d] or continuously[c] with cisplatin plus RT in terms of OS.	OS [Statistical questions P1, P2 and S1 to S6][e]

Footnotes for Table S1:

[a] The definition for LDCR originally specified that the patient should be progression-free; progressions were defined objectively via RECIST and any new lesion occurring anywhere in the body was a sign of objective progression. However, the definition of LDCR was clarified such that new lesions occurring outside of the original irradiated area were not to be considered as a reason for failure of local disease control. Therefore, patients with local disease control were not necessarily progression-free and this text will be excluded from references to local disease control throughout the synopsis and the main study report.

[b] Assessment of tumour response was not a protocolled objective (to compare gefitinib 250 mg and gefitinib 500 mg or placebo used either concomitantly alone or continuously with cisplatin plus RT in terms of tumour response [CR+PR]); however, this assessment was pre-defined in the SAP as a secondary efficacy outcome variable (tumour response [CR+PR] by study closure as per RECIST).

[c] Clarification of study terminology, including reference to treatment given continuously, is included below.

[d] "Concomitantly alone" refers to the first 8 weeks of the study, prior to any treatment in the maintenance phase, when patients received randomised therapy concomitantly with cisplatin and radiotherapy.

[e] The primary and secondary efficacy outcome variables were analysed using a set of statistical questions (2 principal [P1 and P2] and 6 subsidiary [S1 to S6]), which are detailed later in this synopsis.

[f] Calculated using the actual target lesion dimension sizes, the investigator opinion of non-target lesion progression and evidence of occurrence of new lesions.

Note: There was an exploratory objectives in the study (biomarker analyses), which is not reported in the main study report.
AEs: Adverse events; CR: Complete response; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumours; RT: Radiotherapy; SAEs: Serious adverse events; SAP: Statistical analysis plan.

Clarification of study terminology

The aim of this study was to compare the different options of gefitinib treatment on chemoradiotherapy enhancement, given as concomitant therapy (with chemoradiotherapy) or as continuous therapy (continuation of randomised treatment into the maintenance phase). The purpose of this comparison was to assess both whether the use of gefitinib concomitantly is effective and whether the continued use of gefitinib is effective (in addition to concomitant use). To do this, the statistical analysis accounted for the effects of concomitant treatment and maintenance treatment independently of one another. To address the study objectives, the study needed to establish and evaluate 2 effects: the effect of gefitinib versus placebo as concomitant treatment; and the effect of gefitinib versus placebo as maintenance treatment. Consideration of the maintenance effect together with the concomitant effect allows us to assess whether the continuous use of gefitinib is a viable option.

Study design

This was a Phase II, randomised, double-blind, placebo-controlled, parallel group, factorial design, multicentre study. The study evaluated the efficacy and safety of gefitinib or placebo, given either concomitantly, with cisplatin and radiotherapy, or as maintenance in patients with histologically proven, previously untreated Stage III or IV unresected, locally advanced squamous cell carcinoma of the head and neck (SCCHN). Patients were randomised to 1 of 7 treatment arms (2:1:1:1:1:1:1), as described below:

- Treatment Arm A, concomitant treatment with placebo plus cisplatin plus radiotherapy followed by placebo as maintenance treatment;

- Treatment Arm B, concomitant treatment with gefitinib 250 mg plus cisplatin plus radiotherapy followed by placebo as maintenance treatment;
- Treatment Arm C, concomitant treatment with gefitinib 500 mg plus cisplatin plus radiotherapy followed by placebo as maintenance treatment;
- Treatment Arm D, concomitant treatment with gefitinib 250 mg plus cisplatin plus radiotherapy followed by gefitinib 250 mg as maintenance treatment;
- Treatment Arm E, concomitant treatment with gefitinib 500 mg plus cisplatin plus radiotherapy followed by gefitinib 500 mg as maintenance treatment;
- Treatment Arm F, concomitant treatment with placebo plus cisplatin plus radiotherapy followed by gefitinib 250 mg as maintenance treatment;
- Treatment Arm G, concomitant treatment with placebo plus cisplatin plus radiotherapy followed by gefitinib 500 mg as maintenance treatment.

Target patient population and sample size

Female or male patients, aged 18 years and over, with histologically confirmed Stage III or IVa SCCHN that was measurable according to Response Evaluation Criteria in Solid Tumours (RECIST). Patients were not to have received previous surgery to the tumour being studied, chemotherapy or radiotherapy for any tumour, or any previous anti-epidermal growth factor receptor therapy. In addition, patients were to have a life expectancy of ≥12 weeks and a World Health Organisation performance status of 0 or 1.

The primary objective of this study was to compare the treatment arms with respect to local control rate at 2 years. The comparisons of local control rate were made within a logistic model. A contrast within a logistic model comparing at least 55 patients with at least 55 patients will have at least 80% power for a 1-sided 20% significance test to detect the difference between a local control rate of 60% on 1 side of the contrast and a local control rate of 75% on the other side of the contrast. The power of the logistic comparison was approximated by calculating the power of the asymptotically equivalent Pearson's test. No adjustments have been made for multiplicity in this hypothesis-generating study.

The principal questions of interest in this study were: does gefitinib given as maintenance therapy improve 2 year local disease control rate (LDCR); and does gefitinib given as concomitant therapy improve 2 year LDCR. The logistic contrasts corresponding to these 2 principal questions both involved more than 55 patients on each side of the contrast.

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

The gefitinib dose levels for this study were 250 mg and 500 mg with matching gefitinib placebo tablets. All patients received 2 tablets daily: 2 placebo tablets, 1 placebo and 1 gefitinib 250 mg tablet or 2 gefitinib 250 mg tablets, depending on the treatment group to

which they were randomised. Gefitinib and/or matching placebo treatment was taken orally once a day, every day at about the same time, with or without food. If the patient forgot to take a dose, they were to take the last missed dose as soon as they remembered, as long as it was at least 12 hours before the next dose was due. For patients who were unable to swallow the gefitinib or matching placebo tablets, it was possible to disperse the tablet in approximately 50 mL drinking water at room temperature immediately prior to administration. The gefitinib formulation was F012653 and batch numbers were 12328G03, 13005J03, 22121I04, 94367J02, 33116F05, 21063J04, 21510C04, 93809J02 and 10257F03. The matching placebo formulation number was F012647 and the batch numbers were 40935H06, 22626B04, 31281B05, 12520J03, 22034A04, 92984F02, 92994B02 and 91542K02

Cisplatin was administered as a 100 mg/m^2 intravenous infusion on Day 1 of each 3-week cycle; there were 3 cycles over a period of 63 days during the study. Batch numbers are not provided for cisplatin as this is a non-investigational product and was provided from commercial stock. Radiotherapy was administered as 2 Gray (Gy)/day, 5 days/week over a period of 7 weeks (70 Gy in 35 fractions). Equal Estro, who provide independent quality assurance for therapeutic radiology and oncology, performed a prospective quality control of the equipment used and the data obtained for the first patient at each recruiting site and a retrospective quality control analysis for 10% of the remaining patients, randomly selected.

Duration of treatment

Patients received gefitinib and/or placebo tablets daily as concomitant therapy from the day of randomisation (Day 1), including the whole of the week(s) after randomisation until the initiation of cisplatin and radiotherapy (up to 2 weeks after Day 1), until the end of radiotherapy (a total of 8 to 9 weeks). After this, new sets of gefitinib and/or placebo tablets were dispensed as maintenance therapy. Dosing continued until a maximum of 2 years after patient randomisation or until progression, unacceptable toxicity, withdrawal of consent, investigator's decision, study closure or death, if earlier.

Statistical methods

The intention-to-treat (ITT) population comprised all randomised patients, categorised by randomised treatment (gefitinib or matching placebo), and was the analysis population used for all efficacy outcome variables. The safety population comprised all patients who received at least 1 dose of study medication (randomised treatment, cisplatin or radiotherapy), categorised by the treatment actually received.

The statistical questions of interest in this study, with regard to the primary efficacy variable, were:

Principal statistical questions

P1 Does gefitinib, given as maintenance therapy, improve the 2-year LDCR?

P2 Does gefitinib, given as concomitant therapy, improve the 2-year LDCR?

Subsidiary statistical questions

S1 Does maintenance gefitinib 250 mg/day improve 2-year LDCR over matching placebo?

S2 Does maintenance gefitinib 500 mg/day improve 2-year LDCR over matching placebo?

S3 Does concomitant gefitinib 250 mg/day improve 2-year LDCR over matching placebo?

S4 Does concomitant gefitinib 500 mg/day improve 2-year LDCR over matching placebo?

S5 Does maintenance gefitinib 500 mg/day improve 2-year LDCR over maintenance gefitinib 250 mg/day?

S6 Does concomitant gefitinib 500 mg/day improve 2-year LDCR over concomitant gefitinib 250 mg/day?

The same set of questions was also answered for the secondary efficacy variables of LDCR at 1 year, complete response (CR) rate, tumour response rate, progression-free survival (PFS) and overall survival (OS). A logistic modelling strategy was used to analyse LDCR at 2 years, 1 year, CR rate and tumour response rate. A Cox proportional hazards modelling strategy was used to analyse PFS and OS.

The logistic regression model used the ITT population, allowed for the effect of treatment group (Treatment Arms A to G) and included gender, site of primary tumour (hypopharynx or other), and stage of disease (Stage III or IV) as covariates. The odds ratio for each specific treatment contrast was estimated from the model along with its associated 95% confidence interval (CI) and 2-sided p-value. The LDCR, CR rate and tumour response rate were calculated for each treatment arm. In addition, the 1-sided 80% lower confidence limit and 1 sided p-value for the odds ratio at 1 and 2 years were calculated, to reflect the 20% 1-sided significance level used in the sample size calculations.

The Cox proportional hazards model used the ITT population, allowed for the effect of treatment group (Treatment Arms A to G) and included gender, site of primary tumour (hypopharynx or other), and stage of disease (Stage III or IV) as covariates. The hazard ratio for each specific treatment contrast was estimated together with its associated 95% CI and 2-sided p-value. In addition, the 1 sided 80% upper confidence limit and 1-sided p-value for the hazard ratio was calculated. Both PFS and OS were displayed graphically using a Kaplan-Meier plot. The Kaplan-Meier plot was cut-off at 2 years, as patients were not intended to be followed for more than 2 years. Median PFS and the proportion of patients progression-free at 6, 12 and 18 months, and at 2 years were displayed by treatment group and derived from the Kaplan Meier curve; OS was displayed in the same way.

Additional analyses were performed for each level of each covariate of the logistic model for LDCR at 1 and 2 years, CR rate, and tumour response rate; and for the proportional hazards model for PFS and OS. These analyses were only to be performed where sufficient data were available (eg, at least 20 events for PFS and OS); they were performed and presented using the same approach as in the main ITT analyses, except that no p-values were to be presented.

No formal statistical analysis of the safety data was planned.

Patient population

Approximately 224 patients were planned. Overall, 226 patients were randomised from 26 centres in 8 countries to 1 of 7 treatment arms. In total, 108 patients (47.8%) completed the study (2 years post-randomisation) and 83 patients (36.7%) completed the study on randomised treatment. Patient disposition is summarised in Table S2.

Table S2 Patient disposition

	Number (%) of patients							
	Treatment Arm							Total
	A (N=60)	B (N=24)	C (N=31)	D (N=31)	E (N=24)	F (N=34)	G (N=22)	(N=226)
Randomised	60 (100)	24 (100)	31 (100)	31 (100)	24 (100)	34 (100)	22 (100)	226 (100)
Treated (any treatment)	60 (100)	24 (100)	31 (100)	31 (100)	24 (100)	34 (100)	22 (100)	226 (100)
Treated (gefitinib/placebo)	60 (100)	24 (100)	31 (100)	31 (100)	24 (100)	34 (100)	22 (100)	226 (100)
Completed the study	31 (51.7)	11 (45.8)	18 (58.1)	10 (32.3)	10 (41.7)	16 (47.1)	12 (54.5)	108 (47.8)
Completed the study on randomised treatment	25 (41.7)	5 (20.8)	16 (51.6)	9 (29.0)	7 (29.2)	12 (35.3)	9 (40.9)	83 (36.7)
Discontinued from randomised treatment	35 (58.3)	19 (79.2)	15 (48.4)	22 (71.0)	17 (70.8)	22 (64.7)	13 (59.1)	143 (63.3)
Reason for treatment discontinuation[a]								
Adverse event[b]	11 (18.3)	4 (16.7)	6 (19.4)	6 (19.4)	7 (29.2)	6 (17.6)	4 (18.2)	44 (19.5)
Objective disease progression	5 (8.3)	5 (20.8)	3 (9.7)	6 (19.4)	2 (8.3)	9 (26.5)	5 (22.7)	35 (15.5)
Lost to follow-up	0	1 (4.2)	2 (6.5)	2 (6.5)	1 (4.2)	0	1 (4.5)	7 (3.1)
Informed consent withdrawn	4 (6.7)	2 (8.3)	0	3 (9.7)	1 (4.2)	1 (2.9)	0	11 (4.9)
Severe non-compliance	3 (5.0)	2 (8.3)	0	0	2 (8.3)	0	0	7 (3.1)
Clinical progression	4 (6.7)	1 (4.2)	2 (6.5)	2 (6.5)	1 (4.2)	1 (2.9)	2 (9.1)	13 (5.8)
Other	8 (13.3)	4 (16.7)	2 (6.5)	3 (9.7)	3 (12.5)	5 (14.7)	1 (4.5)	26 (11.5)

Table S2 Patient disposition

	Number (%) of patients							
	Treatment Arm							Total
	A (N=60)	B (N=24)	C (N=31)	D (N=31)	E (N=24)	F (N=34)	G (N=22)	(N=226)
Terminated from study	29 (48.3)	13 (54.2)	13 (41.9)	21 (67.7)	14 (58.3)	18 (52.9)	10 (45.5)	118 (52.2)
Reason for study termination								
Lost to follow-up	3 (5.0)	3 (12.5)	4 (12.9)	2 (6.5)	1 (4.2)	0	1 (4.5)	14 (6.2)
Informed consent withdrawn	4 (6.7)	2 (8.3)	2 (6.5)	3 (9.7)	2 (8.3)	1 (2.9)	1 (4.5)	15 (6.6)
Death	22 (36.7)	8 (33.3)	7 (22.6)	15 (48.4)	11 (45.8)	17 (50.0)	8 (36.4)	88 (38.9)
Eligibility criteria not fulfilled	0	0	0	1 (3.2)	0	0	0	1 (0.4)

[a] Discontinuation from gefitinib and/or matching placebo treatment.
[b] For 1 patient (Patient E0104011), who was randomised to Treatment Arm G, the reason for randomised treatment discontinuation was recorded as an adverse event; however, none of the adverse events reported for this patient were listed as leading to permanent discontinuation of randomised treatment. Three adverse events originally listed as leading to permanent discontinuation (excoriation of skin, crusting in nose and conjunctivitis left eye) were amended to temporary discontinuation of randomised treatment following investigation.

The 7 randomised treatment arms were generally well balanced for all important prognostic factors. The patients recruited were typical of a population of untreated patients with unresected locally advanced SCCHN. However, the small number of patients in each treatment group should be considered when making any conclusions, as small differences between treatment groups have a larger impact when the patient population is of a smaller size.

Summary of efficacy results

In this exploratory study, it is important to evaluate the efficacy analysis results in terms of the consistency of the treatment effect (measured by the statistical questions) across each of the 6 outcome variables, since the statistical questions and the outcome variables are inter-related and no account has been taken in the analysis for multiple-testing.

The primary outcome variable was LDCR at 2 years. Gefitinib (250 and 500 mg combined), given as concomitant or maintenance therapy, did not result in evidence of improvement in LDCR at 2 years, compared with placebo (1-sided p-value >0.20) (Table S3, statistical questions P1 and P2).

The results from the analysis of the subsidiary statistical questions (Table S3; statistical questions S1 to S6) for LDCR at 2 years suggest that neither gefitinib 250 mg nor gefitinib 500 mg, given either concomitantly or as maintenance, improved 2-year LDCR compared with placebo (statistical questions S1 to S4). Gefitinib 500 mg may be more effective than gefitinib 250 mg, given either concomitantly or as maintenance, in terms of LDCR at 2 years (statistical questions S5 and S6) (p value <0.20).

Table S3 Comparison of gefitinib 250 mg and 500 mg and placebo in terms of local disease control rate at 2 years (ITT population)

Comparison Treatment arms[a]	N	Patients, n (%)[b]	Odds ratio[c,d]	95% CI (p-value)[c] [2-sided]	80% LCL (p-value)[c] [1-sided]
Gefitinib versus placebo as maintenance therapy (Statistical Question P1)					
D+E+F+G (gefitinib)	111	32 (28.8)	0.684	0.377, 1.241 (0.212)	0.530 (0.894)
A+B+C (placebo)	115	43 (37.4)			
Gefitinib versus placebo as concomitant therapy (Statistical Question P2)					
B+C+D+E (gefitinib)	110	36 (32.7)	0.921	0.508, 1.670 (0.787)	0.713 (0.607)
A+F+G (placebo)	116	39 (33.6)			
Gefitinib 250 mg versus placebo as maintenance therapy (Statistical Question S1)					
D+F (gefitinib 250 mg)	65	16 (24.6)	0.685	0.316, 1.486 (0.339)	0.492 (0.831)
A+B (placebo)	84	28 (33.3)			
Gefitinib 500 mg versus placebo as maintenance therapy (Statistical Question S2)					
E+G (gefitinib 500 mg)	46	16 (34.8)	0.708	0.328, 1.525 (0.378)	0.509 (0.811)
A+C (placebo)	91	36 (39.6)			
Gefitinib 250 mg versus placebo as concomitant therapy (Statistical Question S3)					
B+D (gefitinib 250 mg)	55	14 (25.5)	0.777	0.357, 1.688 (0.523)	0.556 (0.738)
A+F (placebo)	94	30 (31.9)			
Gefitinib 500 mg versus placebo as concomitant therapy (Statistical Question S4)					
C+E (gefitinib 500 mg)	55	22 (40.0)	1.040	0.485, 2.227 (0.920)	0.750 (0.460)
A+G (placebo)	82	30 (36.6)			
Gefitinib 500 mg versus 250 mg as maintenance therapy (Statistical Question S5)					
E+G (gefitinib 500 mg)	46	16 (34.8)	1.557	0.665, 3.646 (0.307)	1.081 (0.154)
D+F (gefitinib 250 mg)	65	16 (24.6)			
Gefitinib 500 mg versus 250 mg as concomitant therapy (Statistical Question S6)					
C+E (gefitinib 500 mg)	55	22 (40.0)	1.773	0.764, 4.116 (0.182)	1.235 (0.091)
B+D (gefitinib 250 mg)	55	14 (25.5)			

[a] The treatment arms are described in the study design section.
[b] "n" refers to the number of patients with local disease control at 2 years.
[c] The odds ratio, CIs and p-values were based on a logistic regression model including gender, randomised treatment, site of primary tumour and stage of disease as covariates.
[d] The odds ratio refers to the first set of treatment groups (first row) versus the second set of treatment groups (second row); an odds ratio of >1 indicates that the first set of treatment groups is more effective.
e This is the probability for the test of superiority of the first set of treatment groups versus the second set of treatment groups; this is equal to the 1-sided p-value (for superiority or inferiority) when the treatment effect favours the first treatment group (odds ratio >1) and to 1 minus the 1-sided p-value (for superiority or inferiority) when the treatment effect favours the second treatment group (odds ratio <1).

CI: Confidence interval; ITT: Intention-to-treat; LCL: Lower confidence limit.

The analysis results suggest that there was no evidence of benefit for gefitinib 250 mg or 500 mg over placebo, or for gefitinib 500 mg over gefitinib 250 mg in terms of LDCR at 1 year, CR, PFS or OS (1-sided p-value >0.20).

Other than for gefitinib 250 mg versus placebo given as maintenance therapy (statistical question S1) (1-sided p-value <0.20), the analysis results did not suggest evidence of benefit for gefitinib 250 mg or 500 mg over placebo, or for 500 mg over 250 mg, for the outcome variable of tumour response (1-sided p-value >0.20).

The results of post-hoc analyses, which assessed the effect of concomitant treatment only on patients who received no further (maintenance) gefitinib treatment and maintenance treatment only in the patients who had not received concomitant gefitinib treatment, were broadly consistent with the main analyses and there was a suggestion of the possible benefit for gefitinib 500 mg versus placebo as concomitant treatment (ie, in patients who received no gefitinib after the concomitant study period).

Summary of safety results

In contrast to the efficacy data, safety data were presented by treatment received over the complete study period (ie, placebo throughout the study, gefitinib as concomitant therapy only, gefitinib as maintenance therapy only, gefitinib as concomitant and maintenance therapy, gefitinib 250 mg as concomitant and maintenance therapy, and gefitinib 500 mg as concomitant and maintenance therapy) and by treatment received in for the concomitant and maintenance phases of the study (ie, placebo, gefitinib 250 mg, gefitinib 500 mg and gefitinib 250 mg or 500 mg).

Over the complete study period, 218 patients (96.5%) received at least 1 dose of gefitinib in the tablet form and 52 patients (23.0%) received at least 1 dose of gefitinib dispersed in drinking water. The mean exposure to randomised treatment ranged from 327.5 to 427.7 days.

All treatments were generally well-tolerated with the majority of AEs being Grade 1 or 2 in both the concomitant period and the maintenance period. In addition, the gefitinib adverse event (AE) profile was consistent with its prescribing information and previous clinical study data in SCCHN cancer. Moreover, adding gefitinib as concomitant therapy did not appreciably worsen the safety and tolerability of chemoradiotherapy; the overall incidence of common SCCHN radiotherapy related toxicities were largely similar between gefitinib and placebo.

The incidence of tumour haemorrhages was very low and similar between gefitinib and placebo. There were no interstitial lung disease-type events reported in the study. Diarrhoea and rash were more commonly reported with gefitinib treatment than with placebo treatment in both the concomitant and maintenance periods of the study, with the higher percentage of events the gefitinib 500 mg arm for both periods.

AEs with an outcome of death were reported at a similar incidence between treatment groups (in the concomitant period, 2.6% in the placebo arm and 1.8% to 3.6% in the gefitinib 250 mg and 500 mg treatment arms, and in the maintenance period 11.7% in the placebo arm and 15.8% to 17.1% in the gefitinib 250 mg and 500 mg treatment arms).

No clinically important changes or imbalances were observed in any of the clinical laboratory safety parameters (haematology, clinical chemistry or urinalysis), vital signs, electrocardiograms or physical findings following dosing with gefitinib 250 mg or 500 mg, given either concomitantly, with cisplatin and radiotherapy, or continuously.

In addition, no new safety concerns associated with the addition of gefitinib to chemoradiotherapy were identified as a result of this study.