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Drug product:	ZD1839	**SYNOPSIS**	
Drug substance(s):	Gefitinib		
Document No.:			
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A PHASE II TRIAL TO EVALUATE ZD1839 (IRESSA™) IN COMBINATION WITH CISPLATIN AND RADIOTHERAPY IN SUBJECTS WITH ADVANCED HEAD AND NECK CARCINOMA (UNRESECTABLE AND INOPERABLE)

Publications

ASCO Annual Meeting (Chicago, Illinois, 1-5 June 2007)

Gefitinib plus concomitant boost accelerated radiation (AFX-CB) and concurrent weekly cisplatin for locally advanced unresectable Squamous Cell Head and Neck Carcinomas (SCCHN): A Phase II Study..

A. Rueda, J.A. Medina, R. Mesía, R. Galiana, M. E. Vega, A. Collado, M. Cobo, J. Contreras, M. Marguelí, E. Alba;
Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 6031

XI Congress Spanish Society of Medical Oncology (SEOM) (Madrid, 3-5 October 2007.
Estudio fase II de gefitinib asociado a radioquimioterapia concomitante en carcinoma escamoso avanzado e irresecable de cabeza y cuello (1839IL/0102).
A. Rueda, J. A. Medina, R. Mesía, R. Galiana, M. E. Vega, A. Collado, M. Cobo, J. Contreras, M. Marguelí, E. Alba;
Clinical & Translational Oncology 7; 9 (Extrord. 2): 67; Abs. P-62

Study dates		**Phase of development**
First subject registered	5 December 2002	Therapeutic exploratory (II)
Last subject completed (i.e., final follow-up)	22 December 2006	

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Objectives

Primary

The primary objective of the trial was to evaluate the disease-free survival rate at 2 years of subjects with advanced head and neck carcinoma treated with ZD1839 250 mg administered once daily in combination with cisplatin and a standard course of radiotherapy.

Secondary

The secondary efficacy objectives of the trial were:

1. To estimate the overall response rate (complete response [CR] and partial response [PR]) at 6 months after the start of treatment
2. To estimate the complete response rate
3. To estimate progression-free survival (PFS) (hereafter referred to as time to progression – TTP)
4. To estimate overall survival

The secondary safety objectives of the trial were:

1. To evaluate the toxicity and the feasibility of treatment with ZD1839 250 mg administered once daily in combination with cisplatin and a standard course of radiotherapy
2. To further characterise the safety profile of ZD1839 at a 250 mg daily dose

The exploratory objective of the trial was to evaluate EGFR and STAT 3 protein in paraffin tissue by immunohistochemistry.

Study design

This was a multi-centre, open-label, non-comparative phase II trial.

An initial cohort of five subjects (**Part A**) enrolled into the trial received ZD1839 and radiotherapy only. The safety and tolerability of the combination was monitored in this cohort before any further subjects were enrolled. If less than 2 subjects experienced dose limiting toxicity (DLT, defined as grade 4 neutropenia lasting more than 5-7 days, febrile neutropenia; grade 4 thrombocytopenia; grade 4 non-haematological toxicity [except untreated alopecia or vomiting without treatment]) during the 6-week radiotherapy treatment period, recruitment to Part B could be started. If two or more subjects experienced DLT the study was to be terminated.
The DLT toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) except mucositis which was evaluated using the Radiation Therapy Oncology Group (RTOG) criteria.
Part B: If the toxicity of ZD1839 and radiotherapy (part A) was acceptable, a total of 42 subjects was to be enrolled to receive ZD1839, radiotherapy and chemotherapy (cisplatin). The toxicity of the combination was to be closely monitored during treatment and recruitment of subjects to ensure that the combination was tolerable.

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Target subject population and sample size

The target population was male or female subjects aged 18 years or older with histologically-confirmed stage III or IV, measurable, extra-laryngeal or inoperable laryngeal head and neck carcinoma.
Five subjects were to be enrolled into Part A, and 42 into Part B.

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

The investigational product was ZD1839 (Iressa^{TM}) in tablets of 250 mg. One 250 mg tablet was to be taken once daily.

Radiotherapy was applied as a total dose of 72 Grays (Gy) delivered over 6 weeks. Daily fractions of 1.8 Gy were delivered to the tumour and cervical and supraclavicular nodules 5 days a week for 6 weeks. In addition, a boost of daily fractions of 1.5 Gy was delivered to the tumour with the last 12 daily fractions of radiotherapy.
The chemotherapy element of the treatment combination was cisplatin 40 mg/m^2 administered as an intravenous (iv) infusion once a week for 4 weeks.

Duration of treatment

ZD1839 commenced 24 hours before the start of radiotherapy/chemoradiation, and continued during radiotherapy/chemoradiation and for 3 months after completion of radiotherapy/chemoradiation. Radiotherapy was delivered for 6 weeks. Cisplatin was administered for 4 weeks.
The dosing schedule for Week 1 to Week 6 is shown below:

Week 1	Week2	Week3	Week 4	Week 5	Week 6
← ZD1839 250 mg once daily, continuous →					
C	C	C	C		
RRRRR	RRRRR	RRRRR	RRRRR	RRRRR	RRRRR
			BB	BBBBB	BBBBB

C = cisplatin 40 mg/m^2 iv infusion
R = radiotherapy 1.8 Gy daily fractions to tumour and cervical and supraclavicular nodules
B = boost radiotherapy 1.5 Gy daily fractions to tumour

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Disease-free survival at 2 years
- Secondary variables:
  - Objective tumour response (CR and PR) at 6 months after the start of treatment based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria

- Incidence of complete response at 6 months
- TTP
- Overall survival

Safety

- 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

Exploratory

To evaluate EGFR protein in paraffin tissue by immunohistochemistry.

Statistical methods

Fleming's method was used to calculate the number of subjects required. A sample size of 42 subjects in Part B of the study was calculated as sufficient to give an 80% probability of rejecting a baseline 2-year disease-free survival rate of 40% with an exact 5% one-sided significance test when the true rate was at the clinically relevant level of 60%. The hypothesis that the 2-year disease-free survival rate is equal to or less than the baseline would be rejected if 23 or more of the 42 subjects were alive and disease-free at 2 years.
The baseline response rate used for the null hypothesis was set at 40%. Rejecting the null hypothesis would indicate that the activity of the combination was at least similar to that observed with concurrent chemotherapy and radiation in this setting, and also that the activity of the combination of chemoradiotherapy was not compromised with the addition of ZD1839, which is associated with a 2-year disease-free survival rate of 41-42% (Suntharalingam 2001).
All subjects that were enrolled and received trial treatment were considered to be the intention-to-treat (ITT) population. The analysis population for all efficacy endpoints was the ITT population in Part B.
The standard summary statistics for continuous variables were: mean, standard deviation, median, quartiles, maximum and minimum. The standard summary statistics for discrete variables were: count and proportion. Response rates were summarised by proportions together with a 95% confidence interval (CI) (the objective response rate also had a 90% CI calculated). Duration of overall survival was summarised by Kaplan-Meier methods. Tolerability was summarised by the appropriate standard summary statistics.

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Subject population

Table S1 Subject population and disposition

		Part A and Part B	
Population			
Part A: N eligible (planned)		5	(5)
Part B: N eligible (planned)		41	(42)
Demographic characteristics (Parts A & B)			
Sex (n and % of subjects)	Male	41	(89.1)
	Female	5	(10.9)
Age (years)	Mean (sd)	56.5	(8.75)
	Range	39 to 75	
Race (n and % of subjects)	Caucasian	46	(100.0)
Baseline characteristics n, (%)			
ECOG performance status			
Fully active (0)		26	(56.5)
Restricted in physically strenuous activity (1)		20	(43.5)
Disposition			
Part A		N = 5	
N (%) of subjects who	Completed	4	(80.0)
	Discontinued	1	(20.0)
Part B		N = 41	
N (%) of subjects who	Completed monotherapy stage	30	(73.9)
	Discontinued	11	(26.8)
N analysed for safety (ITT)		46	
N analysed for efficacy (Part B subgroup of ITT)		41	

Efficacy results

Fourteen subjects (34.1%) were alive and disease-free (i.e., had CR at an assessment at least 700 days after the first dose) at two years from the start of treatment (90% CI 22.0 – 48.1%). Thus the null hypothesis was not rejected and it cannot be claimed that the

activity of the combination is at least similar to that observed with concurrent chemotherapy and radiation in this setting, nor that the activity of the combination of chemoradiotherapy is not compromised with the addition of ZD1839.
Twenty subjects were responders (CR or PR) at 6 months after the start of treatment and the objective response rate was therefore 48.8% (95% CI 32.9 – 64.9%).
Median TTP was estimated by Kaplan-Meier analysis to be 426 days. 95% CI could not be calculated. The proportion of subjects alive and progression-free at 12 months was 50.7% (95% CI 35.3 – 66.2%) and at 24 months was 48.2% (95% CI 32.8 – 63.6%). As the last progression was recorded at 426 days, the estimate of the proportion alive and progression-free at 24 months may be unreliable.
Median survival time could not be calculated as too few subjects died. The proportion of subjects alive at 12 months was 68.3% (95% CI 54.0 – 82.5%), and at 24 months was 53.1% (95% CI 37.7 – 68.5%). There were 20 (48.8%) survivors (95% CI 32.9 – 64.9%) at trial closure; the status of one subject was unknown.

Safety results
The daily administration of ZD1839 at 250 mg combined with routine radiotherapy for 6 weeks did not result in any DLT.
All subjects in Part A and Part B experienced at least one AE, and 36 (78.3%) experienced an AE that was considered by the investigator to be related to ZD1839.
The most frequently occurring AE was mucosal inflammation NOS, in 35 (76.1%) subjects. This was related to ZD1839 in 9 (19.6%) subjects and to other trial therapies in 34 (73.9%) subjects.
Only rash NOS, in 9 (19.6%) subjects and acne NOS, in 5 (10.9%) subjects, were uniquely attributed to ZD1839 by the investigator.
Of 32 (69.6%) subjects who experienced an AE with CTC grade 3 or 4, in only 8 (i.e., 25% of these) was the AE considered to be related to ZD1839.
Seventeen subjects (37.0%) experienced a serious adverse event (SAE); these were considered to be related to ZD1839 in 4 (8.7%) subjects and to other trial therapies in 11 (23.9%). Four subjects died as a result of an AE, but none of these was ZD1839-related.
Ten (21.7%) subjects had haematology-related AEs and 3 (6.5%) had blood chemistry-related AEs. The majority of these AEs were related to other trial therapies and ZD1839 was not considered to uniquely causative for any.
It is concluded that ZD1839 250 mg per day was well tolerated when given in combination with cisplatin and conventional radiotherapy in subjects with inoperable head and neck cancers.
The range of AEs that was considered to be ZD1839-related was representative of the established safety profile of the drug.

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Table S2 **Number (%) of subjects[a] who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)**

Category of adverse event	Part A and Part B N = 46	
Any adverse events	46	(100.0)
Drug-related[b] adverse events	36	(78.3)
Serious adverse events	17	(37.0)
Serious adverse events leading to death	4	(8.7)
Serious adverse events not leading to death	13	(28.3)
Serious drug-related[b] adverse events	4	(8.7)
Discontinuations of study treatment due to adverse events	6	(13.0)
Discontinuations due to drug-related[b] adverse events	1	(2.2)
Discontinuations due to serious adverse events	5	(10.9)
Discontinuations due to serious drug-related[b] adverse events	1	(2.2)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] Investigator considered there was a reasonable possibility that the adverse event was related to ZD1839

Table S3 **Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency (safety analysis set)**

Adverse event (preferred term)	Part A and Part B N = 46	
Mucosal inflammation NOS	35	(76.1)
Dermatitis radiation NOS	26	(56.5)
Dysphagia	26	(56.5)
Asthenia	21	(45.7)
Odynophagia	20	(43.5)
Diarrhoea NOS	19	(41.3)
Anorexia	19	(41.3)
Aptylism	17	(37.0)
Nausea	17	(37.0)
Vomiting NOS	16	(34.8)
Pyrexia	15	(32.6)
Constipation	12	(26.1)
Weight decreased	12	(26.1)
Stomatitis	11	(23.9)
Rash NOS	9	(19.6)
Dysphonia	8	(17.4)
Dermatitis NOS	8	(17.4)
Cough	7	(15.2)
Acne NOS	5	(10.9)
Ear pain	5	(10.9)

[a] Events with a frequency of ≥10% are included in this table.

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Table S4 **Number (%) of subjects with the most commonly reported[a] adverse events considered to be ZD1839-related, sorted by decreasing order of frequency (safety analysis set)**

Preferred term	Part A and Part B (n=46)	
	n	(%)
Mucosal inflammation NOS	9	(19.6)
Rash NOS	9	(19.6)
Asthenia	7	(15.2)
Stomatitis	6	(13.0)
Acne NOS	5	(10.9)
Diarrhoea NOS	5	(10.9)

[a] Events with a frequency of ≥10% are included in this table.

Table S5 **Number (%) of subjects with the most commonly reported[a] adverse events considered to be related to other trial treatments, sorted by decreasing order of frequency (safety analysis set)**

Preferred term	Part A and Part B (n=46)	
	n	(%)
Mucosal inflammation NOS	34	(73.9)
Dermatitis radiation NOS	24	(52.2)
Asthenia	17	(37.0)
Dysphagia	16	(34.8)
Anorexia	16	(34.8)
Diarrhoea NOS	14	(30.4)
Aptylism	13	(28.3)
Nausea	13	(28.3)
Odynophagia	12	(26.1)
Stomatitis	11	(23.9)
Vomiting NOS	9	(19.6)
Dysgeusia	7	(15.2)
Weight decreased	6	(13.0)
Dysphonia	5	(10.9)
Dermatitis NOS	5	(10.9)
Pyrexia	5	(10.9)

[a] Events with a frequency of ≥10% are included in this table.