Drug product:	Iressa	**SYNOPSIS**	
Drug substance(s):	Gefitinib		
Study code:	1839IL/0504		
Date:	30/09/08		

A PHASE II STUDY TO EVALUATE THE SAFETY AND EFFICACY OF THE COMBINATION OF ZD1839 (IRESSA™), DOCETAXEL AND CISPLATIN IN SUBJECTS WITH RECURRENT AND/OR METASTATIC HEAD AND NECK CANCER

Publications

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Preliminary results of a Phase II study to evaluate gefitinib combined with docetaxel and cisplatin in patients with recurrent and/or metastatic squamous-cell carcinoma of the head and neck

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Study dates		**Phase of development**
First subject enrolled	03/07/2003	Therapeutic exploratory (II)
Last subject completed	19/04/2006	

Primary

The primary objective of the study was to evaluate the activity of the combination Gefitinib, docetaxel and cisplatin in subjects with recurrent and/or metastatic head and neck cancer by estimation of the objective response rate (complete response [CR] and partial response [PR]) at study closure.

Secondary

The secondary efficacy objectives of the study were:

1. To estimate the complete response rate
2. To estimate the disease control rate
3. To estimate duration of response
4. To estimate progression-free survival (PFS)
5. To estimate overall survival

The secondary safety objective of the study was:

1. To evaluate the safety and tolerability of the combination Gefitinib, docetaxel and cisplatin

The exploratory objectives of the study were:

1. To investigate the association between epidermal growth factor receptor (EGFR) expression at baseline and the incidence of tumour response
2. To evaluate serial blood (serum) levels of vascular endothelial growth factor (VEGF), HER2 and p53 antibodies as a predictive value of the response with the combination therapy
3. Quality of life (European Organisation for Research on the Treatment of Cancer [EORTC] QLQ-30; QLQ HN 35)

Study design

A multicentre, open-label, phase II study.
An initial cohort of five subjects enrolled into the study received Gefitinib 250 mg orally once daily in combination with docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 every 3 weeks. The safety and tolerability of the combination was to be monitored in this cohort during the first cycle of treatment (3 weeks) before any further subjects were enrolled. If one or no subjects out of five experienced a dose-limiting toxicity (DLT) at this dose level, the combination was to be considered tolerable, and the cohort was to be expanded to 36 subjects.
In the case where two or more of the first five subjects experienced DLT, a further five subjects enrolled received Gefitinib 250 mg orally once daily in combination with docetaxel 60 mg/m^2 and cisplatin 60 mg/m^2 every 3 weeks. If two or more subjects experienced DLT at this lower dose, the study was to be stopped. Alternatively, if one or no subjects experienced DLT at this reduced dose combination, a further 31 subjects were to be recruited at this reduced dose level for evaluation of efficacy.
No intrasubject dose escalation was allowed.
Tolerability was to be determined according to the occurrence of one of the following DLTs:

- Grade 4 neutropenia lasting more than 7 days
- Febrile neutropenia
- Grade 4 thrombocytopenia

Grade 4 non-haematological toxicity (except for alopecia or vomiting without treatment)

Target subject population and sample size

Male or female subjects aged 18 to 70 years, with histologically- or cytologically-confirmed recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). Eligible primary tumour sites were the oral cavity, oropharynx, hypopharynx and larynx. Subjects who have received no previous chemotherapy for recurrent or metastatic disease.
A Fleming single-stage design using 90% power and 5% one-sided alpha with p_0=0.3 and p_1=0.55 (i.e., response rates of 30% and 55%) was to be used. Using this design, a total of 36 subjects were required. Sixteen or more responses in the 36 subjects treated at the highest tolerated dose indicated an active regimen.
The recruitment study was closed before achieving 36 patients. There were included 30 subjects.

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

Investigational product, dosage and mode of administration

Gefitinib (Iressa^{TM}) tablets 250 mg; 250 mg (one tablet) orally once daily.

Combination therapy, dosage and mode of administration

Docetaxel and cisplatin was administered as study therapy.

Docetaxel 75 mg/m^2 was administered as a 1-hour intravenous (iv) infusion every 3 weeks.

Cisplatin 75 mg/m^2 was administered as a 1-hour iv infusion every 3 weeks.

Cisplatin was administered after completion of docetaxel infusion.

In addition, all subjects received ciprofloxacin 500 mg orally twice a day for 10 days starting on Day 2 of each cycle.

Duration of treatment

Gefitinib was to be administered daily and docetaxel and cisplatin were administered every 3 weeks up to 6 cycles in absence of disease progression, unacceptable toxicity or consent withdrawal. After 6 cycles of combination therapy, all subjects with stable or responding disease continued with Gefitinib monotherapy until disease progression, unacceptable toxicity or consent withdrawal.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- **Primary variable:** Objective tumour response (CR and PR) at study closure based on the Response Evaluation Criteria in Solid Tumours (RECIST)
- **Secondary variables**: - Incidence of complete response, controlled disease (CR and PR and stable disease [SD]); duration of response, PFS and Overall survival.
- **Safety**

  Incidence of DLT during the first cycle of study treatment

  Nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

  Incidence and reasons for study drug dose interruptions, study drug dose reductions and withdrawals

  Study drug exposure, laboratory assessments, physical examinations

- **The exploratory objectives of the study were:**

  1. To investigate the association between epidermal growth factor receptor (EGFR) expression at baseline and the incidence of tumour response
  2. To evaluate serial blood (serum) levels of vascular endothelial growth factor (VEGF), HER2 and p53 antibodies as a predictive value of the response with the combination therapy
  3. Quality of life (European Organisation for Research on the Treatment of Cancer [EORTC] QLQ-30; QLQ HN 35)

Statistical methods

All subjects that were enrolled and received study treatment were considered the safety population. All subjects treated at the highest tolerated dose were to be considered the

intention-to-treat (ITT) population. 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 to be summarised by proportions together with a 95% confidence interval (CI; the objective response rate were to be a 90% CI calculated). Durations (PFS, overall survival and response) were to be summarised by Kaplan-Meier methods. Tolerability was to be summarised by the appropriate standard summary statistics. QOL outcome variables were to be summarised by control of longitudinal maintenance of parameters evaluated by the EORTC QLQ C30 and HN 35 questionnaires.

Subject population

The population of trial patients was an acceptable representative group for this Phase II trial. Thirty patients were enrolled and all of them received at least one dose of Gefitinib (250 mg), docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2). All subjects received the study treatment and have been considered intention-to-treat (ITT) population and safety population.
The recruitment was closed before achieving 36 patients.
Eleven patients received 6 cycles of cisplatin, 12 patients received 6 cycles of docetaxel and 16 received at least 6 cycles of Gefitinib; fourteen of these continued monotherapy treatment with Gefitinib. Ten patients (33,3%) received the complete treatment for six o more cycles. One patient discontinued due to an AE, 2 patients due to toxicity, 17 discontinued because of disease progression and 8 because of death.

Table S1 Subject population and disposition

		Total	
Population			
N enrolled (N planned)		30	(36)
Demographic characteristics			
Sex (n and % of subjects)	Male	27	(90.0)
	Female	3	(10.0)
Age (years)	Mean (SD)	54.8	(10.1)
	Range	29 to 69	
Race (n and % of subjects)	Caucasian	30	(100)
	Black	0	(0)
	Oriental	0	(0)
	Other	0	(0)
Baseline characteristics			
ECG overall evaluation	Missing	2	(6.7)
(n and % of subjects)	Normal	26	(86.7)
	Abnormal	2	(6.7)
Any current or past major conditions (n and % of subjects)	No	9	(30.0)
	Yes	21	(70.0)

		Total	
Population			
N enrolled (N planned)		30	(36)
Major surgery (n and % of subjects)	No	12	(40.0)
	Yes	18	(60.0)
Weight (kg)	Mean (SD)	66.17	(15.54)
	Range	41 to 111	
Height (cm)	Mean (SD)	167.03	(6.14)
	Range	155 to 180	
Performance Status (n and % of patients)	0	16	(53.3)
	1	14	(46.7)
Systolic blood pressure	Mean (SD)	117.6	(19.76)
(mmHg, n = 25)	Range	80 to 160	
Diastolic blood pressure	Mean (SD)	68.9	11.94
(mmHg, n = 25)	Range	50 to 100	
Heart rate (BPM, n = 15)	Mean (SD)	80	(12.77)
	Range	56 to 100	
Disposition			
Patients continuing monotherapy at trial end (n and % of subjects)		2	(6.7)
Patients who completed 6 cycles of treatment (n and % of subjects)		10	(33.3)
N analysed for safety [a]		30	
N analysed for efficacy (ITT)[b]		30	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
[b] All subjects treated at the highest tolerated dose
ITT=Intention to treat; N=Number

Efficacy and pharmacokinetic results

Based on the RECIST assessed by head and neck computerised tomography (CT) or nuclear magnetic resonance (NMR), chest x-ray or chest-abdominal CT scan as appropriate, there were 30% of responders:
Objective Response Rate (CR+PR) Confirmed 4 weeks later: : 9 (30.00%); 90% CI (16.63% to 46.51%)
Exact p, true response rate > 30%: 0.568
Objective Response Rate (CR+PR) Not Confirmed 4 weeks later: 14 (46.67%); 90% CI (30.85% to 63.01%)
Exact p, true response rate > 30%: 0.040
Two patients continue on complete response for at least two years.
Median Duration of response was estimated to be 160 days; (95% CI: 127 to 220 days).
Median Progression free survival was estimated to be 154 days; (95% CI: 60 to 212 days).

Proportion alive and progression-free at 6 months was: 42.2% (CI 95% CI: 24.3 to 60.2)
Median Survival Time was estimated to be 256 days (95% CI: 171 to 443)
Proportion alive at 6 months was 63.3% (95% CI: 46.1 to 80.6)

Safety results

Median exposure to Gefitinib (time on treatment) was 119.5 days (range 7 to 801 days) and median exposure to docetaxel and cisplatin was 5 cycles (range 1 to 6). Five patients (16.7%) had one or more interruptions of Gefitinib dose. These interruptions were due to SAE 1 pts (iatrogenic gastroenteritis), Hospitalization 3 pts, Non fulfillment the treatment by patient 1 pts. Thirteen patients (43.3%) had one or more reductions/delays of docetaxel infusions. In 8 patients were due to toxicity. Fifteen patients (50.0%) had one or more reductions/delays of cisplatin infusions, ten of them was due to toxicity.

Ten patients (33.3%) received at least six cycles of study treatment (Gefitinib+docetaxel+cisplatine) and 14 (46.6%) continued receiving Gefitinib monotherapy. One patient discontinued due to an AE (Pneumonia, neutropenia and thrombocytopenia), 2 patients due to toxicity (neutropenia febrile G4, Nausea, vomiting and anaemia G2), 17 discontinued because of disease progression and 8 because of death.

None of the first five patients enrolled experienced DLT during the first administered cycle.

Thirty patients (100.0%) in the trial experienced AEs (all causalities) and 21 (70.0%) experienced SAEs. The most commonly reported AEs were gastrointestinal disorders (29 patients [96.7%]), blood and lymphatic system disorders (26 patients [86.7%]), general disorders and administration site conditions (25 patients [83.3%]), metabolism and nutrition disorders (13 patients [43.3%]) and skin and subcutaneous tissue disorders (12 patients [40.0%]).

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

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]	
Any adverse events	30	(100)
Serious adverse events	21	(70.0)
Serious adverse events leading to death	6	(20.0)
Serious adverse events not leading to death	15	(50.0)
Discontinuations of study treatment due to adverse events	10	(33.3)
Other significant adverse events	0	(0.0)
	Total number of adverse events	
Adverse events	278	
Serious adverse events	44	
Other significant adverse events	0	

[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.

Vomiting was the most commonly reported individual AE, affecting 21 patients (70.0%). Diarrhoea and anaemia was reported for 20 patients (66.7%), asthenia was reported for 18 patients (60.0%), mucosal inflammation and nausea was reported for 14 patients (46.7%), and anorexia was reported for 12 patients (40.0%).

Table S3 Number (%) of subjects with the most commonly reported [a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term) Total (n=30)	Number (%) of subjects who had an adverse event	
Vomiting	21	70.00
Anaemia	20	66.67
Diarrhoea	20	66.67
Asthenia	18	60.00
Mucosal inflammation	14	46.67
Nausea	14	46.67
Anorexia	12	40.00
Pyrexia	11	36.67
Dysphagia	10	33.33
Alopecia	8	26.67
Leukopenia	7	23.33
Neutropenia	7	23.33
Paraesthesia	7	23.33
Rash	7	23.33
Febrile neutropenia	6	20.00
Thrombocytopenia	6	20.00
Odynophagia	5	16.67
Abdominal pain	4	13.33
Tumour haemorrhage	4	13.33
Neck pain	3	10.00
Pruritus	3	10.00
Acne	2	6.67
Constipation	2	6.67
Dyspnoea	2	6.67
Face oedema	2	6.67
Haemorrhage	2	6.67
Malaise	2	6.67
Nephropathy toxic	2	6.67
Renal failure	2	6.67
Trismus	2	6.67
Weight decreased	2	6.67

[a] Events with a total frequency of ≥3% across all treatment groups are included in this table.

SAEs were recorded for 21 patients (70.0%). The most frequent SAEs comprised anaemia in eight patients (36.7%), febrile neutropenia in six patients (20.0%), tumour haemorrhage in four patients (13.3%), asthenia, dysphagia, neutropenia and thrombocytopenia in two patients each (6.7%).

There were six SAEs leadind to death, five of then there were not related to study drug. The other one, neutropenia febrile there were related to chemotherapy treatment, Docetaxel and Cisplatin.

One patient (3.6%) was discontinued from trial treatment because of AE and two patients (7.1%) were discontinued from trial treatment because of toxicity.

Grade 3-4 toxicities were: hand and foot syndrome in 7 patients (23.4%), febrile neutropenia in 6 patients (20.0%), neutropenia in 5 patients (16.7%), anemia and leucopenia in 4 patients (13.3%), nausea/vomiting in 3 patients (10.0%), Diarrhea, mucosal inflammation and asthenia in 2 patients (6.7%) and thrombopenia in 1 patient (3.3%).

Table S4 Number (%) of subjects with the worst CTC-NCI toxicity (safety analysis set)

Toxicity /	Grade 1		Grade 2		Grade 3		Grade 4	
grade NCI-CTC	N	(%)	N	(%)	N	(%)	N	(%)
Anemia	6	(20.0)	11	(36.7)	3	(10.0)	1	(3.3)
Neutropenia	1	(3.3)	1	(3.3)	2	(6.7)	3	(10.0)
Febrile Neutropenia					3	(10.0)	3	(10.0)
Leucopenia	1	(3.3)	2	(6.7)	2	(6.7)	2	(6.7)
Trombopenia	5	(16.7)	1	(3.3)	1	(3.3)		
Hepatic	1	(3.3)						
Rash Cutaneous	4	(13.3)	4	(13.3)				
Diarrhoea	12	(40.0)	6	(20.0)	2	(6.7)		
Nausea/vomiting	12	(40.0)	9	(30.0)	3	(10.0)		
Mucositis	7	(23.3)	5	(16.7)	2	(6.7)		
asthenia	10	(33.3)	5	(16.7)	2	(6.7)		
Anorexia	11	(36.7)	1	(3.3)				
Hand and Foot S.	4	(13.3)	7	(23.3)	5	(16.7)	2	(6.7)