Drug product:	Iressa ™	**SYNOPSIS**	
Drug substance(s):	Gefitinib		
Study code:	1839IL/0505		
Date:	30/06/2008		

A PHASE I/II, MULTICENTRE CLINICAL STUDY OF GEFITINIB (IRESSA™) IN COMBINATION WITH CAPECITABINE (XELODA™) IN SUBJECTS WITH ADVANCED COLORECTAL CARCINOMA AFTER FAILURE OF FIRST-LINE CHEMOTHERAPY

Publications

ASCO Annual Meeting (Orlando, Florida, 13 - 17 May 2005)
Phase I/II trial of capecitabine and gefitinib in patients with advanced colorectal cancer after failure of first-line therapy.
A.Jimeno, I. Sevilla, C. Gravalos, M.E. Vega, P. Escudero, E. Torre, F. Rivera, M.L. García de Paredes, R. Colomer, H. Cortés-Funes.

Journal of Clinical Oncology 2005; 23 (16S Pt. 1): 235s; Abs. 3176

X Congress Spanish Society of Medical Oncology (SEOM) (Zaragoza, 23-25 June 2005),
Estudio fase I/II de la combinación de iressa y capecitabina como tratamiento de segunda línea en cáncer colorrectal avanzado (CCRA).
C. Gravalos, P. Escudero, A. Jimeno, I. Sevilla, Mª E. Vega-Villegas, V. Alonso, I. Juez, R. García-Carbonero, H. Bovio, H. Cortés-Funes
Clinical & Translational Oncology 2005; 7 (Supl. 1): 91; Abs. PD-134

ECCO 13 - Paris, 30 October - 3 November 2005
Phase I/II trial of capecitabine and gefitinib in patients with advanced colorectal cancer after failure of first-line therapy
Cristina Grávalos, Pilar Escudero, Antonio Jimeno, Isabel Sevilla, Mª Eugenia Vega-Villegas, Vicente Alonso, Iñaki Juez, Rocío García-Carbonero, Humberto Bovio, Hernán Cortés-Funes
European Journal of Cancer Supplements 2005; 3(2): 198-99 Abs 700

Phase I/II study of gefitinib and capecitabine in patients with colorectal cancer.
Antonio Jimeno, Cristina Grávalos, Pilar Escudero, Isabel Sevilla, M.ª Eugenia Vega-Villegas, Vicente Alonso, Ignacio Juez, Rocío García-Carbonero, Humberto Bovio, Ramón Colomer, Hernán Cortés-Funes
Clin Transl Oncol (2008) 10:52-57

Study dates		**Phase of development**
First subject enrolled	11/02/2004	Therapeutic exploratory (I/II)
Last subject completed	03/11/2005	

Objectives

The primary objective

- Phase I part: to determine the recommended dose of capecitabine in combination with Gefitinib 250 mg orally once daily .
- Phase II part: to estimate the objective response rate (complete response [CR] and partial response [PR]) for Gefitinib in combination with capecitabine (RECIST).

The secondary objectives

- Phase II part: disease control rate (CR, PR and stable disease [SD]) progression-free survival (PFS), the safety profile of Gefitinib at a 250 mg daily dose and capecitabine

Study design

A multicentre Phase I/II study. The Phase I part of the study was a dose escalation design to establish the recommended dose of capecitabine to be administered in combination with Gefitinib 250 mg orally once daily. The Phase II part was a single-arm, non-comparative, single-stage design to assess the activity of the combination of Gefitinib and capecitabine at the recommended dose of capecitabine determined in the Phase I part of the study. Subjects with advanced or metastatic colorectal cancer received study treatment until disease progression, unacceptable toxicity or withdrawal of consent.

Target subject population and sample size

Subjects with histologically-confirmed colorectal carcinoma. Progressive non-resectable metastatic or locally advanced disease after one prior chemotherapeutic regimen. World Health Organisation (WHO) performance status of 0, 1 or 2 and a life expectancy of at least 12 weeks.
Ten subjects were included in the Phase I part of the study (six subjects at the first dose level and four at the second dose level).
In the Phase II part, Fleming's method was used to determine the number of subjects required. A sample size of 34 subjects on the MTD was sufficient to give 90% probability of rejecting a baseline objective response rate (ORR) of 10% with a 5% one-sided significance test when the true ORR is 30%. If there were seven or more responders out of the 34 at the MTD, the null hypothesis would be rejected and the combination would be considered active.
The recruitment study was closed before to achieve 34 patients at the recommended dose. There were included 26 subjects at the recommended dose.

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.
All subjects received Gefitinib 250 mg (one tablet) orally once daily in combination with capecitabine. The Gefitinib dose level for this study was 250 mg. Study treatment was dispensed to subjects on Day 1 and every 84 days thereafter until the subject withdrew, or completed the study.

Combination therapy, dosage and mode of administration

Capecitabine (Xeloda™) tablets 150 mg and 500 mg.
The total dose was divided in two and administered orally twice daily at approximately 12-hour intervals within 30 minutes of a meal. Capecitabine was administered for 14 days in a 21-day cycle.
The capecitabine dose levels for this study was 1000 mg/m^2 and 1250 mg/m^2 twice daily. Capecitabine was dispensed on Day 1 and every 21 days thereafter until the subject withdrew or closure of the study.

Duration of treatment

Gefitinib and capecitabine were administered until disease progression, unacceptable toxicity or withdrawal of consent.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics Phase II

- Primary variable: Objective tumour response (CR and PR) based on the RECIST
- Secondary variables: Incidence of controlled disease (CR, PR and SD) and PFS

Safety Phase I

- Incidence of DLTs during the first 6 weeks of study treatment.

Safety Phase I/II

- Nature, incidence and severity of adverse events (AEs) and serious adverse events (SAEs).
- Incidence of and reasons for study drug dose interruptions, study drug dose reductions and withdrawals.
- Study drug exposure, laboratory assessments, physical examinations.

Statistical methods

All subjects that were enrolled and received study treatment were considered the safety population. The intention-to-treat (ITT) population consisted of all subjects (in both Phase I and Phase II) who were treated at the MTD. The analysis population for all efficacy outcome variables was the ITT population. The analysis population for all other presentations was the safety 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 and disease control rates have been summarised by proportions together with a 95% confidence interval (CI) (the objective response rate also have a 90% CI calculated). Duration of PFS was summarised by Kaplan-Meier methods. Tolerability was summarised by the appropriate standard summary statistics.

Subject population

The population of trial patients was an acceptable representative group for this Phase I/II trial. There were enrolled ten patients in phase I study, six patients at doses of 250/1000 and 4 patients at doses 250/1250. One patient at the dose 250/1250 died before completing the follow up phase I period.
Because no one objective response happened, the recruitment study was closed before to achieve 34 patients at the recommended dose. There were enrolled 26 patients in phase II study at the recommended dose (four patients were from the second dose level of the Phase I). Due to an incident in the distribution of the study drug, several patients received placebo instead gefitinib at different time intervals. All of the patients received Capecitabine. Three patients received capecitabine plus placebo along the treatment and they were rejected for the ITT efficacy final analysis. Another 3 patients received Capecitabine plus Iressa three months and then changed to Capecitabine plus placebo. Because the principal outcome was Objective response by RECIST, these patients were included in ITT analysis population. Another 2 patients received Iressa from another Iressa study and were included in ITT analysis population..
ITT population were 23 patients for recommended dose.

Table S1 Subject population and disposition

		Total	
Population			
N enrolled (N planned)		23	(34)
Demographic characteristics			
Sex (n and % of subjects)	Male	16	(69.6)
	Female	7	(30.4)
Age (years)	Mean (SD)	66.0	(8.0)
	Range	53 to 81	
Race (n and % of subjects)	Caucasian	22	(95.7)
	Black	1	(4.3)
Baseline characteristics			
WHO performance status	Normal activity	13	(56.5)
	Restricted activity	10	(43.5)
Any current or past major conditions	No	1	(4.3)
	Yes	22	(95.7)
Major surgery	No	6	(26.1)
	Yes	17	(73.9)
Disposition			
N analysed for safety [a]		32	
N analysed for efficacy (ITT)		23	

[a] Number of subjects who took at least 1 dose of study treatment
ITT=Intention to treat; N=Number;

Efficacy and pharmacokinetic results

Phase I/II efficacy. Based on the RECIST, there were no responders by Week 12.

ITT population: Phase II, N=23 patients

Based on RECIST, there were no responders by week 12. RC 0%, 95% CI: 0,00 to 14.82%.

There was SD in 12 patients (52.17%, 95% CI: 30.59% to 73.18%) and PD in 8 patients (34.78%, 95% CI: 16.38% to 57.27%); Three patients were not evaluable .

Median Progression Free Survival was estimated at 117 days (95% CI: 60 to 198 days)

KM progression Free estimate at 6 months: 33% (CI 95%: 13.3% to 52.7%)

N=23; patients with progression or death 20 (87.0%); patients censored 3 (13.0%)

Median Overall survival was estimated at 312 days (95% CI: 147 to 411 days)

Survival estimate at 6 months: 63.6% (CI 95%: 43.5% to 83.7%)

N=23; Number of deaths 15 (68.2%); Number of censored data: 7 (31.8%)

Safety results

Two safety analysis were performed. One in the phase I patients and the other one in the whole safety population.

Phase I: N=10 patients

Median exposure to GEFITINIB was 128 days (range 15 to 276); median 21 day cycles was 6.5 cycles (range 1.0 to 14.0);

Median exposure to Capecitabine was 123 days (range 15 to 265); median 21 days cycles was 6.0 cycles (range 1.0 to 13.0).

Four patients (40%) had one or more interruptions of GEFITINIB dose. These interruptions were due to toxicity in two patients (20%).

Five patients (50%) had one or more interruptions of Capecitabine dose. In four patients it was due to toxicity and two patients needed one reduction of dose.

There was one dose-limiting toxicity at first level of treatment (250/1000). Diarrhoea CTC-NCI grade 2 lasting 3 weeks. Three patients more were recruited at this first level of treatment.

One patient at the second level of treatment (250/1250) died before any follow up study assessments. One patient more was recruited at this second level of treatment.

Ten patients (100.0%) in the trial experienced AEs (all causalities), all of them related to study drug, and 2 (20.0%) experienced SAEs. The most commonly reported AEs (System organ class) were: general disorders and administration site conditions (10 patients [100.0%]), gastrointestinal disorders (9 patients [90.0%]),skin and subcutaneous tissue disorders (9 patients [90.0%]), and nervous system disorders, respiratory, thoracic and mediastinal disorders and metabolism and nutrition disorders (4 patients [40.0%]). Asthenia was the most commonly reported individual AE (preferred term), affecting 8 patients (80.0%). Diarrhoea was reported for 7 patients (70.0%), palmo-plantar erythrodysaesthesia in 6 patients (60.0%), rash in 5 patients (50.0%) and anorexia and mucositis in 4 patients (40.0%).

There were no CTC-NCI grade 4 toxicities. Grade 3 toxicities were: Asthenia, 3 patients (30.0%), increased liver function tests, skin dryness and hiccups 1 patient (10.0%).

Safety population (n=32 patients)

Median exposure to GEFITINIB was 82.0 days (range 10 to 276 days); median 21 day cycles was 4.5 cycles (range 1.0 to 14.0);

Median exposure to Capecitabine was 80.05 days (range 10 to 265); median 21 days cycles was 4.0 cycles (range 1.0 to 13.0).
Seventeen patients (53.1%) had one or more interruptions of GEFITINIB dose. These interruptions were due to toxicity in twelve patients (37.5%).
Twenty-three patients (71.9%) had one or more interruptions of Capecitabine dose. In nineteen (59.4%) patients it was due to toxicity and ten patients (31.3.5%) needed one dose reduction.
Thirty-one patients (96.9%) in the trial experienced AEs (all causalities), thirty of them related to study drug (93.8%), and 13 patients (40.6%) experienced at least one SAE. There were ten patients with AE leading to premature discontinuation.
The most commonly reported AEs (System organ class) were: general disorders and administration site conditions (31 patients [96.88%]), gastrointestinal disorders (28 patients [87.50%]), skin and subcutaneous tissue disorders (21 patients [65.63%]), metabolism and nutrition disorders (13 patients [40.63%]), Respiratory thoracic and mediastinal disorders (11 patients [34.38%]) and nervous system disorders (10 patients [31.25%]).

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	31	(96.9)
Serious adverse events	13	(40.6)
Serious adverse events leading to death	1	(3.1)
Serious adverse events not leading to death	12	(37.5)
Discontinuations of study treatment due to adverse events	4	(12.5)
Other significant adverse events	0	(0.0)
	Total number of adverse events	
Adverse events	354	
Serious adverse events	18	
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.

Asthenia was the most commonly reported individual AE (preferred term), affecting 23 patients (71.88%). Diarrhoea was reported for 19 patients (59.38%), anorexia in 13 patients (40.63%), palmo-plantar erythrodysaesthesia in 11 patients (34.38%), rash in 10 patients (31.25%), mucosal inflammation and nausea in 9 patients (28.13%), pyrexia in 8 patients (25.00%) and vomiting in 7 patients (21.88%).

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)	Number (%) of subjects who had an adverse event	
ASTHENIA	23	(71.88)
DIARRHOEA	19	(59.38)
ANOREXIA	13	(40.63)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	11	(34.38)
RASH	10	(31.25)
MUCOSAL INFLAMMATION	9	(28.13)
NAUSEA	9	(28.13)
PYREXIA	7	(25.00)
VOMITING	7	(21.88)
DRY SKIN	6	(18.75)
ANAEMIA	5	(15.63)
DYSPNOEA	5	(15.63)
ABDOMINAL PAIN	4	(12.50)
SKIN TOXICITY	4	(12.50)
CONSTIPATION	3	(9.38)
COUGH	3	(9.38)
DYSPHAGIA	3	(9.38)
ERYTHEMA	3	(9.38)
GASTRITIS	3	(9.38)
HICCUPS	3	(9.38)
NEUROTOXICITY	3	(9.38)
OEDEMA	3	(9.38)
PRURITUS	3	(9.38)
RECTAL HAEMORRHAGE	3	(9.38)
ABDOMINAL PAIN UPPER	2	(6.25)
ASCITES	2	(6.25)
BACK PAIN	2	(6.25)
BALANITIS	2	(6.25)
DEPRESSION	2	(6.25)
DIZZINESS	2	(6.25)
DYSPEPSIA	2	(6.25)
DYSURIA	2	(6.25)
FACE OEDEMA	2	(6.25)
OEDEMA PERIPHERAL	2	(6.25)
OESOPHAGITIS	2	(6.25)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event	
PERINEAL PAIN	2	(6.25)
PERIPHERAL SENSORY NEUROPATHY	2	(6.25)
STOMATITIS	2	(6.25)

[a] Events with a total frequency of ≥4% are included in this table.

Grade 3-4 toxicities were: Diarrhea in 7 patients (21.9%), Asthenia in 6 patients (18.8%), hand and foot syndrome in 2 patients (6,2%), increased liver function tests, rash, nausea/vomiting and mucosal inflammation in 1 patient (3.1%). Grade 3-4 Hematological toxicity: febrile neutropenia and thrombopenia in 1 patient (3.8). Another 3 patients (9.4%): dysphagia, gastrointestinal syndrome and palmo-plantar dryness.