Drug product:	Iressa	**SYNOPSIS**	
Drug substance(s):	Gefitinib		
Study code:	1839IL/0143		
Date:	29/05/08		

A RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND PHASE IIb STUDY OF RALTITREXED (TOMUDEX®) AND ZD1839 (IRESSA™) VERSUS RALTITREXED ALONE AS SECOND-LINE CHEMOTHERAPY IN SUBJECTS WITH COLORECTAL CARCINOMA

Publications

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A randomised, placebo-controlled, double-blind Phase II study of Raltitrexed (Tomudex®) and Gefitinib (Iressa) vs Raltitrexed alone as 2nd line chemotherapy in subjects with advanced colorectal cancer (CRC). GON group study (Grupo Oncológico del Norte).

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Study dates		**Phase of development**
First subject enrolled	10/12/2003	Therapeutic exploratory (II)
Last subject completed	21/06/2006	

Objectives

The primary objective of the study is to compare the activity of raltitrexed and Gefitinib versus raltitrexed alone as second-line chemotherapy in subjects with colorectal carcinoma by estimating the median progression-free survival (PFS) in each treatment arm.

The secondary efficacy objectives of the study are:

1. To estimate the objective response rate (complete response [CR] and partial response [PR]) at 6 months for each treatment arm
2. To estimate the disease control rate (CR, PR and stable disease [SD]) at 6 months for each treatment arm
3. To estimate overall survival for each treatment arm
4. To estimate duration of response for each treatment arm

The safety objectives of the study are:

1. To further characterise the safety profile of Gefitinib at a 250 mg daily dose

2. To evaluate the safety and tolerability of the combination of raltitrexed and Gefitinib

Study design

A two-arm, randomised, double-blind, placebo-controlled, comparative, Phase IIb study. Subjects will be randomised to one of the following treatment arms:
Treatment arm A: Raltitrexed and Gefitinib
Treatment arm B: Raltitrexed and placebo

Target subject population and sample size

Male or female subjects aged 18 to 75 years, inclusive, with histologically-confirmed metastatic colorectal carcinoma, who have relapsed after first-line treatment for metastatic or locally advanced disease with a fluoropyrimidine-based chemotherapy. 33 subjects per treatment arm.

A study with 33 subjects per treatment arm, all of whom were followed to progression or death, will provide a two-sided test at the 5% level of significance of the equality of PFS in the two treatment arms that will achieve a power of 80% when the median PFS in the ZD1839 arm is twice the median PFS in the placebo arm. To allow for a non-evaluability rate of approximately 12%, a total of 37 subjects per treatment arm will be recruited.

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

Gefitinib (Iressa™) tablets 250 mg and placebo to match.
Treatment arm A: ZD1839 250 mg (one tablet) orally once daily, administered continuously

Treatment arm B: Placebo (one tablet) orally once daily, administered continuously

Combination therapy, dosage and mode of administration

All subjects will receive raltitrexed (Tomudex®) as study therapy. Raltitrexed 3 mg/m^2 will be diluted in 2.5 ml saline fluid and administered as a 20-minute intravenous (iv) infusion on Day 1 of each 3-week cycle.

Duration of treatment

Gefitinib/placebo will be administered daily until disease progression, unacceptable toxicity or withdrawal of consent and raltitrexed will be administered once every 3 weeks until disease progression, unacceptable toxicity, withdrawal of consent or as clinically appropriate. Subjects receiving Gefitinib who are withdrawn for toxicity not considered related to Gefitinib, will be allowed to continue on Gefitinib treatment as open-label therapy.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: Median PFS

- Secondary variables: Objective tumour response (CR and PR) at 6 months, Incidence of controlled disease (CR, PR and SD) at 6 months, Overall survival, Duration of response.

Safety

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 intention-to-treat (ITT) population. The analysis population for all efficacy outcome variables was the 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 also have a 90% CI calculated). Durations (of PFS, overall survival and response) were to be summarised by Kaplan-Meier methods. Tolerability was to be summarised by the appropriate standard summary statistics.

Subject population

Male or female subjects aged 18 to 75 years, inclusive, with histologically-confirmed metastatic colorectal carcinoma, who have relapsed after first-line treatment for metastatic or locally advanced disease with a fluoropyrimidine-based chemotherapy.
The population of trial was an acceptable representative group for this phase II trial. There were 76 enrolled patients, 38 in the experimental arm and 38 in the control arm. The treatment groups were generally well balanced in demographic and baseline characteristis; there were slightly fewer women and abnormal ECG in the Raltitrexed and Gefitinib group.
All subjets that were enrolled and received study treatment were considered the ITT population.

Table S1 Subject population and disposition

		Raltitrexed and Gefitinib		Raltitrexed alone		Total	
Population							
N randomised (N planned)		38	(37)	38	(37)	76	(74)
Demographic characteristics							
Sex (n and % of subjects)	Male	24	(63.2)	22	(57.9)	46	(60.5)
	Female	14	(36.8)	16	(42.1)	30	(39.5)
Age (years)	Mean (SD)	63.0	(7.9)	60.7	(11.7)	61.9	(10.0)
	Range	40 to 76		31 to 75		31 to 76	
Race (n and % of subjects)	Caucasian	38	(100.0)	38	(100.0)	76	(100.0)
Baseline characteristics							
ECG overall evaluation	Normal	35	(92.1)	27	(71.1)	62	(81.6)
(n and % of subjects)	Abnormal	2	(5.3)	7	(18.4)	9	(11.8)
	Missing	1	(2.6)	4	(10.5)	5	(6.6)
Performance Status	0	16	(42.1)	18	(47.4)	34	(44.7)
(n and % of subjects)	1	19	(50.0)	19	(50.0)	38	(50.0)
	2	3	(7.9)	1	(2.6)	4	(5.3)
Any current or past major conditions	No	12	(31.6)	9	(23.7)	21	(27.6)
(n and % of subjects)	Yes	26	(68.4)	29	(76.3)	55	(72.4)
Major surgery	No	20	(52.6)	17	(44.7)	37	(48.7)
(n and % of subjects)	Yes	18	(47.4)	21	(55.3)	39	(51.3)
Disposition							
N analysed for safety[a]		38		38		76	
N analysed for efficacy (ITT)		38		38		76	

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

Efficacy and pharmacokinetic results

The median progression free survival in the combination arm was 63 days (95% CI: 57 - 84 days) versus 72 days (95% CI: 59 – 132 days) in the raltitrexed alone arm. This resulted in a Kaplan Meyer estimate PFS at six months of 9.5 % (95% CI: 0 - 19.3 months) versus 28 % (95% CI: 13.5 - 42.5 months) and median overall survival of 361 days (95% CI: 283-533 days) versus 291 days (95% CI: 255-539 days) respectively. The objective response rate was 7.9% (3 patients) in the combination arm versus 5.3% (2 patients) in the Raltitrexed alone arm.

Table S2 Subject population and disposition

	Raltitrexed and Gefitinib (N = 38)		Raltitrexed alone (N = 38)	
Number (%) of patients with progression or death	36	(97.3)	35	(92.1)
Number (%) of Censored Data	1	(2.7)	3	(7.9)
Progression free survival Median. Days and (95% CI)	63	(57 , 84)	72	(59 , 132)
KM progression free estimate at 6 months. % and (95% CI)	9.5	(0.0 , 19.3)	28	(13.5 , 42.5)
Overall survival Median	361	(283 , 533)	291	(255 , 539)
Objective response rate (CR+PR) N (%) and [95% CI]	3 (7.89)	[1.7 , 21.4]	2 (5.26)	[0.6 , 17.8]

Safety results

Mean time of patients in the study was 85.7 days (range 11 to 328 days) for raltitrexed and Gefitinib group and 113.8 days (range 20 to 273 days) for alone raltitrexed group.

Mean exposure to Gefitinib/placebo (time on treatment) was 84 days (range 12 to 324 days) and 113 days (range 21 to 274 days).

Median exposure to raltitrexed was 3 cycles (range 1 to 13) and 3.5 cycles (range 1 to 13) respectively.

Twelve subjects (31.6 %) had one or more interruptions of Gefitinib/placebo dose in raltitrexed and Gefitinib group and 9 (23.7%) subjects in the raltitrexed group. These interruptions were due to toxicity in 18.4% and 13.1% of patients respectively.

Twelve subjects (31.6%) had one or more reductions/delays in raltitrexed infusions in raltitrexed and Gefitinib group and 14 subjects (36.8%) had one or more reductions/delays of raltitrexed in the raltitrexed group. These interruptions were due to toxicity in 18.4% and 13.1% of patients respectively.

SAEs were recorded for 15 subjects; 7 (18.4%) in the raltitrexed and Gefitinib group and 8 (21.1%) in the raltitrexed group. The most frequent SAEs comprised abdominal pain in one subject (2.6%) for raltitrexed and Gefitinib group and two subjects (5.3%) in the raltitrexed group, diarrhoea in two subjects (5.3%) in the raltitrexed and Gefitinib group and one subject (2.6%) in the raltitrexed group, anorexia, asthenia and vomiting in three subjects each (7.9%) in the raltitrexed group.
Events leading to death were rare (1 case in the raltitrexed group due to Acute renal failure**)**
Serious adverse events were reported by a similar proportion of subjects in both groups.

Table S3 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]					
	Raltitrexed and Gefitinib (n=38)		Raltitrexed alone (n=38)		Total (n=76)	
Any adverse events	35	(92.1)	35	(92.1)	70	(92.1)
Serious adverse events	7	(18.4)	8	(21.1)	15	(19.7)
Serious adverse events leading to death	0	(0.0)	1	(2.6)	1	(1.3)
Serious adverse events not leading to death	0	(0.0)	0	(0.0)	0	(0.0)
Discontinuations of study treatment due to adverse events	0	(0.0)	0	(0.0)	0	(0.0)
Other significant adverse events	0	(0.0)	0	(0.0)	0	(0.0)
	Total number of adverse events					
Adverse events	203		179		382	
Serious adverse events	10		25		35	
Other significant adverse events	0		0		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.

In both groups 35 subjects (92.1%) experienced AEs. The most commonly reported AEs were asthenia (20 [52.6%] / 19 [50.0%]), skin rash (17 [44.7%] / 7 [18.4%]), nausea (14 [36.8%] / 10 [26.3%]), anorexia (9 [23.7%] / 12 [31.6%]), diarrhoea (11 [29.0%] / 9 [23.7%]) and vomiting (8 [21.1%] / 10 [26.3%]) in each study group.

Adverse events were reported by a similar proportion of subjects in both groups; There were no differences in toxicity profile except for the higher incidence of skin toxicity in raltitrexed and ZD1839 group.

Table S4 **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	Number (%) of subjects who had an adverse event					
	Raltitrexed and Gefitinib (n=38)		Raltitrexed alone (n=38)		Total (n=76)	
Asthenia	20	(52.63)	19	(50.00)	39	(51.32)
Skin Rash	17	(44.73)	7	(18.40)	24	(31.58)
Nausea	14	(36.84)	10	(26.32)	24	(31.58)
Anorexia	9	(23.68)	12	(31.58)	21	(27.63)
Diarrhoea	11	(28.95)	9	(23.68)	20	(26.32)
Vomiting	8	(21.05)	10	(26.32)	18	(23.68)
Fever	8	(21.05)	8	(21.05)	16	(21.05)
Abdominal Pain	3	(7.89)	6	(15.79)	9	(11.84)
Pyrosis	5	(13.16)	3	(7.89)	8	(10.53)
Constipation	4	(10.53)	2	(5.26)	6	(7.89)
Dysgeusia	3	(7.89)	2	(5.26)	5	(6.58)
Hepatotoxicity	2	(5.26)	3	(7.89)	5	(6.58)
Anemia	1	(2.63)	3	(7.89)	4	(5.26)
Arthromyalgia	2	(5.26)	1	(2.63)	3	(3.95)
Headache	3	(7.89)	.	.	3	(3.95)
Mucositis	2	(5.26)	1	(2.63)	3	(3.95)
Urinary Infection	3	(7.89)	.	.	3	(3.95)

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

The most frequent drug-related AEs, were asthenia, liver dysfunction and anemia which were encountered in 46.1%, 44.7% and 43.4% of the subjects respectively. In addition, 47.4% of the subjects treated with raltitrexed and Gefitinib experienced skin toxicity. There was a higher incidence of skin toxicity and diarrhoea in subjects treated with raltitrexed and Gefitinib.