Drug Product	IRESSA 250 mg tablet	**SYNOPSIS**	
Drug Substance	IRESSA (gefitinib, ZD1839)		
Study Code	1839IL/0551		
Edition Number	1		
Date	11 June 2009		

A RANDOMIZED, OPEN-LABEL PHASE II STUDY OF ZD1839 (IRESSA™) VERSUS GEMCITABINE AND CARBOPLATIN IN CHEMOTHERAPY-NAIVE PATIENTS WITH ADVANCED (STAGE IIIB OR IV) NON-SMALL CELL LUNG CANCER AND ECOG PERFORMANCE STATUS 2.

Study centre(s)

This study was conducted at 2 centres in Canada.

Publications

None at the time of writing this report

Study dates		**Phase of development**
First subject enrolled	19 Oct 2004	Phase II
Last subject completed	16 June 2008	

The study was terminated prematurely due to slower than expected recruitment with only 35 out of the originally planned 122 patients randomized.

Objectives

The primary objective was to demonstrate in chemotherapy naïve patients with advanced (Stage IIIB or IV) non-small cell lung cancer (NSCLC) and ECOG performance status (PS) 2 non-inferiority in progression free survival (PFS) for ZD1839 compared to gemcitabine/carboplatin

The secondary objectives were:

- To compare symptom improvement rate based on the FACT-L lung cancer subscale (LCS) for ZD1839 compared to gemcitabine/carboplatin
- To compare ZD1839 and gemcitabine/carboplatin in terms of overall survival
- To compare ZD1839 and gemcitabine/carboplatin in terms of overall objective tumour response rate (complete response and partial response)
- To compare QOL for ZD1839 treated patients with that of gemcitabine/carboplatin treated patients, based on the FACT-L with respect to the Treatment Outcome Index (TOI) and FACT-L total score
- To evaluate safety and tolerability in the ZD1839 treatment arm and the gemcitabine/carboplatin treatment arm

Study design

This is a Phase II, multicentre, randomized, open label study. Patients will be randomized in a 1:1 ratio to one of two treatment groups:

Randomize

- Group A: ZD1839 250 mg/day p.o. until objective disease progression
- Group B: Day 1 - Carboplatin AUC 5.0 i.v. and Gemcitabine 1000 mg/m^2 i.v. and Day 8 - Gemcitabine 1000 mg/m^2 i.v, every 3 weeks, for a maximum of 6 cycles, or for 4 cycles for stable disease (or two cycles after best response – PR or CR)

Where possible, patients will be encouraged to crossover from Group A to B or B to A at the time of objective disease progression.

Target patient population

Male or female patients aged 18 or older with a ECOG PS 2, and measurable disease according to RECIST criteria. Patients must be chemotherapy-naive with histologically or cytologically confirmed locally advanced (Stage IIIB not curable with surgery or radiotherapy, or Stage IV) NSCLC.

Patients were entered to this study, initiated in 2004, before the significance of predictive factors such as smoking history, adenocarcinoma histology and mutation status was described.

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

Gefitinib (ZD1839, IRESSA™) 250 mg orally once daily. The formulations (batch) numbers were F12653, (10013118, 10018315, 1001788, 10039176, 10050162). Commercially-available gemcitabine (manufactured by Eli Lilly and Company) and carboplatin (manufactured by Bristol Myers Squibb) was supplied by the Investigators' pharmacies. The batch numbers are listed in Appendix 12.1.6.

Duration of treatment

ZD1839 was administered daily until objective PD, unacceptable toxicity, withdrawal of consent or closure of the study.

Cycles of gemcitabine/carboplatin were repeated every 3 weeks, for 4 cycles for SD, or 2 cycles after best response (PR or CR), but for a maximum of 6 cycles. Chemotherapy was discontinued if there was objective PD, unacceptable toxicity, withdrawal of consent or closure of the study.

Where possible, patients were encouraged to crossover from Group A to B or B to A at the time of objective disease progression.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: PFS (defined as the interval between the date of randomisation and the earliest date of objective disease progression according to The Response Evaluation Criteria in Solid Tumours [RECIST] or death due to any cause in the absence of progression

Safety

- Secondary variables: Nature, incidence and severity of adverse events and serious adverse events

Statistical methods

Efficacy was not evaluated in this abbreviated report. AEs were described using frequency and percentages.

The safety analysis comprised all subjects who took at least one dose of the randomised treatment.

Subject population

Table S1 Subject population and disposition

		ZD1839		Gemcitabine/ Carboplatin		Total	
Population							
N randomised (N planned)		18	(61)	17	(61)	35	(122)
Demographic characteristics							
Sex (N and % of subjects)	Male	12	(66.7)	9	(52.9)	21	(60.0)
	Female	6	(33.3)	8	(47.1)	14	(40.0)
Age (years)	Mean (SD)	66.2	(8.2)	67.8	(6.0)	67.0	(7.2)
	Range	50 to 83		56 to 75		50 to 83	
Race (N and % of subjects)	Caucasian	12	(66.7)	16	(94.1)	28	(80.0)
	Black	0	(0)	1	(5.9)	1	(2.9)
	Oriental	4	(22.2)	0	(0)	4	(11.4)
	Other	2	(11.1)	0	(0)	2	(5.7)
Baseline characteristics							
ECOG performance status	2	17	(94.4)	17	(100)	34	(97.1)
	Unknown	1	(5.6)	0	(0)	1	(2.9)
Disposition							
N analysed for efficacy (ITT)		18		17		35	
N analysed for safety[a]		17		17		34	

ITT=Intention to treat; N=Number; SD=standard deviation

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing

Efficacy and pharmacokinetic results

No analysis of the efficacy results was performed since the study was prematurely terminated.

Table S2 Progression-Free Survival (ITT)

Event		ZD1839 (N=18)	Gemcitabine/ Carboplatin (N=17)
Progression-Free Survival	Number (%) of patients with censored observations	1 (5.6%)	1 (5.9%)
	Median Progression-Free Survival Time	42 days	131 days
	95% CI for Progression-Free Survival Time[a]	35-90 days	66-190 days

CI=confidence intervals
[a] Estimated by Brookmeyer-Crowley method

Safety results

Table S3 Number (%) of subjects during randomised treatment 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]			
	ZD1839 (N=17)		Gemcitabine/ Carboplatin (N=17)	
Any AE	17	(100)	17	(100)
Drug related	11	(64.7)	14	(82.4)
Any SAE (including events with an outcome of death)	2	(11.8)	2	(11.8)
Drug related	0	(0)	1	(5.9)
Any AE leading to discontinuation of treatment	2	(11.8)	0	(0)
Drug related	0	(0)	0	(0)
Any AE leading with outcome of death	2	(11.8)	0	(0)
Drug related	0	(0)	0	(0)
Any CTC grade 3 or 4 AE	8	(47.1)	12	(70.6)
Drug related	1	(5.9)	7	(41.2)

AE=adverse event; CTC=Common Toxicity Criteria; SAE=serious adverse event
[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.

Table S4 Number (%) of subjects during randomised treatment with the most commonly reported[a] adverse events, sorted by decreasing order of frequency in the ZD1839 group (safety analysis set)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event			
	ZD1839 (N=17)		Gemcitabine/ Carboplatin (N=17)	
Diarrhoea	11	(64.7)	1	(5.9)
Dyspnoea	6	(35.3)	10	(58.8)
Nausea	5	(29.4)	8	(47.1)
Vomiting	5	(29.4)	1	(5.9)
Fatigue	4	(23.5)	8	(47.1)
Asthenia	3	(17.6)	5	(29.4)
Headache	3	(17.6)	4	(23.5)
Cough	3	(17.6)	2	(11.8)
Rash	3	(17.6)	2	(11.8)
Anorexia	3	(17.6)	1	(5.9)
Decreased appetite	3	(17.6)	0	(0)
Dry skin	3	(17.6)	0	(0)
Hypoaesthesia	3	(17.6)	0	(0)
Constipation	2	(11.8)	11	(64.7)
Pain in Extremity	2	(11.8)	4	(23.5)
Dizziness	2	(11.8)	3	(17.6)
Sputum discoloured	2	(11.8)	3	(17.6)
Confusional state	2	(11.8)	2	(11.8)
Dysphonia	2	(11.8)	2	(11.8)
Erythema	2	(11.8)	2	(11.8)
Haemoptysis	2	(11.8)	2	(11.8)
Oedema peripheral	2	(11.8)	2	(11.8)
Stomatitis	2	(11.8)	2	(11.8)
Anxiety	2	(11.8)	1	(5.9)
Insomnia	2	(11.8)	1	(5.9)
Pruritus	2	(11.8)	1	(5.9)
Weight decreased	2	(11.8)	1	(5.9)
Acne	2	(11.8)	0	(0)

Table S4 Number (%) of subjects during randomised treatment with the most commonly reported[a] adverse events, sorted by decreasing order of frequency in the ZD1839 group (safety analysis set)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event			
	ZD1839 (N=17)		Gemcitabine/ Carboplatin (N=17)	
Urinary tract infection	2	(11.8)	0	(0)
Wheezing	2	(11.8)	0	(0)
Productive cough	1	(5.9)	3	(17.6)
Catheter site pain	1	(5.9)	2	(11.8)
Decubitus ulcer	1	(5.9)	2	(11.8)
Dyspepsia	1	(5.9)	2	(11.8)
Neutropenia	0	(0)	6	(35.3)
Epistaxis	0	(0)	4	(23.5)
Back pain	0	(0)	2	(11.8)
Muscular weakness	0	(0)	2	(11.8)
Pain	0	(0)	2	(11.8)
Pitting oedema	0	(0)	2	(11.8)
Thrombocytopenia	0	(0)	2	(11.8)
Toothache	0	(0)	2	(11.8)

[a] This table includes those adverse events occurring in at least 6% of the study population, in either treatment group.

Table S5 Number (%) of subjects during crossover treatment 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]			
	ZD1839 (N=9)		Gemcitabine/ Carboplatin (N=6)	
Any AE	8	(88.9)	6	(100)
Drug related	6	(66.7)	3	(50.0)
Any SAE (including events with an outcome of death)	2	(22.2)	2	(33.3)
Drug related	1	(11.1)	1	(16.7)

Table S5 Number (%) of subjects during crossover treatment 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]			
	ZD1839 (N=9)		Gemcitabine/ Carboplatin (N=6)	
Any AE leading to discontinuation of treatment	0	(0)	0	(0)
Drug related	0	(0)	0	(0)
Any AE leading with outcome of death	2	(22.2)	1	(16.7)
Drug related	1	(11.1)	0	(0)
Any CTC grade 3 or 4 AE	7	(77.8)	4	(66.7)
Drug related	3	(33.3)	2	(33.3)

AE=adverse event; CTC=Common Toxicity Criteria; SAE=serious adverse event

[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.

The most commonly reported adverse events by System organ class and Preferred term were similar between randomised treatment and crossover treatment in both treatment groups.