Drug Product	Iressa™	**SYNOPSIS**	
Drug Substance	ZD1839		
Study Code	1839IL/0100		
Date	12 October 2006		

A phase I/II trial to evaluate ZD1839 (Iressa™) in combination with radiotherapy and gemcitabine as first-line treatment in patients with locally advanced, unresectable pancreatic cancer

Publications

Phase I trial of gefitinib with concurrent radiotherapy and fixed 2-h gemcitabine infusion, in locally advanced pancreatic cancer.

International Journal of Radiation OncologyBiologyPhysics, Volume 66, Issue 5, Pages 1391-1398

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Trial dates		**Phase of development**
First patient registered	2 August 2002	I/II
Trial closure	4 April 2005	

Objectives

Primary

The primary objective of the trial was to identify the maximum tolerated dose (MTD) of gemcitabine given as a 2-hour intravenous (iv) infusion that could be administered in combination with ZD1839 250 mg once daily and a standard course (45 Grays [Gy]) of radiotherapy in patients with locally advanced, unresectable pancreatic cancer.

Secondary

The secondary efficacy objectives of the trial were (Part C only):

1. To estimate the overall objective response rate (complete response [CR] and partial response [PR]) at the recommended dose level

2. To estimate the disease control rate

3. To estimate time to progression (TTP)

4. To estimate overall survival

The secondary safety objectives of the trial were (Parts A, B and C):

1. To further characterise the safety profile of ZD1839 at a 250 mg daily dose

2. To evaluate the safety and tolerability of the combination ZD1839, radiotherapy and gemcitabine

Trial design

A multicentre, open-label, non-comparative, dose-finding phase I/II trial in three parts:

Part A: Initial cohort of 6 patients to demonstrate the tolerability of ZD1839 and radiotherapy only

Part B: Cohorts of three to six patients treated at increasing doses of gemcitabine in combination with ZD1839 and radiotherapy

Part C: An additional cohort of 27 patients treated at one dose level below the MTD to provide further safety and tolerability information on the combination and to provide preliminary information on activity. This part of the trial was not undertaken.

Target patient population

Part A: Male or female patients aged 18 years or older with histologically-confirmed, unresectable pancreatic cancer locally advanced (Stage III-IVa) or with residual disease after surgery who have received no previous chemotherapy or radiotherapy.

Part B and Part C: Male or female patients aged 18 years or older with histologically-confirmed, locally advanced, stage III -IVa, unresectable, non-metastatic pancreatic cancer who have received no previous chemotherapy or radiotherapy.

Investigational product, dosage and mode of administration

ZD1839 (Iressa^{TM}) tablets 250 mg; one tablet (250 mg) orally once daily, administered continuously. All patients were to receive the same dose and schedule of ZD1839.

Combination therapy, dosage and mode of administration

Radiotherapy and chemotherapy (gemcitabine) were to be administered concomitantly with ZD1839 as trial therapy.

Part A: An initial cohort of 6 patients was to receive ZD1839 and radiotherapy only. The safety and tolerability of the combination were to be monitored in this cohort before gemcitabine was added to the combination therapy. If there were three or fewer patients with dose-limiting toxicity (DLT) in this initial cohort, the trial was to proceed to Part B with

three patients initially recruited to ZD1839, radiotherapy and gemcitabine according to the dose-escalation schedule below. If two or more patients experienced DLT in Part A, the combination was to be considered intolerable and the trial was to be stopped.

DLT was defined as unacceptable toxicity meeting one of the following criteria: febrile neutropenia, neutropenia grade 4 lasting more than 5-7 days, common toxicity criteria (CTC) grade 4 thrombocytopenia, and grade 4 non-haematological toxicity (except alopecia and vomiting without treatment).

Radiotherapy: Daily fractions of 1.8 Gy delivered 5 days a week for 5 weeks, to a total dose of 45 Gy. All patients were to receive the same dose and schedule of radiotherapy. The following radiotherapy guidelines were to be followed:

- No radiotherapy given to regional lymph nodes. Lymph nodes > 1.5 cm in diameter were to be considered as pathologic and included in the radiotherapy area
- Radiotherapy volume < 500 cm^3, with security borders < 2 cm
- Computerised tomography (CT) scan (TAC) simulation, with cross section 3-5 mm
- Tumoural volume $\geq$ 500cm^3 by scan simulation planification were excluded
- Suitable technique with optimal dosimetry

Part B: Gemcitabine: All patients (except patients in Part A who were to receive ZD1839 and radiotherapy only) were to receive gemcitabine (Gemzar®) administered as a 2-hour iv infusion once a week for 5 weeks. The first cohort of three patients to receive gemcitabine was to be treated with 100 mg/m^2 per week (Dose Level 1). Dose escalation for subsequent cohorts was to proceed according to the following criteria:

- If no patient experienced a DLT, the subsequent cohort of three patients was to be enrolled at the next dose level
- If one patient had a DLT, a further three patients were to be enrolled at the same dose level
- If two or more patients in an initial cohort of three or an expanded cohort of six patients had a DLT, the dose was to be considered to be the MTD and three patients were to be enrolled at the previous dose level to define the toxicity

The dose of gemcitabine was to be increased/decreased according to the following schedule:

Dose level	Gemcitabine (mg/m2/week)
Level -2	50
Level -1	75
Level 1	100
Level 2	150
Level 3	200

Intrapatient dose escalation was not permitted.

Part C: Once the MTD had been identified, a further cohort of 27 patients was to be enrolled at the dose below the MTD (the recommended dose) to provide further safety and tolerability information on the combination and to provide preliminary information on activity. This part of the trial did not proceed.

Duration of treatment

ZD1839: Treatment with ZD1839 was to commence on Day 1 of Week 1, concurrently with the start of radiotherapy (Parts A, B and C) and gemcitabine (Parts B and C only), and was to continue until disease progression, unacceptable toxicity or withdrawal of consent, except in the case of CR or PR (surgical where the patient was eligible for surgical resection) after tumour assessment in Week 11 when, if surgery was planned, ZD1839 treatment was to be terminated 5 days before surgery.

In case of stable disease (SD) or PR where the patient was not eligible for surgical resection, after tumour assessment in Week 11, the patient could continue monotherapy with ZD1839 until disease progression, unacceptable toxicity or withdrawal of consent.

Radiotherapy: Radiotherapy was to be delivered for 5 weeks.

Chemotherapy: Gemcitabine was to be administered once weekly for 5 weeks.

The dosing schedule is shown below:

Week 1	Week 2	Week 3	Week 4	Week 5
← ZD1839 250 mg once daily* →				
G G	G G	G		
RRRRR	RRRRR	RRRRR	RRRRR	RRRRR

G = gemcitabine iv infusion
R = radiotherapy 1.8 Gy daily fractions
* ZD1839: 250 mg continuing until progression or surgical resection.

Trial treatment was to be stopped in cases of disease progression, unacceptable toxicity or withdrawal of consent.

Endpoints

- **Efficacy (for patients treated at the Recommended Dose Level – Part C) – this part of the trial was not performed**

  Secondary endpoints

  – Overall objective tumour response (CR and PR) based on the Response Evaluation Criteria in Solid Tumours (RECIST), assessed by abdominal CT (abdominal scan)

  – Incidence of controlled disease (CR and PR and SD), assessed by abdominal CT (abdominal scan)

  – TTP

  – Overall survival

- **Safety (Parts A, B and C)**

  Primary endpoint

  – Incidence of DLT

  Secondary endpoints

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

  – Incidence of and reasons for trial drug dose interruptions, trial drug dose reductions and withdrawals

  – Trial drug exposure, laboratory assessments, physical examinations

Statistical methods

Patients planned:

Part A: Initial cohort of 6 patients was to receive ZD1839 and radiotherapy only. If two or more patients experienced DLT, the combination was to be considered intolerable and the trial was to be stopped.

Part B: Cohorts of three patients in each dose level, expanded to six patients if one patient experienced DLT.

Part C: An additional cohort of 27 patients was to be recruited at one dose level below the MTD to provide further safety and tolerability information on the combination and to provide preliminary information on activity. This part of the trial was not performed.

Part A and Part B

The primary objective of this trial was to determine the dose combination at which DLT occurred and from this to define the MTD. The number of patients to be recruited was determined by the objective to gain adequate valid safety information while exposing as few patients as possible to sub-optimal or toxic levels of treatment. No formal patient number calculation was performed because it was dependent on the number of dose escalations required to determine the MTD.

Part C (this part of the trial was not performed)

Fleming's method was used to calculate the number of patients required to be able to interpret the preliminary data on activity, and to confirm that the activity of the combination of gemcitabine and radiotherapy was not compromised with the addition of ZD1839. A sample size of 27 patients was sufficient to give an 80% probability of rejecting a baseline response rate of 5% with an exact 5% one-sided significance test when the true response was at the clinically relevant rate of 20%. The hypothesis that the response rate was equal to or less than the baseline was to be rejected if four or more responses were observed out of the 27 patients.

The safety population was to consist of all patients that were enrolled and received trial drug. The intent to treat (ITT) population was to consist of all subjects that were enrolled and received the trial treatment at the recommended dose level in Part C of the trial. The analysis population for all efficacy endpoints was to be the ITT population. All other presentations were to be based on the safety population. However, as Part C of the trial was not performed, the ITT population was redefined as all patients in Parts A and B of the trial who received at least one dose of ZD1839.

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 controlled disease rates were to be summarised by proportions together with a 95% confidence interval. Durations (TTP and overall survival) were to be summarised by Kaplan-Meier methods. Tolerability was to be summarised by the appropriate standard summary statistics.

Patient population

The population of trial patients was an acceptable representative group for this Phase I/II trial. Nineteen patients were screened, of whom 18 were eligible and registered for the trial. All 18 received at least one dose of ZD1839 and comprised the ITT population.

All 18 patients (100.0%) received ZD1839 and radiotherapy. Three patients also received gemcitabine at 100 mg/m^2/wk, six received gemcitabine at 150 mg/m^2/wk and three received gemcitabine at 200 mg/m^2/wk.

Of six patients who did not also receive gemcitabine (Part A), three did not complete the combination phase and the other three entered monotherapy but were not continuing at the end of the trial.

In Part B, all three patients who received gemcitabine at 100 mg/m^2/wk completed combination therapy; one entered monotherapy but was not continuing at trial end. Of six patients who received gemcitabine at 150 mg/m^2/wk, three did not complete combination therapy, one completed combination therapy but did not enter monotherapy, one entered monotherapy but was not continuing at trial end and the sixth continued monotherapy at trial end. Of three patients who received gemcitabine at 200 mg/m^2/wk, two did not complete combination therapy and the third entered monotherapy and continued monotherapy at the end.

Part C was not undertaken.

Tabla S 1 Patient population and disposition

Demographic or baseline characteristic		**Patients (N = 18)**	
Demographic characteristics			
Sex, n and (%) of patients	Male	8	(44.4)
	Female	10	(55.6)
Age (years)	Mean (SD)	60.3	(10.52)
	Range	42 to 76	
Race (n and % of patients)	Caucasian	18	(100.0)
Height (cm, n = 17)	Mean (SD)	161.6	(10.7)
	Range	143 to 182	
Baseline characteristics			
Weight (kg)	Mean (SD)	62.2	(8.85)
	Range	50.1 to 80.0	
Systolic blood pressure (mmHg, n = 14)	Mean (SD)	126.1	(20.49)
	Range	100 to 170	
Diastolic blood pressure (mmHg, n = 14)	Mean (SD)	72.9	(11.22)
	Range	60 to 90	
Heart rate (BPM, n = 15)	Mean (SD)	77.9	(14.03)
	Range	60 to 100	
ECOG (Eastern Cooperative Oncology Group) Performance Status (n and % of patients)	0 1 2	3 14 1	(16.7) (77.8) (5.6)
Disposition		Patients (N = 18)	

Demographic or baseline characteristic	**Patients (N = 18)**	
n (%) continuing monotherapy at trial end	2	(11.1)
n (%) entered monotherapy but not continuing at trial end	5	(27.8)
n (%) completed combination phase but did not enter monotherapy	3	(16.7)
n (%) did not complete combination phase	8	(44.4)
Patients who received ZD1839 and radiotherapy alone (n =6)		
n (% of group) continuing monotherapy at trial end	0	(0.0)
n (% of group) entered monotherapy but not continuing at trial end	3	(50.0)
n (% of group) completed combination phase but did not enter monotherapy	0	(0.0)
n (% of group) did not complete combination phase	3	(50.0)
Patients who received gemcitabine at 100 mg/m2/wk (n = 3)		
n (% of group) continuing monotherapy at trial end	0	(0.0)
n (% of group) entered monotherapy but not continuing at trial end	1	(33.3)
n (% of group) completed combination phase but did not enter monotherapy	2	(66.7)
n (% of group) did not complete combination phase	0	(0.0)
Patients who received gemcitabine at 150 mg/m2/wk (n = 6)		
n (% of group) continuing monotherapy at trial end	1	(16.7)
n (% of group) entered monotherapy but not continuing at trial end	1	(16.7)
n (% of group) completed combination phase but did not enter monotherapy	1	(16.7)
n (% of group) did not complete combination phase	3	(50.0)
Patients who received gemcitabine at 200 mg/m2/wk (n = 3)		
n (% of group) continuing monotherapy at trial end	1	(33.3)
n (% of group) entered monotherapy but not continuing at trial end	0	(0.0)
n (% of group) completed combination phase did but not enter monotherapy	0	(0.0)
n (% of group) did not complete combination phase	2	(66.7)

Efficacy results

Based on the RECIST, as assessed by abdominal CT, there were no responders by Week 11 (0.0%; exact 95% confidence interval (CI) for proportion of responders, 0.0% to 18.5%).

Abdominal scan at Week 11 showed stable disease (SD) in 9 patients (50.0%) and progressive disease (PD) in 7 patients (38.9%); two patients (11.1%) were not evaluable (NE).

One patient (5.6%; exact 95% CI 0.1% to 27.3%) was alive and progression-free at trial closure, two (11.1%) had died without prior documented disease progression and disease progression was reported for the other 15 patients (83.3%).

Median TTP was estimated at 110 days (95% CI 74 to 204 days).

The proportion alive and progression-free at 6 months was 33.3% (95% CI, 11.6% to 55.1%).

Two patients (11.1%; exact 95% CI 1.4% to 34.7%) were alive at trial closure and 16 (88.9%) were dead. Median survival time was estimated at 224 days (95% CI 145 to 374 days). The proportion of patients alive at 6 months was 66.7% (95% CI 44.9% to 88.4%).

Safety results

Median time on trial was 116 days (range 26 to 372 days) and median exposure to ZD1839 (time on treatment) was 98.5 days (range 25 to 372 days). Six patients (33.3%) had one or more interruptions of ZD1839 dose. These interruptions were due to toxicity in five (27.8%) patients. Two patients (11.1%) completed the trial (they were on monotherapy at trial closure), 12 (66.7%) discontinued because of disease progression, and four (22.2%) discontinued because of AEs.

Two patients (11.1%) were recorded with dose-limiting asthenia: this DLT was recorded with onset 7 days after first dose for one patient who received gemcitabine at 150 mg/m^2/week, and with onset 18 days after first dose for the second who received gemcitabine at 200 mg/m^2/week. The AEs, both with worst CTC grade 3, were not considered to be serious and led to withdrawal for one patient only. These AEs were recorded as DLTs in the CRF, although not in accordance with the criteria for DLT specified in the protocol. The MTD for gemcitabine in combination with ZD1839 and radiotherapy was therefore not identified.

Eighteen patients (100.0%) in the trial experienced AEs (all causalities) and 8 (44.4%) experienced SAEs. The most commonly reported AEs were gastrointestinal disorders (17 patients [94.4%]), general disorders and administration site conditions (15 patients [83.3%]), skin and subcutaneous tissue disorders (12 patients [66.7%]), metabolism and nutrition disorders (7 patients [38.9%]) and investigations (five patients [27.8%]). Asthenia was the most commonly reported individual AE, affecting 14 patients (77.8%). Diarrhoea was reported for 11 patients (61.1%), vomiting NOS was reported for 10 patients (55.6%), abdominal pain upper was reported for 8 patients (44.4%), and abdominal pain NOS, anorexia, rash NOS, and pyrexia were reported for 6 patients each (33.3%).

Sixteen (88.9%) patients had drug-related AEs; 6 of these (33.3%) had CTC grade 3 or 4 ZD1839-related AE(s). In general, the profile of ZD1839-related AEs was as expected for ZD1839, with diarrhoea NOS, rash NOS, and abdominal pain being most commonly recorded (7 [38.9%], 6 [33.3%], and five [27.8%] patients, respectively. Only asthenia (7 patients [38.9%]), pyrexia (three patients [16.7%]), and anaemia NOS (two patients [11.1%]) were attributed to other trial therapy alone.

Sixteen patients (88.9%) died during the trial. The deaths of 15 (83.3%) were cancer-related.

SAEs were recorded for 8 patients (44.4%). These comprised gastrointestinal disorders in three patients (16.7%), infections and infestations, blood and lymphatic system disorders, general disorders and administration site conditions, vascular disorders, and hepatobiliary disorders in two patients each (11.1%), and respiratory, thoracic and mediastinal disorders, and skin and subcutaneous disorders in one patient each (5.6%). Individual SAEs were considered to be related to ZD1839 treatment in the case of one patient each (5.6%) with neutropenia and visceral arterial ischaemia, and related to other trial therapy in the case of two patients (11.1%) with anaemia NOS.

Four patients (22.2%) were discontinued from trial treatment because of AEs comprising one case each of asthenia, respiratory failure, vasculitis, and visceral arterial ischaemia (this AE was considered to be ZD1839-related).

Haematology assessments that were categorised as AEs were limited to leukopenia NOS and neutropenia in one patient, leukopenia NOS, neutropenia, and anaemia NOS in a second, and anaemia NOS in a third, whilst blood chemistry abnormalities were recorded as AEs only in one patient each with increased alanine aminotransferase (ALT) and increased γ-glutamyl transferase (GGT) and one patient with hyperglycaemia.

Tabla S 2 Number (%) of patients who had an AE in any category (ITT analysis set)

Category of AE	**Number (%) of patients who had an AE in each categorya**	
Any AE	18	(100.0)
ZD1839-related AEs	16	(88.9)
SAEs	8	(44.4)
Serious ZD1839-related AEs	2	(11.1)
AEs leading to death	1	(5.6)
ZD1839-related AEs leading to death	0	(0.0)
Patient had CTC Grade 3 or 4 AE	10	(55.6)
Patient had CTC Grade 3 or 4 ZD1839-related AE	6	(33.3)
Withdrawal due to AEs	4	(22.2)

Category of AE	**Number (%) of patients who had an AE in each categorya**	
Withdrawal due to SAEs	3	(16.7)
Withdrawal due to ZD1839-related AEs	1	(5.6)
Withdrawal due to serious ZD1839-related AEs	1	(5.6)

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