AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA™
ACTIVE INGREDIENT: gefitinib/ ZD1839

Study No: 1839IL/0118, NCT00239291
A PHASE I/II STUDY OF ZD1839 (IRESSA™) GIVEN CONCURRENTLY WITH RADIOTHERAPY IN PATIENTS WITH NON-METASTATIC PROSTATE CANCER

Developmental phase: Phase I/II
Study Completion Date: 04 May 2006
Date of Report: 04 June 2007

OBJECTIVES:

The primary objective of the Phase I part of the trial was to estimate the safety of 250 mg ZD1839 given concurrently with 3-dimensional conformal radiotherapy (3D-CRT) in patients with non-metastatic prostate cancer.
The primary objective of the Phase II part of the trial was to estimate the safety and tolerability of 250 mg ZD1839 given concurrently with 3D-CRT in patients with non-metastatic prostate cancer.
The exploratory objective of this two-part trial was to assess epidermal growth factor receptor EGFR expression and activation status (autophosphorylation; pEGFRat diagnosis in patients with non-metastatic prostate cancer.

METHODS:

Trial design

A single centre, non-randomised, non-comparative, open-label, two-part trial. Part A of the trial had a safety design to estimate the tolerability of 250 mg ZD1839 given in combination with 3D-CRT in patients with non-metastatic prostate cancer. In Part B of the trial, the safety and tolerability of 250 mg ZD1839 given in combination with 3D-CRT was to be estimated in patients with non-metastatic prostate cancer.

Target patient population

Patients with histologically-confirmed local (T2) or locally advanced (T3) prostate cancer. Lymph node (Nx, N0) and metastasis (M0) negative patients, who were hormone-therapy naïve and whose prostate-specific antigen (PSA) levels were below 20 ng/mL. World Health Organisation (WHO) performance status (PS) of 0 - 1.

Investigational product, dosage and mode of administration

ZD1839 (Iressa™) tablets 250 mg. The first five patients in Part A of the trial were to receive 250 mg (one tablet) orally daily continuously from Day 1. If three or more patients experienced a dose-limiting toxicity (DLT), the maximum tolerated dose (MTD) had been exceeded and no more patients were to be recruited into the trial. If two or fewer of these patients developed DLT, a further seven patients were to be recruited. If five or more patients of the expanded cohort (12) of Part A experienced a DLT then no patients were to be recruited to Part B of the study.
DLT was to include any trial drug-related grade 4 haematological toxicity; any trial drug-related grade 3 non-haematological toxicity; any serious adverse event (SAE; excluding scheduled admissions to hospital); treatment interruption for longer than 14 days due to trial drug-related toxicity; more than three interruptions in treatment (excluding technical failure to deliver radiotherapy due to linear accelerator breakdown or service), or death from any cause.
3D-CRT starting on Day 8, 50.4 Grays (Gy) (1.8 Gy per day) was to be given to the seminal vesicles and to the prostate gland, including all tumour extensions outside the prostate, with about a 1 cm margin in 28 fractions (28 radiation therapy days, 5 days a week). Thereafter, 22 Gy (2 Gy per day) was to be given to the prostate gland and to extraprostatic tumour extension with a 1 cm margin except 0.6 cm margin to the rectum in 11 fractions (11 days). 3D-CRT of the prostate was thereby to consist of 72.4 Gy given in 39 fractions, and the total treatment time was to be about 53 days.

Comparator, dosage and mode of administration

Not applicable.

Duration of treatment

ZD1839 was to be administered from Day 1 continuously throughout the trial period until the end of 3D-CRT (a treatment duration of 60 days) or until unacceptable toxicity or withdrawal of consent.
3D-CRT was to be administered from Day 8 for approximately 53 days or until unacceptable toxicity or withdrawal of consent.

Endpoints

- **Primary endpoint**

Part A (Phase I part of trial)

- Incidence of DLTs

Part B (Phase II part of trial)

- Nature, incidence and severity of AEs and SAEs
- Incidence of and reasons for trial drug dose interruptions, trial drug dose reductions, and withdrawals
- Trial drug exposure, laboratory assessments, physical examinations

- **Exploratory**

Parts A and B

- EGFR expression and activation status at diagnosis

Statistical methods

It was planned to recruit a total of 37 patients on 250 mg ZD1839 (12 from Part A and 25 from Part B). Any AE with an underlying incidence of 7.5 % had a probability of at least 90 % of occurring in one or more of the 37 patients. All patients who were enrolled and received trial treatment were to be considered the intention-to-treat (ITT) population. The analysis population for the assessment of safety and tolerability at the 250 mg dose was to be 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. 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.
Of 53 patients who were screened, 42 were eligible, registered for the trial and received at least one dose of ZD1839. These comprised the ITT population, which was to be the analysis population for assessment of safety and tolerability.

All patients except one had significant past or current medical conditions. None was recorded as having previous treatment for cancer. Overall vital signs were normal at screening for all registered patients except one.
Thirty (71.4%) patients completed trial medication and 12 (28.6%) prematurely discontinued because of AEs.

Table S1 Patient population and disposition

		Patients (N = 42)	
Demographic characteristics			
Sex, n and (%) of patients	Male	42	(100.0)
Age (years)	Mean (SD)	65.9	(6.37)
	Range	47 to 75	
Race (n and % of patients)	Caucasian	42	(100.0)
Height (cm. n = 41)	Mean (SD)	177.4	(6.76)
	Range	163 to 192	
Baseline characteristics			
Weight (kg)	Mean (SD)	85.09	(14.870)
	Range	55.0 to 134.5	
Systolic blood pressure (mmHg. n = 41)	Mean (SD)	158.7	(18.36)
	Range	127 to 208	
Diastolic blood pressure (mmHg. n = 41)	Mean (SD)	90.4	(11.72)

		Patients (N = 42)	
	Range	64 to 122	
Heart rate (BPM)	Mean (SD)	75.5	(14.34)
	Range	49 to 118	
WHO PS (n and % of patients)	PS0	29	(69.0)
	PS1	13	(31.0)
	PS2	0	(0.0)
Disposition (n and % of patients)			
Did not prematurely discontinue trial medication		30	(71.4)
Prematurely discontinued trial medication		12	(28.6)
Prematurely discontinued trial medication because of AEs		12	(28.6)

Data derived from Tables T1.1 to T1.3.5

RESULTS:

Efficacy and pharmacokinetic results

There were no efficacy or pharmacokinetic objectives in this trial.

Safety results

Median time on trial was 154.0 days (range 19 to 197 days) and median exposure to ZD1839 (time on treatment) was 55.0 days (range 19 to 71 days). Thirty (71.4%) patients had one or more interruptions of ZD1839 dose due to toxicity. Thirty-nine (92.9%) patients had one or more interruptions in radiotherapy; these were due to toxicity in four (9.5%) cases. Thirty (71.4%) patients completed the trial and 12 (28.6%) discontinued because of AEs.

None of the stopping rules was activated and thus the MTD was not exceeded With ZD1839 at 250 mg daily. Overall the investigator recorded DLTs in fourteen (33.3%) patients. The most common DLTs were transaminase increases (11 [26.2%] patients had increased ALT, AST or both) as a result of which it was decided not to proceed to the 500 mg dose of ZD1839 as originally planned. One patient had urticara as well as increased transaminases. Of the remaining three patients, one had bladder pain, another had calculus urinary, and the third had gastroenteritis, renal insufficiency, cardiac failure, pyrexia, myocarditis and cardiomegaly.

All 42 (100.0%) patients in the trial experienced AEs; these were considered to be serious in three (7.1%) patients. The most commonly reported AEs were gastrointestinal disorders (40 [95.2%] patients), renal and urinary disorders (36 [85.7%] patients), skin and subcutaneous tissue disorders (34 [81.0%] patients), investigations (17 [40.5%] patients) and general disorders and administration site conditions (13 [31.0%] patients). Proctitis, pollakiuria, diarrhoea and dysuria were the most commonly reported individual AEs, affecting 32 (76.2%), 29 (69.0%), 28 (66.7%) and 24 (57.1%) patients, respectively.

Renal and urinary disorders were commonly reported as AEs probably related to ZD1839 treatment and to other trial therapies, with 29 (69.0%), 24 (57.1%) and 16 (38.1%) patients recorded with drug-related pollakiuria, dysuria and nocturia. Otherwise, in general, the profile of drug-related AEs was as expected for ZD1839, with gastrointestinal and skin and subcutaneous tissue disorders being most commonly recorded (40 and 34 patients, respectively). In most cases (except dyspepsia, nausea [in three of four affected patients], acne, dry skin, eczema and pruritus) these were also attributed to other trial therapies. Increased transaminases, seen in 17 (40.5%) patients, were attributed solely to ZD1839.

AEs with worst CTC grade 3 or 4 comprised seven instances of ALT increased, six of AST increased, five of pollakiuria and one each of cardiac failure, cardiomegaly, myocarditis, pyrexia, gastroenteritis, calculus urinary, dysuria, nocturia, renal insufficiency and urticaria.

Three (7.1%) patients were reported with SAEs; in one patient three SAEs (cardiomegaly, cardiac failure and myocarditis) were considered to have led to death. Other SAEs comprised pyrexia, gastroenteritis and renal insufficiency (in the patient mentioned above), bladder pain and pollakiuria in one patient and calculus urinary in another. All of these AEs were considered by the investigator to be probably related to ZD1839 treatment and to other trial therapy.
Nine other patients (21.4%) were discontinued from trial treatment because of AEs. The AEs comprised nine cases of ALT increased and seven cases of AST increased. These were all considered by the investigator to be related to ZD1839 treatment.
Several patients had some values for individual haematology parameters above or below project specific ranges but none was recorded as an AE. All patients had at least one value for individual clinical chemistry parameters above or below project specific ranges . These were recorded as AEs probably related to ZD1839 treatment for 17 (40.5%) patients with AST increased and 16 (38.1%) with ALT increased. For eight (19.0%) patients, increased ALT and AST were recorded as DLTs. Increased ALT alone was recorded as DLT for three (7.1%) patients.

Table S2 Number (%) of patients who had an adverse event in any category (ITT analysis set)

Category of AE	**Number (%) of patients who had an adverse event in each category[a]**	
Any AEs	42	(100.0)
ZD1839-related AEs	42	(100.0)
SAEs	3	(7.1)
Serious ZD1839-related AEs	3	(7.1)
AEs leading to death	1	(2.4)
ZD1839-related AEs leading to death	1	(2.4)
Patient had CTC grade 3 or 4 AE	13	(31.0)
Patient had CTC grade 3 or 4 ZD1839-related AE	13	(31.0)
Withdrawal due to AEs	12	(28.6)

Category of AE	Number (%) of patients who had an adverse event in each category[a]	
Withdrawal due to ZD1839-related AEs	12	(28.6)
Withdrawal due to SAEs	3	(7.1)
Withdrawal due to serious ZD1839-related AEs	3	(7.1)

Data derived from Table T3.2.1 and Listing Tables G7.1.1 to G7.1.5

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

Table S3 Number (%) of patients with the most commonly reported[a] AEs, sorted by decreasing order of frequency (ITT analysis set)

Preferred term	Number (%) of patients who had an adverse event in each category[a]	
Proctitis	32	(76.2)
Pollakiuria	29	(69.0)
Diarrhoea	28	(66.7)
Dysuria	24	(57.1)
Acne	17	(40.5)
AST increased	17	(40.5)
ALT increased	16	(38.1)
Nocturia	16	(38.1)
Dry skin	13	(31.0)
Flatulence	12	(28.6)
Fatigue	11	(26.2)
Dermatitis	8	(19.0)

[a] This table uses a cut-off of 10%

Data from Table T3.2.2

Table S4 Number (%) of patients who had a dose-limiting toxicity by preferred term (ITT analysis set)

Preferred term	Number (%) of patients who had a dose-limiting toxicity	
Total patients with DLTs	14	(33.3)
ALT increased	11	(26.2)
AST increased	8	(19.0)

Preferred term	Number (%) of patients who had a dose-limiting toxicity	
Bladder pain	1	(2.4)
Calculus urinary	1	(2.4)
Cardiac failure	1	(2.4)
Cardiomegaly	1	(2.4)
Gastroenteritis	1	(2.4)
Myocarditis	1	(2.4)
Pyrexia	1	(2.4)
Renal insufficiency	1	(2.4)
Urticaria	1	(2.4)

Data derived from Table T3.1, Listing Table 7.1.3

Table S5 Number (%) of patients with the most commonly reported drug-related AEs, sorted by decreasing order of frequency and by relationship to ZD1839 or to other trial therapy

System organ class and preferred term[a]	Number (%) of patients who had an adverse event in each category	
AEs related to ZD1839	**42**	**(100.0)**
Gastrointestinal disorders	40	(95.2)
Proctitis	32	(76.2)
Diarrhoea	28	(66.7)
Flatulence	12	(28.6)
Dyspepsia	4	(9.5)
Nausea	4	(9.5)
Renal and urinary disorders	36	(85.7)
Pollakiuria	29	(69.0)
Dysuria	24	(57.1)
Nocturia	16	(38.1)
Haematuria	3	(7.1)
Skin and subcutaneous tissue disorders	34	(81.0)
Acne	17	(40.5)
Dry skin	13	(31.0)
Dermatitis	8	(19.0)
Eczema	3	(7.1)
Pruritus	3	(7.1)

System organ class and preferred term[a]	Number (%) of patients who had an adverse event in each category	
Investigations	17	(40.5)
AST increased	17	(40.5)
ALT increased	16	(38.1)
General disorders and administration site conditions	10	(23.8)
Fatigue	8	(19.0)
Respiratory, thoracic and mediastinal disorders	5	(11.9)
Eye disorders	4	(9.5)
Keratoconjunctivitis sicca	3	(7.1)
Infections and infestations	3	(7.1)
Injury, poisoning and procedural complications	3	(7.1)
Dermatitis radiation	3	(7.1)
Metabolism and nutrition disorders	3	(7.1)
Nervous system disorders	2	(4.8)
Cardiac disorders	1	(2.4)
Reproductive system and breast disorders	1	(2.4)
AEs related to other trial therapy	**41**	**(97.6)**
Gastrointestinal disorders	39	(92.9)
Proctitis	32	(76.2)
Diarrhoea	28	(66.7)
Flatulence	12	(28.6)
Renal and urinary disorders	36	(85.7)
Pollakiuria	29	(69.0)
Dysuria	24	(57.1)
Nocturia	16	(38.1)
Haematuria	3	(7.1)
Skin and subcutaneous tissue disorders	11	(26.2)
Dermatitis	8	(19.0)
General disorders and administration site conditions	12	(28.6)
Fatigue	11	(26.2)
Respiratory, thoracic and mediastinal disorders	1	(2.4)
Psychiatric disorders	2	(4.8)
Infections and infestations	2	(4.8)
Injury, poisoning and procedural complications	3	(7.1)
Dermatitis radiation	3	(7.1)

System organ class and preferred term[a]	Number (%) of patients who had an adverse event in each category	
Metabolism and nutrition disorders	2	(4.8)
Reproductive system and breast disorders	2	(4.8)
Vascular disorders	1	(2.4)
Investigations	1	(2.4)
Cardiac disorders	1	(2.4)

Data from Table T3.2.3

[a]Individual AEs with frequency of > 5% are included in this table

Exploratory Results

Approximately half of the patients with evaluable data (17 patients, 48.6%) had all tumour cells positive for EGFR, and only one (2.6%) had no tumour cells positive for EGFR. No patients had cells positive for NCL-EGFR-TR.

Slightly more than half the patients (18, 51.4%) had an EGFR tumour to normal tissue ratio of 100% and the great majority (34, 97.1%) had an EGFR tumour to normal tissue ratio of 50% or greater.

Four (11.1%) patients had positive EGFR activation; of these 3 had an activation status (% level relative to EGFF1 expression levels) of 20%, and one had an activation status of 90%.

No patients had EGFR gene copy number amplification.