AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Iressa™
ACTIVE INGREDIENT: gefitinib/ZD1839

Study No: 1839IL/0155
AN OPEN LABEL, NON-COMPARATIVE, PHASE II TRIAL OF ZD1839 (IRESSA™) AS FIRST-LINE TREATMENT IN SUBJECTS WITH RELAPSED PROSTATE CANCER FOLLOWING RADICAL PROSTATECTOMY OR RADIOTHERAPY

Developmental phase: Phase II
Study Completion Date: 24 January 2006
Date of Report: 11 March 2009

OBJECTIVES:

Primary

The primary objective of the trial was to evaluate the activity of ZD1839 in subjects with relapsed prostate cancer by estimating the prostate-specific antigen (PSA) response rate (the percentage of subjects experiencing PSA normalisation or a ≥50% reduction in PSA levels sustained for 3 months, i.e., three consecutive PSA measurements) at trial closure.

Secondary

The secondary efficacy objectives of the trial were:

1. To estimate the time to treatment failure (TTF)
2. To estimate the duration of PSA response
3. To estimate the PSA progression-free survival (PSA PFS)

The safety objective of the trial was:

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

METHODS:

Trial design

A single-centre, open-label, non-randomised, non-comparative, Phase II trial.

Target subject population

Male subjects aged 18 years or older with prostate cancer who had either undergone radical prostatectomy or received radiotherapy. Subjects were to have rising PSA levels as determined by two (after prostatectomy) or three (after radiotherapy) consecutive, independent (at least 4 weeks apart) PSA increases (relapse). Lymph node (Nx, N0) and metastasis (M0) negative subjects. Subjects were to have stopped hormonal treatment at least 6 months before entry into the trial, have PSA levels below 10 ng/ml, and a World Health Organisation (WHO) performance status of 0 to 1.

Investigational product, dosage and mode of administration

ZD1839 (gefitinib, Iressa^{TM}) tablets 250 mg. Subjects were to receive 250 mg (one tablet) orally, once daily, administered continuously.

Comparator, dosage and mode of administration

Not applicable.

Duration of treatment

ZD1839 was to be administered daily until PSA progression (defined as doubling in serum PSA levels), unacceptable toxicity or withdrawal of consent. All subjects were to receive ZD1839 for a minimum of 3 months.

Outcome variables

Efficacy

– **Primary outcome variable**:

- PSA response rate at trial closure based on the percentage of subjects experiencing PSA normalisation or a ≥50% reduction in PSA levels compared with trial entry sustained for 3 months (i.e., three consecutive measurements)

– **Secondary outcome variables:**

- TTF (failure defined as a need for additional/alternative therapy due to PSA progression, metastases or adverse events [AEs])
- Duration of PSA response
- PFS (progression defined as doubling in PSA levels compared with the PSA level at trial entry)

Safety

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

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

– Trial drug exposure, laboratory assessments, physical examinations

Statistical methods

Using a single-stage Fleming design, 30 subjects were to be enrolled into the trial. It was assumed that the PSA response rate would be 40% or less. A critical value of 17 would define a test of this assumption with a one-sided significance level of 5% and that achieved a power of 80% against the alternate hypothesis that the PSA response rate was 63% or more.

All the subjects who were enrolled and received trial treatment were considered the intention-to-treat (ITT) population. The analysis population for all efficacy outcome variables 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. The PSA response rate was to be summarised by proportions together with a 95% confidence interval (CI) and a 90% CI. Durations (of TTF, PSA response and PSA PFS) were to be summarised by the appropriate standard summary statistics.

Patients who have not failed at trial closure will be censored.

Subject population

The population of trial subjects was an acceptable representative group for this Phase II trial. Thirty-six subjects were screened, and 30 were eligible for the trial, received at least one dose of ZD1839 and comprised the ITT population. This was the analysis population for safety and efficacy.

Table S1 Subject population and disposition

Demographic or baseline characteristic		**Subjects (N = 30)**	
Demographic characteristics			
Sex, n and (%) of subjects		This was an all-male trial	
Age (years)	Mean (SD)	66.3	(5.92)
	Range	52 to 76	
	<45	0	(0.0%)
	45 – 64	10	(33.3%)
	65 – 74	19	(63.3%)
	>75	1	(3.3%)
Height (cm)[a]	Mean (SD)	177.5	(6.43)
	Range	167 to 194	
Weight (kg)	Mean (SD)	83.23	(11.417)
	Range	69.8 to 114.6	
Baseline characteristics			
Systolic blood pressure (mmHg)	Mean (SD)	166.7	(23.34)
	Range	120 to 204	
Diastolic blood pressure (mmHg)	Mean (SD)	92.1	(10.10)

Demographic or baseline characteristic		Subjects (N = 30)	
	Range	78 to 116	
Heart rate (BPM)	Mean (SD)	68.6	(11.32)
	Range	54 to 102	
ECG evaluation	Normal	21	(70.0%)
	Abnormal	9	(30.0%)
WHO performance status (n and % of subjects)	0	24	(80.0)
	1	6	(20.0)
Free prostate-specific antigen (ng/ml)	Mean (SD)	0.215	(0.2089)
	Range	0.05 – 0.70	
Serum prostate-specific antigen (ng/ml)	Mean (SD)	2.690	(2.3596)
	Range	0.20 – 8.50	
Disposition[b]			
Completed		14	(46.7%)
Discontinued		15	(50.0%)
Unknown		1	(3.3%)
Analysed for safety and efficacy (ITT)		30	(100.0%)

[a] One subject omitted from data

[b] Number of subjects who took at least one dose of trial treatment and had at least one data point after dosing

N=Number

Source Tables 1.1 – 1.6 and Listing 8.7

RESULTS:

Efficacy results

PSA response was recorded for two subjects; PSA response rate was 6.67% (exact 95% CI for PSA response rate – 0.82 to 22.07, exact 90% CI for PSA response rate – 1.20 to 19.53).

Treatment failure was recorded for 22 (73.3%) subjects; eight (26.7%) subjects were censored. Five (16.7% - exact 95% CI 5.64% to 34.72%) subjects continued trial treatment at trial closure. Median time to treatment failure or death was 119 days (95% CI 85.0 to 156 days). Eighteen (60.0% - 95% CI 42.47% to 77.53%) subjects were alive without treatment failure at 3 months.

Two (6.7%) subjects were recorded with PSA response and one (3.3%) subject was censored. Duration of PSA response was not calculated.

Fourteen (46.7%) subjects were recorded with PSA progression and 16 (53.3%) subjects were censored. Sixteen (53.3% - exact 95% CI 34.33% to 71.66%) were PSA progression-free at trial closure. Median time to PSA progression was 179 days (lower exact 95% CI 119.0 [upper not calculable] days). Eighteen (60.0%) subjects were PSA progression-free at 3 months. The proportion of subjects PSA progression-free at 3 months, including those who discontinued before 3 months, was 74.9% (exact 95% CI 58.67% to 91.07%).

Safety results

Median time on ZD1839 treatment was 147.5 days (range 33 to 600 days). Fourteen (46.7%) subjects had one or more interruptions of ZD1839 dose, which were due to toxicity in 3 (10.0%) subjects. Fourteen (46.7%) subjects completed the trial, two (6.7%) discontinued because of disease progression, nine (30.0%) discontinued because of AEs and four (13.3%) discontinued for other reasons. One (3.3%) subject was omitted from the Termination From Trial listing.

All 30 (100.0%) subjects in the trial experienced AEs and all had AEs that were considered by the investigator to be ZD1839-related. Five (16.7%) subjects had CTC grade 3 or 4 AEs – these being considerd by the investigator as ZD1839-related for four (13.3%) subjects. AEs were recorded as severe for four (13.3%) subjects and severe and ZD1839-related for three (10.0%).
The most commonly reported AEs were skin and subcutaneous tissue disorders (26 [86.7%] subjects), gastrointestinal disorders (25 [83.3%] subjects) and infections and infestations (15 [50.0%] subjects). Acne and diarrhoea were the most commonly reported individual AEs, respectively affecting 23 (76.7%) and 17 (56.7%) subjects, and these were considered by the investigator to be ZD1839-related.

In general, the profile of ZD1839-related AEs was as expected.

No deaths were recorded during the trial.
A single SAE was recorded, comprising calculus urinary, which was not considered to be ZD1839-related.

Nine (30.0%) subjects were recorded with AEs leading to discontinuation; five of these (16.7%) had ALT and/or AST increased and all were considered to be ZD1839-related.
Seven (23.2%) subjects had a worst CTC grade of 3 for ALT, and two had a worst grade of 3 for AST. Six (20.0%) subjects experienced AEs of both ALT increased (two each with worst CTC grades 1, 2 and 3) and AST increased (four with worst CTC grade 1 and two with worst grade 2) and in all cases these were considered to be ZD1839-related by the investigator.
There were no clinically important abnormalities in haematology recorded as AEs or as CTC grades 3 or 4.

Table S2 Number (%) of subjects who had an AE in any category (ITT analysis set)

Category of AE	Number (%) of subjects who had an AE in each category[a]	
Any AEs	30	(100.0)
ZD1839-related AEs	30	(100.0)
SAEs	1	(3.3)
Serious ZD1839-related AEs	0	(0.0)
AEs leading to death	0	(0.0)

Category of AE	Number (%) of subjects who had an AE in each category[a]	
Subject had CTC grade 3 or 4 AE	5	(16.7)
Subject had CTC grade 3 or 4 ZD1839-related AE	4	(13.3)
Severe AE	4	(13.3)
Severe ZD1839-related AE	3	(10.0)
Withdrawal due to AEs	9	(30.0)
Withdrawal due to SAEs	0	(0.0)
Withdrawal due to ZD1839-related AEs	9	(30.0)
Withdrawal due to serious ZD1839-related AEs	0	(0.0)

Data derived from Table 6.1

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

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

Preferred term	Number (%) of subjects who had an AE in each category[a]	
Acne	23	(76.7)
Diarrhoea	17	(56.7)
Nausea	7	(23.3)
Constipation	6	(20.0)
Proctitis	6	(20.0)
Influenza	6	(20.0)
ALT increased	6	(20.0)
AST increased	6	(20.0)
Fatigue	4	(13.3)
Dry skin	4	(13.3)
Erythema	4	(13.3)
Cough	3	(10.0)
Onychomycosis	3	(10.0)
Dysgeusia	3	(10.0)
Flatulence	3	(10.0)
Epistaxis	3	(10.0)
Headache	3	(10.0)
Arthralgia	3	(10.0)
Anorexia	3	(10.0)

Preferred term	Number (%) of subjects who had an AE in each category[a]	
Conjunctivitis	3	(10.0)

[a] This table uses a cut-off of 10%
Data from Table 6.2

Table S4 Number (%) of subjects with the most commonly reported[a] ZD1839-related AEs, sorted by decreasing order of frequency (ITT analysis set)

Preferred term	Number (%) of subjects who had an AE in each category[a]	
Acne	23	(76.7)
Diarrhoea	17	(56.7)
Nausea	6	(20.0)
Proctitis	6	(20.0)
ALT increased	6	(20.0)
AST increased	6	(20.0)
Constipation	5	(16.7)
Fatigue	4	(13.3)
Dry skin	4	(13.3)
Erythema	4	(13.3)
Cough	3	(10.0)
Flatulence	3	(10.0)
Onychomycosis	3	(10.0)
Dysgeusia	3	(10.0)
Epistaxis	3	(10.0)
Anorexia	3	(10.0)
Conjunctivitis	3	(10.0)

[a] This table uses a cut-off of 10%
Data from Table 6.5