AstraZeneca

Drug product:	Gefitinib	**SYNOPSIS**	
Drug substance(s):	Gefitinib		
Study code:	1839US/0040		
Date:	02 November 2004		

A phase II, open-label trial to assess the activity of ZD1839 (IRESSA™) in patients with recurrent prostate cancer who have rising serum PSA levels despite serum testosterone < 50 ng/dL

Study centers

This study was conducted in 10 US centers.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	10 May 2001	Therapeutic exploratory (II)
Last patient completed	8 April 2002	

Objectives

Primary objective

- to determine the percentage of patients experiencing a ≥50% decline in serum prostate-specific antigen (PSA)

Secondary objectives

- to evaluate the duration of PSA decline
- to estimate the time to progression (TTP)
- to evaluate the changes in quality of life (QOL)
- to characterize the safety profile of ZD1839

Exploratory objectives

- to evaluate the correlation of epidermal growth factor receptor (EGFR) expression and its relationship to serum PSA decline and TTP
- to assess the steady state exposure to ZD1839 and investigate any relationship between exposure, PSA changes, and other pertinent variables
- to evaluate the PSA slope before and during ZD1839 therapy

Study design

This was an open-label, non-randomized, single-arm, multicenter study.

Target patient population and sample size

This study was conducted in patients with recurrent prostate cancer who had rising serum PSA levels despite serum testosterone below 50 ng/dL, and who had histological or cytological confirmation of original prostate cancer diagnosis.

At least 45 evaluable patients needed to be enrolled in this study in order to observe a 5% response rate if the true response rate was at least 20%, with a power of at least 90% for a 2-sided 5% significance level test. If exactly 45 patients were evaluable, 6 patients would be required to have a PSA decline in order to conclude the response rate was 20% (observed response rate, 13.3%; 95% CI, 5.1% to 26.8%).

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

ZD1839, formulation number F12653, was administered orally in 250-mg tablets, 2 tablets once daily (batch numbers 2000015310, 2000026445) beginning from within 72 hours of enrollment. The dosage was reduced to 250 mg once daily for intolerance to study drug.

Duration of treatment

Patients received ZD1839 for 6 months; ZD1839 administration was allowed to continue as long as patients demonstrated evidence of PSA response and clinical benefit from this treatment.

Criteria for evaluation (main variables)

The primary analysis was performed on data from patients in the evaluable-for-PSA-decline population. The evaluable-for-PSA-decline population is a subset of those patients in the intention-to-treat (ITT) population who remained in the study for at least 84 days, or who were withdrawn from the study at the discretion of the investigator before 84 days because of study drug toxicity or disease progression as determined by radiologic or physical examination. Patients in the ITT population were excluded from the evaluable-for-PSA-decline population if they met any 1 of the following criteria:

- patients withdrew from the study before Visit 5 (ie, who did not receive at least 3 months of ZD1839 pharmacotherapy)
- patients withdrew from the study because of increasing serum PSA concentrations
- patients withdrew their consent to participate in the study (eg, those who withdrew because of toxicity)
- patients without serum PSA concentration values obtained at baseline (Day 1) or within 7 days before baseline during a screening visit
- patients with serum PSA concentrations reported by local laboratories (only concentrations obtained by the central laboratory were evaluable for PSA decline)

Efficacy and pharmacokinetics

- Primary variable: serum PSA concentration as determined by a central laboratory using a third-generation method.
- Secondary variables: duration of decline in serum prostate-specific antigen concentration, TTP, tumor assessment, the Functional Assessment of Cancer Therapy-Prostate (FACT-P) QOL questionnaire, trough concentrations of ZD1839
- Exploratory variable: EGFR expression

Safety

Tolerability was assessed in terms of adverse events, serious adverse events, and laboratory data (hematology, clinical chemistry, urinalysis).

Statistical methods

Efficacy was assessed by analyzing the PSA decline rate with a 1-sided test at a 2.5% significance level. The primary analysis was performed on data from patients in the evaluable-for-PSA-decline population. Secondary analyses of the PSA decline rate were also performed on data from patients in the per-protocol and ITT populations to assess population sensitivity.

No interim analyses were planned or performed for this study.

Patient population

Of 82 men with prostate cancer who were screened to enter this study, 58 enrolled and received study drug; 5 patients completed the study. Fifty-two enrolled patients were evaluable for improvement in QOL, 40 were evaluable for PSA decline, and 5 were in the per-protocol population. The mean serum PSA concentration for 53 men who provided data at baseline was 38 ng/mL, ranging from 5 ng/mL to 187 ng/mL (Table S1).

More than three-quarters of patients were Caucasian. Mean patient age was 73 years, ranging from 54 to 88 years. All but 1 patient had a WHO performance score of 0 or 1 at baseline. More than 20% of patients were previously treated for prostate cancer by at least 1 of the following: medical castration, radiotherapy, surgical castration, or radical prostatectomy. More than 80% of patients previously received anti-prostate cancer treatment by endocrine therapy.

The most frequent medications administered to at least 20% of subjects before entering the study were analgesics and antipyretics, HMG coenzyme A reductase inhibitors (statins), and propionic acid derivatives. The most frequent medications administered to at least 20% of subjects after entering the study were antipropulsives, analgesics and antipyretics, contrast media, HMG CoA reductase inhibitors (statins), vitamin preparations, propionic acid derivatives, and systemic antihistamines.

Table S1 Subject population, demographic and baseline characteristics, and disposition (all patients)

Demographic or baseline characteristic		**N = 58[a]**	
Demographic characteristics			
Age (years)	Mean (SD)	73	(8.3)
	Range	54 to 88	
Race (n and % of patients)	Black	9	(16)
	Caucasian	45	(78)
	Hispanic	4	(7)
Baseline characteristics			
Body mass index	Mean (SD)	29.8	(4.95)
	Range	19.3 to 42.7	
Performance status (n and % of patients)	Normal activity (PS 0)	42	(72)
	Restricted activity (PS 1)	15	(26)
	In bed ≤50% time (PS 2)	1	(2)
	In bed >50% time (PS 3)	0	
	100% bedridden (PS 4)	0	

Table S1 Subject population, demographic and baseline characteristics, and disposition (all patients)

Demographic or baseline characteristic		N = 58[a]	
Previous prostate cancer treatment	Medically castrated	45	(78)
(n and % of patients)	Surgically castrated	13	(22)
	Radiotherapy	25	(43)
	Brachytherapy	4	(7)
	Radical prostatectomy	12	(21)
	Partial prostatectomy	4	(7)
	Cryotherapy	1	(2)
Prior anti-prostate cancer treatment	Endocrine therapy, anti-androgens	52	(90)
(n and % of patients for n≥3)	Endocrine therapy, gonadotropin releasing hormone analogues	48	(83)
	Cytokines and immunomodulators	16	(28)
	Systemic corticosteroids	8	(14)
	Other therapeutic products	6	(10)
	Antiandrogens	3	(5)
Serum prostate-specific antigen	mean (SD)	38	(37.2)
concentration (ng/mL)	median	23	
	range	5 to 187	
	n	53	

[a] Data are summarized for 58 men unless otherwise specified.
SD Standard deviation.

The treatment group was representative of patients with prostate cancer.

Efficacy and pharmacokinetic results

None of the 40 patients evaluable for PSA decline were PSA responders; there was no evidence of anti-tumor activity in this patient population. The mean change from baseline serum PSA concentration at the withdrawal/completion visit was 43 ng/mL, the mean change ranging at any visit from 5 ng/mL at months 5 and 6 to 44 ng/mL at month 3.

The duration of PSA decline could not be determined because none of the patients experienced a PSA decline as defined in the study.

TTP analyses were not performed because of the number of patients who withdrew from the study before month 6 and because most had an increase in PSA throughout; 3 patients had

stable PSA levels through 6 months of therapy. Therefore, estimating TTP would not have provided any useful information.

The rate of change in serum PSA concentrations was not determined because a linear relationship was not found between PSA and time.

The mean change from baseline FACT-P score at the withdrawal/completion visit was –7, which indicates a worsening QOL on average. Mean changes from baseline FACT-P scores decreased continuously from –4.4 at month 1 to –6.3 at month 3, then gradually increased to 1.1 at month 6.

The mean change from baseline Prostate Cancer Subscale (PCS) score at the withdrawal/completion visit was –1; the mean change ranged at any visit from –1.9 at month 2 to 1.4 at month 5.

The mean change from baseline Trial Outcome Index (TOI) score at the withdrawal/completion visit was –6.2, which indicates a decrease in patient functionality.

As a consequence of the lack of response data seen in this study, the investigation of relationships with exposure was not considered appropriate. While no attempt was made to ascertain from each patient's dosing history that these were all true steady-state trough samples, the concentrations determined do not appear to be atypical to those seen in patients on the same dose level 24 to 28 hours following administration of study drug in other ZD1839 monotherapy studies.

Safety results

All but 1 patient experienced an adverse event; 11 (19%) patients withdrew from the study because of adverse events. Eleven (19%) patients experienced 13 serious adverse events, 2 of which occurred before the first administration of study drug (Table S2). No patients died during the study or within 30 days after completing the study.

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

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]	
	N = 58	
Any adverse events	57	(98)
Serious adverse events[b]	11	(19)
Discontinuations of study treatment attributed to adverse events	11	(19)
Other significant adverse event CTC grade 3 or 4 events[c]	17	(29)
	Total number of adverse events while on treatment[d]	
Any adverse events	560	
Serious adverse events [b]	11	
Other significant adverse events CTC grade 3 or 4 events[c]	23	

[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.

[b] Two patients (Patients 2087/0047 and 2043/0039) each experienced a serious adverse event that occurred before the first administration of study drug. These 2 events are not counted in this table, but are listed in Table 12.2.7.4.

[c] One patient (Patient 2087/0047) experienced 2 CTC grade 3 adverse events that occurred before the first administration of study drug. These 2 events are not counted in this table, but are listed in Table 11.3.6.2.3.

[d] Adverse events are counted from the first administration of study drug until 30 days after the last administration of study drug.

The most common adverse events experienced by at least 25% of patients by COSTART body system were skin and appendages, digestive, whole body, respiratory system, metabolic and nutritional, nervous system, special senses, and urogenital.

The most common adverse events experienced by at least 20% of patients were diarrhea, rash, dry skin, nausea, asthenia, acne, and anorexia (Table S3).

Table S3 Number (%) of patients with adverse events with an incidence ≥5%, sorted by decreasing order of frequency (safety analysis set)

COSTART term	N = 58	
	n	(%)
Diarrhea	41	71
Rash	33	57
Dry skin	21	36
Nausea	18	31

Table S3 Number (%) of patients with adverse events with an incidence ≥5%, sorted by decreasing order of frequency (safety analysis set)

COSTART term	N = 58	
	n	(%)
Asthenia	16	28
Acne	14	24
Anorexia	12	21
Pruritus	11	19
Pain	10	17
Epistaxis	9	16
Abdominal pain	8	14
Conjunctivitis	8	14
Peripheral edema	8	14
Pharyngitis	8	14
Dizziness	6	10
Rhinitis	6	10
Back pain	5	9
Cough increased	5	9
Dry mouth	5	9
SGPT increased	5	9
Taste perversion	5	9
Vomiting	5	9
Weight loss	5	9
Amblyopia	4	7
Constipation	4	7
Face edema	4	7
Hyperesthesia	4	7
Hypertonia	4	7
Paresthesia	4	7
Depression	3	5
Ecchymosis	3	5
Flatulence	3	5
Headache	3	5
Hematuria	3	5

Table S3 Number (%) of patients with adverse events with an incidence ≥5%, sorted by decreasing order of frequency (safety analysis set)

COSTART term	N = 58	
	n	(%)
Herpes simplex	3	5
Insomnia	3	5
Kidney function abnormal	3	5
Skin ulcer	3	5
Urinary retention	3	5
Urinary tract infection	3	5

The safety profile of 500 mg of ZD1839 in this study is consistent with that found in other clinical studies of this dosage of ZD1839. No new safety concerns were identified in this study.

Over 80% of patients experienced adverse events relating to skin and appendages and the digestive system, 29% of patients had adverse events relating to special senses. Of the 10 most frequently occurring adverse events experienced by more than 15% of patients, 4 were related to skin and appendages (rash, dry skin, acne, pruritus) and 3 to the digestive system (diarrhea, nausea, anorexia); 8 (14%) patients experienced conjunctivitis. No adverse events resulted in death.

Most adverse events leading to discontinuation were associated with skin and appendages and the digestive systems; most were of mild or moderate intensity, and most were related to study drug. One patient discontinued study drug because of elevated aminotransferases.

Two patients experienced more than 1 serious adverse event. The most common serious adverse events were related to the urogenital system (1 occurrence each of hematuria, urinary tract disorder, and urinary tract infection), the nervous system (2 occurrences of urinary retention), the cardiovascular system (1 occurrence each of sinus bradycardia and elective aneurysm repair), and special senses (1 occurrence each of amblyopia and photophobia in 1 patient). Two of the 13 serious adverse events (wound infection and dehydration) were considered related to study drug by the investigator.

No trends in clinical laboratory results were seen, and there was no evidence of consistent drug-related adverse events associated with study drug.

No vital sign measurement, physical finding, concomitant medication, or change in weight, ECG recording, or WHO performance score suggested any new safety concern for this study drug.