AstraZeneca

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SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA™

ACTIVE INGREDIENT: Gefitinib

Trial title: A PHASE II EXPLORATORY, MULTICENTRE, OPEN-LABEL, NON-COMPARATIVE STUDY OF ZD1839 (IRESSA™) AND RADIOTHERAPY IN THE TREATMENT OF PATIENTS WITH GLIOBLASTOMA MULTIFORME.

Developmental phase: II
First subject recruited: 11 February 2003
Last subject completed: 8 November 2005
Approval date: 09 May 2007

OBJECTIVES

Primary objective:

The primary objective was to evaluate the objective tumour response at 6 months after the end of combination treatment with ZD1839 and irradiation in patients with glioblastoma multiforme (GBM) by computerised tomography (CT) scan or magnetic resonance imaging (MRI) of the brain according to Macdonald criteria.

Secondary objectives

1. To evaluate the disease control rate at 6 months after the end of combination treatment
2. To estimate clinical or radiological time to progression (TTP)
3. To estimate the overall survival
4. To estimate the safety of ZD1839 in combination with radiotherapy

Exploratory objectives

When possible, to analyse EGFR 1-4 expression and markers of EGFR signal pathways in all possible tumours and in skin biopsies using real-time PCR and/or western blot and immunohistochemistry, and to correlate tumour response to EGFR expression. (Analysis of glioma tissues was to be performed on specimens taken at surgery and analysis of skin on specimens obtained before and after initiation of ZD1839 treatment.)

Study design

This was an open, multicentre, non-comparative, Phase II study. The relevant level of therapeutic efficacy considered to be significant was a response rate of 20%. Response was defined as partial or complete response according to Macdonald criteria at 6 months after the end of combination treatment with ZD1839 and irradiation.

The study was to start with a short dose escalation of ZD1839 to establish the tolerated dose of the combination of ZD1839 and radiotherapy.

Target patient population

Male and female patients aged 18 years or above, with histologically- or cytologically- confirmed GBM. The patients in the target population were those patients with verified tumour expressing EGFR. However, all patients otherwise eligible for the study were also to be consecutively included because there was still controversy regarding the efficacy of EGFR analysis. Patients were to be treatment-naïve (excluding surgery) and were to have a World Health Organisation (WHO) performance status (PS) of 0 - 2.

Investigational product, dosage and mode of administration

Patients who met the selection criteria were to receive ZD1839 in combination with radiotherapy as follows: ZD1839 (Iressa^{TM}) 250 mg and 500 mg (two 250 mg tablets). Six patients were to be treated with 250 mg ZD1839 in the first instance. If there were two or fewer grade 3 - 4 toxicity observed, the dose was to be increased to 500 mg. After the sixth patient had been entered, there may have been a break in recruitment whilst the safety assessment was being made. If three or more among the first six patients experienced grade 3 - 4 toxicity at the 250 mg dose the continuation of the study was to be discussed by the AstraZeneca study physician and the co-ordinating Principal Investigator.

If at the 500 mg dose level of ZD1839 there were two or fewer grade 3 - 4 toxicity seen in the first six patients recruited at this dose then 500 mg was to be the dose for the rest of the study. If three or more patients of the six recruited at the 500 mg dose level experienced grade 3 - 4 toxicity, then the 250 mg was to be used for the rest of the study. One/two tablet(s) were to be administered orally once daily for at least 12 months or until disease progression.

Radiotherapy

Irradiation was to be given as 60 Grays (Gy) in 30 fractions over 6 weeks, one fraction per day and five fractions per week. Radiotherapy was not to commence until at least 3 weeks but less than 6 weeks after surgery.

Comparator, dosage and mode of administration

Not applicable.

Duration of treatment

ZD1839 was to be administered daily until disease progression or undue toxicity, however, after 12 months of treatment a decision was to be taken by the study co-ordinator before continuation. Irradiation was to be given over a 6-week period. Treatment was to be withdrawn in the event of progressive disease, unacceptable toxicity or withdrawal of patient consent.

Endpoints

- **Efficacy**
- **Primary endpoint**

    - Objective tumour response (assessed using Macdonald criteria)

- **Secondary endpoints**

    - Disease control rate
    - TTP
    - Overall survival

- **Safety**

    - Nature, incidence and severity of adverse events (AEs)
    - Incidence of and reasons for investigational product dose interruptions, investigational product dose reductions and withdrawals
    - Investigational product exposure, laboratory assessments, physical examinations

- **Exploratory**

    - EGFR expression was to be analysed with real-time PCR and/or western blot and immunohistochemistry in all possible cases

Statistical methods

Fleming's method was to be used to calculate the number of patients required. 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 rejected if four or more responses were observed out of the 27 patients.

All patients who were enrolled and received investigational product were to be considered the intention-to-treat (ITT) population. For all efficacy and safety endpoints, the analysis population was to be the ITT population.

The standard summary statistics for continuous variables were: mean, standard deviation, median, quartiles, minimum and maximum. 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 (CI) (the objective response rate was also to have a 90% CI calculated). Durations (TTP and overall survival) were to be summarised by Kaplan-Meier methods. Tolerability was to be summarised by the appropriate standard summary statistics.

The primary aim was to evaluate tumour regression according to Macdonald criteria and the statistical evaluation was based on the Fleming method. The lowest limit of therapeutic activity considered to be of interest was a response of 20% evaluated after 6 months of the end of irradiation, compared to a postoperative CT/MRI examination. In addition, side effects were to be carefully evaluated.

Patient population

Thirty six patients were screened and registered for the study. Thirty-five received ZD1839 and were considered the ITT population: six (17.1%) of these received 250 mg ZD1839 and 29 (82.9%) received 500 mg. This was the analysis population for safety and efficacy.

Thirty-two (91.4%) patients completed combination therapy; 31 (88.6%) entered the monotherapy phase but did not complete 12 months treatment post radiation. One (2.9%) patient completed 12 months treatment post radiation.

Table S1 Patient population and disposition

Demographic or baseline characteristic		Patients (N = 35)	
Demographic characteristics			
Sex (n and % of patients)	Male	20	(57.1)
	Female	15	(42.9)
Age (years)	Mean (SD)	53.3	(9.79)
	Range	27 to 69	
Race (n and % of patients)	Caucasian	35	(100.0)
Height (cm)	Mean (SD)	173.1	(8.08)
	Range	158 to 185	
Weight (kg. n = 34)	Mean (SD)	74.39	(13.937)
	Range	45.5 to 103.2	
WHO Performance Status (n and % of patients)	PS0	10	(28.6)
	PS1	20	(57.1)
	PS2	5	(14.3)
Disposition (n and %)			
Received ZD1839 250 mg		6	(17.1)
Received ZD1839 500 mg		29	(82.9)
Completed combination therapy		32	(91.4)
Entered monotherapy, did not complete 12 months treatment post radiation		31	(88.6)
Completed 12 months treatment post radiation		1	(2.9)
Analysed for safety and efficacy (ITT)		35	(100.0)

Efficacy results

There were no responders and 35 (100.0%) non-responders at 6 months after the end of combination therapy. Nine (25.7%) patients were recorded with stable disease (SD) but none (0.0%) had complete response (CR) or partial response (PR). Twenty-two (62.9%) were recorded with progressive disease (PD), and the remaining four (11.4%) were not evaluable (NE). At study closure, 33 (94.3%) patients were recorded with disease progression, one (2.9%) had died without prior documented disease progression and the status of the remaining patient (2.9%) was not known (consent had been withdrawn). None was recorded as alive and progression-free.

Median time to progression was 136 days.

The proportion of patients alive and progression-free at 6 months was 26.5%. One (2.9%) patient had censored observations. At study closure, four (11.4%) patients were alive and 30 (85.7%) were dead. The status of the remaining patient (2.9%) was not known (consent had been withdrawn).

Safety results

Median time on study was 128.0 days (range 26 to 412 days) and median time on ZD1839 treatment was 122.0 days (range 20 to 412 days). Of twenty-one (60.0%) patients who had one or more interruptions of ZD1839 dose, these were due to toxicity in seven; six (20.7% of patients assigned to receive 500 mg) patients had reduction of ZD1839 dose because of toxicity. One (2.9%) patient completed 12 months treatment post irradiation, 31 (88.6%) entered monotherapy but did not complete 12 months treatment post irradiation and three (8.6%) did not complete the combination phase.
All 35 (100.0%) patients in the study experienced AEs (any causality). Eighteen (51.4%) had CTC grade 3 or 4 AEs; these were recorded as drug-related for five (14.3%). Rash and diarrhoea were the most commonly reported individual AEs.

In general, the profile of ZD1839-related (as categorised by the investigator) AEs was as expected, with rash and diarrhoea respectively affecting 22 (62.9%) and 17 (48.6%) patients in the combination phase and 23 (65.7%) and 18 (51.4%) patients in the overall study period. Relatively few AEs were attributed to other study therapy; the most common were headache and nausea, which were reported for five (14.3%) and four (11.4%) patients, respectively. There were no marked differences between types of AE reported during combination therapy and the overall study period.

AEs leading to withdrawal were considered by the investigator to be related to ZD1839 treatment for three (8.6%) patients during combination therapy. These comprised two instances of rash and one of thrombocytopenia, the latter being recorded as possibly also related to other study therapy.
The primary cause of death was recorded as malignant neoplasm progression for 31 (88.6%) of 33 patients for whom death was recorded.

SAEs, which were recorded for six (17.1%) and 13 (37.1%) patients during combination therapy and the overall treatment period respectively, comprised mainly single instances of a range of events with the most frequent being convulsion, in five subjects. In the overall treatment period, one instance of convulsion was considered by the investigator to be related to ZD1839 treatment, one instance of skin infection was attributed by the investigator to other study therapy, and one instance of wound infection was attributed to both treatments.

Thrombocytopenia was the only haematological finding classified as an AE. This was not serious but led to withdrawal from the study. The investigator considered it to be possibly related to ZD1839 treatment and to other study therapy. Of fourteen patients who had increases in transaminase levels above the project specific range, two were particularly affected, with 8 and 16 fold increases in ALT activity (9 and 10 times the upper limit of the project specific range, respectively). These were not recorded as AEs.

The overall safety profile of ZD1839 at 500 mg was similar to expectation and did not appear to have been adversely affected by co-treatment with radiotherapy in this study with patients with GBM.

Table S2 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 category[a]	
Any AEs	35	(100.0)
ZD1839-related AEs	31	(88.6)
SAEs	13	(37.1)
ZD1839-related SAEs	2	(5.7)
AEs leading to death	1	(2.9)
ZD1839-related AEs leading to death	0	(0.0)
Patient had CTC grade 3 or 4 AE	18	(51.4)
Patient had CTC grade 3 or 4 ZD1839-related AE	5	(14.3)
Withdrawal due to AEs	6	(17.1)
Withdrawal due to SAEs	1	(2.9)
Withdrawal due to ZD1839-related AEs	3	(8.6)
Withdrawal due to ZD1839-related SAEs	0	(0.0)

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 during combination treatment or in the overall treatment period, sorted by decreasing order of frequency (ITT analysis set)**

Preferred term	Number (%) of patients who had an AE in each category[a]			
	Combination therapy		Overall treatment period	
Rash	22	(62.9)	23	(65.7)
Diarrhoea	18	(51.4)	20	(57.1)
Nausea	10	(28.6)	13	(37.1)
Dry skin	11	(31.4)	12	(34.3)
Convulsion	3	(8.6)	8	(22.9)
Fatigue	6	(17.1)	7	(20.0)
Paronychia	5	(14.3)	7	(20.0)
Headache	6	(17.1)	7	(20.0)
Vomiting	2	(5.7)	6	(17.1)
Urinary tract infection	4	(11.4)	5	(14.3)
Dyspepsia	4	(11.4)	4	(11.4)
Nasopharyngitis	3	(8.6)	4	(11.4)

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

Table S4 **Number (%) of patients with drug-related adverse events in the combination treatment phase and overall study period, sorted by decreasing order of frequency (ITT analysis set)**

Preferred term	Number (%) of patients who had an AE in each category			
	Combination therapy		Overall treatment period	
Related to ZD1839				
Rash	22	(62.9)	23	(65.7)
Diarrhoea	17	(48.6)	18	(51.4)
Dry skin	11	(31.4)	12	(34.3)
Paronychia	5	(14.3)	7	(20.0)
Nausea	4	(11.4)	5	(14.3)
Anorexia	2	(5.7)	2	(5.7)
Dermatitis exfoliative	2	(5.7)	2	(5.7)
Conjunctivitis	1	(2.9)	2	(5.7)
Vomiting	1	(2.9)	2	(5.7)
Rash pustular	-	-	2	(5.7)
Dermatitis acneiform	1	(2.9)	1	(2.9)
Pruritus	1	(2.9)	1	(2.9)
Abdominal pain	1	(2.9)	1	(2.9)
Nasal congestion	1	(2.9)	1	(2.9)
Muscle cramp	1	(2.9)	1	(2.9)
Pyogenic granuloma	1	(2.9)	1	(2.9)
Eye infection	1	(2.9)	1	(2.9)
Otitis externa	1	(2.9)	1	(2.9)
Keratoconjunctivitis sicca	1	(2.9)	1	(2.9)
Urethritis	-	-	1	(2.9)
Alopecia	-	-	1	(2.9)
Convulsion	-	-	1	(2.9)
Headache	-	-	1	(2.9)
Benign neoplasm of thyroid gland	-	-	1	(2.9)
Wound infection	-	-	1	(2.9)
Weight decreased	-	-	1	(2.9)
Decreased appetite	-	-	1	(2.9)
Dry mouth	1	(2.9)	1	(2.9)
Thrombocytopenia	1	(2.9)	1	(2.9)

Related to other study therapy				
Headache	4	(11.4)	5	(14.3)
Nausea	4	(11.4)	4	(11.4)
Fatigue	3	(8.6)	3	(8.6)
Vomiting	1	(2.9)	2	(5.7)
Rash	1	(2.9)	1	(2.9)
Diarrhoea	1	(2.9)	1	(2.9)
Thrombocytopenia	1	(2.9)	1	(2.9)
Dermatitis exfoliative	1	(2.9)	1	(2.9)
Regurgitation of food	1	(2.9)	1	(2.9)
Asthenia	1	(2.9)	1	(2.9)
Urinary incontinence	1	(2.9)	1	(2.9)
Wound infection	-	-	1	(2.9)
Skin infection	-	-	1	(2.9)

Table S5 Number (%) of patients with serious adverse events in the combination therapy phase and overall study period, sorted by decreasing order of frequency (ITT analysis set)

Preferred term	**Number (%) of patients who had a SAE in each category**			
	Combination therapy		**Overall treatment period**	
Total patients	**6**	**(17.1)**	**13**	**(37.1)**
Convulsion	1	(2.9)	5	(14.3)
Pulmonary embolism	3	(8.6)	3	(8.6)
Wound infection	1	(2.9)	2	(5.7)
Abdominal hernia obstructive	1	(2.9)	1	(2.9)
Neoplasm progression	1	(2.9)	1	(2.9)
Partial seizures	-	-	1	(2.9)
Myocardial ischaemia	-	-	1	(2.9)
Gastric ulcer haemorrhage	-	-	1	(2.9)
Dyspnoea	-	-	1	(2.9)
Skin infection	-	-	1	(2.9)
Tooth infection	-	-	1	(2.9)
Drowning	-	-	1	(2.9)
Subdural haematoma	-	-	1	(2.9)
Upper limb fracture	-	-	1	(2.9)
Bursitis	-	-	1	(2.9)
Osteitis	-	-	1	(2.9)

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As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Iressa™ (gefitinib), Healthcare Professionals should view their specific country information.