AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA
ACTIVE INGREDIENT: Gefitinib

Study No: 1839IL/0105
An open-label, non-comparative, phase II trial of ZD1839 (Iressa™) in combination with docetaxel (Taxotere®) in patients with advanced or metastatic non-small cell lung cancer failing or unsuitable for platinum based chemotherapy

Developmental phase: II
Study Completion Date: 15 September 2004
Date of Report: 01 February 2007

OBJECTIVES:

Primary

The primary objective of the trial was to assess the activity of ZD1839 in combination with docetaxel by estimating the overall response rate (complete response [CR] and partial response [PR]) in patients with advanced or metastatic non-small cell lung cancer who had failed, or were unsuitable for, platinum based therapy.

Secondary

The secondary efficacy objectives of the trial were:

1. To estimate the disease control rate
2. To estimate time to progression (TTP)
3. To estimate overall survival

The safety objectives of the trial were:

1. To further characterize the safety profile of ZD1839 at a 250 mg daily dose
2. To evaluate the safety and tolerability of the combination ZD1839 and docetaxel

The exploratory objectives of the trial were:

1. To investigate the association between epidermal growth factor receptor (EGFR) and Her-2-neu expression from initial tumour biopsies and incidence of tumour response
2. To investigate the association between serum EGFR and Her-2-neu levels and incidence of tumour response

METHODS:

Trial design

This was an open-label multiple centre, non-comparative, phase II trial of ZD1839 in combination with docetaxel in patients with advanced or metastatic non-small cell lung cancer who had failed, or were unsuitable for, platinum based therapy. A total of 56 patients were to be recruited, split equally between the two patient populations: 28 patients failing after platinum based chemotherapy, and 28 patients who were unsuitable for platinum based chemotherapy.
All patients were to receive the same treatments, however for administration purposes, the two patient populations were to be clearly noted at the time of enrolment, in order to ensure that sufficient patients were recruited to each group:

Group A: Patients progressing during or after platinum based chemotherapy
Group B: Patients unsuitable for platinum chemotherapy

Population

Male or female patients with histologically- or cytologically-confirmed non-resectable advanced or metastatic (Stage IIIB or IV) non-small cell lung cancer (NSCLC) who had failed, or were unsuitable for, platinum based therapy. Patients were required to have at least one measurable lesion. Patients were also required to have a World Health Organisation (WHO) performance status (PS) of ≤ 2 and a life expectancy of > 3 months.

RESULTS:

Patient population

Of fifty patients who were screened, 48 were enrolled and 47, comprising 32 males and 15 females, received the trial drug. They were assigned to two groups: 30 to Group A, who had failed platinum chemotherapy, and 17 to Group B, who were unsuitable for platinum chemotherapy. Mean age was 55.1 years (range 21 to 68 years) in Group A and 61.1 years (range 44 to 83 years) in Group B. The patients, whose race was not recorded in this trial, had WHO performance status 0 (53.3% in Group A and 11.8% in Group B), 1 (43.3% in Group A, 76.5% in Group B) or 2 (3.3% in Group A and 11.8% in Group B). In total, four patients, three in Group A and one in Group B, were continuing monotherapy at the trial closure.

Table S1 Patient population and disposition

		Group A (failed platinum chemotherapy)		Group B (unsuitable for platinum chemotherapy)		Total	
Population							
N receiving at least one dose (N planned)		30	(28)	17	(28)	47	(56)
Demographic characteristics							
Sex	Male	21	(70.0)	11	(64.7)	32	(68.1)

		Group A (failed platinum chemotherapy)	Group B (unsuitable for platinum chemotherapy)	Total
(n and % of patients)	Female	9 (30.0)	6 (35.3)	15 (31.9)
Age (years)	Mean (SD)	55.1 (9.68)	61.1 (10.53)	57.3 (10.30)
	Range	21 to 68	44 to 83	21 to 83
	Median	55.5	57	57
Race		Race was not recorded in this trial		
Height (cm)	Mean (SD)	171.5 (8.64)	167.8 (8.21)	170.1 (8.59)
	Range	150 to 183	152 to 182	150 to 183
Baseline characteristics				
Weight (kg)	Mean (SD)	68.66 (13.14)	64.06 (11.78)	66.99 (12.73)
	Range	40.0 to 105.0	50.0 to 98.0	40.0 to 105.0
Systolic blood pressure (mmHg)	Mean (SD)	128.6 (16.85)	124.4 (16.49)	127.0 (16.66)
	Range	100 to 170	91 to 158	91 to 170
Diastolic blood pressure (mmHg)	Mean (SD)	76.4 (9.81)	75.3 (8.14)	76.0 (9.15)
	Range	59 to 100	57 to 89	57 to 100
Heart rate (bpm)	Mean (SD)	82.5 (14.90)	90.0 (12.56)	85.3 (14.40)
	Range	60 to 120	73 to 120	60 to 120
WHO performance status (n and % of patients)	PS0	16 (53.3)	2 (11.8)	18 (38.3)
	PS1	13 (43.3)	13 (76.5)	26 (55.3)
	PS2	1 (3.3)	2 (11.8)	3 (6.4)
Disposition				
N (%) of patients who	Completed	3 (10.0)	1 (5.9)	4 (8.5%)
	Discontinued	27 (90.0)	16 (94.1)	43 (91.5)
N analysed for safety and efficacy (ITT)		30	17	47

ITT=Intention to treat; N=Number.

Efficacy results

No patients (0.0%) showed complete response (CR) but partial response (PR) was recorded for seven (23.3%, 95% CI, 9.9 – 42.3%) patients in Group A and two (11.8%, 95% CI, 1.5 - 36.4%) patients in Group B. Controlled disease (CR, PR and stable disease [SD]), was recorded for 19 (63.3%, 95% CI, 43.9% - 80.1%) Group A patients and nine (52.9%, 95% CI, 27.8 – 77.0%) of Group B patients. Twelve (40.0%) and seven (41.2%) patients in Group A or B, respectively, were recorded with SD. Two (6.7%, 95% CI, 0.8 – 22.1%) Group A patients and one (5.9%, 95% CI, 0.1 – 28.7%) Group B patient were alive and progression-free at trial closure. At 6 months, in Groups A and B, respectively, 27.0% (95% CI, 10.1 - 43.9%) and 28.2% (95% CI, 6.2 - 50.2%) were alive and progression free. Median time to progression was 124 days (95% CI, 76 – 158 days) for Group A and 63 days (95% CI, 41 – 225 days) for Group B. Nine (30.0%) Group A patients and three (17.6%) Group B patients were alive at trial closure. Median survival

time was 384 and 135 days respectively for the two groups. Survival at 6 months was not recorded. Results for exploratory variables will be reported separately.

Safety results

All 47 patients (100.0%) in both groups in the trial experienced AEs (all causality). 86.7% of patients in Group A and 70.6% of patients in Group B had ZD1839-related AEs. 33.3% (Group A) and 64.7% (Group B) patients had serious AEs (SAEs). The incidence of ZD1839-related AEs of CTC Grade 3 or 4 was 33.3% in Group A and 23.5% in Group B. Two Group A patients (6.7%) and four Group B patients (23.5%) had SAEs leading to death but none was considered to be drug-related.

The most commonly reported ZD1839-related AEs occurring during the combination therapy stage were diarrhoea NOS (27 patients [57.4%]), dry skin (15 patients [31.9%] and rash NOS (12 patients [25.5%]. The most commonly reported ZD1839-related AEs in the overall treatment period were diarrhoea NOS (27 patients [57.4%]), dry skin (15 [31.9%] patients) and rash NOS (12 [25.5%] patients). Of these, diarrhoea NOS (eight patients [17.0%]) and dry skin (five patients [10.6%]) were also attributed docetaxel, whereas rash NOS was not. The AEs most commonly attributed to docetaxel were alopecia (10 [21.3%] patients, also attributed to ZD 1839 in three [6.4%] patients), nausea (nine [19.1%] patients), diarrhoea NOS (eight patients [17.0%]) and asthenia (eight [17.0%] patients, also attributed to ZD1839 in five [10.6%] patients). Acne NOS (three patients [6.4%]) and erythema (three patients [6.4%]) were, like rash NOS, only attributed to ZD1839.

23.3% of Group A patients and 35.3% of Group B patients had one or more interruptions of ZD1839 dose. These interruptions were due to toxicity in all the Group A patients and in 50.0% of the Group B patients. 26.7% of Group A patients and 17.6% of Group B patients had one or more adjustments in dose for docetaxel infusions (due to toxicity in 75.0% of the Group A patients and in 66.7% of the Group B patients). 40.0% of Group A patients and 23.5% of Group B patients had one or more delays in dose of docetaxel. These delays were due to toxicity in 33.3% of the Group A patients and in 75.0% of the Group B patients. 90.0% of Group A patients and 94.1% of patients in Group B discontinued treatment because of disease progression, AE, death or other reasons.

AEs leading to withdrawal were experienced by 13.3% of patients in Group A and 29.4% in Group B in the combination therapy phase, and one patient from each in the monotherapy phase. AEs leading to withdrawal were considered to be possibly related to ZD1839 treatment in one case of rash NOS and possibly related to ZD1839 and docetaxel in two Group A patients with increased transaminase levels, one Group A patient with lung infiltration NOS, one Group B patient with asthenia and wound infection and one Group B patient with pneumonia NOS.