AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA
ACTIVE INGREDIENT: Gefitinib

Study No: 1839IL/0083
A multicentre, open-label, non-comparative Phase II trial to evaluate the efficacy and safety of ZD1839 (Iressa^{TM}) alone as first-line treatment in patients with ER-negative metastatic breast cancer

Developmental phase: II
Study Completion Date: 12 October 2004
Date of Report: 28 March 2007

OBJECTIVES:

Primary objective

To evaluate the efficacy of oral ZD1839 500 mg once daily administered continuously in patients with oestrogen receptor (ER) negative metastatic breast cancer by estimating the disease control rate (complete response [CR], partial response [PR] and stable disease [SD]).

Secondary objectives

1. To estimate the controlled disease rate at 3 and 6 months after first treatment
2. To estimate the objective tumour response rate (CR and PR)
3. To estimate progression-free survival (henceforth termed time to progression)
4. To estimate survival
5. To estimate duration of response of the objective tumour assessment (CR + PR)

The safety objective of the trial was to further characterise the safety profile of ZD1839 at a 500 mg daily dose
The exploratory objective of the trial was to investigate the association between epidermal growth factor receptor (EGFR) expression at baseline and the incidence of disease control

METHODS:

Trial design

A multicentre, open-label, non-comparative, Phase II trial.

Target patient population

Female patients aged 18 years or older with histologically-confirmed ER-negative, progesterone receptor (PgR)-positive or PgR-negative, metastatic breast cancer that was not considered to be life-threateningwho had received no previous endocrine or cytotoxic treatment for metastatic breast cancer.

Investigational product, dosage and mode of administration

ZD1839 (Iressa^{TM}) tablets 250 mg; 500 mg (two tablets) orally once daily, administered continuously.

Duration of treatment

Treatment was to be administered continuously until disease progression, unacceptable toxicity or withdrawal of consent.

RESULTS:

Population

Seventy-seven patients were planned to be recruited, but AstraZeneca halted recruitment on this trial because of concerns, on the part of the investigators, regarding lack of efficacy of the monotherapy regime. Seventeen patients were screened, registered, received at least one dose of ZD1839 and were included in the ITT population. This was the analysis population for efficacy and safety.

Table S1 Patient population (ITT population) and disposition

Population			
N registered and treated		17	
Demographic characteristics			
Sex (n and % of patients)	Male	0	(0.0)
	Female	17	(100.0)
Age (years)	Mean (SD)	57.8	(13.71)
	Range	34 to 77	
Race (n and % of patients)	Race was not recorded in this trial		
Height (cm)	Mean (SD)	159.3	(7.70)
	Range	140 to 172	
Baseline characteristics			
Weight (kg)	Mean (SD)	66.79	(16.71)
	Range	42.3 to 105.0	
Systolic blood pressure (mmHg. n = 12)	Mean (SD)	129.2	(18.32)
	Range	100 to 160	
Diastolic blood pressure (mmHg. n = 12)	Mean (SD)	75.8	(6.69)
	Range	70 to 90	

Heart rate (BPM. n = 14)	Mean (SD)	82.2	(16.11)
	Range	54 to 109	
WHO Performance Status (n and % of patients)	PS0	13	(76.5)
	PS1	4	(23.5)

Efficacy results

In this trial the disease control rate was based on those patients responding (CR, PR) and those with SD sustained for at least 4 weeks. Overall best response was defined as one assessment of SD or better at least 6 weeks after baseline.

Controlled disease (SD confirmed and sustained for at least 4 weeks, there were no responders) was reported in four (23.5%) patients (exact 90% and 95% CI, respectively, for proportion of controlled disease, 8.5 – 46.1% and 6.8 – 49.9%). At 3 and 6 months, controlled disease was reported in two (11.8%) patients (exact 95% CI for proportion of controlled disease, 1.5 – 36.4%).
None (0.0%) of the patients were recorded as responders (CR or PR). Overall best response of SD was reported in seven (41.2%) patients and progressive disease (PD) was reported for ten (58.8%) patients. At trial closure, none of the patients (0.0%; exact 95% CI, 0.0 – 19.5%) was progression free. Disease progression had been recorded for all 17 (100.0%). Median time to progression was 49 days (95% CI 45 – 96 days). The Kaplan-Meier estimate for the proportion of patients alive and progression-free was 5.9% (95% CI 0.0% - 17.1%).
At trial closure, four (23.5%) patients (exact 95% CI 6.8 – 49.9%) were alive and 13 (76.5%) patients were dead. Median survival time was 568 days (95% CI 285 – 682 days). At 6 months, 14 (82.4%) patients (95% CI 64.2% – 100.0%) were alive.
No analysis was undertaken for duration of response because there were no responders.
One of four patients with controlled disease had tumour cells with EGFR staining, both of the membrane and the cytoplasm. Six of 12 patients with uncontrolled disease had membrane and cytoplasmic staining.
CA15.3 values increased over the period of the trial in eight patients, by approximately 2 – 4 times the baseline value. Of these eight patients, four were recorded as having controlled disease, and four as having uncontrolled disease coinciding with these increases.

Safety results

Median exposure (time on treatment) was 51.0 days (range 28 to 183 days). One (5.9%) patient had one or more dose interruptions due to toxicity. All 17 (100.0%) of the patients prematurely discontinued trial medication, 16 (94.1%) because of disease progression and one (5.9%) because she did not wish to continue treatment.
All 17 patients (100.0%) in the trial experienced drug related AEs. Four (23.5%) patients had SAEs and one (5.9%) had a drug-related SAE. There were no AEs leading to death and no patients (0.0%) were withdrawn because of AEs.
The most commonly reported AEs were gastrointestinal disorders and skin and subcutaneous tissue disorders (15 [88.2%] patients each). Diarrhoea NOS was the most

commonly reported individual AE (11 [64.7%] patients). Acne NOS was reported for nine (52.9%) patients, dry skin for eight (47.1%) and alopecia for five (29.4%). Four (23.5%) patients each suffered constipation and nausea.

The more common drug-related AEs comprised diarrhoea NOS (10 [58.8%] patients), acne NOS (nine [52.9%] patients), dry skin (seven [41.2%] patients, nausea (four [23.5%] patients), asthenia, vomiting NOS and rash NOS (three [17.6%] patients each), and ALT increased, AST increased, conjunctivitis, skin fungal infection NOS and anorexia (two [11.8%] patients each).

Drug-related AEs with a CTC grade of 3 or 4 affected five (29.4%) patients; two (11.8%) with acne NOS and one (5.9%) each with diarrhoea NOS, vomiting NOS and increased ALT.

Thirteen (76.5%) patients died during the trial. The primary cause was stated as disease progression in all cases except for one patient who died from cardiac insufficiency. Four (23.5%) patients experienced SAEs; one each with febrile bone-marrow aplasia, febrile neutropenia, arrhythmia NOS and vomiting NOS. Only the vomiting NOS was considered to be drug-related.