AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA
ACTIVE INGREDIENT: Gefitinib

Study No: 1839IL/0074
A phase II study to evaluate ZD1839 (Iressa™) in second line combination with paclitaxel (Taxol®) and carboplatin (Paraplatin®) in patients with advanced ovarian, peritoneal or fallopian tube adenocarcinoma

Developmental phase: II
Study Completion Date: 06 May 2005
Date of Report: 26 February 2008

OBJECTIVES:

The primary objective of the study was to assess the activity of ZD1839 administered daily in combination with carboplatin and paclitaxel by estimating the overall response rate (complete response [CR] and partial response [PR]) in patients with sensitive or resistant or refractory ovarian, peritoneal or fallopian tube cancer.

The secondary efficacy objectives of the trial were:

1. To estimate the disease control rate (CR, PR and stable disease [SD])
2. To estimate time to progression (TTP)
3. To estimate overall survival
4. To estimate duration of response

The safety objectives of this trial were:

1. To further characterise the safety profile of ZD1839 at a 500 mg daily dose
2. To evaluate the safety and tolerability of the combination ZD1839, carboplatin and paclitaxel

The exploratory objective of this trial was to correlate objective response and epidermal growth factor receptor (EGFR) percentage expression

METHODS:

This was a multicentre, non-randomised, open-label, non-comparative, two-arm phase II study. Two groups of patients were enrolled: platinum-resistant disease (includes platinum-resistant and platinum-refractory disease) and platinum-sensitive disease. A total of 91 subjects was planned (i.e., approximately 13 per centre), 39 in the platinum-sensitive ovarian cancer arm and 52 in the platinum-resistant ovarian, peritoneal or fallopian tube cancer arm.

The primary outcome variable was the overall response rate (CR and PR) based on the RECIST criteria for measurable and Rustin criteria for non-measurable lesions.

The ZD1839 dose level for this trial was 500 mg/day. Study treatment was dispensed to patients on day 1 of each cycle thereafter until the patient withdrew, or until closure of the study. Study treatment was to be taken once daily in the morning, at approximately the same time each day. In case of toxicity, repeat dose interruptions were allowed as required, for a maximum of 14 days on each occasion. If toxicity recurred after drug re-challenge, and further interruptions were considered insufficient to manage the toxicity, dose reduction from 500 mg to 250 mg was permitted. Only one dose reduction per patient was allowed.

Patients were to receive ZD1839 daily until disease progression, unacceptable toxicity, withdrawal of consent or closure of the study.

The paclitaxel dose was 175 mg/m^2, administered first by a 3-hour intravenous infusion every 21 days. Standard pre-medication (e.g. diphenhydramine, methylprednisolone, cimetidine or ranitidine) was to be given 30 minutes before each paclitaxel infusion. Carboplatin was to be administered as a 30-minute iv infusion every 21 days, at AUC 5.

Treatment with ZD1839 and chemotherapy was to continue for 6 cycles or until disease progression, unacceptable toxicity or withdrawal of consent. Monotherapy with ZD1839 could be continued for patients showing evidence of response or clinical benefit until disease progression, unacceptable toxicity or withdrawal of consent.

Target patient population and sample size

The target population comprised female patients aged 18 years or older with histologically-confirmed ovarian, peritoneal or fallopian tube adenocarcinoma with disease progression or relapse after first-line chemotherapy containing platinum (i.e. cisplatin or carboplatin) and paclitaxel, including patients with platinum-refractory, resistant and potentially sensitive disease.

Key inclusion criteria: Histologically-confirmed epithelial ovarian, peritoneal or fallopian tube adenocarcinoma; measurable disease, or non-measurable disease associated with a rise in CA125 > 65 U/ml, which had increased by at least a further 25% at the time of a second sample taken before trial entry; one previous treatment with the combination platinum (cisplatin or carboplatin) and paclitaxel; platinum-sensitive or platinum-refractory or platinum-resistant ovarian, peritoneal or fallopian tube cancer:

Platinum-sensitive patients were defined as those who had relapsed more than 6 months following completion of first-line platinum-based chemotherapy, after an initial response

Platinum-refractory patients were defined as those who progressed on first-line platinum-based chemotherapy

Platinum-resistant patients were defined as those with disease progression within 6 months of completing first-line platinum-based chemotherapy

Sample size: A sample size of 91 was planned: 39 in the platinum-sensitive arm and 52 in the platinum-resistant/refractory arm.

A two-stage design was used for both arms of the trial. Patients were only recruited to the second stage if at least one response was observed in the first stage for resistant/refractory patients and four responses in sensitive patients. The sample size was calculated using a one-sided alpha of 5% and a power of 80%. The number of patients recruited to the first stage was set to maintain a false-negative rate at the end of the first stage of less than 2%.

Resistant/refractory patients

A baseline response rate of 5% and a clinically relevant response rate of 15% were considered appropriate. There were to be 25 patients recruited to the first stage of this arm, and recruitment was to stop if no patient responded. If one or more patients responded in the first stage then 27 patients were to be recruited into the second stage. The hypothesis that the response rate is less than or equal to the baseline rate would be rejected if six or more responses were observed in the two stages combined.

Sensitive patients

A baseline response rate of 30% and a clinically relevant response rate of 50% were considered appropriate. There were to be 15 patients recruited to the first stage of this arm, and recruitment was to stop if no patient responded. If four or more patients responded in the first stage then 24 patients were to be recruited into the second stage. The hypothesis that the response rate is less than or equal to the baseline rate would be rejected if seventeen or more responses were observed in the two stages combined.

Fleming's method was used to calculate the number of patients required for each arm of the trial (Fleming 1982).

RESULTS:

Patient population

A total of 68 patients, 26 patients in the platinum resistant/refractory group and 42 patients in the platinum sensitive group, from eight centres in France were entered into this study. The planned sample size was therefore not achieved. The median age of the patients was 58.0 years (ranging from 37 to 72 years) in the platinum resistant/refractory group and 57.0 years (ranging from 34 to 71 years) in the platinum sensitive group.

All 26 patients in the platinum resistant/refractory group and 42 patients in the platinum sensitive group received at least one dose of ZD1839. 13 platinum resistant/refractory patients and 30 platinum sensitive patients completed the combination phase of the trial. All 26 patients in the platinum resistant/refractory group and 42 patients in the platinum sensitive group were analysed in the ITT population. This was a non-comparative study.

Efficacy Results:

The analyses based on a data cut-off of 6 May 2005 indicate:

There were 5 (19.2%) responders amongst the platinum resistant/refractory patients (95% CI 6.6% - 39.4%). There were 26 (61.9%) responders amongst the platinum sensitive patients (95% CI 45.6%-76.4%). Both analyses showed better responses than the "baseline" ORRs of 5% and 30% for the platinum resistant/refractory patients and the platinum sensitive patients respectively; however, because the sample size was lower than planned the anticipated power of the analysis was not achieved and these differences must not be considered to be significant.

There were 18 (69.2%, 95% CI 48.2%-85.7%) responders (patients with controlled disease) amongst the platinum resistant/refractory patients and 34 (81.0%, 95% CI 65.9%-91.4%) responders amongst the platinum sensitive patients.

At trial closure, 30 patients were alive, 11 platinum resistant/refractory patients and 19 platinum sensitive patients, but only one patient (in the platinum resistant/refractory group) was alive and progression free. All other patients had disease progression except one platinum sensitive patient who died without prior documented disease progression and four platinum sensitive patients for whom the outcome was unknown.

Median time to progression was 183 days (95% CI 120 days – 251 days) for the platinum resistant/refractory patients and 275 days (95% CI 240 days – 342 days) for the platinum sensitive patients. The proportion of patients alive and progression free at 6 months was 50.0% (95% CI 30.8% - 69.2%) for the platinum resistant/refractory patients and 85.0% (95% CI 73.9% – 96.1%) for the platinum sensitive patients.

Median survival time was 506 days (95% CI 371 days – 651 days) for the platinum resistant/refractory patients and 770 days (95% CI 540 days – 894 days) for the platinum sensitive patients.

The median duration of response was 190 days (95% CI 169 days – 248 days) for the platinum resistant/refractory patients and 228 days (95% CI 176 days – 269 days) for the platinum sensitive patients.

The planned sample size was not achieved and thus the analyses were not adequately powered to permit an evaluation of clinical usefulness.

Safety Results:

The profile of AEs considered by the investigator to be ZD1839-related was similar to those observed in previously conducted ZD1839 studies. The AEs reported to be related to other trial therapy were consistent with the established toxicity profile of paclitaxel and carboplatin.

Twelve (46.2%) platinum resistant/refractory patients and 16 (38.1%) platinum sensitive patients had dose interruptions of ZD1839 due to toxicity. Nine (34.6%) and 20 (47.6%) patients in the platinum resistant/refractory and platinum sensitive groups, respectively, had dose reductions. Six (23.0%) platinum resistant/refractory patients and 10 (23.8%) platinum sensitive patients withdrew because of AEs or SAEs [data taken from AE records]. The most common AEs leading to withdrawal were diarrhoea NOS (in five patients) and intestinal obstruction NOS (in four patients).

The majority of patients experienced one or more AEs. Appendix 12.15 provides a list of all AEs, whilst Table S1 presents an overview of AEs reported in this study:

Table S1 Categories of AEs: number (%) of patients who had at least one AE in any category (ITT population)*

Category[a]	**Platinum resistant/refractory n (%)**	**Platinum sensitive n (%)**
All adverse events (AEs)	26 (100.0)	42 (100.0)
Treatment-related[b] AEs	26 (100.0)	42 (100.0)
All serious adverse events (SAEs)	15 (57.7)	17 (40.5)
Treatment-related[b] SAEs	6 (23.1)	12 (28.6)
Non-fatal SAEs	14 (53.8)	15 (35.7)
Deaths due to AEs	1 (3.8)	2 (4.8)
Deaths due to treatment-related[b] AEs	0 (0.0)	2 (4.8)
Discontinuations from study treatment due to AEs	6 (23.1)	10 (23.8)
Due to treatment-related[b] AEs	3 (11.5)	8 (19.0)
Due to SAEs	5 (19.2)	6 (14.3)
Due to treatment-related[b] SAEs	3 (11.5)	4 (9.5)
CTC[c] grade 3 or 4 AEs		
Treatment-related[b] CTC[c] grade 3 or 4 AEs	17 (65.4)	24 (57.1)

* AEs are included which started or worsened on or after the first dose of ZD1839 and within 30 days after the last dose of ZD1839 (up to the date of trial closure). This table reflects the information on the AE form.

[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.

[b] Treatment-related adverse events were those events that the investigator considered to be possibly related to study treatment.

[c] CTC Grade NCI version 2.0.

n Number of patients.

NB 2 patients had AEs, which were indicated as leading to withdrawal, but the reasons for withdrawal stated on the completion form were disease progression and withdrawal of consent

ZD1839 was better tolerated at 250 mg than 500 mg. The most frequently occurring AEs reported as ZD1839-related by the investigator during combination therapy included gastrointestinal disorders (84.6% of platinum resistant/refractory patients and 83.3% of platinum sensitive patients, principally diarrhoea NOS), and skin and subcutaneous tissue disorders (84.6% of platinum resistant/refractory patients and 88.1% of platinum sensitive patients, mainly acne NOS, dry skin and rash NOS). 65.4% of platinum resistant/refractory patients and 57.1% of platinum sensitive patients had CTC grade 3 or 4 AEs that were considered by the investigator to be related to ZD1839.

Overall there were 11 discontinuations and two deaths (myelodysplastic syndrome NOS and acute lymphocytic leukaemia) due to treatment-related SAEs (in both cases the investigator associated the SAEs with ZD1839 and with other trial therapies). The acute lymphocytic leukaemia occurred in the monotherapy period. Another death due to myelodysplastic syndrome was observed before the cut-off period (34 months after study treatment discontinuation). This was considered by the investigator to be related to trial treatments.

No interstitial lung disease (ILD) type events were reported.