AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA
ACTIVE INGREDIENT: Gefitinib

Study No: 1839IL/0058
A randomised phase II and pharmacokinetic study of oral ZD1839 given continuously with oxaliplatin or cisplatin in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck.

Developmental phase: II
Study Completion Date: 30 September 2004
Date of Report: 13 July 2005

OBJECTIVES:

Primary objective was to evaluate the efficacy of oral ZD1839 administered continuously with either cisplatin or oxaliplatin administered once every 3 weeks, in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SCCHN).

The secondary objectives were to examine the effect of combination on the steady state exposure of ZD1839 and cisplatin/oxaliplatin, to characterize the safety profile of the two combinations, and to evaluate epidermal growth factor (EGFR) expression in SCCHN.

METHODS:

This study was a two-arm, open-label, randomized, phase II and pharmacokinetic trial, conducted in two centres in France, evaluating the anti-tumour activity, safety and clinical benefit of daily oral dosing with 500 mg ZD1839 in combination with either cisplatin (Arm A) or oxaliplatin (Arm B) every three weeks. Platinum compounds were to be administered as an IV infusion on day 1 of a three-week cycle.

Criteria for Evaluation

Efficacy:

Objective tumour response, according to RECIST criteria. Patients receiving at least two courses of therapy or who withdrew early due to disease progression or death were evaluable for response. Objective tumour responses (CR or PR) were to be confirmed by a second measurement at least 4 weeks after the initial documented response.

Progression free survival (assessed form the date of first treatment to the date that progression is observed),

Overall survival (assessed as date of randomization to the date of patient death) and duration of response (defined as the interval between the date of first documented response and the date of objective, documented disease progression) were evaluated.
Safety: All patients receiving study drug were evaluated. Adverse events and laboratory abnormalities were evaluated according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), Version 2.
Pharmacokinetics: To evaluate epidermal growth factor receptor (EGFR) expression in SCCHN.

Statistical Methods:
Design: The stage 1 ad hoc rule of Green/Dahlberg was to be used to stop the trial.
A maximum of 22 eligible patients are to be randomised to each arm, with 12 patients included in a first step and 10 in a second.
Interim analysis: An interim assessment was to be performed after the first 12 eligible/evaluable patients in each arm were assessed, and if 2 or more responses were observed, 10 additional patients were to be included per arm based on the predefined study design. With just 16 patients included, this analysis was not performed

RESULTS:

Fifteen of 16 randomised patients were treated in 2 French centres. All treated patients were evaluable for safety. One patient had a major protocol eligibility deviation, having the wrong histology (adenocarcinoma).
Of the 15 treated patients, 12 were evaluable for efficacy. 3 patients were considered not evaluable, one having entered the study with a major protocol violation, two having received less than two cycles of treatment.
Two patients were still receiving ZD1839 at the cut-off date; 6 patients (40%) discontinued for non-fatal disease progression; 5 patients (33%) discontinued due to AEs, 4 of which were treatment-related; 3 patients (20%) withdrew consent, and one patient discontinued having achieved a complete response, observed from the second cycle.

Patient Characteristics:
Patient characteristics at baseline were well balanced between treatment arms. Median age: 62 years (range: 46-70); WHO 0-1: 10 patients (71%), 2: 4 patients (29%).
The median number of disease sites was 1 (range: 0-2); lung: 9 patients (64%), lymph nodes: 7 patients (50%), hypopharynx: 1 patient (7%), skin: 1 patient (7%). Ten patients (71%) had at least one tumour-related symptom; pain being the most frequent symptom at baseline.
Thirteen patients (93%) had received prior radiotherapy, four of whom received concomitant chemotherapy. Two patients received neoadjuvant platinum-based chemotherapy

Efficacy Results
Overall response rate in the 14 eligible and treated patients was 21.4 % [95% CI: 4.7-50.8], with one complete response and one partial response observed in Arm A (ZD1839 + cisplatin), and one partial response in Arm B (ZD1839 + oxaliplatin). An additional patient experienced a partial response, which was not confirmed, as the following tumour assessment showed tumour progression.

Median follow-up was 10.2 months (range, 0.5-20.5); 13 patients have progressed, median progression-free survival was 4.59 months [95%CI: 3.33-5.85]; 11 patients have died, median overall survival was 10.59 months [95% CI: 2.58-18.6].

Safety Results:
Extent of exposure:
ZD1839: 49 treatment cycles were administered, (Arm A: 28; Arm B: 21); the median number of cycles per patient was 3 (range: 1-6). The median cumulative dose of ZD1839 was 22000 mg, representing a relative dose intensity of 62.2% (range 0% to 99%, with 3 patients not receiving ZD1839 at all, due to patient refusal (in two cases) and one patient experiencing early progression). Five patients had dose reductions (3 in Arm A, 2 in Arm B) due to adverse events, including diarrhoea (2 patients), folliculitis, vomiting and glossitis. Four patients experienced 11 interruptions in treatment, ten of which were due to adverse events (9 were treatment-related).
Platinum compounds: relative dose intensities of 97.1% and 99.1% for cisplatin (Arm A) and oxaliplatin (Arm B) respectively. Two patients in Arm A had delays in cisplatin treatment lasting >7 days, one of which was due to grade 2 thrombocytopenia. Three patients had reductions in the platinum dose (2 in Arm A, 1 in Arm B) due to adverse events in each case.

Toxicity (NCI-CTC, Version 2) was similar in both treatment arms. No grade 4 treatment-related non-haematological AEs were reported. The most common related events (grades 1-3) were diarrhoea and skin toxicity, occurring in 9 and 10 patients respectively. Haematological toxicity was not significant, with mostly grade 1 and 2 events; two grade 3 events were recorded (one anaemia, one neutropenia) and no grade 4 events. No febrile neutropenia occurred.
Hepatic and renal laboratory value abnormalities were rare and only mild, with no events more severe than grade 1. Creatinine elevations were observed predominantly in Arm A (5 cases, compared to one in Arm B), whilst liver function test abnormalities were more frequent in Arm B.

SAEs: 10 patients (63%) experienced a total of 23 SAEs, two of which were treatment-related, both occurring in the same patient. No patients died on-study. No study treatment-related death was observed.
Five patients discontinued due to treatment-related adverse events, including 3 patients who discontinued due to elevated serum creatinine levels or reduced creatinine clearance.