AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA
ACTIVE INGREDIENT: gefitinib

Study No: 1839IL/0070 (NCT00233636)
A TWO-PART PHASE II TRIAL TO EVALUATE ZD1839 (IRESSA^{TM}) AND RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED INOPERABLE SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Developmental phase: II
Study Completion Date: 01/Jul/2007
Date of Report: August 2008

OBJECTIVES:

Primary

Part A
The primary objective of the dose-finding part of the trial is to identify the maximum tolerated dose (MTD) of daily ZD1839 when used in combination with a standard radiotherapy regimen.
Part B
The primary objective of the main phase II part of the trial is to assess the activity of the selected dose of ZD1839 in combination with the standard radiotherapy regimen by estimating the overall response rate (complete response [CR] and partial response [PR]) at trial closure.

Secondary

Part B
The secondary efficacy objectives of the main phase II part of this trial are:

1. To estimate progression-free survival (PFS)
2. To estimate overall survival
3. To estimate duration of response

Both parts

The secondary safety objectives of both parts of this trial are:

1. To further characterise the safety profile of ZD1839 at 250 mg and 500 mg daily doses

2. To evaluate the safety and tolerability of the combination ZD1839 and radiotherapy

Exploratory

Part B

The exploratory objective of the main phase II part of this trial is to investigate the association between epidermal growth factor receptor (EGFR) expression at baseline and incidence of tumour response.

METHODS:

Multicenter, open-label, noncomparative, two step phase I/II study, with a dose-finding period to determine the MTD of daily gefitinib administered in combination with a standard radiotherapy regimen, followed by a phase II study to evaluate the therapeutic activity of the combination of the selected dose of gefitinib with a standard radiotherapy regimen. Gefitinib was administered once a day on a continuous basis. The treatment was administered for a maximum of 12 months or until disease progression, unacceptable toxicity or withdrawal of consent. The minimum amount of follow-up was 12 months. Radiotherapy was started concomitantly with gefitinib and was administered in daily fractions of 2.0 Gy according to the standard of each participating center. Cohorts of three patients were treated with gefitinib at the first dose level (250 mg). If one or two patients in the initial cohort had dose-limiting toxicity (DLT), three other patients were enrolled at the same level. Dose escalation proceeded if no patients had DLT, which was defined as grade 3–4 hematologic, neurologic, cardiac, lung, renal, or hepatic toxicity; grade 3–4 weight loss with PS deterioration; and deterioration of visual acuity thought to be associated with gefitinib treatment, grade 3–4 skin or gastrointestinal toxicity, and grade 4 dysphagia. Dose escalation was stopped if more than one-third of patients of a given cohort had DLT. The dose of gefitinib could be interrupted for a maximum of 14 days in the presence of grade 3 or 4 toxicity. Once the adverse event (AE) decreased in severity to grade 1, the patient continued to take the assigned dose. If the AE resolved to grade 2, patients in the 500 mg cohort had their dose reduced to 250 mg, whereas patients in the 250 mg cohort were taken off study.

Patient selection

Eligibility criteria for study entry included histologically confirmed, inoperable, and locally advanced squamous cell carcinoma of the head and neck (undifferentiated nasopharyngeal carcinoma was not allowed) with at least one bidimensionally measurable target lesion; age 18–75 years; WHO performance status (PS) 0 or 1; life expectancy of at least 3 months; and adequate baseline organ function.. Previous surgery was not allowed. Patients were ineligible if they had received earlier radiotherapy or chemotherapy. Patients with a history of other coexisting malignancies or malignancies diagnosed within the last 5 years, with the exception of adequately treated conebiopsed in-situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin, were also ineligible. Pregnancy, lactation, uncontrolled infections, unstable systemic diseases, any evidence of clinically active interstitial lung disease, and any unresolved grade 2 or higher Common Toxicity Criteria version 2.0 were also exclusion criteria. Concomitant use of phenytoin, carbamazepine, barbiturates, rifampicin, or St John's Wort was not allowed. The study was sponsored by AstraZeneca, Basiglio, Italy (study no. 1839IL/0070, Clinical Trials. gov Identifier: NCT00233636). The study was approved by the Ethics Committee of each participating center. Written informed consent was obtained from each patient before registration.

Patient evaluation

At enrollment, patients were evaluated by complete history and physical examination, PS recording, heart rate and blood pressure, complete blood cell (CBC) count, serum chemistries, urinalysis, ECG, chest radiograph, and total body computed tomography scan. Other exams were performed only in the presence of clinical indication. Patients were monitored throughout the treatment by clinical examination, toxicity assessment, CBC counts, biochemistry, concurrent illness, or therapy on day 1 of each week during radiotherapy. ECG and ophthalmic assessment were performed as clinically indicated. During the treatment with single-agent gefitinib, the patients were monitored by clinical examination, toxicity assessment, CBC counts, biochemistry, concurrent illness or therapy, and tumor assessment 4 weeks after the end of radiotherapy and at every 8-week interval thereafter until trial closure. Response was assessed according to Response Evaluation Criteria in Solid Tumors. Responding or stable patients received additional treatment for maximum of 12 months or until progression or unacceptable toxicities. National Cancer Institute Common Toxicity Criteria version 2.0 were used to grade toxicity.

Statistical methods

The standard '3+3' design was used for the phase I study. O'Brien and Fleming's method was used to calculate the number of patients required in the phase II part of the study. A sample size of 28 patients receiving the MTD was to give more than 80% probability of rejecting a baseline response rate of 70% with an exact 5% one-sided significance test when the true response was at clinically relevant rate of 90%. The hypothesis that the response rate was equal to or less than the baseline was rejected if 23 responses or more were observed of the 28 patients.

Response rates were summarized by proportions together with a 95% confidence interval (CI). PFS was calculated from the time of study entry to the first evidence of disease progression; OS was calculated from the time of study entry to patient's death or last followup. The Kaplan–Meier analysis was used for evaluation of PFS and OS.

RESULTS:

Patient characteristics

Between July 2003 and March 2006, 16 patients were enrolled in this study. The planned sample size was not reached owing to the low accrual, which was likely because of the increased awareness that concomitant chemoradiotherapy was the best therapeutic option in this subset of patients. Twelve patients were males, four patients were females. Median age was 58.5 (range: 43–73) years. All patients had stage IV disease. PS was 1 in the majority of patients. Hypopharynx was the most frequent site of primary tumor.

Dose escalation results

Two dose levels were tested. No DLT occurred among the first three patients treated at 250 mg, so gefitinib dose was escalated to 500 mg. Two patients had DLT among the first three patients treated at 500 mg; an additional patient treated at 500 mg had DLT; therefore, the accrual at the higher dose was stopped and further patients were treated at 250 mg. In total, 12 and four patients were enrolled at dose level of 250 mg and 500 mg, respectively. DLT observed at the higher dose included grade 3 stomatitis in three patients and grade 3 liver toxicities in one patient. The dose level of 250 mg was recommended for the phase II study. The occurrence of AEs represented the main cause of gefitinib interruption at both dose levels. Patient decision (in two cases) and liver toxicity, lung toxicity, and low compliance (in one case each) were additional reasons for treatment interruption. The median duration of gefitinib treatment was 100 (range: 36–272) days, and it was 27.4 (range: 9.9–74.5%) of the maximum planned duration. The median total given dose of radiotherapy was 69 (range: 50–104) Gy. Radiotherapy was given for a median of 8 (range: 7–13) weeks, which was slightly more than expected, and mainly owing to the occurrence of toxicities.

Toxicity

Six patients died during the study as a result of AEs (three patients treated at 250 mg and three patients at 500 mg). In particular, two of these patients had a cardiovascular arrest and two other patients died of gastrointestinal toxicity (diarrhea and dysphagia, respectively). The fifth patient passed away after an overwhelming sepsis, whereas the last patient died of an intratumoral hemorrhage. None of these deaths was considered related to gefitinib by any single investigators, whereas dysphagia was considered likely to be related to radiation therapy. Five serious AEs (SAEs) occurred in the subgroup of patients treated at 250 mg; three SAEs were observed in the group of patients treated at 500 mg. The overall incidence of treatment-induced SAEs was 9%. Sixty-eight AEs were considered linked to the combination of gefitinib and radiotherapy.

Response

All sixteen patients were evaluable for response. The median duration of follow-up was 8.3 (range: 2–26) months. At the time of study closure, 11 patients had died and five were alive. Four patients had a complete response, which was confirmed in three cases; eight patients had a PR, which was not confirmed in six patients. SD and disease progression were observed in one and three patients, respectively. Median duration of response was 5.4 (range: 1–21) months. The observed SD lasted 7.4 months. The median PFS was 6.7 months (95% CI: 4.5–12.1) and the median OS was 8.5 months (95% CI: 4.6–not reached).

REFERENCE

Caponigro F, Romano C, Milano A, Solla R, Franchin G, Adamo V, Mari E, Morrica B, Pepe S.A phase I/II trial of gefitinib and radiotherapy in patients with locally advanced inoperable squamous cell carcinoma of the head and neck. Anticancer Drugs. 2008 Aug;19(7):739-44.