AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA
ACTIVE INGREDIENT: gefitinib

Study No: 1839IL/0138 (NCT00233623)
A RANDOMISED, NON-COMPARATIVE, MULTICENTRE, PHASE II, PARALLEL-GROUP TRIAL OF ZD1839 (IRESSA™) IN COMBINATION WITH 5 FLUOROURACIL, LEUCOVORIN AND CPT-11 (IRINOTECAN) IN PATIENTS WITH METASTATIC COLORECTAL CANCER

Developmental phase: II
Study Completion Date: 31/May/2007
Date of Report: November 2008

OBJECTIVES:

Primary

The primary objective of the trial is to estimate progression-free survival (PFS) at trial closure for the combination ZD1839, 5-fluorouracil (5-FU), leucovorin (LV) plus irinotecan (CPT-11) and for the combination 5-fluorouracil (5-FU), leucovorin (LV) plus irinotecan in patients with metastatic colorectal cancer.

Secondary

The secondary efficacy objectives of the trial are:

1. To estimate the objective response rate (complete response [CR] and partial response [PR]) at trial closure using the Response Evaluation Criteria in Solid Tumours (RECIST)
2. To estimate disease control rate (CR, PR and stable disease [SD]) at trial closure
3. To estimate overall survival
4. To estimate duration of response

The safety objectives of the trial is:
1. To evaluate the safety and tolerability of the combination ZD1839, 5-FU, LV plus CPT-11 and of the combination 5-FU, LV plus CPT-11.

METHODS:

The study protocol was approved by the Independent Local Ethics Committee of each participating center and was conducted in accordance with The Declaration of Helsinki and according to the Good Clinical Practice–International Conference on Harmonisation (GCP–ICH) rules (study 1839IL/0138, sponsored by AstraZeneca). Inclusion criteria in the trial were histologically confirmed metastatic adenocarcinoma of the colon or rectum with measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST), life expectancy of at least 12 weeks, age >18 years and Eastern Cooperative Oncology Group performance status of zero or one.

No prior therapy for metastatic disease was allowed; patients may have received one prior course of 5-FU-based adjuvant chemotherapy and/or radiotherapy with the last dose administered at least 6 months before randomization. Patients had to provide written informed consent before the study entry.

This study is a randomized, multicenter, noncomparative phase II, parallel-group trial. The study was initially powered with the primary objective of estimating the ORR at trial closure according to the RECIST, for the combination of gefitinib and FOLFIRI regimen and for FOLFIRI alone, in patients with metastatic CRC. The study was not powered at conventional levels for a formal comparison between arms but was conducted to quantify the response rate, and other outcome data, on each arm. A randomized trial was preferred to a single-arm, uncontrolled trial as randomization serves to provide an internal control and lessens patient selection bias. Gefitinib was administered orally once daily at the dose of 250 mg. A full safety evaluation was conducted when six patients completed one cycle of combination therapy, before further patients were enrolled into the trial. According to FOLFIRI regimen, CPT-11 was administered at the dose of 180 mg/m2 by i.v. infusion over 90 min on day 1; levo-FA was administered at 100 mg/m2 by i.v. infusion over 120 min on days 1 and 2; and 5-FU was administered as a bolus injection at 400 mg/m2 and as 22-h i.v. infusion at 600 mg/m2 on days 1 and 2. Cycles were repeated every 2 weeks. Antiemetic prophylaxis with a 5-hydroxytryptamine3 (5-HT3) receptor antagonist and dexamethasone and anticholinergic prophylaxis with atropine were used. Dose modification was made for myelosuppression, diarrhea, mucositis and skin rash. Treatment was continued for a maximum of 12 cycles or until disease progression, unacceptable toxicity or withdrawal of consent. Patients without disease progression at the end of 12 cycles continued to receive gefitinib alone administered daily until disease progression, unacceptable toxicity or withdrawal of consent. The aim of the study was to investigate the effects of the two treatments and to gather information so that a subsequent phase III study could be designed appropriately. A sample size of 50 patients per arm was calculated in order to give at least an 87% probability of rejecting a baseline response rate of 35% with an exact 5% one-sided significance test when the true response is at the clinically relevant rate of 55%. Patients who have not progressed or died at the time of analysis have been censored at the time of their latest objective tumor assessment, including patients lost to follow-up or who withdraw consent. The study started in October 2002. In May 2004, on the basis of preliminary phase II evidence of the efficacy and tolerability of gefitinib plus a 5-fluorouracil, folinic acid, oxaliplatin (FOLFOX) regimen as first-line therapy for CRC, the protocol for the current study was amended to allow it to be repowered for a primary end point of progression-free survival (PFS). An increase in the sample size of an additional 90 patients (to 190 in total) was calculated under the revised primary comparative end point. The first cohort of 100 patients was enrolled by December 2004, after which recruitment restarted according to the modified sample size. A further 24 of the 90 additional patients were enrolled before the study closing early in March 2006 for reasons of slow recruitment and for changes in the standard of care in first-line CRC, making FOLFIRI no longer appropriate as a control arm. The early closure of the study did not allow to perform the comparative analysis on PFS and the data presented in this paper are for the first cohort of 100 patients. The safety and tolerability of gefitinib plus FOLFIRI were assessed in the first six patients enrolled in the combination arm in a single institution before continuing the recruitment. Pretreatment evaluations included past medical history, demography, assessment of tumor lesions and concurrent illness/therapy, physical examination, hematology, biochemistry, urinalysis, pregnancy test (if appropriate), and electrocardiogram. Tumor assessments were to be carried out every 8 weeks of therapy (four cycles) until progression. According to RECIST, assessments of objective responses must be confirmed a minimum of 4 weeks after the criteria for response are first met. For the purpose of this trial, any detrimental change in a patient's condition, after they enter the trial and during the 30-day follow-up period after the final treatment, was considered an adverse event as well as the development of a new cancer. Adverse events and laboratory values were graded according to the National Cancer Institute Common Toxicity Criteria 2.0 (NCI-CTC). All subjects who were enrolled in the first cohort of 100 patients and received study treatment are the intention-to-treat (ITT) population, considered for all efficacy outcome variables analysis. The ORR for each arm has been calculated. Durations of PFS and OS are analyzed using log-rank and also summarized by Kaplan–Meier methods.

RESULTS:

The study started in October 2002. The safety and tolerability of the combination were assessed in an initial cohort of 11 patients, corresponding to six patients enrolled to FOLFIRI plus gefitinib arm and five patients to FOLFIRI alone. The results of the initial safety analysis demonstrated that the association of gefitinib and FOLFIRI was well tolerated and no dose-limiting toxicity was reported; consequently, the enrollment restarted. From October 2002 to September 2004, the planned 100 patients in the initial cohort were

enrolled from nine Italian hospitals on to this study. The baseline characteristics of the enrolled patients were well balanced between the two randomized arms. A total number of 911 chemotherapy cycles was administered either with or without gefitinib with a median of 12 cycles (range 1–12) in the FOLFIRI-alone arm and 10 cycles (range 1–12) in the FOLFIRI plus gefitinib arm. Overall, 721 cycles were administered at full dose and without delay [401 cycles (86.4%) in the FOLFIRI-alone arm and 320 cycles (71.6%) in the FOLFIRI plus gefitinib arm], 18 cycles were administered at a reduced dose, 142 were delayed, and 30 were administered at a reduced dose and delayed. Gefitinib was temporarily interrupted in 13 patients (25%) due to an adverse event. The primary efficacy end point of this study was the ORR defined as either complete or partial response according to RECIST criteria. One patient randomized to FOLFIRI plus gefitinib arm was found ineligible after randomization and never started the study treatment and was excluded from the ITT analysis. Overall, 96 patients (97.0%) are assessable for the tumor response and three patients (3.0%, two in FOLFIRIalone arm and one in FOLFIRI plus gefitinib arm) withdrew from the trial therapy before the first planned tumor assessment: two patients for adverse event (one patient for cardiomyopathy NCI-CTC grade 3 and one patient for febrile neutropenia NCI-CTC grade 4), and one patient died of an unknown cause. The ORR was 46.5% (46 patients): 47.9% (23 patients) in the FOLFIRI-alone arm and 45.1% (23 patients) in the FOLFIRI plus gefitinib arm. The disease control rate was of 81.8% (81 patients): 83.3% (40 patients) in the FOLFIRI-alone arm and 80.4% (41 patients) in the FOLFIRI plus gefitinib arm. The median duration of tumor response was 6.8 months [95% confidence interval (CI) 5.7–9.2]: 6.2 months (95% CI 4.5–13.4) in the FOLFIRI-alone arm and 7.8 months (95% CI 5.7–9.2) in the FOLFIRI plus gefitinib arm. At the median follow-up of 14.5 months, 78 (78.8%) patients progressed, while in the study, 35 (72.9%) in the FOLFIRI-alone arm and 43 (84.3%) in the FOLFIRI plus gefitinib arm. The median PFS in the FOLFIRI-alone arm was 8.3 months (95% CI 7.1–11.2) and in the FOLFIRI plus gefitinib arm was 8.3 months (95% CI 6.6–10.3). At the cut-off date, 37 patients (37.4%) were alive, 19 (39.6%) in the FOLFIRI-alone arm and 18 (35.3%) in the FOLFIRI plus gefitinib arm. Overall, 57of the 62 deaths (91.9%) were related to CRC. The causes of deaths unrelated to cancer were heart failure (one patient in the FOLFIRI plus gefitinib arm), road accident (one patient in the FOLFIRI-alone arm), suicide (one patient in the FOLFIRIalone arm), and unknown (one patient in each of the two arms). At trial closure, the median OS in the FOLFIRI-alone arm was 18.6 months (95% CI 14.1–29.0) and in the FOLFIRI plus gefitinib arm was 17.1 months (95% CI 13.8–26.5). Thirty patients withdrew from the study for reasons other than progressive disease: 12 patients (25%) in the FOLFIRI arm and 18 (35.3%) in the combination arm. The reasons of withdrawal were adverse events or intolerance to therapies in 15 patients (29.4%) in the combination arm and in 6 patients (12.5%) in the FOLFIRI arm, respectively. The toxicity of the combination of FOLFIRI plus gefitinib was acceptable although drug-related NCI-CTC grades 3–4 adverse events were experienced by 35 (68.6%) patients randomized to FOLFIRI plus gefitinib arm compared with 25 patients (52.1%) in the FOLFIRI-alone arm, serious adverse events by 13 (25.5%) patients randomized to FOLFIRI plus gefitinib arm versus 10 patients (20.8%) in the FOLFIRI-alone arm. Most common drug-related NCI-CTC grades 3–4 adverse events included diarrhea (33.3% of patients in the FOLFIRI plus gefitinib arm versus 2.1% in the FOLFIRI-alone arm) and neutropenia (35.3% of patients in the FOLFIRI plus gefitinib arm versus 22.9% in the FOLFIRI-alone arm). The patients randomized to FOLFIRI plus gefitinib arm experienced more skin toxicity (70.6% versus 35.4%) and bleeding events (15.7% versus 2.1%), while more NCI-CTC grades 1–2 neurologic events were experienced in the FOLFIRI alone arm (22.9% versus 7.8%). The data regarding the additional 24 patients enrolled in the second part of the study and not included in the statistical analysis are consistent with the above-presented results of the first 100 patients.

REFERENCE

Santoro A, Comandone A, Rimassa L, Granetti C, Lorusso V, Oliva C, Ronzoni M, Siena S, Zuradelli M, Mari E, Pressiani T, Carnaghi C. A phase II randomized multicenter trial of gefitinib plus FOLFIRI and FOLFIRI alone in patients with metastatic colorectal cancer. Ann Oncol. 2008 Nov;19(11):1888-93.