AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: IRESSA
ACTIVE INGREDIENT: Gefitinib

Study No:
Randomised, Placebo-Controlled, Phase II Trial of Preoperative Therapy with Gefitinib (Iressa®/ZD1839) and Epirubicin-Cyclophosphamide in Patients with Primary, Operable, (T2-T3), Oestrogen Receptor Negative Breast Cancer (NICE study)

Developmental phase: II
Study Completion Date: 2 May 2007
Date of Report: 2 October 2008

OBJECTIVES:

Primary objective

- To estimate the effect of preoperative gefitinib on the complete pathological tumour response rate (pCR) in primary, oestrogen receptor negative breast cancer at the time of surgery.

Secondary objective

- To estimate the effect of preoperative gefitinib on complete and overall objective tumour response rate in primary, oestrogen receptor negative breast cancer at the time of surgery.

Pharmacokinetic objectives

- To relate the steady-state gefitinib levels with the incidence of pCR.
- To perform pharmacokinetic/pharmacodynamic (PK/PD) analysis of the explorative variables in relation to the steady-state levels of gefitinib.

Explorative objective

- To investigate the association between gene signature profile in tumour tissue, proteomic profile, specific predictive biological markers and incidence of complete pathological response. The specific predictive markers were EGFR, ERBB2, TOP2A and TIMP1. Tissue arrays from the biopsy at baseline and, if possible, from the tumour at definitive surgery were analysed for amplification and/or deletions of the EGFR, ERBB2 and TOP2A genes using FISH. TIMP1 was measured in the plasma samples that had been taken for proteomic analysis at baseline and at time of surgery.

Safety objective

- To estimate tolerability of gefitinib in combination with epirubicin and cyclophosphamide.

METHODS:

The intention to treat (ITT) analysis set included all patients that were enrolled and randomised and received at least one dose of study drug. The per protocol (PP) analysis set included all patients in the ITT analysis set without major protocol deviations. The analysis set for all efficacy endpoints was the PP analysis set. For sensitivity analysis, statistical analyses of all variables could be repeated in the ITT analysis set. The analysis set for safety endpoints comprised all randomised patients.

The primary statistical analysis calculated the frequency of pCR at surgery in the PP population evaluable for pathological response in the 2 treatment arms. A difference of at least 5% higher pCR in the gefitinib arm compared to the placebo arm was an affirmative indication for further evaluation. A 95% confidence interval was calculated to give an impression of the calculated difference using a chi-2 test.
The secondary efficacy variable (proportion of patients with complete objective tumour response and overall objective tumour response) was analysed with the same methodology as the primary variable. Additionally, the change in tumour size from baseline to visit 6 before surgery was compared between treatment arms using analysis of covariance (ANCOVA) with treatment and centre as factors and baseline tumour size as a covariate.
Descriptive statistics were used for the safety variables.

RESULTS:

Summary of efficacy results

Analysis of the primary variable, pCR, showed no difference between treatments at the time of surgery (0.31%, 95% CI 0-14.6) with 11% (8/71) of the gefitinib patients and 11% (8/73) of the placebo patients attaining a pCR. The secondary variables included complete and overall objective tumour response and showed no difference between treatments at the time of surgery (2.27%, 95% CI 0-34.8) with tumour response observed in 70% (50/71) of the gefitinib patients and in 68% (50/73) of the placebo patients. The secondary variables also included reduction of tumour size; no significant difference was shown between the gefitinib and the placebo treatment groups between baseline and surgery (adjusted mean difference -0.08%, 95 CI -0.77 to 0.62, p=0.83).

Summary of pharmacokinetic results

Results will be reported later in a separate appendix.

Summary of pharmacodynamic results

Results will be reported later in a separate appendix.

Summary of pharmacokinetic/pharmacodynamic relationships

Results will be reported later in a separate appendix.

Summary of pharmacogenetic results

Results will be reported later in a separate appendix.

Summary of safety results

The safety profile of gefitinib in this study was consistent with previous studies and no new safety concerns were identified. In general, AEs were mild (CTC grade 1) or moderate (CTC grade 2). The addition of gefitinib was associated with a numerically higher incidence of AEs, SAEs, DAEs and dose interruptions. Nausea, alopecia and fatigue were the most frequently reported AEs in both treatment groups. The incidence of diarrhoea, acne, dry skin and acneiform dermatitis was considerably higher in the gefitinib group than in the placebo group, which is in agreement with the known safety profile of gefitinib. Febrile neutropenia and pyrexia were the most frequently reported SAE in both treatment groups, with a higher incidence of febrile neutropenia in the treatment group receving gefitinib (18.09%) than with placebo (9.20%). 4 patients on gefitinib reported more than one episode of febrile neutropenia, while all the placebo patients with febrile neutropenia reported single episodes. There were no reports of death or interstitial lung disease.
The clinical laboratory results showed a decrease in neutrophils, in keeping with the AE reports of febrile neutropenia, and isolated, asymptomatic increases in liver enzymes in both treatment arms during treatment. A decrease in WHO performance status was observed in the treatment groups, as expected with the current chemotherapy regimen. There were no clinically relevant trends in physical findings.