AstraZeneca

Clinical Study Report Addendum Synopsis	
Drug Substance	Gefitinib (IRESSA™, ZD1839)
Study Code	D791AC00007
Edition Number	1
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Abbreviated Clinical Study Report Addendum for Gefitinib (IRESSA™, ZD1839) Study D791AC00007 (IPASS): Final Survival Analysis Report

An Open Label, Randomised, Parallel Group, Multicentre, Phase III Study to Assess Efficacy, Safety and Tolerability of Gefitinib (IRESSA™) (250 mg tablet) Versus Carboplatin/Paclitaxel Doublet Chemotherapy as First-Line Treatment in Selected Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) in Asia (IPASS)

Study dates:	First subject enrolled: 29 March 2006 Data cut-off date for primary analysis: 14 April 2008 Data cut-off date for final survival analysis: 14 June 2010
Phase of development:	Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

Eighty-seven centres from the following countries participated in this study: China, Hong Kong, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan, and Thailand.

Publications

Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.

Objectives and criteria for evaluation

The purpose of this Clinical Study Report (CSR) addendum synopsis is to report the final analysis of overall survival (OS) up to the data cut-off (DCO) date of 14 June 2010. Also presented is updated information on subsequent anti-cancer treatments and updated safety information. The following objectives and variables are relevant to this addendum synopsis:

- **Secondary objective:** to compare the randomised treatment arms in terms of OS
  - OS was defined as the time from the date of randomisation to the date of death due to any cause or to the last date the patient was known to be alive
  - Note that IPASS was sized and powered to assess non-inferiority for the primary outcome variable of progression-free survival (PFS) in the overall study population
- **Secondary objective:** to compare the safety and tolerability profile of gefitinib at a 250 mg daily dose relative to that of carboplatin/paclitaxel doublet chemotherapy
  - Following the DCO date for analysis of PFS, only information relating to new serious adverse events (SAEs) was to be collected for patients still receiving study treatment (or within 28 days of the last dose); updated information relating to all AEs/SAEs ongoing at the PFS DCO date was also collected.
- **Exploratory objective:** to investigate baseline biomarker data in consenting patients to ascertain if there are any biomarkers that differentiate for a relative treatment effect when comparing the randomised treatment arms
  - Tumour biomarker status was determined for: i) epidermal growth factor receptor (EGFR) mutation, ii) EGFR gene copy number (hereafter referred to as EGFR FISH), and iii) EGFR protein expression
  - For this addendum synopsis, various data (including OS) were summarised by biomarker status and also by EGFR mutation positive subtype
  - Note that no new biomarker data were generated post-PFS DCO date

For details of all other objectives/variables/results/conclusions (including the primary variable of PFS), see the main CSR/synopsis (dated 19 December 2008; PFS DCO date: 14 April 2008). In brief, IPASS exceeded its primary objective and demonstrated superiority of gefitinib relative to carboplatin/paclitaxel in terms of PFS in the overall study population. However, in this clinically-selected population enriched for patients with tumours bearing EGFR mutations, further pre-planned analysis demonstrated that different PFS outcomes were obtained for patients with known EGFR mutation positive (gefitinib benefit) and negative (carboplatin/paclitaxel benefit) tumours. In patients with an unknown EGFR mutation status, the efficacy results were consistent with the overall study population. The safety and tolerability profile of gefitinib was more favourable compared with carboplatin/paclitaxel in each EGFR mutation subgroup.

Study design

An open-label, multicentre, randomised (1:1), parallel-group, Phase-III study comparing gefitinib with carboplatin/paclitaxel doublet chemotherapy for the first-line treatment of non-small cell lung cancer (NSCLC) in clinically-selected patients. Following documentation of progression on first-line randomised treatment, patients were to enter survival follow up and further care and treatment was at the discretion of the treating physician. Although it was the protocol intent that patients progressing on gefitinib were to be treated with carboplatin/ paclitaxel (supplied by AstraZeneca), investigators could decide to treat with another approved therapy if carboplatin/ paclitaxel was considered unsuitable. Following analysis of the data in June 2008, it was agreed that biomarker data for patients ongoing in the study would be released to investigators (if patients consented), as these could have an important impact on decisions relating to the future management of their patients' lung cancer.

Target subject population and sample size

Male or female never smokers or ex-light smokers with Stage IIIB or IV adenocarcinoma of the lung who had not received any previous chemotherapy (excluding non-platinum based adjuvant chemotherapy). The study was conducted in patients in Asia.

The study set out to determine whether gefitinib was non-inferior to carboplatin/paclitaxel in terms of PFS (primary objective), and was sized and powered based on this primary endpoint. In order to give 80% chance (power) of concluding non-inferiority for PFS (if gefitinib was truly non-inferior to carboplatin/paclitaxel), 944 progression events were required; at that point, the DCO date for analysis of PFS occurred. The final OS analysis (secondary objective) was planned for when 944 deaths had occurred (so that the level of maturity was the same as for PFS).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Gefitinib (250 mg daily) and carboplatin (AUC 5.0 or 6.0) / paclitaxel (200 mg/m^2 every 3 weeks) were administered as reported in the main CSR/synopsis. Gefitinib batch numbers are provided in the main CSR/synopsis.

Statistical methods

The primary analysis of OS used a Cox proportional hazards model adjusted for WHO performance status, smoking history, and gender in the intention-to-treat (ITT) population. The hazard ratio (HR; gefitinib:carboplatin/paclitaxel) was estimated together with its 2-sided 95% confidence interval (CI) and p-value. An unadjusted Cox proportional hazards model in the ITT population was performed as a sensitivity analysis; this method produced a p-value equivalent to a log-rank test. Subgroup analyses of OS (clinical and biomarker subgroups) were conducted using an adjusted Cox proportional hazards model similar to that described above. In addition, exploratory analyses of OS were performed by EGFR mutation subtype (Exon 19 deletions and the L858R point mutation in Exon 21, which together account for ~90% of all EGFR mutations observed in NSCLC). Safety data were summarised in the evaluable-for-safety (EFS) population, and according to EGFR mutation status and subtype.

Subject population

As reported in the main CSR/synopsis, 1217 patients were randomised to treatment and included in the ITT population (gefitinib: 609; carboplatin/paclitaxel: 608). The safety population included 1196 patients (98.3%; gefitinib: 99.7%; carboplatin/paclitaxel: 96.9%). Demographic and baseline characteristics were well balanced between the two treatment groups, and the population was representative of the advanced NSCLC population clinically selected for this study.

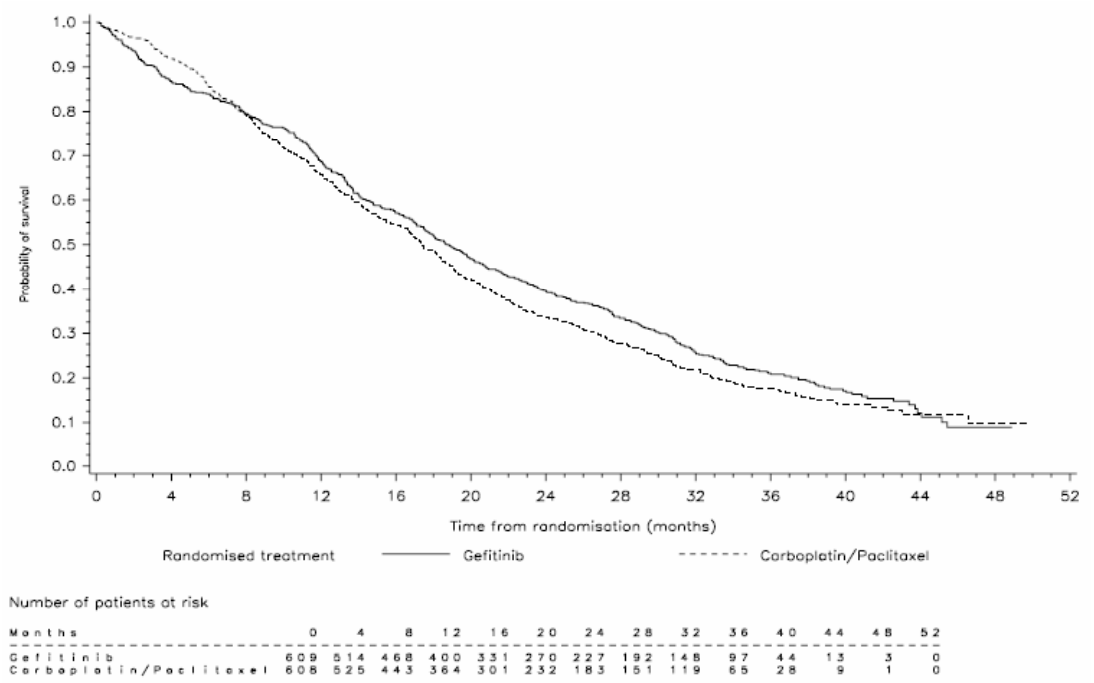
At the PFS DCO date, 694 patients were continuing in the study. Of the 362 patients in the gefitinib group, 149 were still taking gefitinib. Of the 332 patients in the carboplatin/ paclitaxel group, none remained on carboplatin/paclitaxel. At the DCO date for final OS analysis (14 June 2010), 181 patients remained in the study. Of the 97 patients in the gefitinib group, 20 were still taking gefitinib. Of the 84 patients in the carboplatin/paclitaxel group, none remained on carboplatin/paclitaxel (as expected).

Summary of efficacy results at the final OS DCO date

At the final OS DCO date, 954 patients had died (78.4% maturity). Median duration of follow up (time from randomisation until death or censoring) at 14 June 2010 was 17.8 months in the gefitinib arm and 15.7 months in the carboplatin/paclitaxel arm.

There was no statistically significant difference in OS for the gefitinib arm versus the carboplatin/paclitaxel arm in the overall study population (HR 0.901, 95% CI 0.793 to 1.023; p=0.1087; Figure S1). Median OS: gefitinib arm, 18.8 months; carboplatin/paclitaxel arm, 17.4 months. Results of the sensitivity analysis (unadjusted proportional hazards model) were consistent with the primary analysis (HR 0.903, 95% CI 0.796 to 1.026; p=0.1179).

Figure S1 Kaplan-Meier curves for overall survival (ITT population)



Number of patients at risk

Months	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Gefitinib	609	514	468	400	331	270	227	192	148	97	44	13	3	0
Carboplatin/Paclitaxel	608	525	443	364	301	232	183	151	119	65	28	9	1	0

It was anticipated that interpretation of the OS results from this study would be difficult due to the large amounts of subsequent treatment that patients could have received following disease progression on randomised first-line treatment, and the fact that these treatments were likely to have differed between the randomised groups. It was the protocol intent that patients progressing on gefitinib were to receive carboplatin/paclitaxel (if appropriate), and it was expected that many patients progressing on carboplatin/paclitaxel would receive subsequent EGFR tyrosine kinase inhibitors (TKIs; gefitinib or erlotinib) as these are widely available. At the final OS DCO date, the majority of patients had received further systemic therapy following discontinuation of randomised first-line treatment (approximately 69% in the gefitinib arm and 62% in the carboplatin/paclitaxel arm) but the types of subsequent therapies differed between the treatment arms. 301 patients (49.4%) received carboplatin/paclitaxel at some point following randomised gefitinib; 313 patients (51.5%) received EGFR TKIs at some point following randomised carboplatin/paclitaxel.

The OS outcome (no statistically significant difference in OS for the gefitinib arm versus the carboplatin/paclitaxel arm) was consistent across all clinical subgroups (gender, age, WHO performance status, smoking history, and disease stage).

Subgroup analyses of OS by EGFR mutation status showed no significant difference in OS for the gefitinib arm versus the carboplatin/paclitaxel arm in the subgroup of patients with unknown mutation status (HR 0.818, 95% CI 0.696 to 0.962; p=0.0149; median OS 18.9 months vs. 17.2 months), or in the subgroups of patients with known mutation positive (HR 1.002, 95% CI 0.756 to 1.328; p=0.9904; median OS 21.6 months vs.21.9 months) or

negative (HR 1.181, 95% CI 0.857 to 1.628; p=0.3090; median OS 11.2 months vs. 12.7 months) tumours. Please note: for these subgroups, the CIs have not been adjusted to take account of multiple testing of this secondary endpoint. Therefore, the ability to claim statistical significance at the traditional 5% level (ie, 95% CI below 1, and p-value <0.05) does not hold for these analyses; this should be taken into account in the interpretation of the results.

An exploratory subgroup analysis of OS was conducted on patients with tumours bearing the two most common EGFR mutation positive subtypes: Exon 19 deletions (140/1217 patients; 11.5%) and the L858R mutation (111/1217 patients; 9.1%). Differences in the estimated OS treatment effect for the gefitinib arm versus the carboplatin/paclitaxel arm were observed for patients with these mutation subtypes: Exon 19 deletions HR 0.787, 95% CI 0.539 to 1.149; L858R mutation HR 1.441, 95% CI 0.903 to 2.299. Due to the exploratory nature of this analysis and the small patient numbers, these results should be interpreted with caution.

Summary of safety results (at the final OS DCO date)

At the final OS DCO date (14 June 2010), median exposure to randomised gefitinib was 5.9 months (5.6 months at the PFS DCO date). Median exposure to randomised carboplatin/paclitaxel was 4.1 months (same as at the PFS DCO date, as expected, since no patients were still taking randomised carboplatin/paclitaxel at the PFS DCO date).

Cumulative safety data to 14 June 2010 were generally consistent with those presented in the main CSR/synopsis and with the known safety profile of gefitinib; there were no new safety findings for gefitinib (either in the overall study population, the EGFR mutation subgroups, or the subgroups of known mutation positive patients with the most prevalent EGFR mutation subtypes) based on the safety data collected since the previous PFS DCO date: