Clinical Study Report Synopsis

Drug Substance	Gefitinib (IRESSA™, ZD1839)
Study Code	D7913L00071
Edition Number	1
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A Placebo-Controlled, Multicentre, Randomised, Parallel Group trial to Assess the Efficacy, Safety and Tolerability of Gefitinib (Iressa® 250mg) as Maintenance Therapy in Locally Advanced or Metastatic (Stage IIIB/IV) Non Small Cell Lung Cancer (NSCLC) Chinese Patients who Have Not Experienced Disease Progression or Unacceptable Toxicity during Front Line Standard Platinum-Based Chemotherapy

Study dates:	First subject enrolled: 26 September 2008 Last subject last visit: 24 January 2011
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

A total of 27 sites throughout China participated in the study. These centres are those participated in the INFORM and followed patients according to the protocol at the time of study initiation.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
Progression free survival (PFS)	Determine the efficacy of Gefitinib (Iressa® 250 mg) following standard front line platinum- based chemotherapy in IIIB/IV NSCLC compared to placebo by assessment of progression free survival (PFS)
Secondary	**Secondary**
Overall survival (OS)	Determine the efficacy of Gefitinib (Iressa® 250 mg) following standard front line platinum- based chemotherapy in IIIB/IV NSCLC compared to placebo by assessment of overall survival (OS)
ORR and DCR	Determine the efficacy of Gefitinib (Iressa® 250 mg) following standard front line platinum- based chemotherapy in IIIB/IV NSCLC compared to placebo by assessment of objective response rate (ORR: CR plus PR), disease-control rate (DCR: CR plus PR plus sustained SD≥6 weeks
Safety and tolerability	The frequency and grade of toxicity events evaluated by CTCAE version 3.0
LCS	Improvement in LCS will be assessed from the 7-question LCS domain score derived from the FACT-L questionnaire .
Exploratory	**Exploratory**
Investigate the efficacy of gefitinib and placebo as maintenance treatment by tumour biomarker status (including tumour EGFR mutation status; investigate the efficacy of gefitinib and placebo as maintenance treatment by serum biomarker status, and to compare with tumour biomarker analysis.	1.Tissue EGFR mutation status 2 Serum biomarker status, and to compare with tumour biomarker analysis

Study design

This is a double blind, multicentre, randomized, placebo-controlled study. The eligible patients were randomized to receive gefitinib or placebo at 1:1 ratio.

The study drug was continued until objective progression of disease (PD) was documented or discontinuation of treatment for other reason (eg, toxicity, patient refusal). After discontinuing the study drug, the subsequent treatment was at the discretion of the attending physician. Patients who have not objectively progressed (via RECIST) should continue to be assessed for progression (by having RECIST assessments) whether they are still receiving study treatment or not.

Patients continue to be followed for survival. All subsequent chemotherapy, radiation, surgical or other anti-cancer treatments were to be recorded for both arms until death, loss to follow-up, withdrawal of informed consent or final data cut-off for analysis .

Target subject population and sample size

This study recruited around 298 male or female, histologically or cytologically diagnosed locally advanced or metastatic NSCLC patients with a World Health Organization (WHO) Performance Status (PS) 0-2. Patients must have completed 4 cycles of platinum based first line doublet chemotherapy without experiencing disease progression or unacceptable toxicity. The chemotherapy was given every 3 weeks, which included cisplatin or carboplatin, combined with any one of the following: gemcitabine, paclitaxel, docetaxel, vinorelbine.

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

Table S2 Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product	Dosage form and strength	Manufacturer	Batch number
Gefitinib	250mg tablet	AstraZeneca	D7913L00071-001
Placebo sized-matched tablet	placebo	AstraZeneca	D7913L00071-002

AstraZeneca supplied gefitinib to the investigator as brown, film-coated round shaped tablets with matched placebo.

Descriptive information for gefitinib can be found in the Investigator's Brochure.

For all centres, tablets were packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contained 50 tablets, sufficient for 42 days supply plus overage. Gefitinib/placebo was dispensed to patients in the AstraZeneca packaging provided: packaging includes bottles, caps and label.

Duration of treatment

Gefitinib or placebo was administered daily until objective progression or other criteria for discontinuation are met.

Statistical methods

At the final analysis, the primary analysis of PFS is in the ITT population using a Cox proportional hazards model adjusted for the randomisation stratification factors (histology, smoking status, tumour EGFR mutation status) plus best response to first line chemotherapy (CR/PR or SD), and performance status (0-1 vs 2).

Assuming a true hazard ratio (HR; gefitinib:placebo) of 0.7, 247 PFS events would be required to demonstrate superiority at a 2-sided 5% significance level with 80% power. Because an Interim Analysis for futility would be performed which is slightly decrease the power, 265 events were used in the Final Analysis to ensure that total power is about 80%. If 296 patients are recruited uniformly over a 12-month period, 265 events are expected to occur after a minimum follow-up of 9 months.

One interim analysis of PFS for futility is planned. The timing of the planned analysis is event driven. A cut-off date is set to coincide with the time when 50 PFS events have occurred, which is estimated to be after approximately 6 months of recruitment.

Subject population

A total of 298 patients were screened for the study and 296 subsequently randomized. By the time of the data cut-off for progression free survival of 24 January 2011, 268patients in the overall ITT population (90.5%) had progression diseases.

The two treatment groups were well balanced with respect to demographic characteristics and tumour burden, thus enabling valid conclusions to be drawn from the efficacy, QOL and safety analyses. The population was representative of the locally advanced or metastatic Chinese NSCLC population although the proportion of current smoker was slightly smaller than expected. All patients achieved SD, or responded to first-line chemotherapy.

Summary of efficacy results

Efficacy findings from this study were:

The study achieved its primary objective and demonstrated superiority of gefitinib relative to placebo in terms of PFS.

- PFS was significantly longer with gefitinib compared placebo in maintenance setting (HR: =0.42, CI: 0.32-0.54, p<0.0001, median PFS: G 4.8 months, P 2.6 months,). The risk of progression over a given period of time was reduced by 58% on gefitinib compared with placebo.

- ORR and DCR were superior with gefitinib compared with placebo treatment, supporting the PFS results.
- OS was similar for both treatments.
- LCS improvement rate were significantly higher in gefitinib compared to placebo group.
- In the pre-planned analyses of the exploratory biomarker endpoint, the greatest magnitude of effect on PFS, ORR and DCR for gefitinib vs placebo was observed in patients with EGFR mutation positive tumours.

Summary of pharmacokinetic results

NA.

Summary of pharmacodynamic results

NA.

Summary of pharmacokinetic/pharmacodynamic relationships

NA.

Summary of pharmacogenetic results

NA.

Summary of safety results

- The most common AEs with gefitinib were rash (49.7%), diarrhea (25.2%), and ALT increase (21.1%), which were generally mild to moderate.
- AEs with more than 5% difference in the incidence were rash (49.7% in gefitinib, 9.5% in placebo), diarrhea (25.2% in gefitinib, 8.8% in placebo), and ALT increase (21.1% in gefitinib, 8.1% in placebo), AST increase (14.3% in gefitinib, 4.1% in placebo), cough (6.1% in gefitinib, 13.5% in placebo).
- Overall incidence of serious AEs were 6.8% and 3.4% in gefinib and placebo group, respectively
- AEs leading to death were reported in 9 patients in gefitinib and 2 patients in placebo. Of these, 3 patients in gefitinib had AEs considered related to the study treatment.
- ILD was reported in 2 patients in gefitinib and none in placebo. ILD was fatal in 1 case.

- Laboratory findings: Mean ALT and AST were higher in gefitinib compared to placebo. No obvious trend in other laboratory parameters was observed.

Safety profile for gefitinib was consistent with known safety profile.

Conclusion(s)

- The study met its primary objective demonstrating significantly longer PFS for gefitinib compared placebo in the overall population in the maintenance setting.
- Significant improvement in ORR, DCR and LCS improvement rate were observed for gefitinib compared to placebo, supporting the primary PFS results.
- There was no significant difference between treatment groups in OS.
- The greatest magnitude of effect with gefitinib on PFS, ORR and DCR was observed in patients with tissue EGFR mutation positive tumours.
- Safety profile for gefitinib was consistent with known safety profile.