Clinical Study Report Synopsis

Drug Substance	Gefitinib (IRESSA™ [1], ZD1839)
Study Code	D791LC00001
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A Phase III Randomised, Double blind, Placebo controlled, Parallel, Multicentre Study to Assess the Efficacy and Safety of continuing IRESSA™ 250 mg in addition to Chemotherapy versus Chemotherapy alone in Patients who have Epidermal Growth Factor Receptor (EGFR) Mutation Positive Locally advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) and have progressed on First Line IRESSA™.

IMPRESS - (IRESSA™ Mutation Positive Multicentre Treatment Beyond ProgRESSion Study)

Study dates:	First patient enrolled: 15 March 2012
	Last patient enrolled: 09 December 2013
	Primary data cut-off: 05 May 2014
Phase of development:	Phase III

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

[1] IRESSA is a trademark of the AstraZeneca group of companies.

Study centres

It was planned that for this study 71 sites would be initiated in 11 countries. In total, 63 sites were initiated and enrolled patients but only 61 sites randomized patients.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives and outcome variables are presented in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate PFS in patients who had 'acquired resistance' to first line gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.	PFS: Time from randomisation until objective disease progression as defined by RECIST based on the investigator measurements or death (by any cause in the absence of progression).
Secondary	Efficacy	To evaluate OS in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.	OS: Time from the date of randomisation until death due to any cause.
Secondary	Efficacy	To evaluate ORR and DCR in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy compared with cisplatin plus pemetrexed combination chemotherapy alone.	ORR: The number (%) of patients with at least 1 visit response of CR or PR. DCR: Percentage of patients who achieve disease control at 6 weeks following randomisation.
Secondary	PRO	To evaluate symptoms and HRQoL as measured by the FACT-L questionnaire in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.	FACT-L questionnaire subscale scores.
Secondary/ Safety	Safety	To evaluate the safety and tolerability in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination alone.	Adverse events, serious adverse events, laboratory safety assessments (clinical chemistry, haematology, and urine analysis), physical examination, electrocardiogram, vital signs.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Pharmacodynamics/ Biomarker[a]	To investigate biomarkers in samples from patients who had 'acquired resistance' to gefitinib to ascertain if there are any biomarkers that differentiate for a relative treatment effect, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone. Biomarker analysis could include EGFR mutations (including T790M), c-Met amplification and other exploratory biomarkers.	Biomarkers.
Exploratory	PRO	To collect utilities assessed by EQ-5D to support health technology assessment and health economic modelling in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.	EQ-5D data and EQ-5D scores.

[a] Analysis of the exploratory biomarkers would be described in a separate analyses plan and reported separately from this Clinical Study Report.

Abbreviations: c-Met, a proto-oncogene; CR, complete response; CSP, Clinical Study Protocol; DCR, disease control rate; EGFR, epidermal growth factor receptor; EQ-5D, Euro Quality of Life-5 Dimensions; FACT-L, Functional Assessment of Cancer Therapy - Lung; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors (Version 1.1).

Note: Analysis of the exploratory biomarker objective will be described in a separate analyses plan and reported separately from this clinical study report.

Study design

This was a Phase III, double-blind, placebo-controlled, parallel, multi-centre study to assess the efficacy and safety of continuing gefitinib (250 mg, orally once daily) in addition to cisplatin plus pemetrexed chemotherapy (maximum 6 cycles, intravenously on Day 1 of each cycle) versus cisplatin plus pemetrexed chemotherapy alone in patients who had epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) and had progressed on first-line gefitinib. Eligible patients were randomised in a 1:1 ratio using Interactive Web Response System or Interactive Voice Response System to either continue blinded gefitinib or blinded placebo.

Target subject population and sample size

This study included male or female patients aged 18 years or older (20 years or older for Japan) with locally advanced or metastatic NSCLC having an activating EGFR tyrosine kinase mutation and predominantly of other than squamous cell histology. Eligible patients had developed 'acquired resistance' (ie, had received first-line gefitinib treatment for a minimum duration of 4 months for patients achieving complete response or partial response and developed radiological response of disease progression while on continuous treatment with first-line gefitinib within the last 4 weeks from randomisation into the study subsequent to

objective clinical benefit [either partial or complete radiological response or durable stable disease >6 months] after initiation of first-line gefitinib).

Approximately 250 patients were expected to be randomised and followed for progression-free survival (PFS) until 190 progression events had occurred. This number of events would give 90% power at the 5% 2-sided significance level, assuming a hazard ratio (HR) of 0.63, to demonstrate superiority of gefitinib in combination with cisplatin plus pemetrexed chemotherapy versus chemotherapy alone. At the time of the PFS analysis, approximately 125 overall survival (OS) events were expected and OS was analysed.

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

Gefitinib 250 mg in oral tablet form or a matching placebo was administered once daily. In addition, a maximum of 6 cycles of cisplatin plus pemetrexed chemotherapy were administered intravenously according to local guidelines on Day 1 of each chemotherapy cycle. After completion of chemotherapy, patients continued their randomised treatment until disease progression or other discontinuation criterion was met. In total, 308 batches of gefitinib and 295 batches of matching placebo were used in this study. Individual batch numbers and further information are included in the clinical study report.

Duration of treatment

Gefitinib treatment was given until objective disease progression was documented or any other criterion for discontinuation (eg, toxicity, withdrawal of consent) was met. The end of the study was defined as the last visit of the last patient, occurring when the last patient had discontinued study treatment. Provision was made for patients who had not progressed at the time of the data cut-off (DCO) and/or had benefited from the study treatment to continue to be treated with gefitinib outside this clinical study protocol (eg, named patient programme or other supply).

Statistical methods

The study planned to have 2 DCOs: primary DCO for PFS analysis (at the time of approximately 190 PFS events had occurred, ie, 75% PFS maturity was observed) and final DCO for OS analysis (at the time of approximately 175 OS deaths, ie, 70% OS maturity was observed). This study included 3 main analysis populations: full analysis set based on the intention-to-treat principle, safety analysis set and evaluable-for-quality of life (EFQoL) analysis set. The primary analysis population was the full analysis set population used to analyse PFS, OS, objective response rate (ORR), and disease control rate (DCR). All statistical tests were performed at a 2-sided 5% significance level unless otherwise stated. The primary objective of the study was to evaluate PFS and the secondary objectives were to evaluate OS, ORR, DCR, and quality of life in patients who had ‘acquired resistance’ to first-line gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.

Primary variable: At the primary DCO, the primary statistical analysis compared PFS as defined by Response Evaluation Criteria in Solid Tumors (RECIST) based on investigator measurements (site-read [investigator assessment] data) or death using a Cox proportional hazards model allowing for the effect of treatment and adjusted for age (<65, ≥65 years), and prior response to gefitinib (stable disease [SD] versus partial response [PR] and complete response [CR] combined). The HR (gefitinib:placebo) was estimated together with its 95% confidence interval (CI) and p-value. In addition, subgroup analysis (to assess consistency of treatment effect between different subgroups) and several sensitivity analyses (to assess evaluation time bias, attrition bias, and ascertainment bias) were performed for PFS. The PFS was displayed graphically using Kaplan-Meier plots.

Secondary variables: The first OS analysis took place at the same time as the primary PFS analysis using the same methodology as for PFS. A second and final analysis of OS would take place when approximately 175 deaths occur. The ORR and DCR were analysed using logistic regression adjusted for prior response to gefitinib and age. The results of the analysis were expressed in terms of an odds ratio and its associated CIs and p-value.

Symptoms and health-related quality of life (HRQoL) were measured by the Functional Assessment of Cancer Therapy - Lung (FACT-L) questionnaire outcomes (FACT-L total score, trial outcome index [TOI], and lung cancer subscale [LCS]). The analysis of the Trial Outcome Index improvement rates was regarded as the primary analysis of the FACT-L questionnaire with LCS and total FACT-L as supportive. The HRQoL improvement rates were analysed using the same methodology as ORR. The time to worsening data were analysed using a Cox proportional hazards model including terms for treatment received and the covariates as defined for PFS. Kaplan-Meier curves for time to worsening were plotted and the HR along with its 95% CIs and p-value were presented.

Safety variables: Adverse events, serious adverse events, electrocardiograms, vital signs, laboratory parameters, physical examination and treatment exposure data were summarised and listed. The latest available value to the pre-first dose of study treatment was used for listings and summaries of changes from baseline.

Exploratory variable: The Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire data collected from EFQoL population were listed and simple summaries were provided.

Subject population

As planned, the study was conducted in Europe and the Asia Pacific region including Japan. A total of 265 EGFR mutation-positive (EGFRM+) patients with locally advanced or metastatic NSCLC, who had progressed after first-line gefitinib treatment, were enrolled at 61 centres in 11 countries. The primary DCO for the study occurred on 05 May 2014.

A total of 265 patients were randomised: 133 patients to the gefitinib group and 132 patients to the placebo group; all patients were included in the full analysis set. One patient was excluded from the safety analysis set in the gefitinib group because this patient did not receive treatment. In total, 253 patients were included in the EFQoL analysis set (124 patients in the

gefitinib group and 129 patients in the placebo group). Patient disposition in the study is presented in Table S2.

Table S2 Patient disposition (All patients)

	Number (%) of patients		
	Gefitinib 250 mg	**Placebo**	**Total**
Patients enrolled[a]			287
Patients randomised	133 (100.0)	132 (100.0)	265 (100.0)
Patients who were not randomised			22
Eligibility criteria not fulfilled			21
Subject decision			1
Full analysis set	133 (100.0)	132 (100.0)	265 (100.0)
Patients who received treatment	132 (99.2)	132 (100.0)	264 (99.6)
Patients who received gefitinib/placebo	132 (99.2)	132 (100.0)	264 (99.6)
Patients who received cisplatin+pemetrexed	131 (98.5)	132 (100.0)	263 (99.2)
Patients who did not receive treatment	1 (0.8)		1 (0.4)
Eligibility criteria not fulfilled	1 (0.8)		1 (0.4)
Patients ongoing study treatment at DCO	23 (17.3)	18 (13.6)	41 (15.5)
Patients who discontinued study treatment	109 (82.0)	114 (86.4)	223 (84.2)
Adverse event	8 (6.0)	9 (6.8)	17 (6.4)
Objective disease progression	82 (61.7)	98 (74.2)	180 (67.9)
Subject decision	18 (13.5)	4 (3.0)	22 (8.3)
Other	1 (0.8)	3 (2.3)	4 (1.5)
Patients ongoing study	70 (52.6)	86 (65.2)	156 (58.9)
Patients who terminated study	63 (47.4)	46 (34.8)	109 (41.1)
Death	50 (37.6)	37 (28.0)	87 (32.8)
Subject decision	12 (9.0)	7 (5.3)	19 (7.2)
Eligibility criteria not fulfilled	1 (0.8)		1 (0.4)
Adverse event		1 (0.8)	1 (0.4)
Lost to follow-up		1 (0.8)	1 (0.4)

[a] Informed consent received.
Percentages were calculated from the number of patients who were randomised.
Abbreviation: DCO, data cut-off.

Baseline characteristics were representative of the EGFRM+ population and were generally well balanced between the 2 treatment groups. There were slightly more patients in the placebo group who had a previous response (CR/PR) to gefitinib. There were slightly more patients in the gefitinib group who were ≥65 years old and who had brain/central nervous system (CNS) metastases at study baseline.

Summary of efficacy results

Primary endpoint: Progression-free survival

The PFS HR based on site-read (investigator assessment) data demonstrated a numerical advantage for gefitinib but the difference did not demonstrate statistically significant improvement in the gefitinib group relative to the placebo group (HR 0.86, 95% CI 0.65 to 1.13, p-value=0.273). Overall, 77.4% patients had a PFS event and most of the PFS events were RECIST progressions rather than death in the absence of progression. Median PFS was 5.4 months (95% CI 4.5 to 5.7 months) in the gefitinib group compared with 5.4 months (95% CI 4.6 to 5.5 months) in the placebo group, which is consistent with the 6 months hypothesised in the Clinical Study Protocol.

The results from the sensitivity analyses (central review, attrition and evaluation time bias) all supported the primary analysis, and the PFS subgroup analyses were generally consistent with the overall PFS. Significant interactions for region, smoking status, Exon 19 deletion mutations and World Health Organization performance status were observed but these were quantitative in nature and did not achieve statistical significance.

An additional exploratory analysis for PFS was performed adding the covariate (brain/not brain) at baseline to the Cox model and results were generally consistent with the overall PFS results (HR 0.80, 95% CI 0.61 to 1.06, p-value=0.128; PFS HR based on site-read [investigator assessment] data).

Secondary objectives: Overall survival, overall response rate and disease control rate

At the DCO for the primary analysis of this study, 87 patient deaths had occurred. Analysis of OS at primary DCO revealed that OS was statistically significantly lower in the gefitinib group compared with the placebo group (HR 1.62, 95% CI 1.05 to 2.52, p-value=0.029). An additional exploratory analysis for OS was performed adding the covariate (brain/not brain) at baseline to the Cox model and results were consistent with the OS results. Median OS was 14.8 months in the gefitinib group compared with 17.2 months in the placebo group.

The ORR was similar in the gefitinib (31.6% patients) and placebo (34.1% patients) arms (based on site-read [investigator assessment] data); the proportion of patients achieving CR or PR based on site-read (investigator assessment) data was similar in the gefitinib and placebo treatment groups.

Patients in the gefitinib group had a small numerical advantage in DCR compared with the placebo group (84.2% in the gefitinib group and 78.8% in the placebo group) but this difference did not reach statistical significance (odds ratio 1.39, 95% CI 0.74 to 2.62, p-value=0.308).

Overall, approximately 9% more patients received subsequent anti-cancer therapy in the placebo group, mainly platinum-based regimen (gefitinib, 3.8% versus placebo, 14.4%) and EGFR TK1 (gefitinib, 22.6% versus placebo, 33.3%). There was no difference in terms of

standard care in third line setting of single agent chemotherapy between the 2 treatment groups.

In general, FACT-L total score, TOI and LCS scores remained relatively stable over time and were broadly similar between treatment groups.

Summary of safety results

Overall, the actual median exposure to the study drug (gefitinib/placebo) was 150 days in the gefitinib group and 159.5 days in the placebo group. Total median exposure to chemotherapy (cisplatin and pemetrexed) was 117 days in the gefitinib group and 122 days in the placebo group, and the median number of cycles was 5 cycles in both treatment groups.

The proportion of patients reporting any adverse event (AE) was similar in both the gefitinib and placebo groups (95.5% gefitinib and 98.5% placebo). The most common AEs in both treatment groups were nausea (64.4% gefitinib and 61.4% placebo); decreased appetite (49.2% gefitinib and 34.1% placebo group) and vomiting (41.7% gefitinib and 33.3% placebo). Some AEs generally expected with the chemotherapy, ie, vomiting (gefitinib 41.7% versus placebo 33.3%), stomatitis (gefitinib 10.6% versus placebo 3.8%), anaemia (gefitinib 31.8% versus 25.0%) and fatigue (gefitinib 21.2% versus 17.4%) were also reported, with a slightly higher frequency in the gefitinib treatment group. No interstitial lung disease event was reported in this study.

The proportion of patients reporting any AE causally related to study drug only (gefitinib or placebo) was higher in the gefitinib group (35.6% gefitinib versus 24.2% placebo). The most common AEs with causality related to gefitinib or placebo (in combination of cisplatin and pemetrexed) were gastrointestinal disorders (18.2% gefitinib and 6.1% placebo) and skin and subcutaneous tissue disorders (gefitinib 16.7% and placebo 8.3%).

The proportion of patients reporting any AE of Common Terminology Criteria for Adverse Event (CTCAE) grade 3 or higher was similar in both the gefitinib and placebo groups (44.7% gefitinib and 41.7% placebo). The most frequently reported AEs of CTCAE grade 3 or higher were haematology-related events. The CTCAE grade 3 or higher AEs reported were generally consistent with the known safety profile of study treatment and the underlying disease. The proportion of patients reporting any AE of CTCAE grade 3 or higher causally related to study drug or chemotherapy only was similar in the gefitinib and placebo groups (3.8% gefitinib and 2.3% placebo).

The proportion of patients reporting any serious adverse event (SAE) (including events with an outcome of death) was slightly higher in the gefitinib group (28.0% gefitinib versus 21.2% placebo); this difference appears to be mainly driven by events in the infections and infestations system organ class (8.3% gefitinib, 1.5% placebo). Two patients (1each in gefitinib and placebo groups) reported SAEs considered by the investigator to be causally related to study drug. The proportion of any SAE causally related to chemotherapy only was higher in the gefitinib group (9.8% gefitinib versus 5.3% placebo). A total of 2 (1.5%) patients in the gefitinib group and 1 (0.8%) patient in the placebo group reported

SAEs that were considered by the investigator to be causally related to both study drug and chemotherapy. No SAEs leading to discontinuation of study drug were reported to be causally related to study drug only

A lower proportion of patients had AEs with an outcome of death in the gefitinib group (3.8% gefitinib versus 6.1% placebo). The majority of AEs with an outcome of death were reported in the system organ class respiratory, thoracic and mediastinal disorders. Of the AEs with an outcome of death, only 5 events were reported during the treatment period (1 event of pneumonia in the gefitinib group and 4 events in the placebo group [pneumonia, cerebral infarction, dyspnoea and gastric perforation]). All other AEs with an outcome of death were reported in the follow-up treatment period. In the gefitinib group, 1 event with outcome of death (pneumonia) was considered by the investigator to be causally related to both study drug and chemotherapy and 1 event with outcome of death (dyspnoea) was considered by the investigator to be causally related to chemotherapy. In the placebo group, 1 event with outcome of death (haemoptysis) was considered by the investigator to be causally related to chemotherapy. The OS outcome appeared to be not related to toxicities as most deaths were disease-related and most were reported beyond the 30 days after last dose of study treatment; a similar number of deaths were reported in the gefitinib and placebo treatment groups (8% in both treatment groups) during treatment and within 30 days of last dose of study treatment.

The proportion of patients with AEs leading to discontinuation of study drug (gefitinib or placebo) was similar in both treatment groups (gefitinib 7.6% and placebo 9.8%). With the exception of AEs of anaemia and blood creatinine increased (gefitinib group) and decreased appetite and nausea (placebo group), which were reported by 2 (1.5%) patients in both treatment groups, all other AEs leading to discontinuation of study drug were not reported in more than 1 patient in each arm. Only one AE leading to discontinuation of study drug was considered by the investigator to be causally related to study drug (dermatitis acneiform; gefitinib group).

Overall, the mean values for the haematology parameters were similar between gefitinib and placebo groups and there were no notable shifts in specific parameters. An event of white blood cell decreased (gefitinib group) led to the discontinuation of study drug. No new safety concerns were identified from the haematology or clinical chemistry results. Consistent with the known safety profile of gefitinib, shift increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values from baseline over the treatment period were only observed in a few patients. Most of these changes were of CTCAE grade 1 or 2 and no patient fulfilled the criteria for potential Hy's law. Results of the urine analysis variables were consistent with the known safety profile of gefitinib. No clinically important changes in urinalysis were observed.

No clinically relevant trends in vital signs, electrocardiogram or physical examination observations were noted during the study.