AstraZeneca

Drug product:	IRESSA™	**SYNOPSIS**	
Drug substance(s):	Iressa (gefitinib)		
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A Double-blind, Placebo-controlled, Parallel-group, Multicentre, Randomised, Phase III Survival Study Comparing ZD1839 (IRESSA™) (250 mg Tablet) plus Best Supportive Care versus Placebo plus Best Supportive Care in Patients With Advanced NSCLC who Have Received One or Two Prior Chemotherapy Regimens and are Refractory or Intolerant to Their Most Recent Regimen

Study centre(s)

This study was conducted in 210 centres from 28 countries worldwide: Argentina (11), Australia (10), Brazil (10), Bulgaria (6), Canada (6), Estonia (2), Germany (8), Greece (4), Hungary (9), India (7), Ireland (2), Latvia (4), Lithuania (3), Malaysia (5), Mexico (8), Netherlands (7), Norway (12), Philippines (5), Poland (5), Romania (4), Russia (7), Singapore (3), Slovakia (10), Sweden (8), Taiwan (9), Thailand (4), Turkey (10), and United Kingdom (31).

Publications

Thatcher N, Chang A, Parikh P, Pemberton K, Archer V. Results of a Phase III placebo-controlled study (ISEL) of gefitinib (IRESSA) plus best supportive care (BSC) in patients with advanced non-small-cell lung cancer (NSCLC) who had received 1 or 2 prior chemotherapy regimens. Proceedings of the 96th Annual Meeting of the American Association for Cancer Research;2005 Apr 16-20;Anaheim, United States (Abstract LB-6).

Study dates		**Phase of development**
First patient enrolled	15 July 2003	Therapeutic confirmatory (III)
Last patient enrolled	2 August 2004	
Data cut-off date	29 October 2004	

Objectives

The primary objective was to compare overall survival for ZD1839 (IRESSA™, gefitinib) plus best supportive care (BSC) versus placebo plus BSC.

The secondary objectives were to compare gefitinib plus BSC versus placebo plus BSC in terms of:

- time to treatment failure
- investigator assessed overall objective tumour response (complete response [CR] + partial response [PR])
- quality of life changes
- tolerability

An exploratory objective was to investigate the correlation of epidermal growth factor receptor (EGFR) and other related biomarker status with efficacy in those patients where such tumour material was available. With the exception of EGFR expression status, the data from these analyses will be presented in a separate addendum.

Study design

This is a randomised, double-blind, placebo-controlled, parallel-group, international, multicentre study, designed to assess whether the addition of gefitinib (an EGFR tyrosine kinase inhibitor [TKI]) (250 mg daily) to BSC in patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) conferred an overall survival advantage over placebo plus BSC. Patients received the BSC available as judged by the treating investigator and were randomised to receive either gefitinib or placebo in a 2:1 ratio.

Target patient population and sample size

Patients who had received either 1 or 2 prior chemotherapy regimens for treatment of NSCLC who were refractory or intolerant to their most recent regimen. For patients aged <70 years at initial diagnosis, at least 1 prior therapy should have included platinum-based chemotherapy; however, elderly patients (≥70 years of age at initial diagnosis) were not required to have received prior platinum therapy and may have received 1 or 2 prior non-platinum or single-agent regimens.

Key inclusion criteria: locally advanced or metastatic NSCLC that was not amenable to curative surgery or radiotherapy; refractory or intolerant to most recent chemotherapy regimen; performance status (PS) of 0, 1, or 2 (patients of PS 3 were also eligible unless the investigator believed the poor PS was predominantly due to co-existing morbidity, eg, previous cerebrovascular accident, debilitating rheumatoid arthritis or severe cardiac impairment); life expectancy of at least 8 weeks.

Sample size: The study was originally sized to test the hypothesis that gefitinib would confer a statistically significant survival advantage (a 25% reduction in the hazard rate relative to placebo) among patients with adenocarcinoma histology. Approximately 866 patients with adenocarcinoma, accrued over 12 months, were to be recruited into the study, and it was estimated that this would lead to approximately 1299 patients being randomised altogether. The final analysis of survival required a minimum of 696 deaths among patients with adenocarcinoma histology to achieve 90% power at the 2-sided 5% significance level.

However, publication of the BR-21 study of erlotinib (a randomised, placebo-controlled, Phase III study of another EGFR TKI in 731 patients who had failed one or two lines of chemotherapy for advanced NSCLC) demonstrated a survival benefit for erlotinib that was independent of histological subtype. This, together with the recruitment of substantially more non-adenocarcinoma patients than expected to Study 0709 led the Independent Data Monitoring Committee (IDMC) to recommend a change in the protocol to allow the overall study population to be adopted as a co-primary population alongside the adenocarcinoma population. Based on the pattern of survival observed in BR-21 it was calculated that 900 deaths would provide at least 86% power to detect a similar magnitude of effect as with erlotinib at the 2.5% 1-sided significance level. The actual number of patients enrolled in the study was 1692, including 812 patients with adenocarcinoma histology.

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

Gefitinib 250 mg once daily in oral tablet form (a single 250-mg tablet per dose) with matching placebo tablets used for the comparator. The formulation numbers were F012653 and F012647 for the gefitinib 250-mg and placebo tablets, respectively.

Duration of treatment

Patients continued to receive daily gefitinib or placebo until unacceptable toxicity, patient refusal or the investigator considered the patient was no longer deriving clinical benefit. The protocol did not mandate that radiological progression should necessarily lead to discontinuation of study therapy.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: overall survival
- Secondary variables: time to treatment failure (TTF) and objective tumour response (ORR: assessed by Response Evaluation Criteria In Solid Tumour [RECIST] criteria)

Patient-reported outcomes (PROs)

- Quality of life (QOL) (Functional Assessment of Cancer Therapy-Lung [FACT-L], Trial Outcome Index [TOI], and Lung Cancer Subscale [LCS])

Safety

- Type, frequency, and severity of adverse events (AEs), laboratory parameters, and vital signs

Exploratory

- Exploratory variables: EGFR and other related biomarkers

Statistical methods

The primary aim of this study was to detect an overall survival advantage for gefitinib 250 mg plus BSC compared with placebo plus BSC.

The primary statistical analysis of overall survival was conducted in the co-primary populations of all randomised patients and patients with adenocarcinoma histology on an intention-to-treat basis. Treatment groups were compared using a log-rank test with the following stratification factors: histology (adenocarcinoma versus other), gender (male versus female), smoking history (never smoked versus current/former smoker), reason for prior chemotherapy failure (refractory versus intolerant), number of prior chemotherapy regimens (1 versus 2 regimens) and performance status (0 or 1 versus 2 or 3). Pre-planned subgroup analyses were conducted for these stratification factors and for other clinically relevant subsets identified from the Phase II data with gefitinib as well as the subsets explored in BR-21 (TARCEVA™ [erlotinib] US Package Insert). The additional subgroups were prior docetaxel therapy (yes versus no), age at randomisation (<65 years versus ≥65 years), time from diagnosis to randomisation (<6 months, 6 to 12 months, >12 months), racial origin (Asian [excluding those of Indian origin] versus other) and best response to prior chemotherapy (CR/PR versus SD versus PD). The definition of Asian racial origin excludes those of Indian origin and refers to the racial origin of a patient group and not necessarily their place of birth. Hereafter, this subgroup will be referred to as Asian origin. Patients who have never smoked are referred to as non-smokers and current/former smokers are referred to as smokers within the results presentation.

At the request of the IDMC, there was one interim analysis of overall survival conducted at the close of recruitment. An extreme p-value was applied ($p<0.001$) to ensure the trial was only unblinded in the event of a highly convincing result and to preserve the overall type-I error at 5% in the final analysis.

Patient population

The patients who participated in this study were representative of an advanced pre-treated NSCLC population. A total of 1692 patients were randomised to treatment (1129 patients to receive gefitinib 250 mg and 563 patients to receive placebo); these patients were recruited from 210 centres in 28 countries and included 812 patients (48.0%) with adenocarcinoma histology. Overall, 823 patients (48.6%) were second-line, ie, had received one previous chemotherapy regimen and almost all patients had received prior platinum-based therapy. In line with the intent to recruit a highly refractory patient population, approximately 90% of patients were refractory to their most recent prior chemotherapy regimen (ie, had progressed

on or within 90 days of their most recent chemotherapy regimen) and approximately 45% of patients experienced a best response to their last chemotherapy of disease progression. Approximately one-third of patients were female, one-fifth were non-smokers and one-fifth were of Asian racial origin. The median age of the patients was 61 years (ranging from 28 to 90 years).

As would be expected in a large randomised study with stratified randomisation, the two treatment groups were well balanced at baseline with respect to all important prognostic factors, thus enabling valid conclusions to be drawn from the efficacy, QOL, and safety analyses.

This trial was conducted to high quality; the number of major protocol deviations was low (71 patients [4.2%] were excluded from the per-protocol population) with no imbalance across the treatment groups.

Efficacy results

Primary variable: overall survival

The analyses based on a data cut-off of 29 October 2004, by which time 976 deaths had accrued, median follow-up was 7.2 months, and total mortality was 57.7% indicate:

- While there was some improvement in overall survival in favour of gefitinib 250 mg over placebo (with an absolute difference of 4.5% in the number of deaths reported); the magnitude of this effect was less than anticipated and consequently failed to reach statistical significance for the primary stratified log-rank test (overall population: HR 0.89, 95% CI 0.77 to 1.02, p=0.0871); adenocarcinoma population: HR 0.84, 95% CI 0.68 to 1.03, p=0.0885). Despite this, the likelihood that this increase in overall survival was due to a true effect of gefitinib 250 mg is 95.6%.

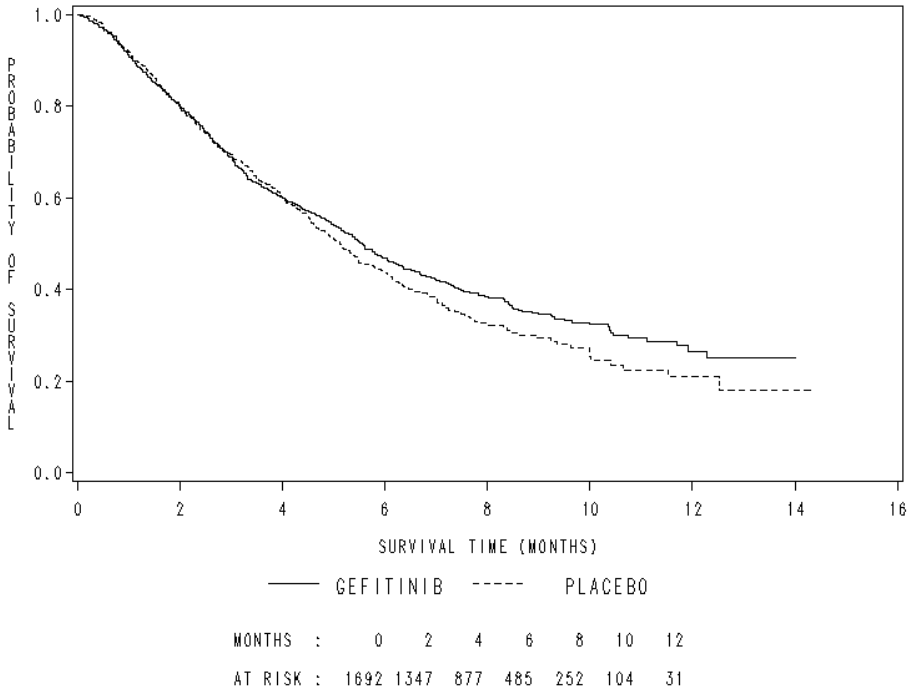
    - the protocolled supportive Cox regression analysis, with covariate adjustment for the same factors employed as strata in the log-rank test, indicated statistically significant treatment effects for both the overall (HR 0.86, 95% CI 0.76 to 0.99, p=0.0299) and adenocarcinoma patient populations (HR 0.81, 95% CI 0.67 to 0.98, p=0.0330)

    - one-year survival was 26.5% and 20.9% for the gefitinib 250-mg and placebo groups, respectively, for the overall ITT population

    - median overall survival was 5.6 months for patients receiving gefitinib 250 mg compared to 5.1 months with placebo in the overall ITT population; it should be noted that separation of the Kaplan-Meier survival curves does not occur until approximately 4 months at 40% overall mortality

    - the low incidence of patients receiving gefitinib therapy following failure of placebo (3%) was unlikely to impact the survival results

Figure S1 Overall survival probability for the ITT overall population



Kaplan-Meier curves for the adenocarcinoma population are similar to the ITT curves.

- pre-planned subgroup analyses revealed general heterogeneity in the treatment effect that was broadly consistent with (1) the gefitinib Phase II programme, (2) the extensive published data for gefitinib, and (3) data for the EGFR TKI erlotinib. Statistically significant treatment-by-covariate interactions were observed for smoking history (non-smokers versus smokers) and racial origin (Asian origin versus non-Asian origin):

  - a survival difference was apparent for gefitinib–treated patients compared to placebo for non-smokers (HR 0.67, 95% CI 0.49 to 0.92, p=0.0124), whereas survival was similar in both treatment groups for smokers (HR 0.92, 95% CI 0.79 to 1.06, p=0.2420)

    - evaluation of the subgroup of non-smokers receiving treatment with gefitinib in comparison to placebo revealed that (1) the risk of death was 33% lower among patients receiving gefitinib 250 mg and (2) median overall survival was prolonged by 2.8 months from 6.1 months for patients receiving placebo to 8.9 months for gefitinib-treated patients

  - similarly, a survival difference was apparent for gefitinib–treated patients compared to placebo for patients of Asian origin (HR 0.66, 95% CI 0.48 to

0.91, p=0.0100), whereas survival was similar in both treatment groups for patients of non-Asian origin (HR 0.92, 95% CI 0.80 to 1.07, p=0.2942)

- evaluation of the subgroup of patients of Asian origin receiving treatment with gefitinib in comparison to placebo revealed that (1) the risk of death was 34% lower among patients receiving gefitinib 250 mg and (2) median overall survival was prolonged by 4 months from 5.5 months for patients receiving placebo to 9.5 months for gefitinib-treated patients

Secondary variables

- efficacy was observed in patients receiving gefitinib 250 mg in terms of the secondary trial endpoints TTF and ORR, with evidence of tumour shrinkage

  – gefitinib 250 mg was associated with a statistically significant 18% reduction in the risk of treatment failure compared with placebo (ITT population: HR 0.82, 95% CI 0.73 to 0.92, p=0.0006).

  – gefitinib 250 mg was associated with a statistically significant 7-fold increase in the ORR compared with placebo (evaluable-for-response population: OR 7.28, 95% CI 3.13 to 16.91, p<0.0001). Objective tumour responses were achieved for 8.0% of patients in the gefitinib 250-mg group compared with 1.3% in the placebo group.

  – similar heterogeneity among subgroups was apparent with greater treatment differences in favour of gefitinib for non-smokers compared with smokers and for patients of Asian origin compared with non-Asian patients.

Exploratory objective

- Evaluation of survival outcomes suggests that patients with EGFR-positive tumours achieve better outcomes than patients with EGFR-negative tumours. The survival benefit for gefitinib-treated patients with EGFR-positive tumours (HR 0.77, 95% CI 0.56 to 1.08, p=0.1258) seems to be somewhat better than for the overall study population while gefitinib 250 mg appears to offer little survival benefit to patients with EGFR-negative tumours (HR 1.57, 95% CI 0.86 to 2.87, p=0.1402), although neither subset analysis was statistically significant. Given this lack of significance coupled with the limited number of patients with available tumour samples overall (n=379, 22.4%) and few samples from never-smokers or patients of Asian racial origin, these data are considered to be inconclusive.

- In the largest subgroup of patients with unknown EGFR expression status, survival outcomes were similar to the overall population (HR 0.84, 95% CI 0.73 to 0.98, p=0.0266).

Patient-reported outcomes

- Quality of life including disease-related symptoms during treatment with gefitinib 250 mg was similar to and no worse than with placebo

  - While results tended to favour gefitinib 250 mg, treatment differences were small:

  - There was a statistically significant difference in symptoms (according to the LCS score) with gefitinib providing more symptomatic control than placebo; the difference was not considered clinically relevant according to the pre-defined criteria of ≥2-point difference in LCS score (Evaluable for QOL population: mean change from baseline in LCS score [gefitinib-placebo] 0.51 points, 95% CI 0.08 to 0.94, p=0.0192)

Safety results

Consistent with the results of previously conducted gefitinib monotherapy studies, the safety data from this study confirm that gefitinib 250 mg has a favourable tolerability profile in terms of the type, frequency, and severity of events:

- The majority of patients experienced one or more AEs. No clinically relevant differences between the treatment groups in the frequency of SAEs or CTC grade 3 or 4 AEs were evident. The frequencies of AEs leading to discontinuation and AEs leading to death were low in both treatment groups (Table S1).

Table S1 Categories of adverse events: number (%) of patients who had at least 1 adverse event in any category (Evaluable for safety population)

Category[a]	Number (%) of patients			
	Gefitinib 250 mg (N=1126)		Placebo (N=562)	
Patients with an adverse event (AE)	927	(82.3)	397	(70.6)
CTC grade 3 or 4 AEs	341	(30.3)	151	(26.9)
Serious AEs	216	(19.2)	98	(17.4)
AE leading to discontinuation	61	(5.4)	13	(2.3)
AE leading to death	55	(4.9)	22	(3.9)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

N Number of patients.

- Consistent with the known toxicity profile for gefitinib, the most frequently reported adverse events for gefitinib 250 mg were diarrhoea, rash and other skin events, nausea, anorexia, and vomiting (Table S2). The majority of these events were of CTC grade 1 (mild) or 2 (moderate). The frequencies of individual CTC grade 3 or 4 AEs were low in both treatment groups.

Table S2 Most common adverse events (those occurring in at least 5% of the study population): evaluable-for-safety population

	Number (%) of patients							
	Gefitinib 250 mg (N=1126)				Placebo (N=562)			
	All CTC grades		CTC grade 3/4		All CTC grades		CTC grade 3/4	
Diarrhoea	309	(27.4)	31	(2.8)	52	(9.3)	5	(0.9)
Rash[a]	295	(26.2)	12	(1.1)	40	(7.1)	0	
Nausea	190	(16.9)	9	(0.8)	90	(16.0)	2	(0.4)
Anorexia	172	(15.3)	25	(2.2)	69	(12.3)	11	(2.0)
Vomiting	152	(13.5)	13	(1.2)	56	(10.0)	2	(0.4)
Dry skin	128	(11.4)	0		20	(3.6)	0	
Constipation	108	(9.6)	13	(1.2)	71	(12.6)	10	(1.8)
Pruritus	81	(7.2)	2	(0.2)	26	(4.6)	1	(0.2)
Pyrexia	79	(7.0)	7	(0.6)	27	(4.8)	2	(0.4)
Asthenia	75	(6.7)	19	(1.7)	36	(6.4)	7	(1.2)
Cough	75	(6.7)	2	(0.2)	45	(8.0)	4	(0.7)
Dyspnoea	75	(6.7)	35	(3.1)	44	(7.8)	21	(3.7)
Stomatitis	68	(6.0)	3	(0.3)	22	(3.9)	1	(0.2)
Fatigue	63	(5.6)	16	(1.4)	27	(4.8)	6	(1.1)

[a] The frequency of rash is based solely on adverse events with the MedDRA preferred term of rash. This is likely to provide an underestimate of the true incidence of skin toxicity associated with gefitinib therapy. When the MedDRA high level term (HLT) acnes is combined with HLT rashes, eruptions and exanthems and preferred terms rash pustular, dermatitis and dermatitis exfoliative, the incidence of skin toxicity is increased to 413 [36.7%] in gefitinib-treated patients and 56 [10.0%] in placebo-treated patients. Similarly, for CTC grade 3 or 4 events, the combined incidence of CTC grade 3 or 4 skin toxicity is 18 [1.6%] in gefitinib-treated patients and 1 [0.2%] in placebo-treated patients.

- The incidence of interstitial lung disease (ILD) type events was approximately 1% in both treatment groups.
- Gefitinib 250 mg was well-tolerated. Dose interruptions were generally of short duration and permanent discontinuations of study treatment due to AEs were low.
- The clinical laboratory results were similar to those seen in previous gefitinib monotherapy studies:
  - No clinically relevant changes in haematology parameters between treatment groups were evident; gefitinib 250 mg was comparable to placebo.
  - A slightly greater proportion of patients had a CTC grade 2 or more change in their creatinine values in the gefitinib 250-mg group (1.3%) compared with the placebo group (0.2%). In several instances the creatinine change occurred concurrently with episodes of diarrhoea and some patients were on concomitant medications known to have an effect on renal parameters.

- The majority of transaminase changes were CTC grade 1 (mild) or 2 (moderate). A slightly higher proportion of gefitinib-treated patients than placebo-treated patients experienced a CTC grade 3 or 4 change in ALT (1.5% vs 0.8%) or AST (1.0% vs 0.6%). These generally asymptomatic changes were not associated with corresponding changes in total bilirubin or alkaline phosphatase.

- Consistent with previous gefitinib monotherapy studies, there was a slightly increased frequency of haematuria (10.4% vs 7.6%) and proteinuria (8.1% vs 5.3%) for gefitinib 250 mg vs placebo.

- Gefitinib 250 mg has a favourable tolerability profile in terms of the type, frequency, and severity of AEs reported by non-smokers and patients of Asian origin:

  - The safety profile for non-smokers was consistent with that of the overall population.

  - Adverse events tended to be more frequently reported in both treatment groups by patients of Asian origin, although generally the types of events were similar to the overall population.