AstraZeneca

Clinical Study Synopsis

Drug substance:	Gefitinib
Document No.:	001
Edition No.:	001
Study code:	1839IL/0710 D7913C00710
Date:	25 April 2005

A Double Blind, Placebo Controlled, Parallel Group, Multicentre, Randomised Phase III Study of Disease-Related Symptoms Comparing ZD1839 (IRESSA™) (250mg Tablet) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Symptomatic Patients with Advanced NSCLC who have Received One or Two Prior Chemotherapy Regimens and are Refractory or Intolerant to Their Most Recent Regimen

Study dates:	First patient enrolled: 01 April 2004 Last patient completed: 22 November 2004
Phase of development:	Therapeutic confirmatory (III)
International Co-ordinating Investigators:	
Sponsor's Responsible Medical Officer:	Nick Botwood BSc MB BS MRCP MFPM Worldwide Medical Director – IRESSA AstraZeneca, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

This study was performed in compliance with Good Clinical Practice.

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A Double Blind, Placebo Controlled, Parallel Group, Multicentre, Randomised Phase III Study of Disease-Related Symptoms Comparing ZD1839 (IRESSA™) (250mg Tablet) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Symptomatic Patients with Advanced NSCLC who have Received One or Two Prior Chemotherapy Regimens and are Refractory or Intolerant to Their Most Recent Regimen

International co-ordinating investigators

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Study centre(s)

In this study, patients were recruited from 25 centres in Austria, Denmark, South Africa, Spain and United Kingdom.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	01 April 2004	Therapeutic confirmatory (III)
Last patient enrolled	10 September 2004	
Date of early study termination	28 September 2004	
Last patient completed	22 November 2004	

Objectives

The primary objective of the study was to compare gefitinib plus best supportive care (BSC) versus placebo plus BSC in terms of pulmonary symptom improvement as measured by the 4 pulmonary questions of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) Lung Cancer Subscale (LCS). Table 1 summarises the objectives and variables of this study, and shows how they relate to the study objectives.

Table 1 Study objectives and variables

Objective	Variable(s)
Primary	
To compare gefitinib + BSC versus placebo + BSC in terms of pulmonary symptom improvement as measured by the 4 pulmonary questions of the FACT-L LCS	The proportion of patients with sustained pulmonary symptom improvement, as measured by the 4 pulmonary items (short of breath; ease of breathing; tightness in chest and cough) of the FACT-L LCS. Pulmonary symptom improvement had to be demonstrated in the absence of clinically significant increases in the use of concomitant medications that, in the opinion of the investigator, could have resulted in improvement
Secondary	
To compare gefitinib + BSC versus placebo + BSC in terms of patient reported functionality and quality of life	Improvement in patient-reported functionality as measured by trial outcome index (TOI [which is comprised of the physical and functional well-being sections and LCS of FACT-L]) and quality of life as measured by the FACT-L total score
To compare gefitinib + BSC versus placebo + BSC in terms of progression free survival	Progression-free rate (PFR) at 4 months, PFR at 6 months and overall progression free survival
To compare gefitinib + BSC versus placebo + BSC in terms of overall objective tumour response (CR + PR)	Overall tumour response rate (Response Evaluation Criteria in Solid Tumours [RECIST] criteria for radiographic response)
To compare gefitinib + BSC versus placebo + BSC in terms of tolerability	Tolerability (type, frequency and severity of adverse events; laboratory parameters)
To compare gefitinib + BSC versus placebo + BSC in terms of survival	Time from randomisation to death
Exploratory	
To compare gefitinib + BSC versus placebo + BSC in terms of Health Resource Utilization including the use of concomitant medications	The use of selected items of resources and concomitant medications including: number of inpatients days (ICU/non ICU); number of invasive procedures eg, epidural analgesia, thoracentesis; palliative radiotherapy; all concomitant medications, including supplemental oxygen therapy (dose, route, schedule, start date, indication, stop date and reason for stopping)

Table 1 Study objectives and variables

Objective	Variable(s)
To compare gefitinib + BSC versus placebo + BSC in terms of patient health status	Patient Health Status as measured by the EuroQuol-5 Dimension (EQ-5D), monthly
To compare gefitinib + BSC versus placebo + BSC in terms of changes in pain and fatigue	Changes in pain and fatigue as measured by the single items from the FACT-L physical well-being domain, weekly
To compare gefitinib + BSC versus Placebo + BSC in terms of changes in World Health Organisation (WHO) Performance Status (PS)	Changes in WHO PS as assessed by the investigator, monthly
To evaluate a patient-reported global assessment of change in pulmonary symptoms, which will potentially provide an anchoring of the pulmonary symptoms endpoint to patient-perceived clinical benefit	Global assessment of change will be explored by asking patients weekly, if they feel their *overall* lung symptoms (referencing the 4 pulmonary items of the FACT-L LCS) are *better*, *about the same* or *worse*, since starting study medication
To investigate the potential correlation between spirometry and pulmonary symptoms	Evaluation of spirometry, twice at baseline and at 4 and 8 weeks after initiation of study therapy
To investigate the correlation of epidermal growth factor receptor (EGFR) and other related biomarker status with efficacy in those patients where such tumour material is available	Epidermal growth factor receptor and related biomarkers

BSC	Best supportive care.
CR	Complete response.
FACT-L	Functional Assessment of Cancer Therapy for Lung Cancer.
ICU	Intensive care unit.
LCS	Lung Cancer Subscale.
PR	Partial response.
PS	Performance status.
WHO	World Health Organisation.

Study design

This was a double blind, placebo controlled, parallel group, international multicentre, phase III randomised study, designed to demonstrate that the addition of gefitinib to BSC confers an improvement in pulmonary symptoms, measured by the 4 pulmonary-specific questions of the FACT-L LCS in patients with previously treated advanced or metastatic non-small cell lung cancer (NSCLC). Patients were stratified according to World Health Organisation (WHO) performance status (PS) (0, 1 versus 2, 3), tumour histology (adenocarcinoma versus other), gender (male versus female), smoking history (smoking or

history of smoking versus never smoked), prior chemotherapy history (intolerant versus refractory) and centre, and randomised to receive either gefitinib or placebo in a ratio of 2:1. The study protocol is provided in Appendix C.

Target patient population and sample size

Male and female patients, aged 18 years or older with advanced or metastatic NSCLC.

Key inclusion criteria:

- locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy, which had been histologically or cytologically confirmed
- at least one moderate (score 1) or severe (score 0) pulmonary item on the pulmonary questions of the FACT-L LCS at baseline
- not considered to require palliative radiotherapy at the time of study entry
- previously received at least one but no more than 2 prior chemotherapy regimens
- refractory or intolerant to most recent prior chemotherapy regimen
- WHO PS 0, 1 or 2. Patients of PS 3 were eligible unless the investigator believed the poor PS was predominantly due to co-existing morbidity
- haemoglobin ≥ 10 g/dL at entry
- life expectancy of at least 8 weeks

A total of 324 patients (216 to receive gefitinib and 108 to receive placebo) were required to achieve 90% power for a 2-sided 5% significance level test. The sample size was estimated assuming a 2:1 randomisation (gefitinib to placebo), a 21% pulmonary symptom improvement rate on the gefitinib arm and a 7% improvement rate on the placebo arm. The sample size parameters were estimated based on data from IDEAL 2, a study performed in a similar population to that planned in this study. The assumptions for the placebo arm were based on the expectation that patients on placebo would perform similarly to the patients on IDEAL 2 who had a best tumour response of progressive disease.

A total of 46 patients were randomised at the time of study closure; 31 patients were randomised to receive gefitinib plus BSC and 15 patients to receive placebo plus BSC.

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

Gefitinib 250 mg tablet, once daily for oral administration (one 250 mg tablet per dose). The formulation number was F12653 and the Analytical Development Macclesfield (ADM) batch number was 93809J02.

Placebo tablet matching the active investigational product, once daily for oral administration. The formulation number was F12647 and the ADM batch number was 91542K02.

Duration of treatment

Patients continued to receive daily gefitinib or placebo until unacceptable toxicity, patient refusal, or the investigator considered the patient to have clear evidence of radiological and/or clinical progression.

Early closure of the study

The Steering Committee for this study met on 2 August 2004 to discuss the options for further study conduct in view of the fact that survival data from the related and recently amended AstraZeneca Study 1839IL/0709 might be available before the end of 2004. Also considered in the discussion were the data from the BR-21 study of erlotinib (another EGFR-tyrosine kinase inhibitor) versus BSC, presented at the American Society of Clinical Oncology (ASCO) 2004 (Shepherd et al 2004). These data were likely to adversely affect the ability of this study to continue to full accrual of 324 patients by June 2005.

The proposals of either continuing the study in its current format (albeit with optimised recruitment) or changing the study design (to mandate that all patients receive active drug after 6 weeks of randomised therapy) were rejected. Neither of these options would have guaranteed that a sufficient number of patients would be randomised before the end of 2004. The Steering Committee was of the unanimous opinion that to knowingly accrue patients to a study that was highly unlikely to complete was unethical. The study would be insufficiently powered to address its primary endpoint and the recommendation was to close the study as soon as possible. The study closed to recruitment in September 2004, and the last patient completed in November 2004.

During the study, treatment was unblinded for 6 (19.4%) of the 31 patients randomised to receive gefitinib, and for 4 (26.7%) of the 15 patients randomised to receive placebo. All 4 patients who initially received placebo crossed over to gefinitib. All patients were unblinded when the study closed to recruitment on 28 September 2004. A further 4 patients who initially received placebo crossed over to receive gefitinib.

Statistical methods

This study was closed early; therefore no statistical analysis was performed.

Patient population

A total of 46 patients (31 patients [67.4%] in the gefitinib plus BSC and 15 patients [32.6%] in the placebo plus BSC group) from 25 centres in 5 countries were randomised in this study.

The demographic characteristics are summarised in Table 2. There were 32 male patients (69.6%) and 14 females (30.4%), ranging from 25 to 82 years in age. A total of 41 patients (89.1%) were Caucasian. The treatment groups were generally well balanced in terms of demographic characteristics.

A total of 46 patients were analysed in the intention-to-treat (ITT) population (ie, all randomised patients) and in the evaluable-for-safety (EFS) population (ie, all patients who received at least one dose of study medication).

Table 2 Summary of demographic characteristics: ITT population

Demographic characteristic		**Gefitinib (N=31)**		**Placebo (N=15)**	
Age (years)	Mean (SD)	57.8	(11.7)	63.7	(10.7)
	Median	59.0		64.0	
	Range	25.0-77.0		38.0-82.0	
Age distribution (n [%])	<45 years	4.0	(12.9)	1.0	(6.7)
	45-64 years	19.0	(61.3)	8.0	(53.3)
	65-74 years	5.0	(16.1)	5.0	(33.3)
	≥75 years	3.0	(9.7)	1.0	(6.7)
Sex (n [%])	Male	22	(71.0)	10	(66.7)
	Female	9	(29.0)	5	(33.3)
Race (n [%])	Caucasian	27	(87.1)	14	(93.3)
	Black	1	(3.2)	0	(0)
	Other	3	(9.7)	1	(6.7)

ITT Intention-to-treat.
N Number of patients.
Data derived from Summary Tables T1.1 and T1.2.

Reasons for discontinuation from the study included study closure (28.3%), objective disease progression (26.1%), symptomatic deterioration (21.7%), death (15.2%), adverse event (6.5%) and patient withdrawal (2.2%).

Efficacy results

This study was closed early; therefore no efficacy data were validated or analysed.

Safety results

All available data are provided in Appendix B (Summary tables) and Appendix E (Data listings). It is difficult to draw conclusions from the small sample size; however the results are consistent with those expected, based on the known safety profile of gefitinib from previously conducted monotherapy studies, and suggest that gefitinib in advanced NSCLC has an acceptable tolerability profile compared to BSC in terms of the type, frequency and severity of events. Table 3 presents an overview of AEs reported in this study.

Table 3 Categories of adverse events: number (%) of patients who had at least one adverse event in any category: EFS population

Category[a]	Gefitinib (N=31)		Placebo (N=15)	
All adverse events (AEs)	24	(77.4)	6	(40.0)
Treatment-related[b] AEs	18	(58.1)	0	(0)
All serious adverse events (SAEs)	6	(19.4)	2	(13.3)
Treatment-related[b] SAEs	2	(6.5)	0	(0)
Non-fatal SAEs	5	(16.1)	2	(13.3)
Deaths due to SAEs	1	(3.2)	0	(0)
Deaths due to treatment-related[b] SAEs	0	(0)	0	(0)
Discontinuations from study treatment due to AEs	3	(9.7)	0	(0)
Due to treatment-related[b] AE	3	(9.7)	0	(0)
Due to SAE	0	(0)	0	(0)
Due to treatment-related[b] SAE	0	(0)	0	(0)
CTC[c] Grade 3 or 4 AEs	7	(22.6)	2	(13.3)
CTC Grade 3 or 4 treatment- related[b] AE	4	(12.9)	0	(0)

[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.
[b] Treatment-related adverse events were those events that the investigator considered to be possibly related to study treatment.
[c] CTC Grade NCI version 2.0.
EFS Evaluable for safety.
N Number of patients.
Data derived from Summary Table T4.1 and Listings G4.3 and G4.4.

- The most frequently reported adverse events for gefitinib, in order of decreasing frequency, were rashes/acnes, diarrhoea and vomiting. The majority of these were of Common Toxicity Criteria (CTC) grade 1 (mild) or 2 (moderate). Table 4 shows the most common AEs, ranked in order of decreasing frequency within each system organ class.

Table 4 Overall adverse events occurring with an incidence of at least 5% in patients treated with gefitinib, by system organ class and preferred term: EFS population

System organ class and preferred term	Number (%) of patients[a]			
	Gefitinib (N=31)		Placebo (N=15)	
Gastrointestinal disorders				
Diarrhoea	7	(22.6)	0	(0)
Vomiting	4	(12.9)	1	(6.7)
Constipation	3	(9.7)	2	(13.3)
Nausea	3	(9.7)	1	(6.7)
General disorders				
Fatigue	3	(9.7)	1	(6.7)
Pyrexia	3	(9.7)	0	(0)
Asthenia	2	(6.5)	0	(0)
Respiratory, thoracic, and mediastinal disorders				
Dyspnoea	3	(9.7)	0	(0)
Skin and subcutaneous disorders				
Rashes/Acnes[b]	10	(32.3)	0	(0)

[a] Percentages are of total patients in each treatment group and do not necessarily add up to 100% within each system organ class. Patients with events in more than 1 category are counted once in each of those categories.

[b] Grouping of the high level terms 'Acnes', 'Rashes, eruptions and exanthems NEC' and the preferred term 'Rash papular'.

EFS Evaluable for safety.

N Number of patients.

Data derived from Summary Tables T4.2 and T4.3.

- Nine patients (19.6%) reported a CTC grade 3 or 4 adverse event (gefitinib: 7 [22.6%]; placebo: 2 [13.3%]).

- Eight patients (17.4%) reported a serious adverse event during the treatment phase (gefitinib: 6 [19.4%]; placebo: 2 [13.3%]). The frequencies of individual events for gefitinib were low and no obvious patterns were apparent. Further details are provided in Summary Listing G4.2 in Appendix E.

- Three patients (9.7%) in the gefitinib group had AEs leading to discontinuation, compared with none in the placebo group. Patients E0250002, E1630007 and E1860001 were discontinued from receiving investigational product due to

treatment-related, non-serious AEs. Further details are provided in Summary Listing G4.3 in Appendix E.

- One patient (2.2%) died as the result of an adverse event. A 60 year old male patient (E1114003) received gefitinib, and stopped taking study treatment due to disease progression. Six days later the patient developed a lower respiratory tract infection. The patient was pyrexic, and had neutophilia and leucophilia. The patient died 2 days later. The investigator considered the event to be unrelated to study treatment.

- The maximum number of days on treatment for gefitinib (including interruptions) was 196 days, and for placebo was 109 days.

Conclusion(s)

- The safety data from this study suggest that gefitinib is well tolerated when used at the 250 mg dose to treat patients with advanced NSCLC. The most commonly reported AEs were consistent with those reported in previous gefitinib monotherapy studies. No new safety findings were evident from this small sample of patients.

References

Shepherd FA, Pereira J, Ciuleanu TE, Tan EH, Hirsh V, Thongprasert S, et al. A randomized placebo-controlled trial or erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial. Proceedings of the 40th Annual Meeting of the American Society of Clinical Oncology; 2004 Jun 5-8; New Orleans, USA (Abstract 7022).

Date of the report

25 April 2005

APPENDICES

Appendix A: Signatures
Appendix B: Summary Tables
Appendix C: Protocol
Appendix D: Important publications referenced in the report
Appendix E: Subject Data Listings
Appendix F: Subject Information and Consent