Clinical trial results:
A Phase II Multicentre Randomised, Parallel Group, Double-Blind, Placebo Controlled Study of ZD1839 (Iressa™) (250mg Tablet) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Chemotherapy Naïve Patients with Advanced (Stage IIIB or IV) Non-Small Cell Lung Cancer
(NSCLC) and Poor Performance Status INSTEP (Iressa NSCLC Trial Evaluating Poor Performance Patients)

Summary

EudraCT number	2004-004206-25
Trial protocol	IE CZ
Global end of trial date	24 April 2016

Results information

Result version number	v1 (current)
This version publication date	15 March 2017
First version publication date	15 March 2017

Trial information

Trial identification

Sponsor protocol code	D7913C00711

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00259064
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	One Medimmune Way, 101 ORD, 2233C, Gaithersburg, United States, MD 20878
Public contact	Yuri Rukazenkov, AstraZeneca, +44 01625 231825, yuri.rukazenkov@astrazeneca.com
Scientific contact	Yuri Rukazenkov, AstraZeneca, +44 01625 231825, yuri.rukazenkov@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 February 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2007
Global end of trial reached?	Yes
Global end of trial date	24 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare gefitinib (IRESSA™, ZD1839) + best supportive care (BSC) versus placebo + BSC in terms of progression-free survival (PFS).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Canada: 114
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	United Kingdom: 40
Worldwide total number of subjects	201
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	36
From 65 to 84 years	147
85 years and over	18

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were screened prior to entry into study & were required to fulfil all inclusion/exclusion criteria which included: a diagnosis of NSCLC, locally advanced or metastatic disease, not amenable to curative surgery, radiotherapy or chemotherapy; Measurable disease according to RECIST; No prior chemotherapy, biological or immunological therapy.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

Patients were randomised in a ratio of 1:1 to receive either gefitinib 250 mg or matching placebo tablets in combination with BSC. Study treatment wasdispensed to patients in a double blind manner on Day 1 and every 12 weeks thereafter until the patient discontinued.

Arms

Are arms mutually exclusive?	Yes
Arm title	Gefitinib

Arm description:

Gefitinib 250 mg plus Best Supportive Care

Arm type	Experimental
Investigational medicinal product name	Gefitinib
Investigational medicinal product code	
Other name	Iressa
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 mg daily

Arm title	Placebo

Arm description:

Matched Placebo plus Best Supportive Care

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet daily

Number of subjects in period 1	Gefitinib	Placebo
Started	100	101
Completed	100	101

Period 2	
Period 2 title	Overall Trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

Patients were randomised in a ratio of 1:1 to receive either gefitinib 250 mg or matching placebo tablets in combination with BSC. Study treatment wasdispensed to patients in a double blind manner on Day 1 and every 12 weeks thereafter until the patient discontinued.

Arms	
Are arms mutually exclusive?	Yes
Arm title	Gefitinib

Arm description:

Gefitinib 250 mg plus Best Supportive Care

Arm type	Experimental
Investigational medicinal product name	Gefitinib
Investigational medicinal product code	
Other name	Iressa
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 mg daily

Arm title	Placebo

Arm description:

Matched Placebo plus Best Supportive Care

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet daily

Number of subjects in period 2	Gefitinib	Placebo
Started	100	101
Completed	99	99
Not completed	1	2
Consent withdrawn by subject	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Gefitinib
Reporting group description: Gefitinib 250 mg plus Best Supportive Care	
Reporting group title	Placebo
Reporting group description: Matched Placebo plus Best Supportive Care	

Reporting group values	Gefitinib	Placebo	Total
Number of subjects	100	101	201
Age Categorical Units: Subjects			
Adults (18-64 years)	19	17	36
From 65-84 years	73	74	147
85 years and over	8	10	18
Age Continuous Units: years			
arithmetic mean	72.3	73.9	
standard deviation	± 9.5	± 9	-
Gender Categorical Units: Subjects			
Female	39	40	79
Male	61	61	122
Race Units: Subjects			
Caucasian	96	97	193
Oriental	4	3	7
other	0	1	1
Smoking history Units: Subjects			
Habitual	19	19	38
Occasional	0	2	2
Ex Smoker	71	71	142
Non Smoker	10	9	19
WHO Performance Status			
World Health Organisation (WHO) performance status is a scale from 0 (fully active) to 5 (dead), indicating patients ability to perform certain activities of daily life. All patients in this study have PS of 2 or 3.			
Units: Subjects			
2: in bed <= 50% of time	55	63	118
3: in bed > 50% of time	45	38	83

End points

End points reporting groups

Reporting group title	Gefitinib
Reporting group description: Gefitinib 250 mg plus Best Supportive Care	
Reporting group title	Placebo
Reporting group description: Matched Placebo plus Best Supportive Care	
Reporting group title	Gefitinib
Reporting group description: Gefitinib 250 mg plus Best Supportive Care	
Reporting group title	Placebo
Reporting group description: Matched Placebo plus Best Supportive Care	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description: Progression Free Survival (PFS) is defined as the interval between the date of randomisation and the earliest date of objective disease progression according to The Response Evaluation Criteria in Solid Tumours [RECIST] or death due to any cause in the absence of progression	
End point type	Primary
End point timeframe: Overall Study - Assessed every 6 weeks from randomisation	

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: days				
median (confidence interval 95%)	43 (39 to 55)	41 (37 to 43)		

Statistical analyses

Statistical analysis title	Primary Analysis: Hazard Ratio
Statistical analysis description: Hazard Ratio(HR) calculated from Cox Proportional hazards model including factors (gender, WHO performance status, histology, smoking history, lung stage classification). The primary analysis does not include progression events, or deaths in the absence of progression, which occur more than 12 weeks after the last evaluable RECIST assessment.	
Comparison groups	Gefitinib v Placebo

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.2165
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.821
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.123

Notes:

[1] - Although medians are presented these estimates of PFS are not reliable in this setting: scans were every 6 wks whilst the population progressed rapidly, over half the patients progressing before their first scan. Therefore medians will be more representative of scan timings, rather than actual progression times which may have occurred before the scan takes place. The HR is a much more accurate reflection of the treatment difference, taking into account all information over the study period.

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective Response Rate is the number of patients who have either a complete response (CR) or partial reponse (PR) as defined by Response Evaluation Criteria In Solid Tumour (RECIST) during the study.

End point type	Secondary

End point timeframe:

Overall Study - Response is assesed every 6 weeks from randomisation

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: Patients	6	1		

Statistical analyses

Statistical analysis title	Comparison of Objective Response Rate

Statistical analysis description:

The objective tumour response rate was compared between gefitinib and placebo using a logistic regression model which included terms for Randomised Treatment, Gender, WHO Performance Status, Histology, Smoking History and Lung Stage Classification. The odds ratio (gefitinib:placebo) was estimated from the model along with its associated 95% CI.

Comparison groups	Gefitinib v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	6.556

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.741
upper limit	58.173

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (time to death) is defined as the interval between the date of randomisation and the date of patient death, due to any cause, or to the last date the patient was known to be alive. Those patients who are known to be alive at study closure will be regarded as censored in the calculation of the median overall survival time for each treatment group.

End point type	Secondary

End point timeframe:

Assessed every 6 weeks from randomisation until study data cut off (DCO) or death

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	101		
Units: months				
median (confidence interval 95%)	3.7 (2.6 to 4.4)	2.8 (2.3 to 3.6)		

Statistical analyses

Statistical analysis title	Comparison of Overall Survival

Statistical analysis description:

Overall survival (time to death) was analysed using a proportional hazards model. The model included terms for Randomised Treatment, Gender, WHO Performance Status, Histology, Smoking History and Lung Stage Classification. The hazard ratio (gefitinib:placebo) was estimated together with its associated 95% confidence interval and p-value.

Comparison groups	Gefitinib v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2722
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.615
upper limit	1.147

Secondary: Pulmonary symptom improvement

End point title	Pulmonary symptom improvement

End point description:

Pulmonary symptom improvement is calculated from the responses to the Pulmonary items on the Functional Assessment of Cancer Therapy (Lung) (FACT-L) questionnaire which are: shortness of breath; ease of breathing; tightness in chest and cough A Pulmonary Symptom improvement is defined as an improvement from baseline in at least 1 moderate (score 1) or severe (score 0) pulmonary item of at least 2 points that is maintained for at least 28 days, ie, symptom improvement from moderate (score 1) to minimal (score 3) or none (score 4); or improvement from severe (score 0) to mild (score 2) or minimal (score 3) or none (score 4).

End point type	Secondary

End point timeframe:

Collected three-weekly via a patient diary for all patients for the 1st 18 weeks, then every 6 weeks at each clinic visit up to and including 6 weeks post disease progression.

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[2]	46[3]		
Units: Patients				
number (not applicable)	15	13		

Notes:

[2] - Patients analysed are those in the Evaluable-for-pulmonary-symptom-improvement population.

[3] - Patients analysed are those in the Evaluable-for-pulmonary-symptom-improvement population.

Statistical analyses

Statistical analysis title	Comparison of pulmonary sysmptom improvement

Statistical analysis description:

The pulmonary symptom improvement rate was compared between gefitinib and placebousing a logistic regression model including terms for Randomised Treatment, Gender, WHO Performance Status, Histology, Smoking History and Lung Stage Classification. The odds ratio (gefitinib:placebo) will be estimated from the model along with its associated 95% CI.

Comparison groups	Gefitinib v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority[4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.986
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.395
upper limit	2.46

Notes:

[4] - Patients analysed are those in the Evaluable-for-pulmonary-symptom-improvement population which included all patients who had at least one LCS pulmonaryitem (shortness of breath, ease of breathing, tightness in chest, or cough) with a baseline score of 0 or 1 (scores ranged from 0 to 4, with a higher score indicating better pulmonary symptoms) and who also had at least 1 evaluable post

baseline assessment.

Secondary: Improvement in Quality of Life as measured by the Trial Outcome Index (TOI)

End point title	Improvement in Quality of Life as measured by the Trial Outcome Index (TOI)

End point description:

Improvement in patient-reported functionality as measured by TOI (trial outcome index), which is comprised of thephysical and functional well being sectionsand LCS of FACT-L. An improvemetnt is defined to be an increase from baseline score of 6 or more points.

End point type	Secondary

End point timeframe:

Collected three-weekly via a patient diary for all patients for the 1st 18 weeks, then every 6 weeks at each clinic visit up to and including 6 weeks post disease progression.

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[5]	65[6]		
Units: patients	12	9		

Notes:

[5] - Patients analysed are those in the Evaluable for Quality of Life population, a subset of the ITT.

[6] - Patients analysed are those in the Evaluable for Quality of Life population, a subset of the ITT.

Statistical analyses

Statistical analysis title	Comparison of QoL improvement measured by the TOI

Statistical analysis description:

The QoL (Quality of Life) improvement rate as measured by TOI (Trial outcome Index) was compared between gefitinib and placebo using a logistic regression model that includes terms for Randomised Treatment, Gender,WHO Performance Status, Histology, Smoking History and Lung Stage Classification. The odds ratio(gefitinib:placebo) was estimated from the model along with its associated 95% CI.

Comparison groups	Gefitinib v Placebo
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.381
upper limit	2.8

Notes:

[7] - Patients analysed are those in the Evaluable for Quality of Life population, including those with a baseline Quality of Life (QoL) assessment and at least one non-missing post-baseline QoL assessment. A subset of the ITT.

Secondary: Improvement in Quality of Life as measured by the total score of the FACT-L questionnaire

End point title	Improvement in Quality of Life as measured by the total score

	of the FACT-L questionnaire

End point description:

Improvement in patient-reported functionality as measured by the total score of the FACT-L. An improvement is defined to be an increase from baseline score of 6 or more points.

End point type	Secondary

End point timeframe:

Collected three-weekly via a patient diary for all patients for the 1st 18 weeks, then every 6 weeks at each clinic visit up to and including 6 weeks post disease progression.

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[8]	65[9]		
Units: patients	16	13		

Notes:

[8] - Patients analysed are those in the Evaluable for Quality of Life population, a subset of the ITT.

[9] - Patients analysed are those in the Evaluable for Quality of Life population, a subset of the ITT.

Statistical analyses

Statistical analysis title	Comparison of QoL improvement measured by FACT-L

Statistical analysis description:

The QoL(Quality of Life) improvement rate measured by the total score of the FACT-L will be compared between gefitinib and placebo using a logistic regression model that includes terms for Randomised Treatment, Gender,WHO Performance Status, Histology, Smoking History and Lung Stage Classification. The odds ratio(gefitinib:placebo) will be estimated from the model along with its associated 95% CI.

Comparison groups	Gefitinib v Placebo
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.421
upper limit	2.408

Notes:

[10] - Patients analysed are those in the Evaluable for Quality of Life population, including those with a baseline Quality of Life (QoL) assessment and at least one non-missing post-baseline QoL assessment. A subset of the ITT.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs are collected every 21 days for 1st 18 wks, then every 42 days until discontinuation of study drug. At discontinuation, patients are followed up for all existing & new AEs for 30 days; all AEs, toxicities & SAEs should be followed until resolution.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Matched Placebo plus Best Supportive Care

Reporting group title	Gefitinib

Reporting group description:

Gefitinib 250 mg plus Best Supportive Care

Serious adverse events	Placebo	Gefitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 101 (24.75%)	25 / 100 (25.00%)	
number of deaths (all causes)	85	84	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			

subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 101 (0.99%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung consolidation			

subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Impaired self-care			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rib fracture			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular tachycardia			

subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral disorder			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Convulsion			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Somnolence			

subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Small intestinal obstruction			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Muscular weakness			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess intestinal			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal abscess			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis viral			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterium avium complex			

infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 101 (2.97%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia viral			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Gefitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 101 (91.09%)	89 / 100 (89.00%)	
Investigations			
Weight decrease			
subjects affected / exposed	3 / 101 (2.97%)	6 / 100 (6.00%)	
occurrences (all)	3	6	

Nervous system disorders			
Dizzines			
subjects affected / exposed	7 / 101 (6.93%)	4 / 100 (4.00%)	
occurrences (all)	8	4	
Headache			
subjects affected / exposed	4 / 101 (3.96%)	5 / 100 (5.00%)	
occurrences (all)	6	7	
Dysgeusia			
subjects affected / exposed	1 / 101 (0.99%)	5 / 100 (5.00%)	
occurrences (all)	1	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 101 (0.99%)	6 / 100 (6.00%)	
occurrences (all)	1	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 101 (6.93%)	9 / 100 (9.00%)	
occurrences (all)	7	10	
Fatigue			
subjects affected / exposed	22 / 101 (21.78%)	14 / 100 (14.00%)	
occurrences (all)	22	14	
Oedema peripheral			
subjects affected / exposed	13 / 101 (12.87%)	13 / 100 (13.00%)	
occurrences (all)	14	17	
Pyrexia			
subjects affected / exposed	4 / 101 (3.96%)	6 / 100 (6.00%)	
occurrences (all)	4	6	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 101 (0.00%)	5 / 100 (5.00%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 101 (8.91%)	11 / 100 (11.00%)	
occurrences (all)	9	11	
Constipation			

subjects affected / exposed	19 / 101 (18.81%)	17 / 100 (17.00%)	
occurrences (all)	22	19	
Diarrhoea			
subjects affected / exposed	20 / 101 (19.80%)	50 / 100 (50.00%)	
occurrences (all)	24	65	
Dyspepsia			
subjects affected / exposed	3 / 101 (2.97%)	6 / 100 (6.00%)	
occurrences (all)	3	6	
Dysphagia			
subjects affected / exposed	4 / 101 (3.96%)	5 / 100 (5.00%)	
occurrences (all)	4	5	
Nausea			
subjects affected / exposed	31 / 101 (30.69%)	30 / 100 (30.00%)	
occurrences (all)	35	37	
Stomatitis			
subjects affected / exposed	5 / 101 (4.95%)	9 / 100 (9.00%)	
occurrences (all)	5	9	
Vomiting			
subjects affected / exposed	14 / 101 (13.86%)	21 / 100 (21.00%)	
occurrences (all)	15	24	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 101 (10.89%)	6 / 100 (6.00%)	
occurrences (all)	13	6	
Dyspnoea			
subjects affected / exposed	13 / 101 (12.87%)	17 / 100 (17.00%)	
occurrences (all)	13	17	
Epistaxis			
subjects affected / exposed	2 / 101 (1.98%)	6 / 100 (6.00%)	
occurrences (all)	2	9	
Haemoptysis			
subjects affected / exposed	5 / 101 (4.95%)	4 / 100 (4.00%)	
occurrences (all)	5	5	
Skin and subcutaneous tissue disorders			

Decubitis ulcer			
subjects affected / exposed	1 / 101 (0.99%)	5 / 100 (5.00%)	
occurrences (all)	1	5	
Dermatitis acneiform			
subjects affected / exposed	2 / 101 (1.98%)	6 / 100 (6.00%)	
occurrences (all)	2	6	
Dry skin			
subjects affected / exposed	1 / 101 (0.99%)	19 / 100 (19.00%)	
occurrences (all)	1	23	
Pruritis			
subjects affected / exposed	2 / 101 (1.98%)	9 / 100 (9.00%)	
occurrences (all)	3	11	
Rash			
subjects affected / exposed	10 / 101 (9.90%)	34 / 100 (34.00%)	
occurrences (all)	14	41	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 101 (4.95%)	9 / 100 (9.00%)	
occurrences (all)	5	9	
Confusional state			
subjects affected / exposed	9 / 101 (8.91%)	6 / 100 (6.00%)	
occurrences (all)	9	6	
Depression			
subjects affected / exposed	5 / 101 (4.95%)	2 / 100 (2.00%)	
occurrences (all)	6	2	
Insomnia			
subjects affected / exposed	4 / 101 (3.96%)	11 / 100 (11.00%)	
occurrences (all)	4	12	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 101 (7.92%)	7 / 100 (7.00%)	
occurrences (all)	9	7	
Muscular weakness			
subjects affected / exposed	5 / 101 (4.95%)	7 / 100 (7.00%)	
occurrences (all)	5	7	
Musculoskeletal pain			

subjects affected / exposed	5 / 101 (4.95%)	7 / 100 (7.00%)	
occurrences (all)	5	7	
pain in extremity			
subjects affected / exposed	5 / 101 (4.95%)	4 / 100 (4.00%)	
occurrences (all)	8	4	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	7 / 101 (6.93%)	11 / 100 (11.00%)	
occurrences (all)	7	13	
Oral candidiasis			
subjects affected / exposed	5 / 101 (4.95%)	3 / 100 (3.00%)	
occurrences (all)	5	3	
Urinary tract infection			
subjects affected / exposed	8 / 101 (7.92%)	8 / 100 (8.00%)	
occurrences (all)	8	8	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	17 / 101 (16.83%)	20 / 100 (20.00%)	
occurrences (all)	19	21	
Dehydration			
subjects affected / exposed	5 / 101 (4.95%)	5 / 100 (5.00%)	
occurrences (all)	5	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2005	Amendment included: Extension of recruitment period due to slow recruitment from 11 months to 27 months; Clarification of exploratory objectives, planned biomarker analyses and confirmation of the biomarkers to be investigated; Change to allow patients to continue receiving study medication following disease progression, if the patient is deriving clinical benefit; Updated information regarding ZD1839 exposure, including ISEL clinical study data and rodent carcinogenicity data; Clarification of timings for visit 1 and visit 2; Clarification of Exclusion Criteria, Item 2 (radiotherapy, to allow discrimination between wide field and local irradiation.); Confirmation that proteomics no longer applicable to this protocol; Clarification of the reporting requirements for overdose; confirmation that no germline genetic analysis will be performed on any tumour tissue from this study; correction of volume of blood sampling to be taken at baseline.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported