Clinical trial results:
A Phase III Randomised, Double blind, Placebo controlled, Parallel, Multicentre Study to Assess the Efficacy and Safety of continuing IRESSATM 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 IRESSATM.

Summary

EudraCT number	2011-004942-16
Trial protocol	ES DE IT HU
Global end of trial date	20 November 2019

Results information

Result version number	v1 (current)
This version publication date	10 October 2020
First version publication date	10 October 2020

Trial information

Trial identification

Sponsor protocol code	D791LC00001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	One Medimmune Way, 101 ORD, 2233C, Gaithersburg, MD 20878, United States, 20878
Public contact	Haiyi Jiang/Asia Medical Director, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
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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	16 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate Progression Free Survival (PFS) in patients who have acquired resistance to first line gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.

Protection of trial subjects:

Following documentation of progression, patients were due to enter survival follow-up. The final OS analysis was planned for when 175 deaths had occurred.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 118
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Japan: 23
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 42
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Taiwan: 18
Worldwide total number of subjects	265
EEA total number of subjects	57

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	188
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 265 (100%) patients randomised were from 61 centres in 11 countries: 133 patients to the gefitinib group and132 patients to the placebo group. Patients received maximum of 6 cycles cisplatin plus pemetrexed chemotherapy in addition to the randomised treatment (gefitinib or placebo).

Pre-assignment

Screening details:

A total of 287 patients were enrolled, however only 265 patients were randomised. Randomised patients had epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) and who had progressed on first-line gefitinib treatment

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gefitinib

Arm description:

Gefitinib 250mg and cisplatin plus pemetrexed combination chemotherapy

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

Dosage and administration details:

250mg

Arm title	Placebo

Arm description:

Placebo and cisplatin plus pemetrexed combination chemotherapy.

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

Dosage and administration details:

0mg

Number of subjects in period 1	Gefitinib	Placebo
Started	133	132
Received treatment	132	132
Completed	26	38
Not completed	107	94
Consent withdrawn by subject	12	10
Adverse event, non-fatal	-	1
Death	94	82
Did not receive treatment	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Gefitinib
Reporting group description:	
Gefitinib 250mg and cisplatin plus pemetrexed combination chemotherapy	
Reporting group title	Placebo
Reporting group description:	
Placebo and cisplatin plus pemetrexed combination chemotherapy.	

Reporting group values	Gefitinib	Placebo	Total
Number of subjects	133	132	265
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	90	98	188
From 65-84 years	43	34	77
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.3	57.0	
standard deviation	± 10.63	± 11.25	-
Gender, Male/Female Units: Participants			
Female	87	84	171
Male	46	48	94
Age, Customized Units: Subjects			
<65 years	90	98	188
>=65 years	43	34	77
Race/Ethnicity, Customized Units: Subjects			
Asian	104	102	206
Black or African American	0	1	1
White	29	29	58

End points

End points reporting groups

Reporting group title	Gefitinib
Reporting group description:	
Gefitinib 250mg and cisplatin plus pemetrexed combination chemotherapy	
Reporting group title	Placebo
Reporting group description:	
Placebo and cisplatin plus pemetrexed combination chemotherapy.	

Primary: Overall survival (OS) at the time of overall survival analysis

End point title	Overall survival (OS) at the time of overall survival analysis
End point description:	
OS is the time from the date of randomisation until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.	
End point type	Primary
End point timeframe:	
Following progression survival data was collected every 8 weeks until documentation of death, withdrawal of consent, loss to follow-up or the final data cut-off, whichever occurs first.	

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: Number of patients with an OS event	94	82		

Statistical analyses

Statistical analysis title	Overall survival (OS)
Comparison groups	Gefitinib v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.016
Method	Cox Proportional Hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.94

Secondary: Median overall survival (OS) at time of overall survival analysis

End point title	Median overall survival (OS) at time of overall survival analysis

End point description:

OS is the time from the date of randomisation until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

End point type	Secondary

End point timeframe:

Following progression survival data was collected every 8 weeks until documentation of death, withdrawal of consent, loss to follow-up or the final data cut-off, whichever occurs first.

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: Months				
median (confidence interval 95%)	13.4 (10.7 to 18.0)	19.5 (15.6 to 21.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) at 9 months

End point title	Overall survival (OS) at 9 months

End point description:

OS is the time from the date of randomisation until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

End point type	Secondary

End point timeframe:

Following progression survival data was collected every 8 weeks until documentation of death, withdrawal of consent, loss to follow-up or the final data cut-off, whichever occurs first.

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: Percentage				
number (confidence interval 95%)	66.7 (57.5 to 74.2)	79.4 (71.3 to 85.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) at 12 months

End point title	Overall survival (OS) at 12 months

End point description:

OS is the time from the date of randomisation until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

End point type	Secondary

End point timeframe:

Following progression survival data was collected every 8 weeks until documentation of death, withdrawal of consent, loss to follow-up or the final data cut-off, whichever occurs first.

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: Percentage				
number (confidence interval 95%)	54.1 (44.8 to 62.5)	68.8 (59.9 to 76.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) at 18 months

End point title	Overall survival (OS) at 18 months

End point description:

OS is the time from the date of randomisation until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

End point type	Secondary

End point timeframe:

Following progression survival data was collected every 8 weeks until documentation of death, withdrawal of consent, loss to follow-up or the final data cut-off, whichever occurs first.

End point values	Gefitinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: Percentage				
number (confidence interval 95%)	41.2 (32.3 to 49.9)	52.9 (43.6 to 61.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug until last study visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Gefitinib 250 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Gefitinib 250 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 132 (28.79%)	28 / 132 (21.21%)	
number of deaths (all causes)	94	82	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Circulatory collapse			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			

alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
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			

Asthma			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 132 (3.03%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemoptysis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemothorax			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 132 (2.27%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Psychiatric disorders			
Delirium			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wolff-Parkinson-White syndrome			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cognitive disorder			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorder			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 132 (3.03%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Urinary tract infection			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Gefitinib 250 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 132 (94.70%)	127 / 132 (96.21%)	
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 132 (3.79%)	11 / 132 (8.33%)	
occurrences (all)	5	17	
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 132 (6.06%)	10 / 132 (7.58%)	
occurrences (all)	10	16	
Blood creatinine increased			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	12 / 132 (9.09%)	12 / 132 (9.09%)	
occurrences (all)	14	17	
Haemoglobin decreased			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 132 (6.06%)	4 / 132 (3.03%)	
occurrences (all)	10	5	
Neutrophil count decreased			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	16 / 132 (12.12%)	22 / 132 (16.67%)	
occurrences (all)	31	47	
Platelet count decreased			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	9 / 132 (6.82%)	3 / 132 (2.27%)	
occurrences (all)	15	6	

White blood cell count decreased			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	17 / 132 (12.88%)	13 / 132 (9.85%)	
occurrences (all)	38	24	
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	9 / 132 (6.82%)	6 / 132 (4.55%)	
occurrences (all)	9	6	
Dysgeusia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 132 (2.27%)	7 / 132 (5.30%)	
occurrences (all)	3	10	
Headache			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	11 / 132 (8.33%)	18 / 132 (13.64%)	
occurrences (all)	14	24	
Paraesthesia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 132 (3.79%)	7 / 132 (5.30%)	
occurrences (all)	6	8	
Peripheral sensory neuropathy			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	9 / 132 (6.82%)	10 / 132 (7.58%)	
occurrences (all)	12	12	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	40 / 132 (30.30%)	32 / 132 (24.24%)	
occurrences (all)	56	40	
Bone marrow failure			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 132 (3.03%)	8 / 132 (6.06%)	
occurrences (all)	7	21	
Leukopenia			

alternative dictionary used: MedDRA 18			
subjects affected / exposed	27 / 132 (20.45%)	22 / 132 (16.67%)	
occurrences (all)	61	53	
Neutropenia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	29 / 132 (21.97%)	28 / 132 (21.21%)	
occurrences (all)	59	69	
Thrombocytopenia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	7 / 132 (5.30%)	9 / 132 (6.82%)	
occurrences (all)	11	11	
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	15 / 132 (11.36%)	30 / 132 (22.73%)	
occurrences (all)	27	43	
Fatigue			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	28 / 132 (21.21%)	23 / 132 (17.42%)	
occurrences (all)	37	31	
Malaise			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	10 / 132 (7.58%)	9 / 132 (6.82%)	
occurrences (all)	10	15	
Pyrexia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	21 / 132 (15.91%)	14 / 132 (10.61%)	
occurrences (all)	24	15	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	7 / 132 (5.30%)	4 / 132 (3.03%)	
occurrences (all)	7	4	
Abdominal pain upper			
alternative dictionary used:			

MedDRA 18			
subjects affected / exposed	12 / 132 (9.09%)	13 / 132 (9.85%)	
occurrences (all)	16	16	
Constipation			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	34 / 132 (25.76%)	35 / 132 (26.52%)	
occurrences (all)	58	56	
Diarrhoea			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	43 / 132 (32.58%)	19 / 132 (14.39%)	
occurrences (all)	71	22	
Nausea			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	84 / 132 (63.64%)	80 / 132 (60.61%)	
occurrences (all)	180	160	
Stomatitis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	14 / 132 (10.61%)	5 / 132 (3.79%)	
occurrences (all)	15	8	
Vomiting			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	54 / 132 (40.91%)	43 / 132 (32.58%)	
occurrences (all)	96	75	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	20 / 132 (15.15%)	15 / 132 (11.36%)	
occurrences (all)	23	18	
Dyspnoea			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	12 / 132 (9.09%)	9 / 132 (6.82%)	
occurrences (all)	13	10	
Hiccups			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	7 / 132 (5.30%)	7 / 132 (5.30%)	
occurrences (all)	11	10	
Productive cough			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	10 / 132 (7.58%)	10 / 132 (7.58%)	
occurrences (all)	10	11	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	9 / 132 (6.82%)	5 / 132 (3.79%)	
occurrences (all)	9	5	
Dermatitis acneiform			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 132 (6.06%)	4 / 132 (3.03%)	
occurrences (all)	11	4	
Dry skin			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	12 / 132 (9.09%)	8 / 132 (6.06%)	
occurrences (all)	12	8	
Pruritus			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 132 (6.06%)	7 / 132 (5.30%)	
occurrences (all)	9	8	
Rash			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	15 / 132 (11.36%)	11 / 132 (8.33%)	
occurrences (all)	20	12	
Psychiatric disorders			
Insomnia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	10 / 132 (7.58%)	7 / 132 (5.30%)	
occurrences (all)	12	7	
Musculoskeletal and connective tissue disorders			

Arthralgia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 132 (6.06%)	7 / 132 (5.30%)	
occurrences (all)	9	9	
Back pain			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	11 / 132 (8.33%)	14 / 132 (10.61%)	
occurrences (all)	11	15	
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 132 (6.06%)	2 / 132 (1.52%)	
occurrences (all)	10	2	
Myalgia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	9 / 132 (6.82%)	
occurrences (all)	1	15	
Infections and infestations			
Conjunctivitis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 132 (0.76%)	8 / 132 (6.06%)	
occurrences (all)	1	8	
Nasopharyngitis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 132 (3.79%)	8 / 132 (6.06%)	
occurrences (all)	7	9	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	64 / 132 (48.48%)	45 / 132 (34.09%)	
occurrences (all)	92	74	
Hypocalcaemia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 132 (6.06%)	2 / 132 (1.52%)	
occurrences (all)	9	2	
Hypokalaemia			

alternative dictionary used: MedDRA 18			
subjects affected / exposed	13 / 132 (9.85%)	5 / 132 (3.79%)	
occurrences (all)	21	9	
Hyponatraemia			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	11 / 132 (8.33%)	3 / 132 (2.27%)	
occurrences (all)	17	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2012	Amendment1: Measures to identify Hy's law events. Exclusion criteria updated: exclusion of breast feeding, clarity on birth control.
27 July 2012	Amendment 2: To provide better clarity on definition of the end of the study
08 April 2013	Amendment 3: Update inclusion criteria (prior treatment and concomitant medications) based on the Steering Committee recommendation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported