Clinical trial results:
A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Oral E7080 in Addition to Best Supportive Care (BSC) versus BSC Alone in Patients with Locally Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer Who Have Failed at Least Two Systemic Anticancer Regimens

Summary

EudraCT number	2011-002347-10
Trial protocol	HU GB CZ IT BE
Global end of trial date	27 June 2015

Results information

Result version number	v1 (current)
This version publication date	19 January 2019
First version publication date	19 January 2019

Trial information

Trial identification

Sponsor protocol code	E7080-703

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01529112
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Medical Research Inc.
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, United States,
Public contact	Medical Information, Eisai Ltd, +44 08000014612, Lmedinfo@eisai.net
Scientific contact	Medical Information, Eisai Ltd, +44 08000014612, Lmedinfo@eisai.net

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	27 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the overall survival (OS) of patients receiving E7080 + best supportive care (BSC) with those receiving placebo + BSC

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:
- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal
Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 November 2011
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	United Kingdom: 19
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	135
EEA total number of subjects	92

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)	73
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The participant flow is based on data cut-off date of 21 January 2014 as the study is ongoing.

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

Blinding implementation details:

The study was unblended after primary analysis. Placebo had the same appearance of lenvatinib, but with no active pharmaceutical ingredients.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenvatinib

Arm description:

Participants received lenvatinib 24 mg orally, once daily continuously in each 28-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received lenvatinib 24 mg orally, once daily continuously in each 28-day treatment cycle.

Arm title	Lenvatinib matched placebo

Arm description:

Participants received lenvatinib matched placebo orally, once daily continuously in each 28-day treatment cycle.

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:

Participants received lenvatinib matched placebo orally, once daily continuously in each 28-day treatment cycle.

Number of subjects in period 1	Lenvatinib	Lenvatinib matched placebo
Started	89	46
Completed	20	5
Not completed	69	41
Consent withdrawn by subject	7	3
Adverse event, non-fatal	2	-
Protocol violation	1	-
Death	59	38

Baseline characteristics

Reporting groups	
Reporting group title	Lenvatinib
Reporting group description:	
Participants received lenvatinib 24 mg orally, once daily continuously in each 28-day treatment cycle.	
Reporting group title	Lenvatinib matched placebo
Reporting group description:	
Participants received lenvatinib matched placebo orally, once daily continuously in each 28-day treatment cycle.	

Reporting group values	Lenvatinib	Lenvatinib matched placebo	Total
Number of subjects	89	46	135
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	63	63.5	
full range (min-max)	41 to 82	44 to 77	-
Gender categorical Units: Subjects			
Female	44	19	63
Male	45	27	72

End points

End points reporting groups

Reporting group title	Lenvatinib
Reporting group description:	
Participants received lenvatinib 24 mg orally, once daily continuously in each 28-day treatment cycle.	
Reporting group title	Lenvatinib matched placebo
Reporting group description:	
Participants received lenvatinib matched placebo orally, once daily continuously in each 28-day treatment cycle.	
Subject analysis set title	Phamacokinetic Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The analysis was performed using the pharmacokinetic (PK) analysis set defined as all subjects who received at least one dose of study drug and had evaluable PK data.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from the date of randomization until the date of death from any cause. The analysis was performed using the Intent-to-Treat Population, defined as all randomized subjects.	
End point type	Primary
End point timeframe:	
From date of randomization (Day 1) until occurrence of 90 deaths in the study (cut off date 26 November 2013), approximately 22 months	

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Weeks				
median (confidence interval 95%)	38.4 (26.57 to 47.86)	24.1 (15.29 to 36.43)		

Statistical analyses

Statistical analysis title	Statistical analysis of overall survival
Comparison groups	Lenvatinib matched placebo v Lenvatinib
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065
Method	based on Kaplan Meier estimation
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.03

Secondary: Number of participants with Treatment emergent non-serious adverse events (AEs) and Treatment emergent serious adverse events (SAEs)

End point title	Number of participants with Treatment emergent non-serious adverse events (AEs) and Treatment emergent serious adverse events (SAEs)

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant administered with an investigational product. A SAE was defined as any untoward medical occurrence that at any dose; resulted in death, was life-threatening (i.e., the subject was at a risk of death at the time of the event; this did not include an event that hypothetically might have caused death if it had been more severe), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, or was a congenital abnormality/birth defect. In this study, treatment emergent adverse events (TEAEs) (defined as an AE (serious/non-serious) that started/increased in severity on/after the first dose of study medication up to 30 days after the final dose of study medication) were assessed. Safety Analysis Set was used.

End point type	Secondary

End point timeframe:

For each participant, from the first dose till 30 days after the last dose or up to approximately 2 years (data cut-off date of 21 January 2014)

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Participants				
number (not applicable)				
Treatment-emergent non-serious AEs	83	42		
Treatment-emergent SAEs	46	21		

Statistical analyses

No statistical analyses for this end point

Secondary: 6-Month Survival rate

End point title	6-Month Survival rate

End point description:

Event-free survival rate was calculated using Kaplan Meier estimations. The percentage of participants with event free survival up to 6 months and the corresponding 95% confidence interval were estimated for each treatment group. The data presented is based on the data cut-off date of 26 November 2013 while the study is still ongoing. The analysis was performed using the Intent-to-Treat Population, defined as all randomized subjects.

End point type	Secondary

End point timeframe:

From date of randomization (Day 1) up to 6 months

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Percentage of Participants				
number (confidence interval 95%)	61.6 (50.24 to 71.1)	49 (33.49 to 62.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: 1-year Survival rate

End point title	1-year Survival rate

End point description:

Event-free survival rate was calculated using Kaplan Meier estimations. The percentage of participants with event free survival up to 1 year and the corresponding 95% confidence interval were estimated for each treatment group. The data presented is based on the data cut-off date of 26 November 2013 while the study is still ongoing. The analysis was performed using the Intent-to-Treat Population, defined as all randomized subjects.

End point type	Secondary

End point timeframe:

From date of randomization (Day 1) up to 1 year

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Percentage of Participants				
number (confidence interval 95%)	35.8 (25.13 to 46.54)	20.5 (9.96 to 33.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was defined as the time from the date of the randomization until the date of first documented disease progression according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 or date of death from any cause (whichever occurred first), assessed based on investigator's assessment. Disease progression per RECIST v1.1 was defined as at least a 20% relative increase and 5 mm absolute increase in the sum of diameters of target lesions (taking as reference the smallest sum on study), recorded since the treatment started or the appearance of 1 or more new lesions. The data presented is based on the data cut-off date of 21 January 2014 while the study is still ongoing.

End point type	Secondary

End point timeframe:

From date of randomization (Day 1) until date of first documentation of disease progression or death from any cause (whichever occurred first) or up to approximately 2 years (data cut-off date of 21 January 2014)

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Weeks				
median (confidence interval 95%)	20.9 (15.86 to 23.86)	7.9 (7.43 to 8.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)

End point description:

ORR, defined as the percentage of participants who had best overall response (BOR) of complete response (CR) or partial response (PR) as determined by investigator using RECIST 1.1. CR was defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) had to have reduction in short axis to less than 10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. ORR = CR + PR. The data presented is based on the data cut-off date of 21 January 2014 while the study is still ongoing. The analysis was performed using the Intent-to-Treat Population, defined as all randomized subjects.

End point type	Secondary

End point timeframe:

From date of randomization (Day 1) until disease progression or death, development of unacceptable toxicity, withdrawal of consent, withdrawal by Investigator, or up to approximately 2 years (data cut-off date of 21 January 2014)

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Percentage of Participants				
number (confidence interval 95%)	10.1 (4.7 to 18.3)	2.2 (0.1 to 11.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response duration (RD)

End point title	Response duration (RD)

End point description:

Response duration, defined as the time from the date of the first assessment demonstrating a CR or PR to the date of the first assessment demonstrating progressive disease or death, whichever occurred first. This is an investigator assessed outcome, measured using RECIST 1.1. CR was defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) had to have reduction in short axis to less than 10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Response duration was summarized by including only subjects with events. The data presented is based on the data cut-off date of 21 January 2014 while the study is still ongoing. The analysis was performed using subjects with events.

End point type	Secondary

End point timeframe:

From date of randomization (Day 1) until disease progression or death, development of unacceptable toxicity, withdrawal of consent, withdrawal by Investigator, or up to approximately 2 years (data cut-off date of 21 January 2014)

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[1]	1[2]		
Units: Weeks				
median (confidence interval 95%)	24.2 (12.71 to 33.14)	43.3 (43.3 to 43.3)		

Notes:

[1] - The analysis was performed using subjects with events.

[2] - The analysis was performed using subjects with events.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

The percentage of participants with CR, PR, or stable disease (SD) for greater than or equal to 12

weeks. CR was defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) had to have reduction in short axis to less than 10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Stable disease was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on the study. The data presented is based on the data cut-off date of 21 January 2014 while the study is still ongoing. The analysis was performed using the Intent-to-Treat Population, defined as all randomized subjects.

End point type	Secondary

End point timeframe:

From date of randomization (Day 1) until disease progression or death, development of unacceptable toxicity, withdrawal of consent, withdrawal by Investigator, or up to approximately 2 years (data cut-off date of 21 January 2014)

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Percentage of Participants				
number (confidence interval 95%)	42.7 (32.3 to 53.6)	19.6 (9.4 to 33.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of participants with The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Symptom Scores Achieving Clinically Significant Deterioration on Quality of Life (QOL)

End point title	The Percentage of participants with The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Symptom Scores Achieving Clinically Significant Deterioration on Quality of Life (QOL)

End point description:

The EORTC QLQ-C30 symptom score, a cancer specific self-reporting questionnaire was composed of 9-symptom scales assessing fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties. All of the multi-item scales and single-item measures ranged in score from 0 to 100. For each domain and item, a linear transformation was applied to standardize the raw score to a range from 0 to 100, with a higher scale score representing a higher response level/ high level of symptomatology / problems. The data is presented as percentage of participants with EORTC QLQ-C30 symptom score achieving clinically significant deterioration on QOL. Participants were considered as deteriorated for a given symptom if the change in score from Baseline was 10 points or higher at any time point after Baseline. The data presented is based on the data cut-off date of 21 January 2014 while the study is still ongoing. The Intent-to-Treat population was used.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1 (prior to treatment in Cycle 1)), every 4 weeks during treatment, and 4 weeks after completing treatment or up to approximately 2 years (data cut-off date of 21 January 2014)

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Percentage of participants				
number (not applicable)				
Appetite Loss (N=82, 39)	59.8	66.7		
Constipation (N=82, 40)	43.9	52.5		
Diarrhea (N=81, 40)	48.1	17.5		
Dyspnea (N=82, 40)	43.9	47.5		
Insomnia (N=82, 40)	53.7	35		
Nausea and Vomiting (N=82, 40)	46.3	40		
Pain (N= 82, 40)	74.4	65		
Fatigue (N= 82, 40)	63.4	67.5		
Financial Difficulties (N= 81, 40)	34.6	30		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of participants with The European Organization for Research and Treatment of Cancer (EORTC) module QLQ-LC13 (lung cancer 13) Symptom Scores Achieving Clinically Significant Deterioration on QOL

End point title	The Percentage of participants with The European Organization for Research and Treatment of Cancer (EORTC) module QLQ-LC13 (lung cancer 13) Symptom Scores Achieving Clinically Significant Deterioration on QOL

End point description:

The EORTC module QLQ-LC13 symptom score was a self-reporting cancer-specific questionnaire composed of 13 questions incorporated into 1 multi-item scale designed to evaluate dyspnea and a series of single items assessing different types of pain, as well as, cough, hemoptysis, dysphagia, sore mouth, alopecia, and peripheral neuropathy. For each domain and item, a linear transformation was applied to standardize the raw score to a range from 0 to 100, with 100 representing the best possible function/QOL, and highest burden of symptoms for symptom domains and single items. The data is presented as percentage of participants with EORTC module QLQ-C13 symptom score achieving clinically significant deterioration on QOL. Participants were considered as deteriorated for a given symptom if the change in score from Baseline was 10 points or higher at any time point after Baseline. The data presented is based on the data cut-off date of 21 January 2014 while the study is still ongoing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1 (prior to treatment in Cycle 1)), every 4 weeks during treatment, and 4 weeks after completing treatment or up to approximately 2 years (data cut-off date of 21 January 2014)

End point values	Lenvatinib	Lenvatinib matched placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	46		
Units: Percentage of participants				
number (not applicable)				
Alopecia (Hair Loss) (N= 80, 39)	16.3	15.4		

Dysphagia (Trouble Swallowing) (N= 80, 39)	43.8	23.1		
Haemoptysis (Coughing Up Blood) (N=80, 39)	15	10.3		
How Much Cough (N=80, 39)	33.8	28.2		
Medicine For Pain (N=43, 21)	41.9	28.6		
Pain In Arm Or Shoulder (N=80, 39)	55	43.6		
Pain In Chest (N=80, 39)	37.5	28.2		
Pain In Other Parts Of Body (N=79, 39)	51.9	38.5		
Peripheral Neuropathy-Tingling Hands/Feet(N=80,39)	36.3	41		
Short Of Breath When Climbed Stairs (N=80, 39)	45	46.2		
Short Of Breath When Rested (N=80, 39)	36.3	41		
Short Of Breath When Walked (N=80, 39)	45	51.3		
Sore Mouth Or Tongue (N=80, 39)	60	5.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) profile of lenvatinib in subjects with Non Small Cell Lung Cancer (NSCLC)

End point title	Pharmacokinetic (PK) profile of lenvatinib in subjects with Non Small Cell Lung Cancer (NSCLC)

End point description:

Blood samples were collected for lenvatinib PK analysis. Lenvatinib concentrations from sparse PK sampling were measured. The data is presented as mean nanograms per milliliter +/- Standard deviation of lenvatinib serum concentration. The analysis was performed using the pharmacokinetic (PK) analysis set defined as all subjects who received at least one dose of study drug and had evaluable PK data.

End point type	Secondary

End point timeframe:

Cycle 1/Day 1 (between 0.5 and 4 hours postdose and 6 and 10 hours postdose), Cycle 1/Day 15 (predose, between 0.5 and 4 hours postdose, and 6 and 10 hours postdose), and Day 1 of Cycles 2 though 4 (predose and between 2 and 12 hours postdose)

End point values	Phamacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (0.5 to 4 hours postdose); N=47	93.4 (± 125.66)			
Cycle 1 Day 1 (6 to 10 hours postdose); N=46	229 (± 114.06)			
Cycle 1 Day 15 (Pre-dose); N=43	77.8 (± 84.73)			
Cycle 1 Day 15 (0.5 to 4 hours postdose); N=44	134.3 (± 119.44)			

Cycle 1 Day 15 (6 to 10 hours postdose); N=39	230.7 (± 106.29)			
Cycle 2 Day 1 (Pre-dose); N=42	68.6 (± 73.53)			
Cycle 2 Day 1 (2 to 12 hours postdose); N=41	260.4 (± 176.26)			
Cycle 3 Day 1 (Pre-dose); N=34	53.5 (± 49.2)			
Cycle 3 Day 1 (2 to 12 hours postdose); N=31	255.3 (± 173.79)			
Cycle 4 Day 1 (Pre-dose); N=29	46.2 (± 34.94)			
Cycle 4 Day 1 (2 to 12 hours postdose); N=27	217.7 (± 167.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each participant, from the first dose till 30 days after the last dose or up to approximately 2 years (data cut-off date of 21 January 2014)

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs), defined as an AE (serious/non-serious) that started/increased in severity on/after the first dose of study medication up to 30 days after the final dose of study medication are presented in this section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Lenvatinib

Reporting group description:

Participants received lenvatinib 24 mg orally, once daily continuously in each 28-day treatment cycle.

Reporting group title	Lenvatinib matched placebo

Reporting group description:

Participants received lenvatinib matched placebo orally, once daily continuously in each 28-day treatment cycle.

Serious adverse events	Lenvatinib	Lenvatinib matched placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 89 (51.69%)	21 / 46 (45.65%)	
number of deaths (all causes)	59	38	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	2 / 89 (2.25%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	4 / 89 (4.49%)	3 / 46 (6.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 3	
Chest pain			

subjects affected / exposed	3 / 89 (3.37%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 89 (2.25%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	2 / 89 (2.25%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
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			
Dyspnoea			
subjects affected / exposed	7 / 89 (7.87%)	4 / 46 (8.70%)	
occurrences causally related to treatment / all	1 / 7	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Haemoptysis			
subjects affected / exposed	3 / 89 (3.37%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 89 (3.37%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bronchial polyp			

subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (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 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 89 (1.12%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Productive cough			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			

subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	2 / 89 (2.25%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 89 (1.12%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (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	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			

subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			

subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 89 (1.12%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (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			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	7 / 89 (7.87%)	3 / 46 (6.52%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Lower respiratory tract infection			
subjects affected / exposed	2 / 89 (2.25%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 89 (2.25%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
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	2 / 89 (2.25%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Lenvatinib	Lenvatinib matched placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	83 / 89 (93.26%)	42 / 46 (91.30%)	
Investigations Platelet count decreased subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 11	0 / 46 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	13 / 89 (14.61%) 14	0 / 46 (0.00%) 0	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	40 / 89 (44.94%) 63	4 / 46 (8.70%) 5	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	17 / 89 (19.10%) 18	6 / 46 (13.04%) 6	
Lethargy subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 10	2 / 46 (4.35%) 2	
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 6	0 / 46 (0.00%) 0	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	16 / 89 (17.98%) 26	1 / 46 (2.17%) 1	
Chest pain subjects affected / exposed occurrences (all)	8 / 89 (8.99%) 8	6 / 46 (13.04%) 6	
Fatigue			

subjects affected / exposed	24 / 89 (26.97%)	8 / 46 (17.39%)	
occurrences (all)	31	8	
Malaise			
subjects affected / exposed	5 / 89 (5.62%)	0 / 46 (0.00%)	
occurrences (all)	7	0	
Mucosal inflammation			
subjects affected / exposed	5 / 89 (5.62%)	0 / 46 (0.00%)	
occurrences (all)	5	0	
Oedema peripheral			
subjects affected / exposed	9 / 89 (10.11%)	2 / 46 (4.35%)	
occurrences (all)	12	3	
Pyrexia			
subjects affected / exposed	10 / 89 (11.24%)	4 / 46 (8.70%)	
occurrences (all)	15	4	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 89 (1.12%)	3 / 46 (6.52%)	
occurrences (all)	1	3	
Abdominal pain			
subjects affected / exposed	15 / 89 (16.85%)	1 / 46 (2.17%)	
occurrences (all)	18	1	
Abdominal pain upper			
subjects affected / exposed	5 / 89 (5.62%)	1 / 46 (2.17%)	
occurrences (all)	6	1	
Constipation			
subjects affected / exposed	17 / 89 (19.10%)	8 / 46 (17.39%)	
occurrences (all)	19	8	
Diarrhoea			
subjects affected / exposed	27 / 89 (30.34%)	3 / 46 (6.52%)	
occurrences (all)	43	4	
Dry mouth			
subjects affected / exposed	7 / 89 (7.87%)	2 / 46 (4.35%)	
occurrences (all)	7	2	
Dyspepsia			
subjects affected / exposed	13 / 89 (14.61%)	1 / 46 (2.17%)	
occurrences (all)	16	1	

Nausea			
subjects affected / exposed	26 / 89 (29.21%)	6 / 46 (13.04%)	
occurrences (all)	36	9	
Stomatitis			
subjects affected / exposed	27 / 89 (30.34%)	4 / 46 (8.70%)	
occurrences (all)	34	4	
Vomiting			
subjects affected / exposed	23 / 89 (25.84%)	3 / 46 (6.52%)	
occurrences (all)	27	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 89 (17.98%)	10 / 46 (21.74%)	
occurrences (all)	21	12	
Dysphonia			
subjects affected / exposed	19 / 89 (21.35%)	0 / 46 (0.00%)	
occurrences (all)	21	0	
Dyspnoea			
subjects affected / exposed	16 / 89 (17.98%)	4 / 46 (8.70%)	
occurrences (all)	18	4	
Haemoptysis			
subjects affected / exposed	7 / 89 (7.87%)	1 / 46 (2.17%)	
occurrences (all)	8	2	
Oropharyngeal pain			
subjects affected / exposed	6 / 89 (6.74%)	1 / 46 (2.17%)	
occurrences (all)	6	1	
Productive cough			
subjects affected / exposed	10 / 89 (11.24%)	4 / 46 (8.70%)	
occurrences (all)	14	5	
Rhinorrhoea			
subjects affected / exposed	5 / 89 (5.62%)	1 / 46 (2.17%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	9 / 89 (10.11%)	0 / 46 (0.00%)	
occurrences (all)	9	0	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	14 / 89 (15.73%)	0 / 46 (0.00%)	
occurrences (all)	21	0	
Pruritus			
subjects affected / exposed	9 / 89 (10.11%)	1 / 46 (2.17%)	
occurrences (all)	11	1	
Rash			
subjects affected / exposed	5 / 89 (5.62%)	2 / 46 (4.35%)	
occurrences (all)	9	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 89 (7.87%)	3 / 46 (6.52%)	
occurrences (all)	7	3	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	33 / 89 (37.08%)	3 / 46 (6.52%)	
occurrences (all)	66	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 89 (19.10%)	5 / 46 (10.87%)	
occurrences (all)	23	5	
Back pain			
subjects affected / exposed	13 / 89 (14.61%)	3 / 46 (6.52%)	
occurrences (all)	13	4	
Muscular weakness			
subjects affected / exposed	5 / 89 (5.62%)	1 / 46 (2.17%)	
occurrences (all)	6	1	
Musculoskeletal pain			
subjects affected / exposed	8 / 89 (8.99%)	3 / 46 (6.52%)	
occurrences (all)	8	3	
Myalgia			
subjects affected / exposed	10 / 89 (11.24%)	1 / 46 (2.17%)	
occurrences (all)	13	1	
Pain in extremity			
subjects affected / exposed	5 / 89 (5.62%)	1 / 46 (2.17%)	
occurrences (all)	7	1	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	31 / 89 (34.83%) 36	11 / 46 (23.91%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2011	• Clarified that in countries where erlotinib was approved and marketed for the treatment of NSCLC, subjects must have received erlotinib treatment for their NSCLC and in countries where crizotinib was approved and marketed, subjects must have received crizotinib treatment for NSCLC that was ALK-positive • PK sampling was added • Provided a new IND number on the face page (changed from 72,010 to 113,533) • New information was provided regarding drug-drug interactions with CYP3A4 inducers and inhibitors • A section on PK and pharmacodynamics was added • Some minor errors and inconsistencies were corrected
31 July 2012	• Clarified the requirement for prior erlotinib or gefitinib treatment to require prior erlotinib (or gefitinib for subjects outside the US) only for subjects with activating EGFR mutations • Added that subjects with hypertension and/or proteinuria (Grade ≥ 2) must have BP and urine protein tested (i.e., dipstick) every two weeks, or more frequently as clinically indicated • Stipulated that subjects of unknown EGFR status who had not received prior erlotinib (or gefitinib) should be tested for EGFR activating mutations prior to study entry • Clarified that the End of Treatment visit should be within 30 to 37 days after the last dose • Clarified that following dose delays, treatment could be restarted after resolution to Grade 0, Grade 1, or Baseline without waiting until the start of the next cycle. Scheduled assessments should have continued according to the initial cycle schedule (i.e., treatment assessments should not have been delayed following a dose delay) • Clarified that localized palliative radiotherapy was allowed if there was no clinical evidence of disease progression and after discussion with the Medical Monitor • Clarified RECIST language to be consistent with RECIST 1.1 • Some minor errors and inconsistencies were corrected
16 January 2014	• Updated and expanded the management of hepatotoxicity and thromboembolic events • Stipulated that survival information would continue to be collected after the unblinding of the study in order to further evaluate overall survival

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported