Clinical trial results:
An Open-Label, Single-Arm, Multicenter Phase 2 Study of E7080 [Lenvatinib] in Subjects with Advanced Endometrial Cancer and Disease Progression Following First-Line Chemotherapy

Summary

EudraCT number	2009-016858-41
Trial protocol	HU BG BE
Global end of trial date	10 October 2015

Results information

Result version number	v1
This version publication date	30 October 2016
First version publication date	30 October 2016

Trial information

Trial identification

Sponsor protocol code	E7080-G000-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01111461
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, United States,
Public contact	Eisai Call Center, Eisai Inc., 888 422-4743,
Scientific contact	Eisai Call Center, Eisai Inc., 888 422-4743,

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	21 May 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2012
Global end of trial reached?	Yes
Global end of trial date	10 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the objective response rate (ORR: complete response + partial response [CR+ PR]) of E7080 in subjects with unresectable endometrial cancer and disease progression following platinum-based, first-line chemotherapy.

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 Conference 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 Conference on Harmonisation 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	03 March 2010
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	Poland: 7
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	United States: 58

Worldwide total number of subjects	133
EEA total number of subjects	35

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)	81
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 167 participants were screened for entry into the study. Of these 167 participants, 133 participants met inclusion/exclusion criteria and were treated with at least 1 dose of lenvatinib 24 mg.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Lenvatinib

Arm description:

Lenvatinib 24 mg was administered orally, once daily continuously in 28-day cycles

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	Lenvima
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib hard capsules, 24 mg (two 10-mg capsules and one 4-mg capsule) were self-administered orally once a day in the morning (without regard to food intake) in 28-day cycles. Dose reduction or interruption was allowed for participants who experienced lenvatinib-related toxicity.

Number of subjects in period 1	Lenvatinib
Started	133
Completed	82
Not completed	51
Participant choice	11
Consent withdrawn by subject	1
Adverse event, non-fatal	32
Not specified	6
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Lenvatinib
Reporting group description:	
Lenvatinib 24 mg was administered orally, once daily continuously in 28-day cycles	

Reporting group values	Lenvatinib	Total	
Number of subjects	133	133	
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			
geometric mean	62.7		
standard deviation	± 8.75	-	
Gender categorical Units: Subjects			
Female	133	133	
Male	0	0	

End points

End points reporting groups

Reporting group title	Lenvatinib

Reporting group description:

Lenvatinib 24 mg was administered orally, once daily continuously in 28-day cycles

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

ORR (ORR=CR + PR) was defined as the percentage of participants with best overall response (BOR) of complete response (CR) or partial response (PR) based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 for target lesions assessed by magnetic resonance imaging/computed tomography (MRI/CT) scans, as determined by independent radiologic review (IRR). A BOR of CR was confirmed by a subsequent CR assessment at least 4 weeks later. A BOR of PR was confirmed by a subsequent CR or PR assessment at least 4 weeks later. 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 <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. The Full Analysis Set (Intent-to-Treat [ITT] Analysis Set) was used and included all participants who received at least 1 dose lenvatinib.

End point type	Primary

End point timeframe:

From the date of first administration of study treatment until all participants completed a minimum of 6 cycles (28-day cycles) or discontinued treatment prior to the end of Cycle 6 (as of 21 May 2012 data cut-off)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The null hypothesis that ORR (CR + PR) was ≤10% was tested using the 1-sided exact test of a single proportion, at the 1-sided 0.05 level. ORR (CR + PR) was presented with corresponding 2-sided, 95% confidence interval (CI).

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	133[2]			
Units: Percentage of participants				
number (confidence interval 95%)	14.3 (8.8 to 21.4)			

Notes:

[2] - Full Analysis Set (ITT population)-all participants who received at least 1 dose of lenvatinib.

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 measured as the time from the date of first administration of study treatment until the date of first documentation of disease progression or date of death (whichever occurred first), as determined by IRR and Investigator based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. 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.

End point type	Secondary

End point timeframe:

From date of first administration of study treatment until the date of first documentation of disease progression or date of death, if death occurred prior to disease progression or up to approximately 26 months (as of 21 May 2012 data cut-off)

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	133[3]			
Units: Months				
median (confidence interval 95%)				
Determined by IRR	5.6 (3.7 to 6.3)			
Determined by Investigator	5.4 (3.7 to 6.7)			

Notes:

[3] - Full Analysis Set (ITT population)-all participants who received at least 1 dose of lenvatinib.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was the length time in months from the date of first treatment until the date of death from any cause. If death was not observed, OS was censored at the last known alive date or data cut-off. Additional survival follow-up data was collected for all participants who had not withdrawn consent and were alive at the time of the initial survival follow-up as of 26 Nov 2012 data cut-off. Participants who were lost to follow-up at the time of the initial assessment may have been contacted again at the investigator's discretion. Updated survival (based on 26 Nov 2012 cut-off) was derived for these participants if the contact was made successfully.

End point type	Secondary

End point timeframe:

From date of first administration of study treatment until the date of death, or up to approximately 32 months (as of 26 Nov 2012 data cut-off)

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	133[4]			
Units: Months				
median (confidence interval 95%)	10.6 (8.9 to 14.9)			

Notes:

[4] - Full Analysis Set (ITT population)-all participants who received at least 1 dose of lenvatinib.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

DCR was defined as the percentage of participants with BOR of CR or PR or stable disease (SD) based on RECIST 1.1 and SD lasting greater than or equal to 7 weeks, as determined by IRR and Investigator.

End point type	Secondary

End point timeframe:

From date of first administration of study treatment until the date of first documentation of disease progression or date of death, if death occurred prior to disease progression, or up to approximately 26 months (as of 21 May 2012 data cut-off)

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	133[5]			
Units: Percentage of participants				
number (confidence interval 95%)				
Determined by IRR	60.9 (52.1 to 69.2)			
Determined by Investigator	66.2 (57.5 to 74.1)			

Notes:

[5] - Full Analysis Set (ITT population)-all participants who received at least 1 dose of lenvatinib.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR was defined as the percentage of participants with BOR of CR or PR or durable stable disease (dSD) [CR + PR + dSD] based on RECIST 1.1. The dSD rate was defined as the percentage of participants with dSD (based on RECIST 1.1 and defined as SD lasting greater than or equal to 23 weeks), as determined by the IRR and Investigator.

End point type	Secondary

End point timeframe:

From date of first administration of study treatment until the date of first documentation of disease progression or date of death, if death occurred prior to disease progression, or up to approximately 26 months (as of 21 May 2012 data cut-off)

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	133[6]			
Units: Percentage of participants				
number (confidence interval 95%)				
Determined by IRR	37.6 (29.3 to 46.4)			
Determined by Investigator	44.4 (35.8 to 53.2)			

Notes:

[6] - Full Analysis Set (ITT population)-all participants who received at least 1 dose of lenvatinib.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse events (AEs) /Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Lenvatinib

End point title	Number of Participants with Adverse events (AEs) /Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Lenvatinib

End point description:

Safety was assessed by monitoring and recording all AEs and SAEs, regular monitoring of hematology, clinical chemistry, and urine values, regular measurement of vital signs, electrocardiograms (ECGs), and echocardiograms.

End point type	Secondary

End point timeframe:

From the administration of first dose up to 30 days after the last dose, or up to data cut-off (21 May 2012), or up to approximately 26 months.

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: Participants				
number (not applicable)				
AEs	126			
SAEs	62			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Summary of Plasma Concentration of Lenvatinib

End point title	Summary of Plasma Concentration of Lenvatinib

End point description:

A total of 6 blood samples for pharmacokinetic (PK) analysis were collected from each participant who received lenvatinib once daily. The PK analysis set was used and included all participants with an evaluable plasma concentration.

End point type	Other pre-specified

End point timeframe:

Predose and 2 hours postdose on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	133			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1, Day 1 (Pre-dose) n=132	0 (± 0)			
Cycle 1, Day 1 (2-hour Post-dose) n=132	318.9 (± 242.16)			
Cycle 1, Day 8 (Pre-dose) n=122	105.6 (± 121.66)			
Cycle 1, Day 8 (2-hour Post-dose) n=123	352.6 (± 243.88)			
Cycle 2, Day 1 (Pre-dose) n=107	88.63 (± 78.768)			
Cycle 2, Day 1 (2-hour Post-dose) n=102	336.8 (± 222.56)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage Change from Baseline for the Imaging Biomarker Parameter of the Area Under the Plasma Concentration Curve Blood Normalized (90) (AUCBN (90)) Median for Total Volume

End point title	Percentage Change from Baseline for the Imaging Biomarker Parameter of the Area Under the Plasma Concentration Curve Blood Normalized (90) (AUCBN (90)) Median for Total Volume

End point description:

The antiangiogenic and direct antitumor effects of lenvatinib were assessed by analyses of 2 dynamic contrast-enhanced magnetic resonance imaging/diffusion-weighted magnetic resonance imaging (DCE-MRI/DWI MRI) scans obtained on evaluable participants at Baseline and Cycle 1 Day 5. The scans were obtained using standardized acquisition across sites. DWI sequences totaling approximately 30 seconds were acquired during the DCE-MRI scans. Centralized analysis metrics for DCE-MRI included percentage change in initial area under the gadolinium contrast agent time-concentration curve (first 90 seconds, blood normalized) from baseline. Imaging biomarker analysis set included those participants who received at least 1 dose of lenvatinib and had, at minimum, a baseline and 1 postbaseline evaluable imaging assessment.

End point type	Other pre-specified

End point timeframe:

Cycle 1 Day 5

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	4[7]			
Units: Median for total volume				
arithmetic mean (standard deviation)	-34 (± 18.98)			

Notes:

[7] - n = number of participants with evaluable data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage Change from Baseline in the Contrast Volume Transfer Coefficient (Ktrans) Median

End point title	Percentage Change from Baseline in the Contrast Volume Transfer Coefficient (Ktrans) Median

End point description:

The antiangiogenic and direct antitumor effects of lenvatinib were assessed by analyses of two DCE-MRI/DWI MRI scans obtained on evaluable participants at Baseline and Cycle 1 Day 5. The scans were obtained using standardized acquisition across sites. DWI sequences totaling approximately 30 seconds were acquired during the DCE-MRI scans. Centralized analysis metrics for DCE-MRI included the percentage change in Ktrans for gadolinium chelate movement from the vasculature into the tissue extracellular space from baseline. Imaging biomarker analysis set included those participants who received at least 1 dose of lenvatinib and had, at a minimum, a baseline and 1 postbaseline evaluable imaging assessment.

End point type	Other pre-specified

End point timeframe:

Cycle 1 Day 5

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	4[8]			
Units: 1/minute				
arithmetic mean (standard deviation)	-41.5 (± 22.02)			

Notes:

[8] - n = number of participants with evaluable data

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage Change from Baseline in the Apparent Diffusion Coefficient (ADC) Median

End point title	Percentage Change from Baseline in the Apparent Diffusion Coefficient (ADC) Median

End point description:

The antiangiogenic and direct antitumor effects of lenvatinib were assessed by analyses of two DCE-MRI/DWI MRI scans obtained on evaluable participants at Baseline and Cycle 1 Day 5. The scans were obtained using standardized acquisition across sites. DWI sequences totaling approximately 30 seconds were acquired during the DCE-MRI scans. Centralized analysis metrics for DCE-MRI included the

percentage change in Ktrans for gadolinium chelate movement from the vasculature into the tissue extracellular space from baseline. Imaging biomarker analysis set included those participants who received at least 1 dose of lenvatinib and had, at a minimum, a baseline and 1 postbaseline evaluable imaging assessment.

End point type	Other pre-specified

End point timeframe:

Cycle 1 Day 5

End point values	Lenvatinib			
Subject group type	Reporting group			
Number of subjects analysed	2[9]			
Units: AUM2/s				
arithmetic mean (standard deviation)	2.1 (± 2.27)			

Notes:

[9] - n = number of participants with evaluable data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of administration of first dose up to 30 days after the last dose, or up to data cut-off (21 May 2012), or up to approximately 26 months.

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) and serious TEAEs were collected and reported. Safety analysis set included all participants who received at least one dose of study drug. AEs were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Lenvatinib

Reporting group description:

Lenvatinib 24 mg was administered orally, once daily continuously in 28-day cycles

Serious adverse events	Lenvatinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 133 (46.62%)		
number of deaths (all causes)	57		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm malignant			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tumour necrosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			

subjects affected / exposed	6 / 133 (4.51%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	4 / 133 (3.01%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	6 / 133 (4.51%)			
occurrences causally related to treatment / all	7 / 8			
deaths causally related to treatment / all	1 / 1			
General physical health deterioration				
subjects affected / exposed	3 / 133 (2.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 3			
Device leakage				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				

subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Female genital tract fistula				
subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	5 / 133 (3.76%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Tachypnoea				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Ejection fraction decreased				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Rib fracture				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia				

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tachycardia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Headache			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences causally related to treatment / all	4 / 10		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	5 / 133 (3.76%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	4 / 133 (3.01%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	3 / 133 (2.26%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal fistula				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileitis				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal perforation				

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	6 / 133 (4.51%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 1		
Azotaemia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal disorder			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peridiverticular abscess			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proctitis infectious			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urosepsis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	6 / 133 (4.51%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic disorder			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Lenvatinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 133 (93.98%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	71 / 133 (53.38%)		
occurrences (all)	151		
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	30 / 133 (22.56%)		
occurrences (all)	47		
Fatigue			
subjects affected / exposed	55 / 133 (41.35%)		
occurrences (all)	110		
Oedema peripheral			
subjects affected / exposed	20 / 133 (15.04%)		
occurrences (all)	23		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	8 / 133 (6.02%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 133 (14.29%)		
occurrences (all)	27		
Dysphonia			
subjects affected / exposed	27 / 133 (20.30%)		
occurrences (all)	30		
Dyspnoea			
subjects affected / exposed	17 / 133 (12.78%)		
occurrences (all)	19		
Epistaxis			
subjects affected / exposed	13 / 133 (9.77%)		
occurrences (all)	17		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	7		
Investigations			
Blood thyroid stimulating hormone increased			
subjects affected / exposed	8 / 133 (6.02%)		
occurrences (all)	13		
Weight decreased			

subjects affected / exposed	27 / 133 (20.30%)		
occurrences (all)	51		
Nervous system disorders			
Dizziness			
subjects affected / exposed	20 / 133 (15.04%)		
occurrences (all)	29		
Dysgeusia			
subjects affected / exposed	16 / 133 (12.03%)		
occurrences (all)	18		
Headache			
subjects affected / exposed	35 / 133 (26.32%)		
occurrences (all)	58		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 133 (10.53%)		
occurrences (all)	20		
Thrombocytopenia			
subjects affected / exposed	11 / 133 (8.27%)		
occurrences (all)	14		
Eye disorders			
Vision blurred			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	9		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	14		
Abdominal pain			
subjects affected / exposed	33 / 133 (24.81%)		
occurrences (all)	50		
Abdominal pain upper			
subjects affected / exposed	17 / 133 (12.78%)		
occurrences (all)	33		
Constipation			
subjects affected / exposed	25 / 133 (18.80%)		
occurrences (all)	34		
Diarrhoea			

subjects affected / exposed	46 / 133 (34.59%)		
occurrences (all)	106		
Dry mouth			
subjects affected / exposed	15 / 133 (11.28%)		
occurrences (all)	16		
Dyspepsia			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	9		
Flatulence			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	41 / 133 (30.83%)		
occurrences (all)	67		
Stomatitis			
subjects affected / exposed	30 / 133 (22.56%)		
occurrences (all)	60		
Vomiting			
subjects affected / exposed	32 / 133 (24.06%)		
occurrences (all)	59		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	9		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	10 / 133 (7.52%)		
occurrences (all)	20		
Rash			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	17		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	10		
Proteinuria			

subjects affected / exposed occurrences (all)	28 / 133 (21.05%) 73		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 23 / 133 (17.29%) 29		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 9 / 133 (6.77%) 11 16 / 133 (12.03%) 21 8 / 133 (6.02%) 10		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 17 / 133 (12.78%) 25		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	 45 / 133 (33.83%) 79 8 / 133 (6.02%) 8 17 / 133 (12.78%) 18 11 / 133 (8.27%) 17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2010	Amendment 01: 1) Addition of DWI-MRI-based metrics; originally protocols included only DCE-MRI-based metrics. 2) Updated inclusion criterion with regards to baseline blood pressures and renal function to be consistent with other lenvatinib Phase 2 protocols. 3) Clarified that only Grade 2 toxicities judged to be intolerable required a dose adjustment and that the dose adjustment for intolerable Grade 2 toxicities was the same as for Grade 3. 4) Updated management of hypertension and proteinuria to be consistent with lenvatinib Phase 2 program. 5) Added pharmacogenomics as an exploratory endpoint. 6) Added clarification that the analysis of the primary endpoint (ORR) would be based on IRR. 7) Clarified the number of subjects required for the ITT analysis (130) based on Simon's Optimal 2-Stage Design. 8) Permitted skeletal x-ray for documenting tumor progression. 9) Stipulated that progressive disease should not be recorded as an AE and that the severity of each AE should be assessed using CTCAE. 10) Expanded the window for screening/baseline tumor assessments. 11) Updated the FIGO staging classification for endometrial carcinoma. Rationale: To provide clarification and to be consistent with other Phase 2 studies in the lenvatinib program.
11 July 2011	Amendment 02 1) Clarified treatment requirements after disease progression prior to study inclusion. 2) Clarified size of lesion to qualify as measurable disease. 3) Clarified that subjects with any malignancy (except for endometrial cancer, basal or squamous cell carcinoma of the skin, melanoma in situ, or carcinoma in situ of the cervix) would be excluded. 4) Allowed a 48-hour window to assess hematology and clinical chemistry results. 5) Clarified that blood pressure and heart rate were to be assessed immediately prior to echocardiogram. 6) Increased the number of sites. Rationale: To provide clarification; the number of sites was updated throughout the revised protocol to reflect the actual number of sites that were used.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported