Clinical trial results:
LUX-Bladder 1: Phase II open label single arm exploratory trial of oral afatinib monotherapy following platinum failure for patients with advanced/metastatic urothelial tract carcinoma with genetic alterations in ERBB receptors.

Summary

EudraCT number	2015-005427-10
Trial protocol	ES FR
Global end of trial date	24 September 2018

Results information

Result version number	v4 (current)
This version publication date	14 November 2021
First version publication date	18 September 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1200.261

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02780687
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany,
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the anti-tumour activity and safety of afatinib monotherapy in patients with urothelial tract carcinoma who show mutations in ERBB2 or ERBB3 or amplification in ERBB2 (Cohort A), or EGFR amplification (Cohort B), progressing despite previous platinum-based chemotherapy.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2015
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	Spain: 48
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	17
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was a Phase II open label single arm exploratory trial of oral afatinib monotherapy following platinum failure for patients with advanced/metastatic urothelial tract carcinoma with genetic alterations in ERBB receptors.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

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

Blinding implementation details:

The trial is an open label single arm exploratory Trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

Afatinib monotherapy in patients with urothelial tract carcinoma who progressed after first line of platinum-based chemotherapy and who show mutations in ERBB2 or ERBB3 or amplification in ERBB2 (Erythroblastic leukaemia viral oncogene homolog of the human epidermal growth factor family of receptors). Therapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib monotherapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.

Arm title	Cohort B

Arm description:

Afatinib monotherapy in patients with urothelial tract carcinoma who progressed after first line of platinum-based chemotherapy and who show EGFR (Epidermal Growth Factor Receptor) amplification. Therapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib monotherapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.

Number of subjects in period 1[1]	Cohort A	Cohort B
Started	34	8
Completed	0	0
Not completed	34	8
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	1
Switched to commercial program (in CTP)	2	-
Progressive disease	29	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all enrolled subjects were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
Afatinib monotherapy in patients with urothelial tract carcinoma who progressed after first line of platinum-based chemotherapy and who show mutations in ERBB2 or ERBB3 or amplification in ERBB2 (Erythroblastic leukaemia viral oncogene homolog of the human epidermal growth factor family of receptors). Therapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.	
Reporting group title	Cohort B
Reporting group description:	
Afatinib monotherapy in patients with urothelial tract carcinoma who progressed after first line of platinum-based chemotherapy and who show EGFR (Epidermal Growth Factor Receptor) amplification. Therapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.	

Reporting group values	Cohort A	Cohort B	Total
Number of subjects	34	8	42
Age categorical			
The treated set (TS) included all patients who took at least 1 afatinib dose.			
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)	10	2	12
From 65-84 years	24	6	30
85 years and over	0	0	0
Age Continuous			
The treated set (TS) included all patients who took at least 1 afatinib dose.			
Units: years			
arithmetic mean	66.4	70.0	
standard deviation	± 10.3	± 6.9	-
Sex: Female, Male			
The treated set (TS) included all patients who took at least 1 afatinib dose.			
Units: Participants			
Female	4	2	6
Male	30	6	36
Race (NIH/OMB)			
The treated set (TS) included all patients who took at least 1 afatinib dose.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	0	0	0
White	34	8	42
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Biomarker status - ERBB2 mutation			
The treated set (TS) included all patients who took at least 1 afatinib dose.			
Units: Subjects			
with ERBB2 mutation	8	0	8
without ERBB2 mutation	26	8	34
Biomarker status - ERBB3 mutation			
The treated set (TS) included all patients who took at least 1 afatinib dose.			
Units: Subjects			
with ERBB3 mutation	11	0	11
without ERBB3 mutation	23	8	31
Biomarker status - ERBB2 amplification			
The treated set (TS) included all patients who took at least 1 afatinib dose.			
Units: Subjects			
with ERBB2 amplification	20	0	20
without ERBB2 amplification	14	8	22
Biomarker status - EGFR amplification			
The treated set (TS) included all patients who took at least 1 afatinib dose.			
Units: Subjects			
with EGFR amplification	3	8	11
without EGFR amplification	31	0	31

End points

End points reporting groups

Reporting group title	Cohort A

Reporting group description:

Afatinib monotherapy in patients with urothelial tract carcinoma who progressed after first line of platinum-based chemotherapy and who show mutations in ERBB2 or ERBB3 or amplification in ERBB2 (Erythroblastic leukaemia viral oncogene homolog of the human epidermal growth factor family of receptors). Therapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.

Reporting group title	Cohort B

Reporting group description:

Afatinib monotherapy in patients with urothelial tract carcinoma who progressed after first line of platinum-based chemotherapy and who show EGFR (Epidermal Growth Factor Receptor) amplification. Therapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.

Primary: Progression-free survival rate at 6 months (PFS6) in Cohort A

End point title	Progression-free survival rate at 6 months (PFS6) in Cohort

End point description:

Progression-free survival rate at 6 months for Cohort A defined as the number of patients who were alive and without disease progression at 24-week tumour assessment. Tumour response was assessed based on local radiological image (Computerised tomography (CT) or Magnetic resonance imaging (MRI)) evaluation by the investigators according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. Baseline imaging was to be performed within 28 days before afatinib treatment start, if the patient already had a tumour assessment within this timeframe, this test was not repeated. Progression is defined as at least a 20% increase in sum of longest diameter (LD) of target lesions taking as reference the smallest sum LD since the treatment started, together with an absolute increase in the sum of LD of at least 5 millimeter OR The appearance of one or more new lesions.

End point type	Primary

End point timeframe:

From start of treatment till assesment at week 24.

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: Endpoint was only planned to be analyzed descriptively.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only applies to Cohort A

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	34[3]			
Units: Participants				
Without progression/death at 24th week	4			

Notes:

[3] - all patients who took at least 1 afatinib dose and with ERBB-deregulated tumours (cohort A).

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed objective response rate (ORR) in Cohort A

End point title	Confirmed objective response rate (ORR) in Cohort A[4]

End point description:

Confirmed objective response rate by investigator review for Cohort A was defined as the number of patients with confirmed complete response (CR, disappearance of all target lesions) or confirmed partial response (PR, at least a 30% decrease in sum of longest diameter (LD) of target lesions, reference is baseline sum LD). Tumour response was assessed based on local radiological image (Computerised tomography (CT) or Magnetic resonance imaging (MRI)) evaluation by the investigators according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. Baseline imaging was to be performed within 28 days before afatinib treatment start, if the patient already had a tumour assessment within this timeframe, this test was not repeated.

End point type	Secondary

End point timeframe:

Scans every 8 (±1) weeks from start till end of treatment. Afterwards, if discontinuation was not for progression: every 8 (±1) weeks until month 6, every 12 (±2) weeks thereafter. Until documented disease progression, i.e., up to ~ 20 Months.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only applies to Cohort A

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	34[5]			
Units: Participants				
Objective response	2			

Notes:

[5] - all patients who took at least 1 afatinib dose and with ERBB-deregulated tumours (cohort A).

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) in Cohort A

End point title	Progression-free survival (PFS) in Cohort A[6]

End point description:

Progression-free survival was defined as the time (months) from the date of the first afatinib administration to the date of disease progression or death (if the patient died without progression). The date of progression for the primary analyses was determined based on investigator assessment. Tumour response was assessed based on local radiological image (Computerised tomography (CT) or Magnetic resonance imaging (MRI)) evaluation by the investigators according to RECIST version 1.1. Baseline imaging was to be performed within 28 days before afatinib treatment start, if the patient already had a tumour assessment within this timeframe, this test was not repeated. Progression is defined as at least a 20% increase in sum of longest diameter (LD) of target lesions taking as reference the smallest sum LD since the treatment started, together with an absolute increase in the sum of LD of at least 5 millimeter OR The appearance of one or more new lesions.

End point type	Secondary

End point timeframe:

Scans every 8 (±1) weeks from start till end of treatment. Afterwards, if discontinuation was not for progression: every 8 (±1) weeks until month 6, every 12 (±2) weeks thereafter. Until documented disease progression, i.e., up to ~ 20 Months.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only applies to Cohort A

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	34[7]			
Units: Weeks				
median (confidence interval 95%)	9.8 (7.9 to 16.0)			

Notes:

[7] - all patients who took at least 1 afatinib dose and with ERBB-deregulated tumours (cohort A).

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) in Cohort A

End point title	Overall survival (OS) in Cohort A[8]

End point description:

Overall survival (OS) defined as the time from start of treatment of afatinib until death from any cause.

End point type	Secondary

End point timeframe:

From start of treatment of afatinib until death from any cause, i.e. up to approximately 20 Months.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only applies to Cohort A

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	34[9]			
Units: Weeks				
median (confidence interval 95%)	30.1 (17.4 to 47.0)			

Notes:

[9] - all patients who took at least 1 afatinib dose and with ERBB-deregulated tumours (cohort A).

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) in Cohort A

End point title	Disease control rate (DCR) in Cohort A[10]

End point description:

Disease control rate was calculated as the number of patients with complete response (CR, disappearance of all target lesions), partial response (PR, at least a 30% decrease in sum of longest diameter (LD) of target lesions, reference is baseline sum LD), or stable disease (SD, neither sufficient shrinkage to qualify for PR, taking as reference the baseline sum of diameters (SoD), nor sufficient increase to qualify for PD taking as reference the smallest SoD since the treatment started). Tumour response was assessed based on local radiological image (Computerised tomography (CT) or Magnetic resonance imaging (MRI)) evaluation by the investigators according to Response Evaluation Criteria In

Solid Tumours (RECIST) version 1.1. Baseline imaging was to be performed within 28 days before afatinib treatment start, if the patient already had a tumour assessment within this timeframe, this test was not repeated.

End point type	Secondary

End point timeframe:

Scans every 8 (±1) weeks from start till end of treatment. Afterwards, if discontinuation was not for progression: every 8 (±1) weeks until month 6, every 12 (±2) weeks thereafter. Until documented disease progression, i.e., up to ~ 20 Months.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only applies to Cohort A

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	34[11]			
Units: Participants				
Yes	17			
No	17			

Notes:

[11] - all patients who took at least 1 afatinib dose and with ERBB-deregulated tumours (cohort A).

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of disease control in Cohort A

End point title	Duration of disease control in Cohort A[12]

End point description:

For patients with disease control, duration of disease control was defined as the time from afatinib treatment start to disease progression (or death if the patient died before progression).
Disease control was defined as a having a complete response (CR, disappearance of all target lesions), partial response (PR, at least a 30% decrease in sum of longest diameter (LD) of target lesions, reference is baseline sum LD), or stable disease (SD, neither sufficient shrinkage to qualify for PR, taking as reference the baseline sum of diameters (SoD), nor sufficient increase to qualify for PD taking as reference the smallest SoD since the treatment started). Tumour response was assessed based on local radiological image (CT or MRI) evaluation by the investigators according to RECIST version 1.1. Baseline imaging was to be performed within 28 days before afatinib treatment start, if the patient already had a tumour assessment within this timeframe, this test was not repeated.

End point type	Secondary

End point timeframe:

Scans every 8 (±1) weeks from start till end of treatment. Afterwards, if discontinuation was not for progression: every 8 (±1) weeks until month 6, every 12 (±2) weeks thereafter. Until documented disease progression, i.e., up to ~ 20 Months.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only applies to Cohort A

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	34[13]			
Units: Weeks				
median (confidence interval 95%)	22.7 (15.1 to 36.1)			

Notes:

[13] - all patients who took at least 1 afatinib dose and with ERBB-deregulated tumours (cohort A).

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with tumour shrinkage in Cohort A

End point title	Number of patients with tumour shrinkage in Cohort A[14]

End point description:

Number of patients with tumour shrinkage, tumour shrinkage from baseline was defined by the maximum percentage decrease from baseline in the sum of the longest diameters of target lesions. Tumour response was assessed based on local radiological image (Computerised tomography (CT) or Magnetic resonance imaging (MRI)) evaluation by the investigators according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. Baseline imaging was to be performed within 28 days before afatinib treatment start, if the patient already had a tumour assessment within this timeframe, this test was not repeated.

End point type	Secondary

End point timeframe:

Scans every 8 (±1) weeks from start till end of treatment. Afterwards, if discontinuation was not for progression: every 8 (±1) weeks until month 6, every 12 (±2) weeks thereafter. Until documented disease progression, i.e., up to ~ 20 Months.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint only applies to Cohort A

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	34[15]			
Units: Participants				
Patients with Shrinkage	9			

Notes:

[15] - all patients who took at least 1 afatinib dose and with ERBB-deregulated tumours (cohort A).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of first drug administration till the end of treatment + 30 days (REP), up to approximately 20 Months.

Adverse event reporting additional description:

The treated set (TS) included all patients who took at least 1 afatinib dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Cohort A

Reporting group description:

Afatinib monotherapy in patients with urothelial tract carcinoma who progressed after first line of platinum-based chemotherapy and who show mutations in ERBB2 or ERBB3 or amplification in ERBB2 (Erythroblastic leukaemia viral oncogene homolog of the human epidermal growth factor family of receptors). Therapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.

Reporting group title	Cohort B

Reporting group description:

Afatinib monotherapy in patients with urothelial tract carcinoma who progressed after first line of platinum-based chemotherapy and who show EGFR (Epidermal Growth Factor Receptor) amplification. Therapy consists of 40 mg film-coated tablets taken orally once a day continuously. The dose could be reduced to 30 mg or, in a second step, to 20 mg once daily. No dose increase was allowed after a dose reduction.

Serious adverse events	Cohort A	Cohort B	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 34 (44.12%)	6 / 8 (75.00%)	
number of deaths (all causes)	26	7	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cardiac failure			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
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			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (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			
Asthenia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	4 / 34 (11.76%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (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 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal disorder			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (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			
Escherichia pyelonephritis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pelvic abscess			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (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 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 34 (11.76%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort A	Cohort B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 34 (100.00%)	8 / 8 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 34 (55.88%)	3 / 8 (37.50%)	
occurrences (all)	24	4	

Malaise			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Mucosal inflammation			
subjects affected / exposed	10 / 34 (29.41%)	3 / 8 (37.50%)	
occurrences (all)	13	3	
Oedema peripheral			
subjects affected / exposed	2 / 34 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	3 / 34 (8.82%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Pyrexia			
subjects affected / exposed	7 / 34 (20.59%)	1 / 8 (12.50%)	
occurrences (all)	8	1	
Xerosis			
subjects affected / exposed	3 / 34 (8.82%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 34 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Haemoptysis			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 34 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Blood creatinine increased			
subjects affected / exposed	2 / 34 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	3	4	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Platelet count decreased			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	5	
Transaminases increased			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Neuropathy peripheral			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	

Paraesthesia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Speech disorder			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 34 (29.41%)	2 / 8 (25.00%)	
occurrences (all)	16	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	10 / 34 (29.41%)	1 / 8 (12.50%)	
occurrences (all)	13	1	
Diarrhoea			
subjects affected / exposed	23 / 34 (67.65%)	5 / 8 (62.50%)	
occurrences (all)	50	6	
Dry mouth			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	3 / 34 (8.82%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Faeces soft			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Glossitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	9 / 34 (26.47%)	1 / 8 (12.50%)	
occurrences (all)	11	1	
Stomatitis			

subjects affected / exposed	9 / 34 (26.47%)	2 / 8 (25.00%)	
occurrences (all)	9	2	
Vomiting			
subjects affected / exposed	7 / 34 (20.59%)	1 / 8 (12.50%)	
occurrences (all)	11	1	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	2 / 34 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	5	1	
Dermatitis acneiform			
subjects affected / exposed	4 / 34 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	6	2	
Dry skin			
subjects affected / exposed	3 / 34 (8.82%)	1 / 8 (12.50%)	
occurrences (all)	3	1	
Pruritus			
subjects affected / exposed	5 / 34 (14.71%)	2 / 8 (25.00%)	
occurrences (all)	6	2	
Rash			
subjects affected / exposed	11 / 34 (32.35%)	1 / 8 (12.50%)	
occurrences (all)	14	1	
Skin erosion			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	2 / 34 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Skin toxicity			
subjects affected / exposed	4 / 34 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	4	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Haematuria			

subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	4	0	
Leukocyturia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Oliguria			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Renal failure			
subjects affected / exposed	3 / 34 (8.82%)	0 / 8 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 34 (20.59%)	0 / 8 (0.00%)	
occurrences (all)	7	0	
Bone pain			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	3 / 34 (8.82%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Paronychia			
subjects affected / exposed	3 / 34 (8.82%)	3 / 8 (37.50%)	
occurrences (all)	4	4	
Respiratory tract infection			

subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Skin candida			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	6 / 34 (17.65%)	3 / 8 (37.50%)	
occurrences (all)	7	4	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Decreased appetite			
subjects affected / exposed	15 / 34 (44.12%)	2 / 8 (25.00%)	
occurrences (all)	21	2	
Hyperkalaemia			
subjects affected / exposed	1 / 34 (2.94%)	1 / 8 (12.50%)	
occurrences (all)	1	2	
Hypoalbuminaemia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Hypomagnesaemia			
subjects affected / exposed	4 / 34 (11.76%)	1 / 8 (12.50%)	
occurrences (all)	4	1	
Hyponatraemia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Hypophosphataemia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 8 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2017	Several minor changes throughout the CTP improved the readability and comprehensibility. Several eligibility criteria were modified. Inclusion criteria 4 and 5 were reworded, specifying 'line of chemotherapy' and 'previous treatment'. Exclusion criterion 4 was reworded regarding 'previous radiotherapy' to align with RECIST 1.1. Exclusion criterion 8 was reworded to add incidental localised prostate cancer as allowed malignancy. Exclusion criteria 14 and 15 were reworded; the text about women of child-bearing potential was aligned with project standards and current ICH guidelines. The futility analysis criterion to assess ORR as well as PFS6 was amended. A refined statistical model and new statistical assumptions in the sample size calculations resulted in an increased number of patients to be included in Stage 2 of the trial. The afatinib treatment duration was refined as well as the criteria for treatment discontinuation. For the dose reduction scheme, it was clarified that only renal impairment related to dehydration caused by diarrhoea should lead to afatinib dose reduction. The CTCAE version was changed to version 4.03 throughout the CTP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Duration of confirmed objective response was not analysed because only 2 patients showed a confirmed objective response. Instead, duration of disease control was analysed.

Notes: