



## Clinical trial results:

**An open label trial of afatinib (Giotrif®) in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)**

### Summary

EudraCT number	2009-017661-34
Trial protocol	CZ HU IT ES AT GR PT PL
Global end of trial date	06 March 2024

### Results information

Result version number	v1 (current)
This version publication date	16 March 2025
First version publication date	16 March 2025

### Trial information

#### Trial identification

Sponsor protocol code	1200.55
-----------------------	---------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01853826
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, 001 18002430127, <a href="mailto:clintrriage.rdg@boehringer-ingelheim.com">clintrriage.rdg@boehringer-ingelheim.com</a>
Scientific contact	Boehringer Ingelheim, Call Center, 001 18002430127, <a href="mailto:clintrriage.rdg@boehringer-ingelheim.com">clintrriage.rdg@boehringer-ingelheim.com</a>

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2018
Global end of trial reached?	Yes
Global end of trial date	06 March 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability and efficacy of afatinib (Giotrif®) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-tyrosine kinase inhibitors.

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 tumor associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Austria: 26
Country: Number of subjects enrolled	Czechia: 22
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Italy: 168
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Russian Federation: 85
Country: Number of subjects enrolled	Spain: 85
Worldwide total number of subjects	495
EEA total number of subjects	370

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)	245
From 65 to 84 years	245
85 years and over	5

---

## Subject disposition

### Recruitment

Recruitment details:

Open-label, multicentre, single-arm trial to evaluate the safety, tolerability and efficacy of afatinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutation(s) who had never been treated with an EGFR tyrosine kinase inhibitor (TKI).

### Pre-assignment

Screening details:

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

### Period 1

Period 1 title	Entered Patients
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This study was conducted open label.

### Arms

Arm title	Afatinib treated-patients
-----------	---------------------------

Arm description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Arm type	No intervention
----------	-----------------

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Afatinib treated-patients
Started	481
Completed	479
Not completed	2
Not signed privacy consent form	2

**Period 2**

Period 2 title	Treated patients
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This study was conducted open-label.

**Arms**

<b>Arm title</b>	Afatinib treated-patients
------------------	---------------------------

Arm description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

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

Dosage and administration details:

Patients received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The baseline period is on the treated set represented by the treated patient's period.

<b>Number of subjects in period 2<sup>[2]</sup></b>	Afatinib treated-patients
Started	479
Completed	0
Not completed	479
Other adverse events (AE)	62
Patients who switched to commercial drug	11
Worsening or AE of underlying cancer disease	24
Patient refused to continue medication	21
Non-compliant with protocol	4
Lost to follow-up	2
Progressive disease	342
Other than listed	13

---

Notes:

[2] - 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: From the 495 patients screened, 479 started the trial treatment.

## Baseline characteristics

### Reporting groups

Reporting group title	Afatinib treated-patients
-----------------------	---------------------------

Reporting group description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Reporting group values	Afatinib treated-patients	Total	
Number of subjects	479	479	
Age categorical			
Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	238	238	
From 65-84 years	236	236	
85 years and over	5	5	
Age Continuous			
Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.			
Units: years			
arithmetic mean	64.2		
standard deviation	± 10.9	-	
Sex: Female, Male			
Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.			
Units: Subjects			
Female	314	314	
Male	165	165	
Race (NIH/OMB)			
Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	10	10	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	3	3	
White	465	465	

More than one race	0	0	
Unknown or Not Reported	0	0	

---

## End points

### End points reporting groups

Reporting group title	Afatinib treated-patients
-----------------------	---------------------------

Reporting group description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Reporting group title	Afatinib treated-patients
-----------------------	---------------------------

Reporting group description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

### Primary: Number of patients with adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

End point title	Number of patients with adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 <sup>[1]</sup>
-----------------	---

End point description:

Number of patients with any treatment emergent adverse event (AE) according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

The analysis was performed on the treated set. The treated set is defined by all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.

End point type	Primary
----------------	---------

End point timeframe:

From first drug administration to last drug administration plus 28 days of residual effect period. Up to 3866 days.

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: This endpoint was analyzed only descriptively.

End point values	Afatinib treated-patients			
Subject group type	Reporting group			
Number of subjects analysed	479			
Units: Participants	478			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration.

Adverse event reporting additional description:

Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	27.0
--------------------	------

### Reporting groups

Reporting group title	Afatinib 40 mg
-----------------------	----------------

Reporting group description: -

<b>Serious adverse events</b>	Afatinib 40 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	210 / 479 (43.84%)		
number of deaths (all causes)	127		
number of deaths resulting from adverse events	71		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chromophobe renal cell carcinoma			

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial sarcoma			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningioma			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningioma benign			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	11 / 479 (2.30%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 1		
Metastases to liver			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			

subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
<b>Metastases to pancreas</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Metastasis</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Ovarian granulosa cell tumour</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Prostate cancer</b>			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Transitional cell carcinoma</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Malignant neoplasm progression</b>			
subjects affected / exposed	36 / 479 (7.52%)		
occurrences causally related to treatment / all	0 / 36		
deaths causally related to treatment / all	0 / 29		
<b>Vascular disorders</b>			
<b>Venous thrombosis</b>			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Deep vein thrombosis</b>			

subjects affected / exposed	4 / 479 (0.84%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
<b>Haematoma</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Peripheral ischaemia</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Peripheral vascular disorder</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Superior vena cava syndrome</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Thrombophlebitis</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Vena cava thrombosis</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Surgical and medical procedures</b>			
Surgery			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>General disorders and administration site conditions</b>			

Death				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Disease progression				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fatigue				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Condition aggravated				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Chest pain				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	11 / 479 (2.30%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 4			
Hyperpyrexia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Multiple organ dysfunction syndrome</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pain</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pyrexia</b>			
subjects affected / exposed	4 / 479 (0.84%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
<b>Reproductive system and breast disorders</b>			
<b>Cervical dysplasia</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cystocele</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Uterine prolapse</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Acute respiratory distress syndrome</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Acute respiratory failure				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Atelectasis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	11 / 479 (2.30%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	16 / 479 (3.34%)			
occurrences causally related to treatment / all	0 / 17			
deaths causally related to treatment / all	0 / 0			
Pleurisy				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				

subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
<b>Pneumothorax</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pulmonary embolism</b>			
subjects affected / exposed	13 / 479 (2.71%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 3		
<b>Pulmonary thrombosis</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Respiratory failure</b>			
subjects affected / exposed	6 / 479 (1.25%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 6		
<b>Hydrothorax</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Psychiatric disorders</b>			
<b>Behaviour disorder</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Bradyphrenia</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Confusional state</b>			

subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

C-reactive protein increased subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Radius fracture subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Patella fracture subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Femur fracture				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Craniofacial fracture				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Accidental poisoning				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral nerve injury				

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
Acute coronary syndrome			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ventricular hypokinesia			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left ventricular dilatation			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiopulmonary failure			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac failure acute</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Cardiac failure</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac arrest</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Atrial fibrillation</b>			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac tamponade</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Nervous system disorders</b>			
<b>Hemiparesis</b>			
subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
<b>Aphasia</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cerebral haemorrhage</b>			

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cerebral infarction</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cerebrovascular accident</b>			
subjects affected / exposed	5 / 479 (1.04%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 4		
<b>Cerebrovascular disorder</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Cognitive disorder</b>			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
<b>Dementia</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Dizziness</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Embolic stroke</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Epilepsy</b>			

subjects affected / exposed	4 / 479 (0.84%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
<b>Generalised tonic-clonic seizure</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Headache</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Seizure</b>			
subjects affected / exposed	4 / 479 (0.84%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
<b>Neuropathy peripheral</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Spinal cord compression</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Transient ischaemic attack</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Ischaemic stroke</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Memory impairment</b>			

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Myelopathy</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Neurological decompensation</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Somnolence</b>			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Blood and lymphatic system disorders</b>			
<b>Thrombocytopenia</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Coagulopathy</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Disseminated intravascular coagulation</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Eye disorders</b>			
<b>Glaucoma</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	16 / 479 (3.34%)			
occurrences causally related to treatment / all	17 / 18			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	7 / 479 (1.46%)			
occurrences causally related to treatment / all	6 / 9			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haematoma				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal obstruction				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Odynophagia				

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Nausea</b>			
subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
<b>Lower gastrointestinal haemorrhage</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Intestinal obstruction</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Intestinal infarction</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
<b>Gastritis erosive</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Gastritis</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Gastric perforation</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Duodenal ulcer</b>			

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 479 (0.84%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		

Hydronephrosis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	8 / 479 (1.67%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 1		
Urinary retention			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	9 / 479 (1.88%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 3		

Pneumocystis jirovecii infection				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paronychia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Enterocolitis bacterial				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear infection bacterial				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Conjunctivitis				

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Clostridium difficile colitis</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Clostridial infection</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cellulitis</b>			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Cavernous sinus thrombosis</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>COVID-19</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Bacteraemia</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Abscess neck</b>			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Abscess</b>			

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	5 / 479 (1.04%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	6 / 479 (1.25%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrolyte imbalance			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron deficiency			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Afatinib 40 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	268 / 479 (55.95%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	35 / 479 (7.31%)		
occurrences (all)	101		
Mucosal inflammation			
subjects affected / exposed	54 / 479 (11.27%)		
occurrences (all)	145		
Pyrexia			
subjects affected / exposed	30 / 479 (6.26%)		
occurrences (all)	76		
Asthenia			
subjects affected / exposed	52 / 479 (10.86%)		
occurrences (all)	173		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	238 / 479 (49.69%)		
occurrences (all)	3275		
Nausea			
subjects affected / exposed	32 / 479 (6.68%)		
occurrences (all)	111		
Stomatitis			
subjects affected / exposed	42 / 479 (8.77%)		
occurrences (all)	126		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 479 (7.52%)		
occurrences (all)	112		
Dyspnoea			
subjects affected / exposed	30 / 479 (6.26%)		
occurrences (all)	98		
Skin and subcutaneous tissue disorders			
Skin fissures			

subjects affected / exposed occurrences (all)	27 / 479 (5.64%) 78		
Dermatitis acneiform subjects affected / exposed occurrences (all)	28 / 479 (5.85%) 69		
Dry skin subjects affected / exposed occurrences (all)	49 / 479 (10.23%) 111		
Pruritus subjects affected / exposed occurrences (all)	29 / 479 (6.05%) 74		
Rash subjects affected / exposed occurrences (all)	143 / 479 (29.85%) 501		
Rash papular subjects affected / exposed occurrences (all)	27 / 479 (5.64%) 52		
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	41 / 479 (8.56%) 100		
Paronychia subjects affected / exposed occurrences (all)	85 / 479 (17.75%) 236		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	27 / 479 (5.64%) 103		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2013	Global amendment 1: Clarifications, corrections, and administrative changes, or updates to background information were made. In addition the following was implemented: - cardiac assessments (electrocardiogram (ECG) and left ventricular ejection fraction (LVEF)) were to be performed only if clinically indicated. Left ventricular dysfunction has been associated with HER2 inhibition. Based on the available clinical trial data, there as no suggestion that afatinib caused an adverse effect on cardiac contractility. However, afatinib had not been studied in patients with abnormal LVEF or those with significant cardiac history. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during afatinib treatment, should be considered. In patients that developed relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.; - reporting of serious adverse events (SAEs) after the follow-up period was clarified. The investigator did not need to actively monitor patients for AEs once the clinical trial had ended. However, if the investigator became aware of an SAE that occurred after the patient had completed the clinical trial (including any protocol required residual effect period (REP) and / or follow-up), it was to be reported by the investigator to the sponsor if considered relevant by the investigator;
05 November 2013	Global amendment 1 (continued) - new safety information was added: patients who presented with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye were to be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis was confirmed, treatment with afatinib was to be interrupted or discontinued. If keratitis was diagnosed, the benefits and risks of continuing treatment with afatinib were to be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration; - acceptable methods of birth control were to be used for 28 days after the end of active treatment (rather than 14 days as originally specified).
17 August 2017	Global amendment 2: In addition to clarifications, corrections, and administrative changes, or updates to background information, the following main changes, were implemented: the duration of treatment was updated to ensure an on-going supply to patients who have not yet met the criteria for ceasing study treatment and to allow completion of the trial; a planned interim analysis was added.
08 February 2021	Global amendment 3: In addition to clarifications, corrections, and administrative changes, or updates to background information, the following main changes, were implemented: shipment of medication to patients' homes (or dispensing enough medication for 2 cycles) was permitted to allow flexibility in visit conduct in case required due to pandemic or other exceptional situations to ensure patients safety by ensuring continuous treatment; the risk assessment was updated in line with updates to the Investigator Brochure, to note that gastrointestinal perforation, including fatalities, had been reported during treatment with afatinib in 0.2% of patients across all randomised controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. Patients who develop gastrointestinal perforation while taking afatinib, should permanently discontinue treatment.

---

Notes:

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported