Clinical trial results:
A phase Ib open label clinical trial of continuous once daily oral treatment using BIBW 2992 plus cetuximab (Erbitux®) in patients with non-small cell lung cancer with progression following prior erlotinib (Tarceva®) or gefitinib (Iressa®)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2009-015911-42
Trial protocol	NL
Global end of trial date	08 August 2014

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	1200.71

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01090011
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173 , 55216 Ingelheim am Rhein , Germany,
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim , +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim , +1 8002430127, 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	07 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2013
Global end of trial reached?	Yes
Global end of trial date	08 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the maximum tolerated dose (MTD) and recommended Phase II doses and evaluate the safety and preliminary anti-tumor activity for the combination of BIBW 2992 and cetuximab in patients with non-small cell lung cancer and acquired resistance to erlotinib, gefitinib or BIBW 2992.

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. Close monitoring of all subjects was adhered to throughout the trial conduct. Symptomatic treatment of tumour-associated symptoms, such as radiation therapy with palliative intent was allowed. Concomitant medications, or therapy to provide adequate supportive care, were allowed as clinically necessary. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) was required to exclude interstitial lung disease (ILD). Study drugs were to be interrupted pending investigation of these symptoms. If ILD was diagnosed, study drug was to be permanently discontinued and appropriate treatment instituted as necessary.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 37
Country: Number of subjects enrolled	United States: 164
Worldwide total number of subjects	201
EEA total number of subjects	37

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)	146
From 65 to 84 years	54
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (Subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the entry criteria were violated. Therefore 171 patients were treated in this study.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Combination Arm -Afa40+Ctx250

Arm description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with Acquired Resistance (AR) to erlotinib or gefitinib)

Afatinib 40 mg + cetuximab 250 mg/m2 (Afa40+Ctx250)

Arm type	Experimental
Investigational medicinal product name	afatinib
Investigational medicinal product code	BIBW 2992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuous once daily oral treatment using 40 mg BIBW 2992 plus cetuximab 250 mg/m2 every two weeks (q2wk) up to 28 days

Arm title	Combination Arm - Afa40+Ctx500

Arm description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with AR to
erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m2 (Afa40+Ctx500)

Arm type	Experimental
Investigational medicinal product name	afatinib
Investigational medicinal product code	BIBW 2992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuous once daily oral treatment using 40 mg BIBW 2992 plus cetuximab 500mg q2wk up to 28 days.

Arm title	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)

Arm description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the Maximum Tolerated Dose (MTD) determined in the

combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

Afatinib 40 mg (Afa40 Mono)

Arm type	Experimental
Investigational medicinal product name	afatinib
Investigational medicinal product code	BIBW 2992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Monotherapy afatinib daily 40 mg orally taken

Arm title	Sequential Arm - Combination Therapy (Afa40+Ctx500)

Arm description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the MTD determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m2 (Afa40+Ctx500)

Arm type	Experimental
Investigational medicinal product name	afatinib
Investigational medicinal product code	BIBW 2992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuous once daily oral treatment using 40 mg BIBW 2992 plus cetuximab 500mg q2wk

Number of subjects in period 1	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)
Started	4	126	37
Completed	0	0	0
Not completed	4	126	37
Adverse event, serious fatal	-	7	1
Consent withdrawn by subject	1	3	-
Adverse event, non-fatal	2	16	-
'other reason not found above '	-	-	-
Progressive disease	1	99	36
Protocol deviation	-	1	-

Number of subjects in period 1	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Started	36
Completed	0
Not completed	36
Adverse event, serious fatal	1

Consent withdrawn by subject	1
Adverse event, non-fatal	5
'other reason not found above '	5
Progressive disease	24
Protocol deviation	-

Baseline characteristics

Reporting groups[1]	
Reporting group title	Treatment period
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Reporting group values	Treatment period	Total	
Number of subjects	171	171	
Age categorical Units: Subjects			
Age continuous			
Treated set (TS): all patients who received at least one dose of afatinib+ cetuximab following afatinib monotherapy were included in the analysis.			
Units: years			
arithmetic mean	58.1		
standard deviation	± 10.5	-	
Gender categorical Units: Subjects			
Female	119	119	
Male	52	52	

End points

End points reporting groups

Reporting group title	Combination Arm -Afa40+Ctx250

Reporting group description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with Acquired Resistance (AR) to erlotinib or gefitinib)

Afatinib 40 mg + cetuximab 250 mg/m2 (Afa40+Ctx250)

Reporting group title	Combination Arm - Afa40+Ctx500

Reporting group description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with AR to
erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m2 (Afa40+Ctx500)

Reporting group title	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)

Reporting group description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the Maximum Tolerated Dose (MTD) determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

Afatinib 40 mg (Afa40 Mono)

Reporting group title	Sequential Arm - Combination Therapy (Afa40+Ctx500)

Reporting group description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the MTD determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m2 (Afa40+Ctx500)

Primary: The Occurrence of Dose Limiting Toxicity (DLT)

End point title	The Occurrence of Dose Limiting Toxicity (DLT)[1][2]

End point description:

A DLT was defined as an AE or laboratory abnormality that a) related to the study regimen; b) or met any of the following criteria:
• CTCAE Grade 2 or higher decrease in cardiac left ventricular function
• CTCAE Grade 2 diarrhea lasting for 7 or more days, despite appropriate use of standard anti-diarrheal therapy
• CTCAE Grade ≥3 diarrhea despite appropriate use of standard anti-diarrheal therapy for at least 2 days
• CTCAE Grade ≥3 nausea and/or vomiting despite appropriate use of standard anti-emetics for at least 3 days
• CTCAE Grade ≥3 rash despite standard medical management
• CTCAE Grade ≥3 fatigue lasting for more than 7 days
• CTCAE Grade 4 hypomagnesaemia or Grade 3 hypomagnesaemia with clinical significant sequelae
• All other toxicities of CTCAE Grade ≥3 (except alopecia, and allergic reaction) leading to an interruption of afatinib and/or cetuximab for more than 14 days until recovery to baseline or Grade 1, whichever was higher.

End point type	Primary

End point timeframe:

from day 1 treatment until progression or undue toxicity, up to 28 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 evaluated only descriptively. Thus, no statistical hypothesis were tested.

[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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[3]	6[4]		
Units: participants	0	0		

Notes:

[3] - Treatment Set for cohort one. Cohort one is the first treatment cycle that 4 pats recieved afa+ce250

[4] - Treatment Set for cohort one. Cohort one is the first treatment cycle that 6 pats recieved afa+ce500

Statistical analyses

No statistical analyses for this end point

Secondary: Highest CTCAE Grade

End point title	Highest CTCAE Grade

End point description:

Safety of afatinib when administered together with cetuximab as indicated by intensity and incidence of adverse events, graded according to the U.S. National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Version (v) 3.0

Results were based on Treated set (TS). 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[5]	126[6]	37[7]	36[8]
Units: percentage of participants				
number (not applicable)				
Patients with highest CTCAE grade 1	0	0.8	10.8	2.8
Patients with highest CTCAE grade 2	25	26.2	24.3	19.4
Patients with highest CTCAE grade 3	50	54	48.6	52.8
Patients with highest CTCAE grade 4	25	4	5.4	8.3
Patients with highest CTCAE grade 5	0	15.1	10.8	16.7

Notes:

[5] - TS

[6] - TS

[7] - TS
[8] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Patients [N(%)] With Possible Clinically Significant Abnormalities for Selected Laboratory Parameters

End point title	Frequency of Patients [N(%)] With Possible Clinically Significant Abnormalities for Selected Laboratory Parameters

End point description:

Frequency of patients [N(%)] with possible clinically significant abnormalities for haemoglobin - low, white blood cell ct. - low, neutrophils - low, sodium - low, sodium - high, potassium - low, potassium - high, calcium - low, calcium - high, magnesium - low, AST/GOT, SGOT - high, ALT/GPT, SGPT - high, alkaline phosphatase - high

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

99999=Not calculable

End point type	Secondary

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[9]	126[10]	37[11]	36[12]
Units: percentage of participants				
number (not applicable)				
Haemoglobin - low (N=4,124,35,35)	0	12.9	20	2.9
White blood cell ct. - low (N=4,124,35,35)	0	3.2	0	2.9
Neutrophils - low (N=4,124,35,35)	0	4	0	2.9
Sodium - low (N=4,124,35,35)	0	5.6	0	2.9
Sodium - high (N=4,124,35,35)	0	0.8	0	0
Potassium - low (N=4,124,35,35)	0	5.6	2.9	5.7
Potassium - high (N=4,124,35,35)	0	4	0	0
Calcium - low (N=4,124,35,35)	0	6.5	8.6	5.7
Calcium - high (N=4,124,35,35)	0	1.6	0	0
Magnesium - low (N=4,124,34,35)	0	9.7	0	11.4
AST/GOT, SGOT - high (N=4,123,35,35)	0	3.3	0	2.9
ALT/GPT, SGPT - high (N=4,123,35,35)	0	11.4	0	8.6

Alkaline phosphatase - high (N=4,124,35,35)	25	4.8	2.9	5.7
Blood urea nitrogen - high (N=missing, 105, 28,28)	99999	5.7	3.6	0
Creatinine - high (N=4,123,33,35)	0	2.4	0	0
Creatinine clearance - low (N=4,123,33,35)	0	3.3	0	2.9
Bilirubin, total - high (N=4,124,35,35)	0	4.8	2.9	5.7

Notes:

[9] - TS

[10] - TS

[11] - TS

[12] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency (%) of Patients With Adverse Events Leading to Dose Reduction

End point title	Frequency (%) of Patients With Adverse Events Leading to Dose Reduction

End point description:

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[13]	126[14]	37[15]	36[16]
Units: Percentage of participants				
number (not applicable)	25	37.3	13.5	22.2

Notes:

[13] - TS

[14] - TS

[15] - TS

[16] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency (%) of Patients With Adverse Events Leading to Treatment Discontinuation

End point title	Frequency (%) of Patients With Adverse Events Leading to

	Treatment Discontinuation

End point description:

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[17]	126[18]	37[19]	36[20]
Units: percentage of participants				
number (not applicable)	50	23.8	2.7	19.4

Notes:

[17] - TS

[18] - TS

[19] - TS

[20] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency (%) of Patients With Adverse Events Leading to Death

End point title	Frequency (%) of Patients With Adverse Events Leading to Death

End point description:

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[21]	126[22]	37[23]	36[24]
Units: percentage of participants				
number (not applicable)	0	15.1	10.8	16.7

Notes:

[21] - TS

[22] - TS

[23] - TS

[24] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency (%) of Patients With Related Serious Adverse Events

End point title	Frequency (%) of Patients With Related Serious Adverse Events

End point description:

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake intake up to 915 days

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[25]	126[26]	37[27]	36[28]
Units: percentage of participants				
number (not applicable)	0	10.3	5.4	2.8

Notes:

[25] - TS

[26] - TS

[27] - TS

[28] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve (AUC) on Day 15 of Plasma Afatinib for the Combination Arm

End point title	Area Under the Concentration-time Curve (AUC) on Day 15 of Plasma Afatinib for the Combination Arm[29]

End point description:

Area Under the Concentration-time Curve (AUC) of Afatinib in plasma at steady state over a uniform dosing interval tau (15 days) (AUCtau,ss) after oral administration of Afatinib and cetuximab combination therapy.

The pharmacokinetic set (PKS) consisted of all patients, who received at least one dose of afatinib or cetuximab and for whom at least one observation was available.

End point type	Secondary

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[29] - 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: Reporting statistics are only presented for selected arms by the protocol.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[30]	20[31]		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1300 (± 21.8)	935 (± 59.8)		

Notes:

[30] - Pharmacokinetic Set (PKS)

[31] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Afatinib in Plasma for the Combination Arm

End point title	Concentration of Afatinib in Plasma for the Combination Arm[32]

End point description:

Minimum measured concentration of Afatinib in plasma at steady state over 15 day dosing interval (Cmin,ss). Maximum measured concentration of Afatinib in plasma at steady state over 15 day dosing interval (Cmax,ss).

End point type	Secondary

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[32] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[33]	24[34]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cmin,ss,15	33.9 (± 19.6)	24.4 (± 53.7)		
Cmax,ss,15	83.8 (± 19.8)	52.3 (± 73.2)		

Notes:

[33] - PKS

[34] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Peak-trough Fluctuation (PTF)

End point title	Peak-trough Fluctuation (PTF)[35]

End point description:

Peak-trough fluctuation (PTF) of plasma afatinib for the combination arm. PTF = 100*(Cmax-Cmin)/Caverage where Caverage = AUC/time, where time equals 24 hours.

End point type	Secondary

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[35] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[36]	20[37]		
Units: % of average concentration				
geometric mean (geometric coefficient of variation)	91.6 (± 15.9)	73.8 (± 55.2)		

Notes:

[36] - PKS

[37] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2,ss

End point title	t1/2,ss[38]

End point description:

Terminal half-life of Afatinib in plasma at steady state (t1/2,ss)

Data entry = "99999" stands for missing value.

End point type	Secondary

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[38] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[39]	21[40]		
Units: hour				
geometric mean (geometric coefficient	22.4 (± 24.5)	99999 (±		

of variation)	99999)

Notes:

[39] - PKS

[40] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: MRTpo,ss

End point title	MRTpo,ss[41]

End point description:

Mean residence time of Afatinib in the body at steady state after oral administration (MRTpo,ss) for 15 days.

Data entry = "99999" stands for missing value.

End point type	Secondary

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[41] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[42]	20[43]		
Units: hour				
geometric mean (geometric coefficient of variation)	32.6 (± 23.4)	99999 (± 99999)		

Notes:

[42] - PKS

[43] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: CL/F,ss,15

End point title	CL/F,ss,15[44]

End point description:

Apparent clearance of afatinib in plasma at steady state after extravascular multiple dose administration (CL/F,ss)

End point type	Secondary

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[44] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[45]	20[46]		
Units: mL/min				
geometric mean (geometric coefficient of variation)	511 (± 21.8)	713 (± 59.8)		

Notes:

[45] - PKS

[46] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Vz/F,ss

End point title	Vz/F,ss[47]

End point description:

Apparent volume of distribution during the terminal phase λz at steady state following extravascular administration (Vz/F,ss) for 15 days

Data entry = "99999" stands for missing value.

End point type	Secondary

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[47] - 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: Reporting statistics are only presented for selected arms by the protocol.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[48]	21[49]		
Units: Liter				
geometric mean (geometric coefficient of variation)	991 (± 44.8)	99999 (± 99999)		

Notes:

[48] - PKS

[49] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Plasma Concentrations of Afatinib for the Combination Arm

End point title	Predose Plasma Concentrations of Afatinib for the Combination Arm[50]

End point description:

Predose plasma concentrations (Cpre,ss) of Afatinib at Course 1, Visit 2, 3, 4 and 5, at Course 2, Visit 1 and 2 and at Course 3, Visit 1.

Data entry = "99999" stands for missing values.

End point type	Secondary

End point timeframe:

Up to 57 days

Notes:

[50] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[51]	28[52]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cpre,ss,8 (N=4,25)	33.2 (± 38.3)	28.3 (± 62.3)		
Cpre,ss,15 (N=3,28)	33.9 (± 19.6)	27.1 (± 51.3)		
Cpre,ss,16 (N=3,0)	36.4 (± 15.8)	99999 (± 99999)		
Cpre,ss,22 (N=3,21)	33.5 (± 1.3)	28.3 (± 64.3)		
Cpre,ss,29 (N=3,20)	33.4 (± 21.8)	27.7 (± 56.8)		
Cpre,ss,43 (N=3,19)	33.5 (± 14.9)	26 (± 98.4)		
Cpre,ss,57 (N=3,0)	36.6 (± 4.51)	99999 (± 99999)		

Notes:

[51] - PKS

[52] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (CR, PR and Stable Disease (SD) Determined by RECIST v1.1)

End point title	Disease Control (CR, PR and Stable Disease (SD) Determined by RECIST v1.1)

End point description:

Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Progressive Disease (PD), At least a 20% increase in the sum of the longest diameter of target lesions or the appearance of new lesion(s); Stable Disease (SD), Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Disease control = CR + PR + SD.
Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section.

End point type	Secondary

End point timeframe:

up to 116 weeks

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[53]	126[54]	37[55]	36[56]
Units: percentage of participants				
number (confidence interval 95%)	75 (19.4 to 99.4)	70.6 (61.9 to 78.4)	56.8 (39.5 to 72.9)	50 (32.9 to 67.1)

Notes:

[53] - Treated set.

[54] - TS

[55] - TS

[56] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Tumor Response (Complete Response [CR] and Partial Response [PR])

End point title	Objective Tumor Response (Complete Response [CR] and Partial Response [PR])

End point description:

Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Progressive Disease (PD), At least a 20% increase in the sum of the longest diameter of target lesions or the appearance of new lesion(s); Stable Disease (SD), Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Objective tumor response = CR + PR.

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

up to 116 weeks

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[57]	126[58]	37[59]	36[60]
Units: Percentage of participants				
number (confidence interval 95%)	0 (0 to 60.2)	28.6 (20.9 to 37.3)	5.4 (0.7 to 18.2)	11.1 (3.1 to 26.1)

Notes:
[57] - TS
[58] - TS
[59] - TS
[60] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (According to RECIST v1.1)

End point title	Duration of Objective Response (According to RECIST v1.1)

End point description:

Duration of objective response was measured from the time measurements criteria were met for CR/PR (whichever was first recorded) until the first date that recurrent or PD was objectively documented (taking as reference for PD the smallest measurements recorded since treatment started).

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

up to 116 weeks

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[61]	126[62]	37[63]	36[64]
Units: months				
arithmetic mean (standard deviation)	0 (± 0)	9 (± 6.94)	3.9 (± 0.07)	5.8 (± 2.36)

Notes:
[61] - TS
[62] - TS
[63] - TS
[64] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease Control (According to RECIST v1.1)

End point title	Duration of Disease Control (According to RECIST v1.1)

End point description:

Duration of disease control was defined as the time from the start of treatment to the time of progression or death (whichever occurred first), among patients with evidence SD, PR or CR.

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to

treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

up to 116 weeks

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[65]	126[66]	37[67]	36[68]
Units: months				
arithmetic mean (standard deviation)	7.4 (± 5.54)	7.4 (± 5.45)	4.9 (± 3.08)	5.9 (± 4.51)

Notes:

[65] - TS

[66] - TS

[67] - TS

[68] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Time

End point title	Progression-Free Survival (PFS) Time

End point description:

Progression-Free Survival was defined as the duration of time from start of treatment until the day of objective tumour progression confirmed by tumour imaging (PD according to RECIST 1.1) or death.

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

End point type	Secondary

End point timeframe:

up to 116 weeks

End point values	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)	Sequential Arm - Combination Therapy (Afa40+Ctx500)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[69]	126[70]	37[71]	36[72]
Units: months				
median (confidence interval 95%)	4.2 (1.4 to 13.8)	4.6 (4.2 to 6.3)	2.7 (1.1 to 3.7)	2.9 (1.8 to 4.8)

Notes:
[69] - TS
[70] - TS
[71] - TS
[72] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 915 days

Adverse event reporting additional description:

32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Combination Arm -Afa40+Ctx250

Reporting group description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with Acquired Resistance (AR) to erlotinib or gefitinib)

Afatinib 40 mg + cetuximab 250 mg/m2 (Afa40+Ctx250)

Reporting group title	Combination Arm - Afa40+Ctx500

Reporting group description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with AR to
erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m2 (Afa40+Ctx500)

Reporting group title	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)

Reporting group description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the Maximum Tolerated Dose (MTD) determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

Afatinib 40 mg (Afa40 Mono)

Reporting group title	Sequential Arm - Combination Therapy (Afa40+Ctx500)

Reporting group description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the MTD determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m2 (Afa40+Ctx500)

Serious adverse events	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	63 / 126 (50.00%)	12 / 37 (32.43%)
number of deaths (all causes)	0	38	11
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	2 / 4 (50.00%)	6 / 126 (4.76%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 6	0 / 2
Metastasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm progression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Pain management			

subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgery			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 126 (0.79%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	3 / 126 (2.38%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mucosal inflammation			

subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	3 / 126 (2.38%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	14 / 126 (11.11%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	2 / 16	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 3	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	4 / 126 (3.17%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Lung infiltration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	6 / 126 (4.76%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hallucination			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Biopsy lung			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 4 (0.00%)	4 / 126 (3.17%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug withdrawal headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic cerebral infarction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Diplopia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	4 / 126 (3.17%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	2 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	4 / 126 (3.17%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	4 / 6	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	6 / 126 (4.76%)	3 / 37 (8.11%)
occurrences causally related to treatment / all	0 / 0	3 / 7	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Steroid withdrawal syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cystitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 126 (2.38%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	5 / 126 (3.97%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	2 / 5	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Sequential Arm -		

	Combination Therapy (Afa40+Ctx500)		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 36 (41.67%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Metastasis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm progression			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Pain management			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgery			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

General physical health deterioration			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal			

disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infiltration			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Biopsy lung			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural			

complications			
Fall			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Convulsion			

subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug withdrawal headache				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Embolic cerebral infarction				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal distension			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Dysphagia				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				

subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Steroid withdrawal syndrome			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Spinal pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infectious pleural effusion			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningitis aseptic			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Streptococcal infection				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	0 / 36 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				

subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 36 (2.78%)		
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 %

Non-serious adverse events	Combination Arm - Afa40+Ctx250	Combination Arm - Afa40+Ctx500	Sequential Arm - Afatinib Monotherapy (Afa40 Mono)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	126 / 126 (100.00%)	36 / 37 (97.30%)
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 4 (25.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	7 / 126 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	8	0
Hot flush			
subjects affected / exposed	1 / 4 (25.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Intra-abdominal haematoma			
subjects affected / exposed	1 / 4 (25.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	7 / 126 (5.56%)	1 / 37 (2.70%)
occurrences (all)	0	7	1
Chest discomfort			
subjects affected / exposed	0 / 4 (0.00%)	4 / 126 (3.17%)	0 / 37 (0.00%)
occurrences (all)	0	4	0
Chest pain			

subjects affected / exposed	2 / 4 (50.00%)	6 / 126 (4.76%)	1 / 37 (2.70%)
occurrences (all)	3	8	1
Chills			
subjects affected / exposed	0 / 4 (0.00%)	14 / 126 (11.11%)	2 / 37 (5.41%)
occurrences (all)	0	14	2
Face oedema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	3 / 4 (75.00%)	69 / 126 (54.76%)	16 / 37 (43.24%)
occurrences (all)	4	95	16
Feeling cold			
subjects affected / exposed	0 / 4 (0.00%)	7 / 126 (5.56%)	1 / 37 (2.70%)
occurrences (all)	0	7	1
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	32 / 126 (25.40%)	4 / 37 (10.81%)
occurrences (all)	0	58	5
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	12 / 126 (9.52%)	3 / 37 (8.11%)
occurrences (all)	0	12	4
Pain			
subjects affected / exposed	1 / 4 (25.00%)	14 / 126 (11.11%)	1 / 37 (2.70%)
occurrences (all)	1	14	1
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	21 / 126 (16.67%)	8 / 37 (21.62%)
occurrences (all)	0	24	9
Xerosis			
subjects affected / exposed	0 / 4 (0.00%)	53 / 126 (42.06%)	0 / 37 (0.00%)
occurrences (all)	0	85	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	9 / 126 (7.14%)	0 / 37 (0.00%)
occurrences (all)	0	9	0
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 4 (50.00%)	41 / 126 (32.54%)	10 / 37 (27.03%)
occurrences (all)	2	68	10
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	10 / 126 (7.94%)	3 / 37 (8.11%)
occurrences (all)	0	12	3
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	33 / 126 (26.19%)	7 / 37 (18.92%)
occurrences (all)	1	45	7
Epistaxis			
subjects affected / exposed	2 / 4 (50.00%)	25 / 126 (19.84%)	5 / 37 (13.51%)
occurrences (all)	2	35	7
Hiccups			
subjects affected / exposed	1 / 4 (25.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	2 / 37 (5.41%)
occurrences (all)	0	2	3
Nasal dryness			
subjects affected / exposed	0 / 4 (0.00%)	3 / 126 (2.38%)	3 / 37 (8.11%)
occurrences (all)	0	3	3
Oropharyngeal pain			
subjects affected / exposed	1 / 4 (25.00%)	13 / 126 (10.32%)	2 / 37 (5.41%)
occurrences (all)	1	13	2
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Pulmonary embolism			

subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	3 / 37 (8.11%)
occurrences (all)	0	2	3
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	15 / 126 (11.90%)	4 / 37 (10.81%)
occurrences (all)	0	17	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Depression			
subjects affected / exposed	0 / 4 (0.00%)	5 / 126 (3.97%)	2 / 37 (5.41%)
occurrences (all)	0	5	2
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	11 / 126 (8.73%)	5 / 37 (13.51%)
occurrences (all)	0	11	5
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	3 / 126 (2.38%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Weight decreased			
subjects affected / exposed	1 / 4 (25.00%)	10 / 126 (7.94%)	5 / 37 (13.51%)
occurrences (all)	1	10	5
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	17 / 126 (13.49%)	6 / 37 (16.22%)
occurrences (all)	0	19	6
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	10 / 126 (7.94%)	0 / 37 (0.00%)
occurrences (all)	0	10	0
Headache			
subjects affected / exposed	1 / 4 (25.00%)	53 / 126 (42.06%)	10 / 37 (27.03%)
occurrences (all)	1	68	10
Memory impairment			

subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)	11 / 126 (8.73%)	0 / 37 (0.00%)
occurrences (all)	0	16	0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences (all)	1	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	7 / 126 (5.56%)	1 / 37 (2.70%)
occurrences (all)	1	8	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	5 / 126 (3.97%)	2 / 37 (5.41%)
occurrences (all)	0	5	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences (all)	1	2	0
Ear pruritus			
subjects affected / exposed	1 / 4 (25.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	13 / 126 (10.32%)	2 / 37 (5.41%)
occurrences (all)	0	15	2
Eye irritation			
subjects affected / exposed	0 / 4 (0.00%)	9 / 126 (7.14%)	1 / 37 (2.70%)
occurrences (all)	0	10	1
Lacrimation increased			
subjects affected / exposed	0 / 4 (0.00%)	9 / 126 (7.14%)	0 / 37 (0.00%)
occurrences (all)	0	9	0
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)	8 / 126 (6.35%)	2 / 37 (5.41%)
occurrences (all)	0	8	2
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	10 / 126 (7.94%)	0 / 37 (0.00%)
occurrences (all)	0	11	0
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	4 / 126 (3.17%)	0 / 37 (0.00%)
occurrences (all)	1	4	0
Aphthous stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 126 (1.59%)	2 / 37 (5.41%)
occurrences (all)	1	2	2
Cheilitis			
subjects affected / exposed	0 / 4 (0.00%)	13 / 126 (10.32%)	3 / 37 (8.11%)
occurrences (all)	0	15	3
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	32 / 126 (25.40%)	3 / 37 (8.11%)
occurrences (all)	1	46	3
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	92 / 126 (73.02%)	27 / 37 (72.97%)
occurrences (all)	3	244	34
Dry mouth			
subjects affected / exposed	1 / 4 (25.00%)	14 / 126 (11.11%)	0 / 37 (0.00%)
occurrences (all)	1	14	0
Glossodynia			
subjects affected / exposed	1 / 4 (25.00%)	5 / 126 (3.97%)	1 / 37 (2.70%)
occurrences (all)	1	7	1
Haemorrhoids			
subjects affected / exposed	0 / 4 (0.00%)	4 / 126 (3.17%)	1 / 37 (2.70%)
occurrences (all)	0	4	1
Large intestinal haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Lip dry			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	64 / 126 (50.79%)	11 / 37 (29.73%)
occurrences (all)	4	116	12

Oral pain			
subjects affected / exposed	0 / 4 (0.00%)	8 / 126 (6.35%)	0 / 37 (0.00%)
occurrences (all)	0	8	0
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	16 / 126 (12.70%)	4 / 37 (10.81%)
occurrences (all)	1	23	4
Tongue ulceration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	51 / 126 (40.48%)	7 / 37 (18.92%)
occurrences (all)	1	89	9
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 4 (25.00%)	16 / 126 (12.70%)	2 / 37 (5.41%)
occurrences (all)	1	16	2
Dermatitis acneiform			
subjects affected / exposed	1 / 4 (25.00%)	22 / 126 (17.46%)	7 / 37 (18.92%)
occurrences (all)	1	30	8
Dry skin			
subjects affected / exposed	2 / 4 (50.00%)	39 / 126 (30.95%)	5 / 37 (13.51%)
occurrences (all)	2	46	5
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	14 / 126 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	15	0
Exfoliative rash			
subjects affected / exposed	1 / 4 (25.00%)	3 / 126 (2.38%)	1 / 37 (2.70%)
occurrences (all)	1	4	1
Hair growth abnormal			
subjects affected / exposed	0 / 4 (0.00%)	3 / 126 (2.38%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Hirsutism			
subjects affected / exposed	0 / 4 (0.00%)	17 / 126 (13.49%)	0 / 37 (0.00%)
occurrences (all)	0	21	0
Hyperhidrosis			

subjects affected / exposed	1 / 4 (25.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Pain of skin			
subjects affected / exposed	0 / 4 (0.00%)	10 / 126 (7.94%)	0 / 37 (0.00%)
occurrences (all)	0	11	0
Photosensitivity reaction			
subjects affected / exposed	0 / 4 (0.00%)	8 / 126 (6.35%)	0 / 37 (0.00%)
occurrences (all)	0	8	0
Pruritus			
subjects affected / exposed	1 / 4 (25.00%)	50 / 126 (39.68%)	1 / 37 (2.70%)
occurrences (all)	1	66	1
Rash			
subjects affected / exposed	1 / 4 (25.00%)	106 / 126 (84.13%)	14 / 37 (37.84%)
occurrences (all)	1	243	19
Rash erythematous			
subjects affected / exposed	2 / 4 (50.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences (all)	2	2	0
Rash macular			
subjects affected / exposed	2 / 4 (50.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	2	1	0
Skin fissures			
subjects affected / exposed	1 / 4 (25.00%)	78 / 126 (61.90%)	5 / 37 (13.51%)
occurrences (all)	1	130	5
Skin hypertrophy			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Skin irritation			
subjects affected / exposed	0 / 4 (0.00%)	7 / 126 (5.56%)	0 / 37 (0.00%)
occurrences (all)	0	7	0
Skin reaction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 4 (25.00%)	9 / 126 (7.14%)	0 / 37 (0.00%)
occurrences (all)	1	11	0

Haemoglobinuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	17 / 126 (13.49%)	1 / 37 (2.70%)
occurrences (all)	0	20	1
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	27 / 126 (21.43%)	9 / 37 (24.32%)
occurrences (all)	3	31	10
Flank pain			
subjects affected / exposed	0 / 4 (0.00%)	5 / 126 (3.97%)	2 / 37 (5.41%)
occurrences (all)	0	7	2
Muscle spasms			
subjects affected / exposed	1 / 4 (25.00%)	14 / 126 (11.11%)	3 / 37 (8.11%)
occurrences (all)	1	20	3
Musculoskeletal pain			
subjects affected / exposed	1 / 4 (25.00%)	11 / 126 (8.73%)	2 / 37 (5.41%)
occurrences (all)	1	11	2
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	12 / 126 (9.52%)	1 / 37 (2.70%)
occurrences (all)	0	12	1
Pain in extremity			
subjects affected / exposed	1 / 4 (25.00%)	12 / 126 (9.52%)	1 / 37 (2.70%)
occurrences (all)	1	13	1
Pain in jaw			
subjects affected / exposed	1 / 4 (25.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Candida infection			
subjects affected / exposed	0 / 4 (0.00%)	3 / 126 (2.38%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Eye infection			

subjects affected / exposed	0 / 4 (0.00%)	4 / 126 (3.17%)	0 / 37 (0.00%)
occurrences (all)	0	4	0
Eyelid infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Impetigo			
subjects affected / exposed	0 / 4 (0.00%)	12 / 126 (9.52%)	0 / 37 (0.00%)
occurrences (all)	0	14	0
Localised infection			
subjects affected / exposed	0 / 4 (0.00%)	5 / 126 (3.97%)	0 / 37 (0.00%)
occurrences (all)	0	6	0
Nail infection			
subjects affected / exposed	0 / 4 (0.00%)	5 / 126 (3.97%)	2 / 37 (5.41%)
occurrences (all)	0	7	2
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	9 / 126 (7.14%)	1 / 37 (2.70%)
occurrences (all)	0	9	1
Paronychia			
subjects affected / exposed	2 / 4 (50.00%)	62 / 126 (49.21%)	6 / 37 (16.22%)
occurrences (all)	2	87	6
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	6 / 126 (4.76%)	2 / 37 (5.41%)
occurrences (all)	0	6	2
Skin infection			
subjects affected / exposed	0 / 4 (0.00%)	6 / 126 (4.76%)	0 / 37 (0.00%)
occurrences (all)	0	8	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	6 / 126 (4.76%)	3 / 37 (8.11%)
occurrences (all)	0	7	3
Urinary tract infection			

subjects affected / exposed	0 / 4 (0.00%)	11 / 126 (8.73%)	5 / 37 (13.51%)
occurrences (all)	0	14	5
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	2 / 4 (50.00%)	28 / 126 (22.22%)	7 / 37 (18.92%)
occurrences (all)	3	31	7
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	2 / 126 (1.59%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Hypercalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 126 (0.79%)	0 / 37 (0.00%)
occurrences (all)	3	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 126 (2.38%)	0 / 37 (0.00%)
occurrences (all)	0	6	0
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	9 / 126 (7.14%)	0 / 37 (0.00%)
occurrences (all)	0	16	0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	23 / 126 (18.25%)	3 / 37 (8.11%)
occurrences (all)	0	33	3
Hypomagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	37 / 126 (29.37%)	3 / 37 (8.11%)
occurrences (all)	2	64	3
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	5 / 126 (3.97%)	2 / 37 (5.41%)
occurrences (all)	0	5	2
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 126 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Sequential Arm - Combination Therapy (Afa40+Ctx500)		

Total subjects affected by non-serious adverse events subjects affected / exposed	36 / 36 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Intra-abdominal haematoma			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Chest discomfort			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Face oedema			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	14 / 36 (38.89%)		
occurrences (all)	14		
Feeling cold			

subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	6		
Xerosis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 36 (30.56%)		
occurrences (all)	11		
Dysphonia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	9		
Epistaxis			

subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Hiccups			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Hypoxia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Nasal dryness			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		

Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	4		
Weight decreased			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	8		
Dysgeusia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	10 / 36 (27.78%)		
occurrences (all)	11		
Memory impairment			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Ear pruritus			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Eye irritation			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Aphthous stomatitis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Cheilitis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	7		
Diarrhoea			

subjects affected / exposed	13 / 36 (36.11%)		
occurrences (all)	18		
Dry mouth			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Glossodynia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Large intestinal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Lip dry			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	12 / 36 (33.33%)		
occurrences (all)	15		
Oral pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Tongue ulceration			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		

Dermatitis acneiform			
subjects affected / exposed	9 / 36 (25.00%)		
occurrences (all)	9		
Dry skin			
subjects affected / exposed	13 / 36 (36.11%)		
occurrences (all)	13		
Erythema			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Exfoliative rash			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Hair growth abnormal			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Hirsutism			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Photosensitivity reaction			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	17 / 36 (47.22%)		
occurrences (all)	40		
Rash erythematous			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		

Rash macular			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Skin fissures			
subjects affected / exposed	16 / 36 (44.44%)		
occurrences (all)	17		
Skin hypertrophy			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Skin irritation			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Skin reaction			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Haemoglobinuria			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	6		
Back pain			
subjects affected / exposed	10 / 36 (27.78%)		
occurrences (all)	10		
Flank pain			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Musculoskeletal pain			

subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Pain in jaw			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Candida infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Eye infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Eyelid infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Fungal infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Impetigo			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Localised infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Nail infection			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		

Nasopharyngitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	12 / 36 (33.33%)		
occurrences (all)	13		
Pneumonia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	8 / 36 (22.22%)		
occurrences (all)	8		
Dehydration			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		
Hypercalcaemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Hyperglycaemia			

subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Hypomagnesaemia			
subjects affected / exposed	11 / 36 (30.56%)		
occurrences (all)	14		
Hyponatraemia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Hypophosphataemia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2010	• An exclusion criterion was added, whereby patients who required treatment with any prohibited medication were to be excluded from study participation. This change resulted from a Phase I study (1200.79) of the effects of ritonavir, a potent P-gp inhibitor, on the single-dose PK of 20 mg afatinib, a P-gp substrate, which indicated that, although the median tmax and terminal half-life of afatinib were not affected, the rate and extent of afatinib absorption was increased by co-treatment with ritonavir. • Potent P-gp inhibitors or inducers were identified and added to the list of prohibited medications based on results of Study 1200.79.
03 August 2010	• The protocol was amended to: • Extend the screening period, skip the unnecessary physical examination and safety laboratory tests at study entry, mandate the availability of safety laboratory test results prior to cetuximab infusion if clinically indicated, to clarify the CT scan field and the schedule, and to stress on a confirmation scan in case of response • Broaden the tumour material used for EGFR mutation test • Redefine DLT for hypomagnesaemia • Specify the contraception duration • Mandate the availability of safety laboratory test results when clinically indicated • Clarify the administration of cetuximab • Allow more flexibility in dose modification and management of AEs more • Allow directing sequencing for EGFR mutation test
21 January 2011	The protocol was amended to: • Increase the combination arm to better assess the safety as well as the preliminary anti-tumour activity of the combination therapy (afatinib and cetuximab) in EGFR T790M+ and EGFR T790M- NSCLC following the observation of confirmed objective responses in the currently enrolled patients. • Clarify the timing of biopsy after development of acquired resistance, to include blood EGFR plasma DNA analysis and to clarify the PK sample requirement for the enlarged combination arm • Shorten the erlotinib/gefitinib washout period during screening and reduce the surgery time restriction prior to study treatment • Add plasma EGFR mutation analysis • Modify the criterion for removal of patients from the study, patients with radiographic disease progression while achieving clinical benefit may remain on study and receive palliative therapy
14 September 2011	• The protocol was amended to: • Further evaluate safety and preliminary efficacy in patients with EGFR mutation positive NSCLC and acquired resistance to erlotinib/gefitinib. • Evaluate safety and preliminary efficacy in patients with EGFR mutation positive NSCLC with acquired resistance to afatinib (BIBW 2992). • Introduce Grade 2 intolerable rash and paronychia as dose reduction criteria; to revise dose modification scheme. • Add progression-free survival, duration of disease control and duration of objective response as secondary endpoints. • Add protocol clarifications as indicated (e.g. patients with hypersensitivity reaction to the drug may discontinue the causal drug only; patients with disease progression may continue either afatinib or both drugs if established benefit and no other preferable treatment options, DLT reporting time frame). • Introduce optional rebiopsy and test serum EGFR mutation upon disease progression.

08 November 2012	• The protocol was amended to: • Modify the timing for the primary analysis to when the last patient in the combination arm had started treatment with afatinib plus cetuximab for 6 months, and when at least 80% of patients on the sequential arm had either withdrawn from the trial, progressed on the combination of afatinib plus cetuximab, or initiated afatinib and cetuximab combination therapy for at least 6 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported