Clinical trial results:
A randomized, open-label Phase II study of BIBW 2992 versus cetuximab (Erbitux®) in patients with metastatic or recurrent Head and Neck Squamous Cell Carcinoma (HNSCC) after failure of platinum-containing therapy with a cross-over period for progressing patients.

Summary

EudraCT number	2008-007097-38
Trial protocol	BE ES FR
Global end of trial date	26 July 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	16 July 2015

Trial information

Trial identification

Sponsor protocol code	1200.28

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00514943
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173 , Ingelheim am Rhein , Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG , + 1 800 243 0127 , clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG , + 1 800 243 0127 , 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 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy and safety of afatinib compared with cetuximab (Erbitux®) in patients with metastatic or recurrent head and neck cancer after failure of platinum-containing therapy.

The primary endpoint is Tumor Shrinkage before cross-over (Stage 1) of the trial: maximum decrease in the sum of the longest diameters of the target lesions (according to RECIST) compared to baseline, with baseline defined as the sum of tumor measurement of the target lesion longest diameters measured before the patient start the first administration of the randomized treatment.

Protection of trial subjects:

Only subjects who were considered eligible by investigators based on the protocol-specific inclusion and 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.
For patients who experienced CTCAE (version 3.0) grade ≥3 drug-related adverse events (AEs) despite appropriate supportive care, or grade ≥2 AEs, a dose reduction scheme was followed after a treatment pause to allow the AE to decrease to CTCAE grade ≤1 (within a maximum of 14 days). Further dose reduction instructions related to diarrhea, nausea and vomiting, and rash, respectively were provided.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	146
EEA total number of subjects	82

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)	104
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strict inclusion/exclusion criteria. Thus, out of 146 screened patients, 22 patients failed screening.

Period 1

Period 1 title	Stage 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1

Arm description:

Patients were randomized to Afatinib monotherapy 50mg once daily (q.d.) in Stage 1 and if the patients had disease progression or
intolerable AEs were given the option to cross over to Cetuximab 250 mg/m2 given as 400mg/m2 once in the first week (load) followed by 250mg/m2
weekly thereafter in Stage 2.

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

Dosage and administration details:

50 mg Once daily Oral as tablet or dispersion via gastric feeding tube

Arm title	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1

Arm description:

Patients were randomized to Cetuximab 250 mg/m2 received 400mg/m2 once in the first week followed by 250 mg/m2 weekly
thereafter in Stage 1 and if the patients had disease progression or intolerable AEs were given the option to cross over to Afatinib 50 mg once daily
(q.d.) for Stage 2

Arm type	Treatment sequence
Investigational medicinal product name	Cetuximab (Erbitux®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m2 in the first week given over 120 minutes; 250 mg/m2 weekly thereafter given over 60 minutes. Intravenous.

Number of subjects in period 1[1]	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1
Started	62	62
Completed	32	36
Not completed	30	26
Adverse event, serious fatal	6	3
Adverse event, non-fatal	10	3
Other	1	7
Patient refused to continue study meds	8	3
Progressive disease	4	8
Not treated	1	2

Notes:

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

Period 2

Period 2 title	Stage 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2

Arm description:

Patients were randomized to Afatinib monotherapy 50mg once daily (q.d.) in Stage 1 and if the patients had disease progression or
intolerable AEs were crossed over to Cetuximab 250 mg/m2 given as 400mg/m2 once in the first week (load) followed by 250mg/m2
weekly thereafter in Stage 2.

Arm type	Treatment sequence
Investigational medicinal product name	Cetuximab (Erbitux®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg Once daily Oral as tablet or dispersion via gastric feeding tube

Arm title	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2

Arm description:

Patients were randomized to Cetuximab 250 mg/m2 received 400mg/m2 once in the first week followed by 250 mg/m2 weekly
thereafter in Stage 1 and if the patients had disease progression or intolerable AEs were crossed over to Afatinib 50 mg once daily
(q.d.) for Stage 2

Arm type	Treatment sequence

Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m2 in the first week given over 120 minutes; 250 mg/m2 weekly thereafter given over 60 minutes. Intravenous.

Number of subjects in period 2	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2
Started	32	36
Completed	0	0
Not completed	32	36
Adverse event, serious fatal	1	5
Adverse event, non-fatal	2	5
'Refused to continue medication '	2	-
Progressive disease	27	24
'Reasons other than already stated '	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1
Reporting group description:	
Patients were randomized to Afatinib monotherapy 50mg once daily (q.d.) in Stage 1 and if the patients had disease progression or intolerable AEs were given the option to cross over to Cetuximab 250 mg/m2 given as 400mg/m2 once in the first week (load) followed by 250mg/m2 weekly thereafter in Stage 2.	
Reporting group title	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1
Reporting group description:	
Patients were randomized to Cetuximab 250 mg/m2 received 400mg/m2 once in the first week followed by 250 mg/m2 weekly thereafter in Stage 1 and if the patients had disease progression or intolerable AEs were given the option to cross over to Afatinib 50 mg once daily (q.d.) for Stage 2	

Reporting group values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1	Total
Number of subjects	62	62	124
Age categorical Units: Subjects			
Adults (18-64 years)	45	46	91
From 65-84 years	17	16	33
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	57.9	58.8	
standard deviation	± 9.4	± 8.7	-
Gender categorical Units: Subjects			
Female	7	10	17
Male	55	52	107
Prior chemotherapies (CT)for recurrent/metastatic disease (R/M) Units: Subjects			
Yes	42	41	83
No	20	21	41
Baseline sum of longest diameters (SLD) of target lesions by investigator assessments			
Baseline measures were available for only 61 patients in the Afatinib/Cetuximab group and only 60 patients in the Cetuximab/Afatinib group			
Units: millimeter(s)			
arithmetic mean	71.4	65.4	
standard deviation	± 44.6	± 44.2	-

End points

End points reporting groups

Reporting group title	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1

Reporting group description:

Patients were randomized to Afatinib monotherapy 50mg once daily (q.d.) in Stage 1 and if the patients had disease progression or
intolerable AEs were given the option to cross over to Cetuximab 250 mg/m2 given as 400mg/m2 once in the first week (load) followed by 250mg/m2
weekly thereafter in Stage 2.

Reporting group title	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1

Reporting group description:

Patients were randomized to Cetuximab 250 mg/m2 received 400mg/m2 once in the first week followed by 250 mg/m2 weekly
thereafter in Stage 1 and if the patients had disease progression or intolerable AEs were given the option to cross over to Afatinib 50 mg once daily
(q.d.) for Stage 2

Reporting group title	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2

Reporting group description:

Patients were randomized to Afatinib monotherapy 50mg once daily (q.d.) in Stage 1 and if the patients had disease progression or
intolerable AEs were crossed over to Cetuximab 250 mg/m2 given as 400mg/m2 once in the first week (load) followed by 250mg/m2
weekly thereafter in Stage 2.

Reporting group title	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2

Reporting group description:

Patients were randomized to Cetuximab 250 mg/m2 received 400mg/m2 once in the first week followed by 250 mg/m2 weekly
thereafter in Stage 1 and if the patients had disease progression or intolerable AEs were crossed over to Afatinib 50 mg once daily
(q.d.) for Stage 2

Subject analysis set title	Afatinib 40 mg - Stage 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients were randomised to receive Afatinib 50 mg once daily (q.d.) in Stage 1, and had sequential dose reduction to 40 mg in stage 1.

This is not a defined treatment group, this is for patients who required dose reduction in Afatinib.

This group is only applicable for the pharmaco-kinetic endpoints.

Primary: Tumor Shrinkage Before Crossover (Stage 1) of the Trial as Per Investigator Assessment

End point title	Tumor Shrinkage Before Crossover (Stage 1) of the Trial as Per Investigator Assessment

End point description:

Tumor shrinkage before crossover was defined as the change from baseline in the smallest post-randomisation sum of the longest diameters of target lesions (SLD), calculated as the smallest SLD after randomisation but before crossover minus SLD at baseline. Baseline was the SLD measured before randomisation. A negative value means the smallest post-randomisation SLD was smaller than baseline (decreased since baseline); a positive value means tumor size increased since baseline.

Mean calculated is the Adjusted mean. Adjusted mean is obtained from fitting an ANCOVA model including treatment,
stratification factor prior chemotherapy for recurrent/metastatic disease and the baseline sum of longest distance of target lesions as covariates.

Randomised set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not. However, patients without baseline or post-baseline tumor measurements were excluded.

End point type	Primary

End point timeframe:

From randomization until start of Stage 2 treatment, or within 28 days after the termination of Stage 1. Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[1]	55[2]		
Units: millimeter(s)				
least squares mean (standard error)	-3.86 (± 3.62)	-2.37 (± 3.47)		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Tumor Shrinkage Before Crossover (Stage 1)

Statistical analysis description:

Statistical Analysis for Tumor Shrinkage Before Crossover (Stage 1) of the Trial as Per Investigator Assessment. Receipt of prior chemotherapy for recurrent/metastatic disease and the baseline sum of longest distance for target lesions are covariates. Mean difference calculated is the adjusted mean difference (Afatinib - Cetuximab).

Comparison groups	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1 v Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7606 [3]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.188
upper limit	8.202

Notes:

[3] - P-value obtained from fitting an ANCOVA model including treatment, stratification factor prior chemotherapy for recurrent/metastatic disease and the baseline sum of longest distance of target lesions.

Secondary: Tumor Shrinkage After Crossover (Stage 2) as Per Investigator Assessments

End point title	Tumor Shrinkage After Crossover (Stage 2) as Per Investigator Assessments

End point description:

Tumor shrinkage after crossover was defined as the change from baseline in the smallest post-crossover sum of the longest diameters of target lesions (SLD), calculated as the smallest SLD after crossover minus SLD at baseline. Baseline was the SLD measured at the time of crossover, or the closest measurement before the patient started stage 2 treatment. A negative value means the smallest post-crossover SLD was smaller than baseline (decreased after crossover), a positive value means tumor size

increased after crossover.

Patients treated in stage 2: This analysis set included all patients who received treatment: 32 pateints in the cetuximab arm and 36 patients in the afatinib.

End point type	Secondary

End point timeframe:

From baseline assessed prior to first dose of Stage 2 study medication to 28 days after termination of Stage 2 treatment. For stage 2 first assessment was done 28 days (4 weeks) after treatment then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[4]	29[5]		
Units: millimeter(s)				
arithmetic mean (standard deviation)	16 (± 30)	2 (± 15)		

Notes:

[4] - Patients treated in stage 2

[5] - Patients treated in stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Per Investigator Assessment for Stage 1 (as Confirmed Disease Control (Clinical Benefit) and Objective Response Are Simply Categories of RECIST Assessment).

End point title	Best RECIST Assessment as Per Investigator Assessment for Stage 1 (as Confirmed Disease Control (Clinical Benefit) and Objective Response Are Simply Categories of RECIST Assessment).

End point description:

Best RECIST Assessment is defined as confirmed Disease control (complete response (CR), partial response (PR) and Stable disease (SD)), Objective response (complete response (CR) or partial response
(PR)) assessed by the investigator according to the RECIST 1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined from randomization until patient started Stage 2 or within 28 days after termination of Stage 1 treatment. Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[6]	62[7]		
Units: Number of participants				
Disease control (CR, PR, SD)	31	35		

Objective response (CR, PR)	10	4		
Complete response (CR)	0	2		
Partial response (PR)	10	2		
Stable disease (SD)	21	31		
Progressive disease (PD)	16	19		
Not evaluable	5	1		
Missing	10	7		

Notes:

[6] - RS

[7] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Per ICR for Stage 1 (as Confirmed Disease Control (Clinical Benefit) and Objective Response Are Simply Categories of RECIST Assessment)

End point title	Best RECIST Assessment as Per ICR for Stage 1 (as Confirmed Disease Control (Clinical Benefit) and Objective Response Are Simply Categories of RECIST Assessment)

End point description:

Best RECIST Assessment is defined as confirmed Disease control (complete response (CR), partial response (PR) and Stable disease
(SD)), Best objective response (complete response (CR) or partial response (PR)) as assessed by the independent central review (ICR)
according to the RECIST 1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined from randomization until patient started Stage 2 or within 28 days after termination of Stage 1 treatment. Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[8]	62[9]		
Units: Number of participants				
Disease control (CR, PR, SD)	29	30		
Objective response (CR,PR)	5	6		
Complete response (CR)	0	0		
Partial response (PR)	5	6		
Stable disease (SD)	24	24		
Progressive disease (PD)	21	21		
Not evaluable	2	3		
Missing	10	8		

Notes:

[8] - RS

[9] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Per Investigator Assessment for Stage 2 (as Confirmed Disease Control (Clinical Benefit) and Objective Response Are Simply Categories of RECIST Assessment)

End point title	Best RECIST Assessment as Per Investigator Assessment for Stage 2 (as Confirmed Disease Control (Clinical Benefit) and Objective Response Are Simply Categories of RECIST Assessment)

End point description:

Best RECIST Assessment is defined as confirmed Disease control (complete response (CR), partial response (PR) and Stable disease
(SD)), Objective response (complete response (CR) or partial response (PR)) assessed by the investigator according to the RECIST 1.0
criteria.

End point type	Secondary

End point timeframe:

Response determined during Stage 2 or within 28 days after termination of Stage 2 treatment. For stage 2 first assessment was done 28 days (4 weeks) after treatment then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[10]	36[11]		
Units: Number of participants				
Disease control (CR, PR, SD)	6	14		
Objective response (CR,PR)	2	1		
Complete response (CR)	0	1		
Partial response (PR)	2	0		
Stable disease (SD)	4	13		
Progressive disease (PD)	20	16		
Not evaluable	4	1		
Missing	2	5		

Notes:

[10] - Patients treated in stage 2

[11] - Patients treated in stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Per ICR for Stage2 (as Confirmed Disease Control (Clinical Benefit) and Objective Response Are Simply Categories of RECIST Assessment)

End point title	Best RECIST Assessment as Per ICR for Stage2 (as Confirmed Disease Control (Clinical Benefit) and Objective Response Are Simply Categories of RECIST Assessment)

End point description:

Best RECIST Assessment is defined as confirmed Disease control (complete response (CR), partial response (PR) and Stable disease

(SD)), Best objective response (complete response (CR) or partial response (PR)) as assessed by the independent central review (ICR)
according to the RECIST 1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined during Stage 2 or within 28 days after termination of Stage 2 treatment. For stage 2 first assessment was done 28 days (4 weeks) after treatment then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[12]	36[13]		
Units: Number of participants				
Disease control (CR, PR, SD)	6	12		
Objective response	0	0		
Complete response (CR)	0	0		
Partial response (PR)	0	0		
Stable disease (SD)	6	12		
Progressive disease (PD)	21	18		
Not evaluable	4	1		
Missing	1	5		

Notes:

[12] - Patients treated in stage 2

[13] - Patients treated in stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Onset of Confirmed Objective Response as Per Investigator Assessment for Stage 1

End point title	Best RECIST Assessment as Onset of Confirmed Objective Response as Per Investigator Assessment for Stage 1

End point description:

Best RECIST Assessment as onset of confirmed objective response as per Investigator assessment for Stage 1.

End point type	Secondary

End point timeframe:

Response determined from randomization until patient started Stage 2 or within 28 days after termination of Stage 1 treatment. Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[14]	4[15]		
Units: Number of participants				
Week 4 (Day 1 − 42)	3	0		
Week 8 (Day 43 − 84)	1	3		
Week 16 (Day 85 − 140)	4	1		
Week 24 (Day 141 − 196)	2	0		

Notes:

[14] - RS

[15] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Onset of Confirmed Objective Response as Per ICR for Stage 1

End point title	Best RECIST Assessment as Onset of Confirmed Objective Response as Per ICR for Stage 1

End point description:

Best RECIST Assessment as onset of confirmed objective response as per the independent central review (ICR) according to the RECIST
1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined from randomization until patient started Stage 2 or within 28 days after termination of Stage 1 treatment. Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[16]	6[17]		
Units: Number of participants				
Week 4 (Day 1 − 42)	1	0		
Week 8 (Day 43 − 84)	2	3		
Week 16 (Day 85 − 140)	2	2		
Week 24 (Day 141 − 196)	0	1		

Notes:

[16] - RS

[17] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Onset of Confirmed Objective Response as

Per Investigator Assessment for Stage 2

End point title	Best RECIST Assessment as Onset of Confirmed Objective Response as Per Investigator Assessment for Stage 2

End point description:

Best RECIST Assessment as onset of confirmed objective response as per Investigator assessment according to the RECIST 1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined during Stage 2 or within 28 days after termination of Stage 2 treatment (Week 2, 4 and 12). For stage 2 first assessment was done 28 days (4 weeks) after treatment then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[18]	1[19]		
Units: Number of participants				
Week 2 (Day 1 − 14)	0	0		
Week 4 (Day 15 − 56)	1	1		
Week 12 (Day 57 − 112)	1	0		

Notes:

[18] - Patients treated in stage 2

[19] - Patients treated in stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Confirmed Duration of Objective Response and Disease Control as Per Investigator Assessment for Stage 1

End point title	Best RECIST Assessment as Confirmed Duration of Objective Response and Disease Control as Per Investigator Assessment for Stage 1

End point description:

Best RECIST Assessment as duration of confirmed objective response and disease control as per Investigator assessment according
to the RECIST 1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined from randomization until patient started Stage 2 or within 28 days after termination of Stage 1 treatment. Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[20]	62[21]		
Units: Weeks				
arithmetic mean (standard deviation)				
Duration of objective response (N=10; N=4)	21.4 (± 12.2)	58.9 (± 98.1)		
Duration of disease control (N=31; N=35)	25.1 (± 13.9)	30.3 (± 35.8)		

Notes:

[20] - RS

[21] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Confirmed Duration of Confirmed Objective Response and Disease Control as Per ICR for Stage 1

End point title	Best RECIST Assessment as Confirmed Duration of Confirmed Objective Response and Disease Control as Per ICR for Stage 1

End point description:

Best RECIST Assessment as duration of confirmed objective response and disease control as per the independent central review
(ICR) according to the RECIST 1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined from randomization until patient started Stage 2 or within 28 days after termination of Stage 1 treatment. Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Weeks				
arithmetic mean (standard deviation)				
Duration of objective response (N=5; N=6)	28 (± 12.6)	55.1 (± 76.6)		
Duration of disease control(N=29; N=30)	22.8 (± 11)	28.8 (± 38.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Confirmed Duration of Objective Response and Disease Control as Per Investigator Assessment for Stage 2

End point title	Best RECIST Assessment as Confirmed Duration of Objective Response and Disease Control as Per Investigator Assessment for Stage 2

End point description:

Best RECIST Assessment as confirmed duration of objective response and disease control as per Investigator assessment according
to the RECIST 1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined during Stage 2 or within 28 days after termination of Stage 2 treatment. For stage 2 first assessment was done 28 days (4 weeks) after treatment then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[22]	36[23]		
Units: Weeks				
arithmetic mean (standard deviation)				
Duration of objective response (N=1; N=2)	19.4 (± 21.1)	24.7 (± 0)		
Duration of disease control(N=14; N=6)	21.5 (± 12.3)	21.8 (± 6.1)		

Notes:

[22] - Patients treated in stage 2

[23] - Patients treated in stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Best RECIST Assessment as Confirmed Duration of Disease Control as Per ICR for Stage 2

End point title	Best RECIST Assessment as Confirmed Duration of Disease Control as Per ICR for Stage 2

End point description:

Best RECIST Assessment as confirmed duration of disease control as per the independent central review (ICR) assessment according to the RECIST 1.0 criteria.

End point type	Secondary

End point timeframe:

Response determined during Stage 2 or within 28 days after termination of Stage 2 treatment. For stage 2 first assessment was done 28 days (4 weeks) after treatment then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[24]	36[25]		
Units: Weeks				
arithmetic mean (standard deviation)	18.4 (± 10)	17.4 (± 5)		

Notes:

[24] - Patients treated in stage 2

[25] - Patients treated in stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Before Crossover Based on Investigator Assessment

End point title	Progression Free Survival (PFS) Before Crossover Based on Investigator Assessment

End point description:

PFS is defined as time from randomisation to until the occurrence of tumor progression or death, whichever occurred first, during Stage 1 of the trial.
Median is calculated from the Kaplan−Meier curve for each treatment group.

End point type	Secondary

End point timeframe:

From randomisation to disease progression in Stage 1 or death whichever occurred first before crossover . Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[26]	62[27]		
Units: Weeks				
median (confidence interval 95%)	15.86 (10.29 to 17.14)	15.14 (8.29 to 19.29)		

Notes:

[26] - RS

[27] - RS

Statistical analyses

Statistical analysis title	PFS Before Crossover Based on IA

Statistical analysis description:

Progression Free Survival (PFS) Before Crossover Based on Investigator Assessment (IA).

Hazard ratio, 95% CI and p−value are calculated from the Cox proportional hazards model stratified by the number of prior chemotherapies for R/M setting (0 or >=1)

Comparison groups	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1 v Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.764
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.942
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.387

Secondary: Progression Free Survival (PFS) After Crossover Based on Investigator Assessment

End point title	Progression Free Survival (PFS) After Crossover Based on Investigator Assessment

End point description:

PFS is defined as time from first administration study medication after cross over until the occurrence of tumor progression or death,
whichever came first, during Stage 2 of the trial.
Median is calculated from the Kaplan−Meier curve for each treatment group.

End point type	Secondary

End point timeframe:

From first administration of study medication after cross over to disease progression in Stage 2 or death whichever came first after crossover. For stage 2 first assessment was done 28 days (4 weeks) after treatment then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[28]	36[29]		
Units: Weeks				
median (confidence interval 95%)	6.43 (4.14 to 8.29)	7.93 (4.29 to 14.43)		

Notes:

[28] - Patients treated in stage 2

[29] - Patients treated in stage 2

Statistical analyses

Statistical analysis title	PFS After Crossover Based on IA

Statistical analysis description:

Progression Free Survival (PFS) After Crossover Based on Investigator Assessment (IA).
Hazard ratio, 95% CI and p−value are calculated from the Cox proportional hazards model stratified by the number of prior chemotherapies for R/M setting (0 or >=1)

Comparison groups	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2 v Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.219
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.434
upper limit	1.212

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as time from randomisation to death.

Median is calculated from the Kaplan−Meier curve for each treatment group.

End point type	Secondary

End point timeframe:

From randomisation to data cut-off date (07-MAR-2014).

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Weeks				
median (confidence interval 95%)	35.86 (25.71 to 45)	47.14 (24.14 to 64.17)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)

Statistical analysis description:

Hazard ratio, 95% CI and p−value are calculated from the Cox proportional hazards model stratified by the number of prior chemotherapies for R/M setting (0 or >=1)

Comparison groups	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1 v Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.758
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.708
upper limit	1.608

Secondary: Time to Deterioration in HRQoL - Stage 1

End point title	Time to Deterioration in HRQoL - Stage 1

End point description:

Health related Quality of Life (HRQoL) for Time to deterioration was assessed using the the European Organization for Research and
Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC30) and the Head and Neck Cancer Module (H&N35).

Time to deterioration in HRQoL (defined as a 10-point change towards worsening from the baseline score on a 0-100 point scale) was determined for:
-global health status (Questions 29 and 30 in EORTC QLQ C30)
-pain (Questions 9 and 19 in EORTC QLQ C30)
-swallowing (Questions 35 to 38 in EORTC QLQ-H&N35)

End point type	Secondary

End point timeframe:

From randomisation to deterioration in HRQoL scores before crossover. Evaluations were done for stage 1 after 2 cycles (8 weeks) then every 8 weeks thereafter.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[30]	62[31]		
Units: Months				
median (confidence interval 95%)				
global health status (N=37; N=38)	2.83 (1.91 to 5.85)	3.94 (2.96 to 7.39)		
pain (N=34; N=33)	2.73 (1.48 to 5.88)	4.63 (2.92 to 8.61)		
swallowing (N=33; N=34)	5.59 (2.07 to 7.36)	6.6 (2.92 to 8.48)		

Notes:

[30] - RS

[31] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Patients With AEs Resulting in Diarrhea, Skin Rash, Dose Reduction, Treatement Discontinuation and Decreased Cardiac Left Ventricular Function

End point title	Patients With AEs Resulting in Diarrhea, Skin Rash, Dose Reduction, Treatement Discontinuation and Decreased Cardiac Left Ventricular Function

End point description:

Patients with adverse events (AEs) resulting in Diarrhea, Skin Rash, dose reduction, treatment discontinuation and decreased cardiac left ventricular function.

Treated set in stage 1 (TS stage 1): This analysis set included the randomized patients who took at least 1 dose of the ramdomized treatment (61 afatinib and 60 cetuximab patients).
Treated set in stage 2 (TS stage 2): This analysis set included all patients who received treatment in stage 2 (36 patients in the afatinib and 32 patients in the cetuximab arm).

Note: To asses the Decreased Cardiac left ventricular function, Left ventricular ejection fraction (LVEF) was assessed in patients treated with afatinib in Stage 1 and Stage 2 . And no patients in either group had a significant change in LVEF during Stage 1 or Stage 2 of the trial.

End point type	Secondary

End point timeframe:

First administration of trial medication until 28 days after last drug administration.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61[32]	60[33]	32[34]	36[35]
Units: Number of participants				
With AE leading to Diarrhea	49	15	2	22
With AE leading to skin rash	48	46	14	23
With AE leading to dose reduction	18	2	0	11
With AE leading to treatement discontinuation	23	11	6	8

Notes:

[32] - TS stage 1

[33] - TS stage 1

[34] - TS stage 2

[35] - TS stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and Intensity of Adverse Events With Grading According CTCAE

End point title	Incidence and Intensity of Adverse Events With Grading According CTCAE

End point description:

Incidence and intensity of Adverse Events with grading according to the Common Terminology Criteria for Adverse Events (CTCAE
version 3.0).

End point type	Secondary

End point timeframe:

First administration of trial medication until 28 days after last drug administration

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61[36]	60[37]	32[38]	36[39]
Units: Percentage of participants				
number (not applicable)				
CTCAE grade 1	3.3	5	9.4	5.6
CTCAE grade 2	24.6	41.7	37.5	25
CTCAE grade 3	39.3	28.3	25	25
CTCAE grade 4	8.2	6.7	9.4	13.9
CTCAE grade 5	24.6	16.7	15.6	30.6

Notes:

[36] - TS stage 1

[37] - TS stage 1

[38] - TS stage 2

[39] - TS stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Concentration of Afatinib in Plasma for Dose 40mg and 50mg at Steady State on Day 15 (Cpre,ss,15)

End point title	Pre-dose Concentration of Afatinib in Plasma for Dose 40mg and 50mg at Steady State on Day 15 (Cpre,ss,15)[40]

End point description:

Cpre,ss,15 represents the pre-dose concentration of afatinib in plasma at steady state on day 15.

Pharmacokinetic set (PK): The PK analysis was based on all patients who were treated with afatinib and who had evaluable plasma concentration data, which consisted of data for 60 patients in Stage 1 and 35 patients in Stage 2.

Note: At day 15, values for Afitanib 40 mg no values reported in stage 1 and stage 2.

End point type	Secondary

End point timeframe:

Day 15

Notes:

[40] - 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 comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[41]	26[42]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	39.3 (± 70.1)	46.6 (± 81.4)		

Notes:

[41] - PKS from stage 1

[42] - PKS from stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Concentration of Afatinib in Plasma for Dose 40mg and 50mg at Steady State on Day 29 (Cpre,ss,29)

End point title	Pre-dose Concentration of Afatinib in Plasma for Dose 40mg and 50mg at Steady State on Day 29 (Cpre,ss,29)[43]

End point description:

Cpre,ss,29 represents the pre-dose concentration of afatinib in plasma at steady state on day 29.

Note: At day 29, values for Afitanib 40 mg no values reported in stage 2.

End point type	Secondary

End point timeframe:

Day 29

Notes:

[43] - 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 comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2	Afatinib 40 mg - Stage 1	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33[44]	22[45]	9[46]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	31.7 (± 97.7)	45.9 (± 48.9)	8.84 (± 206)	

Notes:

[44] - PK set

[45] - PK set

[46] - PK set

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Concentration of Afatinib in Plasma for Dose 40mg and 50mg at Steady State on Day 57 (Cpre,ss, 57)

End point title	Pre-dose Concentration of Afatinib in Plasma for Dose 40mg and 50mg at Steady State on Day 57 (Cpre,ss, 57)[47]

End point description:

Cpre,ss,57 represents the pre-dose concentration of afatinib in plasma at steady state on day 57.

End point type	Secondary

End point timeframe:

Day 57

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

End point values	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2	Afatinib 40 mg - Stage 1	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16[48]	10[49]	7[50]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	19.9 (± 94.4)	46.5 (± 67.2)	32.7 (± 25.3)	

Notes:

[48] - PK set

[49] - PK set

[50] - PK set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First administration of trial medication until 28 days after last administration of trial medication, up to 1493 days

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1

Reporting group description:

Patients were randomized to Afatinib monotherapy 50mg once daily (q.d.) in Stage 1 and if the patients had disease progression or intolerable AEs were crossed over to Cetuximab 250 mg/m2 given as 400mg/m2 once in the first week (load) followed by 250mg/m2 weekly thereafter in Stage 2.

Reporting group title	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1

Reporting group description:

Patients were randomized to Cetuximab 250 mg/m2 received 400mg/m2 once in the first week followed by 250 mg/m2 weekly thereafter in Stage 1 and if the patients had disease progression or intolerable AEs were crossed over to Afatinib 50 mg once daily (q.d.) for Stage 2

Reporting group title	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2

Reporting group description:

Patients were randomized to Cetuximab 250 mg/m2 received 400mg/m2 once in the first week followed by 250 mg/m2 weekly thereafter in Stage 1 and if the patients had disease progression or intolerable AEs were crossed over to Afatinib 50 mg once daily (q.d.) for Stage 2

Reporting group title	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2

Reporting group description:

Patients were randomized to Afatinib monotherapy 50mg once daily (q.d.) in Stage 1 and if the patients had disease progression or intolerable AEs were crossed over to Cetuximab 250 mg/m2 given as 400mg/m2 once in the first week (load) followed by 250mg/m2 weekly thereafter in Stage 2.

Serious adverse events	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 61 (59.02%)	26 / 60 (43.33%)	18 / 36 (50.00%)
number of deaths (all causes)	21	19	31
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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

Linitis plastica			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Malignant neoplasm progression			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to central nervous system			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Metastatic pain			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Tumour compression			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Tumour haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tumour pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Vascular disorders			

Haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypotension			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Gastrointestinal tube insertion			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Chills			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Face oedema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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 physical health deterioration			
subjects affected / exposed	6 / 61 (9.84%)	3 / 60 (5.00%)	6 / 36 (16.67%)
occurrences causally related to treatment / all	3 / 7	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 4	0 / 3	0 / 5

Mucosal inflammation			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
Pain			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 61 (3.28%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Asphyxia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Aspiration			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cough			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
Dyspnoea			
subjects affected / exposed	4 / 61 (6.56%)	3 / 60 (5.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Hypoxia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
Interstitial lung disease			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
Pleural effusion			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 61 (3.28%)	1 / 60 (1.67%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Productive cough			

subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Pulmonary embolism			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Respiratory distress			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Anxiety			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Confusional state			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Disorientation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Hallucination, auditory			

subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Investigations			
Weight decreased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Overdose			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Post procedural haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Cardio-respiratory arrest			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiopulmonary failure			
subjects affected / exposed	2 / 61 (3.28%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Endocarditis noninfective			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Myocardial infarction			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Pericarditis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Sinus bradycardia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
Cerebrovascular accident			

subjects affected / exposed	0 / 61 (0.00%)	2 / 60 (3.33%)	0 / 36 (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
Convulsion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Ischaemic stroke			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Somnolence			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Vocal cord paralysis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 61 (3.28%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	8 / 61 (13.11%)	0 / 60 (0.00%)	3 / 36 (8.33%)
occurrences causally related to treatment / all	8 / 8	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	3 / 61 (4.92%)	1 / 60 (1.67%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 61 (0.00%)	2 / 60 (3.33%)	0 / 36 (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
Vomiting			
subjects affected / exposed	0 / 61 (0.00%)	2 / 60 (3.33%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rash			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 61 (4.92%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	3 / 61 (4.92%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular necrosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Fistula			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			

subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue necrosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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			
Abscess limb			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Bacteraemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Bronchitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Cellulitis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Device related sepsis			

subjects affected / exposed	0 / 61 (0.00%)	2 / 60 (3.33%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Endocarditis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Lobar pneumonia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Lung infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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 staphylococcal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Pneumonia			
subjects affected / exposed	5 / 61 (8.20%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Septic shock			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (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
Toxic shock syndrome			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
Urinary tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	8 / 61 (13.11%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	7 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			

subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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	1 / 61 (1.64%)	2 / 60 (3.33%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypernatraemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Hypokalaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	0 / 36 (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
Hypophagia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	0 / 36 (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
Malnutrition			

subjects affected / exposed	2 / 61 (3.28%)	0 / 60 (0.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 32 (40.63%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Linitis plastica			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metastases to central nervous system			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastatic pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tongue neoplasm malignant stage unspecified			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour compression			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Gastrointestinal tube insertion			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Chest pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Face oedema			
subjects affected / exposed	0 / 32 (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	3 / 32 (9.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Mucosal inflammation			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			

Hypersensitivity				
subjects affected / exposed	0 / 32 (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	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asphyxia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Interstitial lung disease			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Obstructive airways disorder			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Productive cough			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Alcohol abuse				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disorientation				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hallucination, auditory				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Weight decreased				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Infusion related reaction				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Post procedural haemorrhage				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound haemorrhage				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis noninfective				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				

subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain oedema				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Somnolence				

subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vocal cord paralysis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Periorbital oedema				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain upper				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Mouth haemorrhage				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal tubular necrosis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue necrosis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	0 / 32 (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 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				

subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Meningitis staphylococcal				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic shock syndrome				

subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection				
subjects affected / exposed	0 / 32 (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 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypernatraemia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophagia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 1	Cetuximab 250 mg/m2 / Afatinib 50 mg - Stage 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 61 (100.00%)	59 / 60 (98.33%)	34 / 36 (94.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 61 (3.28%)	1 / 60 (1.67%)	2 / 36 (5.56%)
occurrences (all)	2	1	2
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences (all)	1	1	0

Hypotension			
subjects affected / exposed	5 / 61 (8.20%)	2 / 60 (3.33%)	0 / 36 (0.00%)
occurrences (all)	5	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 61 (16.39%)	9 / 60 (15.00%)	3 / 36 (8.33%)
occurrences (all)	10	11	3
Fatigue			
subjects affected / exposed	18 / 61 (29.51%)	19 / 60 (31.67%)	5 / 36 (13.89%)
occurrences (all)	19	20	5
Mucosal inflammation			
subjects affected / exposed	14 / 61 (22.95%)	11 / 60 (18.33%)	7 / 36 (19.44%)
occurrences (all)	17	14	8
Pyrexia			
subjects affected / exposed	4 / 61 (6.56%)	11 / 60 (18.33%)	3 / 36 (8.33%)
occurrences (all)	8	13	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 61 (9.84%)	12 / 60 (20.00%)	3 / 36 (8.33%)
occurrences (all)	6	13	3
Dysphonia			
subjects affected / exposed	6 / 61 (9.84%)	2 / 60 (3.33%)	1 / 36 (2.78%)
occurrences (all)	6	2	1
Dyspnoea			
subjects affected / exposed	5 / 61 (8.20%)	9 / 60 (15.00%)	0 / 36 (0.00%)
occurrences (all)	6	12	0
Epistaxis			
subjects affected / exposed	9 / 61 (14.75%)	5 / 60 (8.33%)	2 / 36 (5.56%)
occurrences (all)	9	5	2
Haemoptysis			
subjects affected / exposed	6 / 61 (9.84%)	2 / 60 (3.33%)	1 / 36 (2.78%)
occurrences (all)	6	2	1
Rhinorrhoea			
subjects affected / exposed	4 / 61 (6.56%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences (all)	5	1	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	2 / 61 (3.28%)	1 / 60 (1.67%)	2 / 36 (5.56%)
occurrences (all)	2	1	2
Confusional state			
subjects affected / exposed	4 / 61 (6.56%)	3 / 60 (5.00%)	0 / 36 (0.00%)
occurrences (all)	5	3	0
Insomnia			
subjects affected / exposed	4 / 61 (6.56%)	5 / 60 (8.33%)	1 / 36 (2.78%)
occurrences (all)	4	5	1
Investigations			
Weight decreased			
subjects affected / exposed	9 / 61 (14.75%)	8 / 60 (13.33%)	5 / 36 (13.89%)
occurrences (all)	11	9	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 61 (8.20%)	7 / 60 (11.67%)	1 / 36 (2.78%)
occurrences (all)	5	9	1
Dysgeusia			
subjects affected / exposed	3 / 61 (4.92%)	1 / 60 (1.67%)	2 / 36 (5.56%)
occurrences (all)	3	1	2
Headache			
subjects affected / exposed	4 / 61 (6.56%)	5 / 60 (8.33%)	3 / 36 (8.33%)
occurrences (all)	6	5	3
Paraesthesia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 60 (1.67%)	3 / 36 (8.33%)
occurrences (all)	0	1	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 61 (14.75%)	10 / 60 (16.67%)	3 / 36 (8.33%)
occurrences (all)	17	11	3
Neutropenia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Eye disorders			
Conjunctivitis			
subjects affected / exposed	4 / 61 (6.56%)	7 / 60 (11.67%)	4 / 36 (11.11%)
occurrences (all)	6	7	5

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 61 (6.56%)	1 / 60 (1.67%)	0 / 36 (0.00%)
occurrences (all)	4	1	0
Cheilitis			
subjects affected / exposed	4 / 61 (6.56%)	2 / 60 (3.33%)	1 / 36 (2.78%)
occurrences (all)	4	2	1
Constipation			
subjects affected / exposed	6 / 61 (9.84%)	17 / 60 (28.33%)	2 / 36 (5.56%)
occurrences (all)	6	27	3
Diarrhoea			
subjects affected / exposed	45 / 61 (73.77%)	15 / 60 (25.00%)	21 / 36 (58.33%)
occurrences (all)	58	18	26
Dry mouth			
subjects affected / exposed	2 / 61 (3.28%)	5 / 60 (8.33%)	0 / 36 (0.00%)
occurrences (all)	2	5	0
Dyspepsia			
subjects affected / exposed	1 / 61 (1.64%)	5 / 60 (8.33%)	2 / 36 (5.56%)
occurrences (all)	1	7	2
Dysphagia			
subjects affected / exposed	6 / 61 (9.84%)	8 / 60 (13.33%)	2 / 36 (5.56%)
occurrences (all)	6	9	2
Nausea			
subjects affected / exposed	22 / 61 (36.07%)	17 / 60 (28.33%)	8 / 36 (22.22%)
occurrences (all)	23	24	8
Oral pain			
subjects affected / exposed	4 / 61 (6.56%)	2 / 60 (3.33%)	0 / 36 (0.00%)
occurrences (all)	4	2	0
Stomatitis			
subjects affected / exposed	5 / 61 (8.20%)	4 / 60 (6.67%)	4 / 36 (11.11%)
occurrences (all)	5	4	5
Vomiting			
subjects affected / exposed	15 / 61 (24.59%)	12 / 60 (20.00%)	7 / 36 (19.44%)
occurrences (all)	15	17	10
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	8 / 61 (13.11%)	8 / 60 (13.33%)	3 / 36 (8.33%)
occurrences (all)	11	10	3
Decubitus ulcer			
subjects affected / exposed	0 / 61 (0.00%)	0 / 60 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Dermatitis			
subjects affected / exposed	0 / 61 (0.00%)	3 / 60 (5.00%)	2 / 36 (5.56%)
occurrences (all)	0	4	2
Dermatitis acneiform			
subjects affected / exposed	12 / 61 (19.67%)	8 / 60 (13.33%)	3 / 36 (8.33%)
occurrences (all)	13	8	3
Dry skin			
subjects affected / exposed	9 / 61 (14.75%)	16 / 60 (26.67%)	4 / 36 (11.11%)
occurrences (all)	10	16	4
Erythema			
subjects affected / exposed	2 / 61 (3.28%)	2 / 60 (3.33%)	2 / 36 (5.56%)
occurrences (all)	2	2	2
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 61 (3.28%)	2 / 60 (3.33%)	5 / 36 (13.89%)
occurrences (all)	2	2	6
Pruritus			
subjects affected / exposed	8 / 61 (13.11%)	5 / 60 (8.33%)	1 / 36 (2.78%)
occurrences (all)	8	7	1
Rash			
subjects affected / exposed	26 / 61 (42.62%)	25 / 60 (41.67%)	10 / 36 (27.78%)
occurrences (all)	36	30	11
Skin fissures			
subjects affected / exposed	3 / 61 (4.92%)	11 / 60 (18.33%)	1 / 36 (2.78%)
occurrences (all)	5	18	1
Skin toxicity			
subjects affected / exposed	2 / 61 (3.28%)	3 / 60 (5.00%)	4 / 36 (11.11%)
occurrences (all)	2	4	5
Xeroderma			

subjects affected / exposed	4 / 61 (6.56%)	3 / 60 (5.00%)	0 / 36 (0.00%)
occurrences (all)	4	3	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 61 (3.28%)	5 / 60 (8.33%)	1 / 36 (2.78%)
occurrences (all)	2	6	1
Muscle spasms			
subjects affected / exposed	1 / 61 (1.64%)	0 / 60 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Neck pain			
subjects affected / exposed	3 / 61 (4.92%)	5 / 60 (8.33%)	3 / 36 (8.33%)
occurrences (all)	3	5	3
Pain in extremity			
subjects affected / exposed	1 / 61 (1.64%)	4 / 60 (6.67%)	0 / 36 (0.00%)
occurrences (all)	1	5	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 61 (6.56%)	2 / 60 (3.33%)	0 / 36 (0.00%)
occurrences (all)	5	3	0
Paronychia			
subjects affected / exposed	3 / 61 (4.92%)	4 / 60 (6.67%)	3 / 36 (8.33%)
occurrences (all)	3	5	3
Upper respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)	1 / 60 (1.67%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 61 (19.67%)	11 / 60 (18.33%)	7 / 36 (19.44%)
occurrences (all)	13	13	7
Hypokalaemia			
subjects affected / exposed	6 / 61 (9.84%)	6 / 60 (10.00%)	1 / 36 (2.78%)
occurrences (all)	7	9	1
Hypomagnesaemia			
subjects affected / exposed	2 / 61 (3.28%)	2 / 60 (3.33%)	3 / 36 (8.33%)
occurrences (all)	2	3	3

Non-serious adverse events	Afatinib 50 mg / Cetuximab 250mg/m2 - Stage 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 32 (90.63%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	7		
Mucosal inflammation			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Dysphonia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dyspnoea			

subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	6		
Paraesthesia			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Cheilitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Nausea			

subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Oral pain				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Stomatitis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Vomiting				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Skin and subcutaneous tissue disorders				
Acne				
subjects affected / exposed	4 / 32 (12.50%)			
occurrences (all)	4			
Decubitus ulcer				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Dermatitis				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Dermatitis acneiform				
subjects affected / exposed	3 / 32 (9.38%)			
occurrences (all)	3			
Dry skin				
subjects affected / exposed	3 / 32 (9.38%)			
occurrences (all)	4			
Erythema				
subjects affected / exposed	0 / 32 (0.00%)			
occurrences (all)	0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Pruritus				

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	7		
Skin fissures			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Skin toxicity			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Xeroderma			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Paronychia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	 6 / 32 (18.75%) 6 0 / 32 (0.00%) 0 3 / 32 (9.38%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2008	The duration of the study period (planned dates of trial) was lengthened, the number of study centers was increased, and the potential for inclusion of study centers in Europe was added. Modified exclusion criterion 1 to change the length of time between prior therapy for localized/locoregionally advanced disease and PD from 6 months to 3 months as a significant portion of patients' progress within 6 months after completion of curative intent treatment. Modified inclusion criterion 2 to allow enrollment of patients with well-differentiated (keratinizing) nasopharyngeal cancer, well-differentiated squamous cell carcinomas of the head and neck, and patients with squamous cell carcinomas metastatic to the neck from an unknown head and neck primary site. Modified exclusion criterion 3 to clarify that therapies refer to regimens, ie, more than 2 chemotherapeutic regimens for R/M disease. Removed exclusion criterion 5 that disallowed administration of afatinib via a gastric-tube as an estimated 20% to 30% of the target population only swallow by gastric-tubes and could potentially benefit from anti-EGFR therapy. Applicable information on route and instructions added on how to disperse afatinib in saline and administer it via a gastric-tube. Added guidance for the management of skin rash to dose reduction scheme. Appropriate information was added on drug supply (cetuximab), and applicable packaging according to EU law. Added analysis of pharmacokinetics and biomarkers to secondary endpoints. Updated the primary and secondary endpoints to improve distinction between observations required for endpoints and to correct placement in endpoint sections. Updated guidance for management of diarrhea, nausea and vomiting, and rash to agree with recommendations incorporated across all afatinib protocols. Clarified RECIST categories and defined additional response categories. Split flow chart into 2 flow charts and updated as appropriate to include changes to procedures.
06 February 2009	Added information on cetuximab solution (ie, 5 mg/mL concentration) available in Europe. Specified that all patients must have a baseline MUGA or echocardiography prior to randomization, not only those randomized to afatinib. Updated total sample size to require randomization to continue until 80 patients (40 per group) underwent at least 1 post-randomization tumor assessment, or until a maximum of 100 patients were randomized.
03 April 2009	Added exclusion criterion 21 to exclude patients with known preexisting ILD because ILD is a rare and serious AE reported with other EGFR tyrosine kinase inhibitors. Added background and safety information on ILD throughout the protocol, as applicable.
26 May 2010	Added information and restrictions for concomitant use of medications with afatinib that were potent P-gp inhibitors and inducers. Removed the 100 patient restriction on number of patients to be randomized; randomization was to continue until 80 patients underwent at least 1 post-randomization tumor assessment. Provided additional guidance for patients presenting with acute pulmonary symptoms which are similar to symptoms related to ILD. Provided guidance on compliance related to cetuximab therapy. Updated information on drug formulation provided, available dosage strengths, and labeling of afatinib used in the trial. Clarified that the analyses of trial data performed on an ongoing basis would be used for planning of future trials.

31 January 2011	Added information on role of HPV in HNSCC. Updated General Aim - Objectives to clarify the role of biomarkers that may predict tumor response, rather than limit it to the influence of EGFR genotype on tumor response. Updated the biomarker section based on changes to plan for analysis of samples. Updated information on formulation and labeling of afatinib used in the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported