Clinical trial results:
A randomised, open-label, phase III study to evaluate the efficacy and safety of oral afatinib (BIBW 2992) versus intravenous methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed after platinum-based therapy

Summary

EudraCT number	2011-000391-34
Trial protocol	BE DK FR DE GR ES AT CZ SE IT
Global end of trial date	06 December 2016

Results information

Result version number	v2 (current)
This version publication date	13 December 2021
First version publication date	21 December 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1200.43

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01345682
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, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2014
Global end of trial reached?	Yes
Global end of trial date	06 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of afatinib versus methotrexate therapy in patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) who have progressed during or after platinum-based therapy given for R/M HNSCC.

Protection of trial subjects:

Regular and frequent assessments of clinical benefit throughout the trial ensured that patients not deriving clinical benefit were withdrawn from study medication. Furthermore, an independent data monitoring committee (DMC) evaluated the safety of patients on an ongoing basis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 46
Country: Number of subjects enrolled	Japan: 49
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Belgium: 38
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 131
Country: Number of subjects enrolled	Germany: 76
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Italy: 63
Country: Number of subjects enrolled	Russian Federation: 37
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	South Africa: 8

Worldwide total number of subjects	593
EEA total number of subjects	401

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)	428
From 65 to 84 years	162
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening visit was to be performed within 14 days prior to the first administration of study medication. Eligible patients were to be randomised and treatment was to be started within 4 calendar days after randomisation.

Period 1

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

Blinding implementation details:

Randomised, multicenter, open-label, active-control study with 2 parallel arms.

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib (BIBW 2992)

Arm description:

Oral administration of Afatinib (film-coated tablets). Starting dose 40 milligram (mg) once daily; escalation to 50 mg/day and / or dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

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

Dosage and administration details:

Starting dose 40 mg once daily; escalation to 50 mg/day and / or dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

Arm title	Methotrexate

Arm description:

Intravenous bolus injection of Methotrexate Starting dose 40 milligram per square meter mg/m² weekly; escalation to 50 mg/m² and / or dose reduction to 40 mg/m² (if applicable), 30 mg/m², and 20 mg/m² (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Starting dose 40 mg/m² weekly; escalation to 50 mg/m² and / or dose reduction to 40 mg/m² (if applicable), 30 mg/m², and 20 mg/m² (according to the protocol-defined dose escalation and dose reduction scheme) if required.
No dose increase was allowed after a dose reduction.

Number of subjects in period 1[1]	Afatinib (BIBW 2992)	Methotrexate
Started	322	161
Completed	0	0
Not completed	322	161
Refused to continue trial medication	16	9
Non-compliance with protocol	-	1
Adverse event, serious fatal	29	19
Worsening of underlying cancer disease	23	12
Adverse event, non-fatal	22	22
Progressive disease per RECIST	226	93
Reason other than those specified above	4	3
Lost to follow-up	-	1
Not treated	2	1

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 dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib (BIBW 2992)
Reporting group description:	
Oral administration of Afatinib (film-coated tablets). Starting dose 40 milligram (mg) once daily; escalation to 50 mg/day and / or dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.	
Reporting group title	Methotrexate
Reporting group description:	
Intravenous bolus injection of Methotrexate Starting dose 40 milligram per square meter mg/m² weekly; escalation to 50 mg/m² and / or dose reduction to 40 mg/m² (if applicable), 30 mg/m², and 20 mg/m² (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.	

Reporting group values	Afatinib (BIBW 2992)	Methotrexate	Total
Number of subjects	322	161	483
Age categorical			
The randomised set (RS) included all patients who were randomised to receive treatment, whether treated or not			
Units: Subjects			
Age Continuous			
The randomised set (RS) included all patients who were randomised to receive treatment, whether treated or not			
Units: years			
arithmetic mean	60.0	59.3	
standard deviation	± 8.8	± 9.7	-
Gender, Male/Female			
The randomised set (RS) included all patients who were randomised to receive treatment, whether treated or not			
Units: Subjects			
Female	47	24	71
Male	275	137	412

End points

End points reporting groups

Reporting group title	Afatinib (BIBW 2992)

Reporting group description:

Oral administration of Afatinib (film-coated tablets). Starting dose 40 milligram (mg) once daily; escalation to 50 mg/day and / or dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

Reporting group title	Methotrexate

Reporting group description:

Intravenous bolus injection of Methotrexate Starting dose 40 milligram per square meter mg/m² weekly; escalation to 50 mg/m² and / or dose reduction to 40 mg/m² (if applicable), 30 mg/m², and 20 mg/m² (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

Primary: Progression-free survival (PFS) based on central independent review

End point title	Progression-free survival (PFS) based on central independent review

End point description:

PFS was defined as the time from the date of randomisation to disease progression or death, whichever occurred first. The primary analysis of PFS considered PFS events as assessed by central independent review, including all data collected until the study completion (06 December 2016). The date of disease progression was recorded based on RECIST version 1.1. Unequivocal progression of disease was determined if at least one of the following criteria applied: - At least 20% increase in the SoD of target lesions taking as reference the smallest SoD recorded since the treatment started, together with an absolute increase in the SoD of at least 5 mm - Appearance of one or more new lesions - Unequivocal progression of existing non-target lesions.
The randomised set (RS) included all patients who were randomised to receive treatment, whether treated or not.

End point type	Primary

End point timeframe:

From randomization until disease progression, death or study completion date (06Dec2016); Up to 60 months

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322[1]	161[2]		
Units: months				
median (confidence interval 95%)	2.63 (2.10 to 2.73)	1.74 (1.48 to 2.40)		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard ratio from Cox proportional hazards model stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0257 [3]
Method	Stratified Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.792
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.643
upper limit	0.977

Notes:

[3] - Log−rank test stratified by baseline Eastern Cooperative Oncology Group (ECOG) Performance score (PS)(0 or 1) and prior use of Epidermal Growth Factor Receptor (EGFR)−targeted antibody in the Recurrent and/or Metastatic (R/M) setting (Yes or No).

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS) was a key secondary endpoint of this trial. OS was defined as the time from randomisation to death (irrespective of the cause of death). Patients for whom there was no evidence of death at the study completion date (06 December 2016) were to be censored on the date that they were last known to be alive.

End point type	Secondary

End point timeframe:

From randomization until death or study completion date (06Dec2016); Up to 60 months

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322[4]	161[5]		
Units: months				
median (confidence interval 95%)	6.87 (6.14 to 7.79)	6.01 (5.16 to 7.75)		

Notes:

[4] - RS

[5] - RS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard ratio from Cox proportional hazards model stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6755 [6]
Method	Stratified Log-rank test

Parameter estimate	Hazard ratio (HR)
Point estimate	0.958
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.786
upper limit	1.169

Notes:

[6] - Log−rank test stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No).

Secondary: Objective Response (OR)

End point title	Objective Response (OR)

End point description:

OR is defined as the best overall response of complete response (CR) and partial response (PR) according to RECIST version 1.1, CR for target lesions (TL): Disappearance of all target lesions. CR for non-target lesions (NTL): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10mm short axis). PR for TL: At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Other factors which add to the overall response of an imaging timepoint as PR are as below:- • CR in TL, but non-CR/Non-PD in NTL leads to PR • CR in TL, but not evaluated NTL leads to PR • PR in TL, but non-PD NTL or not all evaluated NTL leads to PR; All the above scenarios should also satisfy 'No occurrence of new lesions'.

End point type	Secondary

End point timeframe:

Tumour imaging was to be performed every 6 weeks during the first 24 weeks of treatment, and hereafter every 8 weeks (data cut-off 07May2014); Up to 28 months

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322[7]	161[8]		
Units: percentage of participants				
number (confidence interval 95%)	10.2 (7.16 to 14.09)	5.6 (2.58 to 10.34)		

Notes:

[7] - RS

[8] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio, 95% CI and p−value (two−sided) from logistic regression stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.101
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	4.14

Secondary: Disease Control (DC)

End point title	Disease Control (DC)

End point description:

DC is defined as the best overall response of CR, PR, stable disease (SD) and non-CR/non-PD. CR for target lesions (TL): Disappearance of all target lesions. CR for non-target lesions (NTL): Disappearance of all non-target lesions . All lymph nodes must be non-pathological in size (<10mm short axis). PR for TL: At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Other factors which add to the overall response of an imaging timepoint as PR are as below:- • CR in TL, but non-CR/Non-PD in NTL leads to PR • CR in TL, but not evaluated NTL leads to PR • PR in TL, but non-PD NTL or not all evaluated NTL leads to PR; SD for TL: change in the sum of diameters does not satisfy PR or PD. SD in TL, non-PD in NTL lead to overall response of SD, provided there is no appearance of new lesions.

End point type	Secondary

End point timeframe:

Tumour imaging was to be performed every 6 weeks during the first 24 weeks of treatment, and hereafter every 8 weeks (data cut-off 07May2014); Up to 28 months

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322[9]	161[10]		
Units: percentage of participants				
number (confidence interval 95%)	49.1 (43.48 to 54.67)	38.5 (30.95 to 46.49)		

Notes:

[9] - RS

[10] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio, 95% CI and p−value (two−sided) from logistic regression stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0353
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.52
Confidence interval	

level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.26

Secondary: Tumour shrinkage

End point title	Tumour shrinkage

End point description:

Tumour shrinkage, defined as the maximum decrease from baseline in the sum of diameters of the target lesions, as measured by central imaging. The longest diameter of target lesions was recorded, except for lymph nodes, which were measured by their short axis. Negative values indicate a reduction in the sum of target lesion diameters and positive values an increase. Percentage of Participants with Tumour shrinkage as per the categories (>=20% increase, >=0 − <20% increase, >0 − <30% decrease, >=30 − <50% decrease, >=50% decrease) are presented.

End point type	Secondary

End point timeframe:

Tumour imaging was to be performed every 6 weeks during the first 24 weeks of treatment, and hereafter every 8 weeks (data cut-off 07May2014); Up to 28 months

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248[11]	121[12]		
Units: percentage of participants				
number (not applicable)				
>=20% increase	16.5	21.1		
>=0 − <20% increase	24.2	31.1		
>0 − <30% decrease	23.6	16.1		
>=30 − <50% decrease	6.2	4.3		
>=50% decrease	5.0	1.9		

Notes:

[11] - RS (Only patients with observed cases (OC) values were analysed)

[12] - RS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Health related quality of life (HRQOL)- Change in Pain scores over time

End point title	Health related quality of life (HRQOL)- Change in Pain scores over time

End point description:

The HRQOL analyses focused on pain, swallowing, and global health status measured by the European Organisation for Research and Treatment of Cancer [EORTC] quality of life questionnaires Core 30 [QLQ-C30], and head and neck cancer specific supplementary module EORTC QLQ-H&N35: Pain scale from H&N35, Swallowing scale from H&N35 and Global health status/QoL scale from C30. Pain scale includes items 31-34 from H&N 35; Swallowing scale includes items 35-38 from H&N35 and Global health status/QoL scale includes items 29-30 from C30. The scores of these scales were averaged from the scores of the component items, transformed and analyzed on 0 - 100 scale. For pain and swallowing scales, higher scores represent worse outcome; for the global health/QoL scale, higher scores represent better outcome. Changes in scores over time were assessed using longitudinal models. The analyses of

HRQOL are presented for the 07 May 2014 cut-off date.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265[13]	117[14]		
Units: scores on a scale				
arithmetic mean (standard error)	11.8 (± 3.16)	16.2 (± 3.43)		

Notes:

[13] - RS (Only patients with observed cases (OC) values were analysed)

[14] - RS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Changes in scores over time were assessed using longitudinal models, i.e. mixed effects growth curve models with the average profile over time for each endpoint described by a piecewise linear model adjusted for the fixed effects baseline ECOG performance score (PS) and prior use of EGFR-targeted antibody for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.03 [16]
Method	longitudinal models
Parameter estimate	Adjusted mean difference
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.31
upper limit	-0.42
Variability estimate	Standard error of the mean
Dispersion value	2.01

Notes:

[15] - Afatinib (BIBW 2992) vs Methotrexate

[16] - Adjusted for baseline ECOG performance score (0 or 1) and prior use of EGFR−targeted antibody for R/M HNSCC (Yes or No).

Secondary: Health related quality of life (HRQOL)- Change in Swallowing scores over time

End point title	Health related quality of life (HRQOL)- Change in Swallowing scores over time

End point description:

The HRQOL analyses focused on pain, swallowing, and global health status measured by the European Organisation for Research and Treatment of Cancer [EORTC] quality of life questionnaires Core 30 [QLQ-C30], and head and neck cancer specific supplementary module EORTC QLQ-H&N35: Pain scale from H&N35, Swallowing scale from H&N35 and Global health status/QoL scale from C30. Pain scale includes

items 31-34 from H&N 35; Swallowing scale includes items 35-38 from H&N35 and Global health status/QoL scale includes items 29-30 from C30. The scores of these scales were averaged from the scores of the component items, transformed and analyzed on 0 - 100 scale. For pain and swallowing scales, higher scores represent worse outcome; for the global health/QoL scale, higher scores represent better outcome. Changes in scores over time were assessed using longitudinal models. The analyses of HRQOL are presented for the 07 May 2014 cut-off date.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257[17]	112[18]		
Units: scores on a scale				
arithmetic mean (standard error)	20.0 (± 3.40)	20.1 (± 3.66)		

Notes:

[17] - RS (Only patients with observed cases (OC) values were analysed)

[18] - RS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Changes in scores over time were assessed using longitudinal models, i.e. mixed effects growth curve models with the average profile over time for each endpoint described by a piecewise linear model adjusted for the fixed effects baseline ECOG PS and prior use of EGFR-targeted antibody for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.9773 [20]
Method	longitudinal models
Parameter estimate	Adjusted mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	4.18
Variability estimate	Standard error of the mean
Dispersion value	2.16

Notes:

[19] - Afatinib (BIBW 2992) vs Methotrexate

[20] - Adjusted for baseline ECOG performance score (0 or 1) and prior use of EGFR−targeted antibody for R/M HNSCC (Yes or No).

Secondary: Health related quality of life (HRQOL)- Change in Global health scores over time

End point title	Health related quality of life (HRQOL)- Change in Global health scores over time

End point description:

The HRQOL analyses focused on pain, swallowing, and global health status measured by the European Organisation for Research and Treatment of Cancer [EORTC] quality of life questionnaires Core 30 [QLQ-C30], and head and neck cancer specific supplementary module EORTC QLQ-H&N35: Pain scale from H&N35, Swallowing scale from H&N35 and Global health status/QoL scale from C30. Pain scale includes items 31-34 from H&N 35; Swallowing scale includes items 35-38 from H&N35 and Global health status/QoL scale includes items 29-30 from C30. The scores of these scales were averaged from the scores of the component items, transformed and analyzed on 0 - 100 scale. For pain and swallowing scales, higher scores represent worse outcome; for the global health/QoL scale, higher scores represent better outcome. Changes in scores over time were assessed using longitudinal models. The analyses of HRQOL are presented for the 07 May 2014 cut-off date.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267[21]	117[22]		
Units: scores on a scale				
arithmetic mean (standard error)	28.7 (± 3.54)	28.2 (± 3.76)		

Notes:

[21] - RS (Only patients with observed cases (OC) values were analysed)

[22] - RS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Changes in scores over time were assessed using longitudinal models, i.e. mixed effects growth curve models with the average profile over time for each endpoint described by a piecewise linear model adjusted for the fixed effects baseline ECOG PS and prior use of EGFR-targeted antibody for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.7767 [24]
Method	longitudinal models
Parameter estimate	Adjusted mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	4.39
Variability estimate	Standard error of the mean
Dispersion value	1.95

Notes:

[23] - Afatinib (BIBW 2992) vs Methotrexate

[24] - Adjusted for baseline ECOG performance score (0 or 1) and prior use of EGFR−targeted antibody for R/M HNSCC (Yes or No).

Secondary: Status change in pain scale

End point title	Status change in pain scale

End point description:

Distribution of patients with improved, stable or worsened HRQOL: Improvement was defined as a score improved by at least 10 points from baseline (on the 0-100 point scale) at any time during the trial. If a patient had not improved, worsening was defined as a 10-point worsening at any time during the trial. Otherwise, a patient was considered as stable.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265[25]	117[26]		
Units: percentage of participants				
number (not applicable)				
Improved	26.4	23.1		
Stable	32.1	31.6		
Worsened	41.5	45.3		

Notes:

[25] - RS (Only patients with observed cases (OC) values were analysed)

[26] - RS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio, 95% CI and p−value (two−sided) from logistic regression stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.494
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.717
upper limit	1.99

Secondary: Status change in swallowing scale

End point title	Status change in swallowing scale

End point description:

Distribution of patients with improved, stable or worsened HRQOL: Improvement was defined as a score improved by at least 10 points from baseline (on the 0-100 point scale) at any time during the trial. If a patient had not improved, worsening was defined as a 10-point worsening at any time during the trial. Otherwise, a patient was considered as stable.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257[27]	112[28]		
Units: percentage of participants				
number (not applicable)				
Improved	26.1	23.2		
Stable	34.2	29.5		
Worsened	39.7	47.3		

Notes:

[27] - RS (Only patients with observed cases (OC) values were analysed)

[28] - RS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio, 95% CI and p−value (two−sided) from logistic regression stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.584
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.687
upper limit	1.95

Secondary: Status change in global health status scale

End point title	Status change in global health status scale

End point description:

Distribution of patients with improved, stable or worsened HRQOL: Improvement was defined as a score improved by at least 10 points from baseline (on the 0-100 point scale) at any time during the trial. If a

patient had not improved, worsening was defined as a 10-point worsening at any time during the trial. Otherwise, a patient was considered as stable.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267[29]	117[30]		
Units: percentage of participants				
number (not applicable)				
Improved	30.3	29.1		
Stable	26.6	25.6		
Worsened	43.1	45.3		

Notes:

[29] - RS (Only patients with observed cases (OC) values were analysed)

[30] - RS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio, 95% CI and p−value (two−sided) from logistic regression stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.816
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.657
upper limit	1.705

Secondary: Time to deterioration in Pain

End point title	Time to deterioration in Pain

End point description:

The time to deterioration was defined as the time from randomisation to a score increased (i.e. worsened) by at least 10 points from baseline (0-100 point scale). If score is missing, and patient died within 28 days after scheduled time for completion, the patient was considered deteriorated. In this case, time to deterioration is time to death.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322[31]	161[32]		
Units: months				
median (confidence interval 95%)	3.02 (2.83 to 3.75)	2.30 (1.64 to 3.32)		

Notes:

[31] - RS

[32] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio from Cox proportional hazards model stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No).

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0217 [33]
Method	Stratified Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.96

Notes:

[33] - Log−rank test stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No).

Secondary: Time to deterioration in Swallowing

End point title	Time to deterioration in Swallowing

End point description:

The time to deterioration was defined as the time from randomisation to a score increased (i.e. worsened) by at least 10 points from baseline (0-100 point scale). If score is missing, and patient died within 28 days after scheduled time for completion, the patient was considered deteriorated. In this case, time to deterioration is time to death.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322[34]	161[35]		
Units: months				
median (confidence interval 95%)	3.75 (2.83 to 4.30)	2.10 (1.48 to 3.32)		

Notes:

[34] - RS

[35] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio from Cox proportional hazards model stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004 [36]
Method	Stratified Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.89

Notes:

[36] - Log−rank test stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No).

Secondary: Time to deterioration in global health status

End point title	Time to deterioration in global health status

End point description:

The time to deterioration was defined as the time from randomisation to a score decreased (i.e. worsened) by at least 10 points from baseline (0-100 point scale). If score is missing, and patient died within 28 days after scheduled time for completion, the patient was considered deteriorated. In this case, time to deterioration is time to death.

End point type	Secondary

End point timeframe:

From randomization until one month after discontinuation of study medication, death or data cut-off (07May2014); Up to 28 months.

End point values	Afatinib (BIBW 2992)	Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322[37]	161[38]		
Units: months				
median (confidence interval 95%)	3.25 (2.83 to 4.01)	2.69 (1.61 to 2.86)		

Notes:

[37] - RS

[38] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio from Cox proportional hazards model stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No). Afatinib (BIBW 2992) vs Methotrexate

Comparison groups	Afatinib (BIBW 2992) v Methotrexate
Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0268 [39]
Method	Stratified Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.97

Notes:

[39] - Log−rank test stratified by baseline ECOG PS (0 or 1) and prior use of EGFR−targeted antibody in the R/M setting (Yes or No).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of study medication (afatinib or methotrexate) and within 28 days after the last administration of study medication (data cut-off 17 January 2017); Up to 61 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Afatinib (BIBW 2992)

Reporting group description:

Oral administration of Afatinib (film-coated tablets). Starting dose 40 mg once daily; escalation to 50 mg/day and / or dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

Reporting group title	Methotrexate

Reporting group description:

Intravenous bolus injection of Methotrexate Starting dose 40 mg/m² weekly; escalation to 50 mg/m² and / or dose reduction to 40 mg/m² (if applicable), 30 mg/m², and 20 mg/m² (according to the protocol-defined dose escalation and dose reduction scheme) if required. No dose increase was allowed after a dose reduction.

Serious adverse events	Afatinib (BIBW 2992)	Methotrexate	
Total subjects affected by serious adverse events			
subjects affected / exposed	168 / 320 (52.50%)	73 / 160 (45.63%)	
number of deaths (all causes)	299	150	
number of deaths resulting from adverse events	70	31	
Vascular disorders			
Angiopathy			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 320 (0.00%)	4 / 160 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	

deaths causally related to treatment / all	0 / 0	0 / 3	
Hypotension			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant neoplasm progression			
subjects affected / exposed	40 / 320 (12.50%)	9 / 160 (5.63%)	
occurrences causally related to	0 / 40	0 / 9	

treatment / all			
deaths causally related to treatment / all	0 / 35	0 / 9	
Metastases to liver			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	11 / 320 (3.44%)	4 / 160 (2.50%)	
occurrences causally related to treatment / all	0 / 15	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Tumour pain			
subjects affected / exposed	3 / 320 (0.94%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour ulceration			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	6 / 320 (1.88%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	3 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Face oedema			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 320 (0.94%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	27 / 320 (8.44%)	8 / 160 (5.00%)	
occurrences causally related to treatment / all	1 / 29	1 / 8	
deaths causally related to treatment / all	0 / 16	1 / 3	
Hyperpyrexia			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal haemorrhage			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	3 / 320 (0.94%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pain			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 320 (2.19%)	5 / 160 (3.13%)	
occurrences causally related to treatment / all	1 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatomegaly			

subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body aspiration			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning deliberate			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	3 / 320 (0.94%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal haemorrhage			

subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure orthostatic decreased			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
False positive investigation result			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	2 / 320 (0.63%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	3 / 320 (0.94%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	

deaths causally related to treatment / all	1 / 1	1 / 1	
Bronchial obstruction			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	15 / 320 (4.69%)	4 / 160 (2.50%)	
occurrences causally related to treatment / all	0 / 15	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 320 (0.00%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	4 / 320 (1.25%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased bronchial secretion			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal obstruction			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laryngeal oedema			
subjects affected / exposed	1 / 320 (0.31%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung disorder			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngeal stenosis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 320 (1.25%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 5	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	3 / 320 (0.94%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 320 (0.63%)	3 / 160 (1.88%)	

occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory depression			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	4 / 320 (1.25%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	6 / 320 (1.88%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stridor			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 320 (0.94%)	8 / 160 (5.00%)	
occurrences causally related to treatment / all	1 / 3	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 320 (0.63%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 320 (0.31%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 320 (0.00%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	

deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombocytopenia			
subjects affected / exposed	3 / 320 (0.94%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	5 / 320 (1.56%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis recurrent laryngeal nerve			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	16 / 320 (5.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	17 / 17	1 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	9 / 320 (2.81%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	2 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Melaena			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	5 / 320 (1.56%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	5 / 320 (1.56%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 320 (0.94%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	10 / 320 (3.13%)	1 / 160 (0.63%)	

occurrences causally related to treatment / all	8 / 11	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 320 (0.94%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	6 / 320 (1.88%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	2 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal impairment			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin haemorrhage			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin reaction			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 320 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rotator cuff syndrome			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trismus			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 320 (0.31%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	7 / 320 (2.19%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	5 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	9 / 320 (2.81%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	6 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food aversion			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	3 / 320 (0.94%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	3 / 320 (0.94%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	6 / 320 (1.88%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	5 / 320 (1.56%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess oral			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	4 / 320 (1.25%)	0 / 160 (0.00%)	

occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 320 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 320 (1.25%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oral infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 320 (4.06%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	1 / 15	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pulmonary sepsis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	4 / 320 (1.25%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 320 (0.94%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 2	1 / 1	
Septic shock			
subjects affected / exposed	2 / 320 (0.63%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Skin infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Staphylococcal infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	1 / 320 (0.31%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	3 / 320 (0.94%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	1 / 320 (0.31%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Afatinib (BIBW 2992)	Methotrexate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	309 / 320 (96.56%)	146 / 160 (91.25%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	9 / 320 (2.81%)	10 / 160 (6.25%)	
occurrences (all)	9	11	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	25 / 320 (7.81%)	9 / 160 (5.63%)	
occurrences (all)	28	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	66 / 320 (20.63%)	41 / 160 (25.63%)	
occurrences (all)	77	57	
Fatigue			
subjects affected / exposed	72 / 320 (22.50%)	42 / 160 (26.25%)	
occurrences (all)	88	57	
Mucosal inflammation			
subjects affected / exposed	74 / 320 (23.13%)	42 / 160 (26.25%)	
occurrences (all)	98	55	
Pyrexia			
subjects affected / exposed	38 / 320 (11.88%)	27 / 160 (16.88%)	
occurrences (all)	44	34	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	21 / 320 (6.56%)	7 / 160 (4.38%)	
occurrences (all)	21	7	
Insomnia			
subjects affected / exposed	27 / 320 (8.44%)	8 / 160 (5.00%)	
occurrences (all)	29	9	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 320 (1.25%)	19 / 160 (11.88%)	
occurrences (all)	4	21	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 320 (1.88%)	20 / 160 (12.50%)	
occurrences (all)	7	25	
Weight decreased			
subjects affected / exposed	69 / 320 (21.56%)	25 / 160 (15.63%)	
occurrences (all)	80	27	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	61 / 320 (19.06%)	42 / 160 (26.25%)	
occurrences (all)	75	55	
Leukopenia			
subjects affected / exposed	3 / 320 (0.94%)	13 / 160 (8.13%)	
occurrences (all)	4	21	
Neutropenia			
subjects affected / exposed	1 / 320 (0.31%)	30 / 160 (18.75%)	
occurrences (all)	1	41	
Thrombocytopenia			
subjects affected / exposed	2 / 320 (0.63%)	10 / 160 (6.25%)	
occurrences (all)	2	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 320 (12.81%)	23 / 160 (14.38%)	
occurrences (all)	53	27	
Dyspnoea			
subjects affected / exposed	45 / 320 (14.06%)	21 / 160 (13.13%)	
occurrences (all)	55	21	
Epistaxis			
subjects affected / exposed	32 / 320 (10.00%)	5 / 160 (3.13%)	
occurrences (all)	40	5	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 320 (8.13%)	16 / 160 (10.00%)	
occurrences (all)	54	21	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	39 / 320 (12.19%)	28 / 160 (17.50%)	
occurrences (all)	56	33	
Abdominal pain			
subjects affected / exposed	27 / 320 (8.44%)	5 / 160 (3.13%)	
occurrences (all)	64	5	
Dyspepsia			
subjects affected / exposed	31 / 320 (9.69%)	4 / 160 (2.50%)	
occurrences (all)	41	6	

Diarrhoea			
subjects affected / exposed	239 / 320 (74.69%)	28 / 160 (17.50%)	
occurrences (all)	629	36	
Dysphagia			
subjects affected / exposed	42 / 320 (13.13%)	12 / 160 (7.50%)	
occurrences (all)	44	12	
Nausea			
subjects affected / exposed	89 / 320 (27.81%)	43 / 160 (26.88%)	
occurrences (all)	120	70	
Stomatitis			
subjects affected / exposed	73 / 320 (22.81%)	28 / 160 (17.50%)	
occurrences (all)	79	47	
Vomiting			
subjects affected / exposed	63 / 320 (19.69%)	26 / 160 (16.25%)	
occurrences (all)	95	39	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	68 / 320 (21.25%)	4 / 160 (2.50%)	
occurrences (all)	93	5	
Acne			
subjects affected / exposed	28 / 320 (8.75%)	2 / 160 (1.25%)	
occurrences (all)	36	2	
Dry skin			
subjects affected / exposed	47 / 320 (14.69%)	5 / 160 (3.13%)	
occurrences (all)	48	6	
Pruritus			
subjects affected / exposed	29 / 320 (9.06%)	1 / 160 (0.63%)	
occurrences (all)	49	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	19 / 320 (5.94%)	3 / 160 (1.88%)	
occurrences (all)	22	3	
Rash			
subjects affected / exposed	134 / 320 (41.88%)	11 / 160 (6.88%)	
occurrences (all)	188	12	
Skin fissures			
subjects affected / exposed	40 / 320 (12.50%)	0 / 160 (0.00%)	

occurrences (all)	51	0	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	17 / 320 (5.31%)	5 / 160 (3.13%)	
occurrences (all)	17	5	
Neck pain			
subjects affected / exposed	17 / 320 (5.31%)	9 / 160 (5.63%)	
occurrences (all)	18	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	60 / 320 (18.75%)	39 / 160 (24.38%)	
occurrences (all)	69	41	
Hypokalaemia			
subjects affected / exposed	20 / 320 (6.25%)	10 / 160 (6.25%)	
occurrences (all)	26	10	
Hyponatraemia			
subjects affected / exposed	17 / 320 (5.31%)	4 / 160 (2.50%)	
occurrences (all)	22	4	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	25 / 320 (7.81%)	4 / 160 (2.50%)	
occurrences (all)	29	4	
Folliculitis			
subjects affected / exposed	24 / 320 (7.50%)	1 / 160 (0.63%)	
occurrences (all)	31	1	
Paronychia			
subjects affected / exposed	51 / 320 (15.94%)	0 / 160 (0.00%)	
occurrences (all)	58	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2011	-A conversion factor was introduced in order to check the total sum of platinum dose administered for patients who were switched from cisplatin to carboplatin (or vice versa) in the first-line R/M setting. -The exclusion criterion on patients with known HIV, active hepatitis B and/or hepatitis C infection was expanded by "other known severe infections, including but not limited to tuberculosis, as judged by the investigator" -The exclusion criteria regarding the use of adequate contraception was changed from 'three months after end of treatment' to 'six months after end of treatment', in order to follow the most stringent criteria regarding pregnancy after end of treatment. -The criterion for methotrexate dose continuation and escalation was changed to 'mucositis common terminology criteria for adverse events (CTCAE) grade ≤1' and for methotrexate dose reduction to 'mucositis CTCAE grade >1'.
23 July 2012	- For the inclusion criteria, it was clarified that platinum based therapy can be a combination therapy. - The handling of patients that were screened but the screening images did not show progression according to Response Evaluation Criteria in Solid Tumours (RECIST) after platinum based therapy was clarified.
15 April 2014	Amendment 3 to the clinical trial protocol only involved logistical and administrative aspects of the trial.
25 March 2015	- The option to continue treatment beyond disease progression was removed because only a small fraction of the patients continued randomised treatment beyond disease progression - Visit frequency during the treatment period was reduced from weekly visits to visits every 4 weeks. - With the implementation of the amendment, tumour assessment frequency was to be according to site local standard, but not less frequently than every 16 weeks. - With the implementation of the amendment, the trial was to be considered completed after all patients had progressed and/or permanently ended study medication and the required number of death events had occurred.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported