Clinical trial results:
LUX-Breast 1: An open-label, randomised phase III trial of BIBW 2992 and vinorelbine versus trastuzumab and vinorelbine in patients with metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-overexpressing breast cancer failing one prior trastuzumab teatment

Summary

EudraCT number	2009-015476-98
Trial protocol	NL BE DE SK PT CZ FR AT IT ES FI LT LV SI GB IE NO
Global end of trial date	06 July 2018

Results information

Result version number	v1
This version publication date	20 July 2019
First version publication date	20 July 2019

Trial information

Trial identification

Sponsor protocol code	1200.75

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01125566
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55612
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 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	30 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2013
Global end of trial reached?	Yes
Global end of trial date	06 July 2018
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 in combination with vinorelbine with trastuzumab in combination with vinorelbine as treatment in patients with metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-overexpressing breast cancer failing 1 prior trastuzumab treatment.

Protection of trial subjects:

Only participants that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All participants were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all participants was adhered to throughout the trial conduct. Rescue medication was allowed for all participants as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2010
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	Japan: 3
Country: Number of subjects enrolled	China: 141
Country: Number of subjects enrolled	Taiwan: 74
Country: Number of subjects enrolled	Korea, Republic of: 82
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Belarus: 13
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Ireland: 14
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Russian Federation: 21

Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Egypt: 2
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	India: 53
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	South Africa: 17
Worldwide total number of subjects	745
EEA total number of subjects	204

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)	628
From 65 to 84 years	107
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Randomised, active-controlled, open-label, parallel-group trial in participants with metastatic human epidermal growth factor receptor2(HER2)-overexpressing breast cancer failing one prior trastuzumab treatment. 508 randomized, 2 were not treated. 75 were switched treatment in which 1 was wrongly classified as discontinued prior to the switch.

Pre-assignment

Screening details:

Participants were treated in the study until disease progression, undue toxicity, or withdrawal of consent. The cut-off date for RECIST-based efficacy was 08 June 2013; a second analysis (primarily for assessing Overall Survival (OS)) contains all data until final database lock (30 July 2018).

Period 1

Period 1 title	Patients before the switch (26Apr2013)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open label trial. Blinding was not performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib + Vinorelbine (AV)

Arm description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine. 339 participants were randomised to the AV arm, however 2 were not treated and 1 center with 5 participants was excluded from the analysis. Consequently, number of subjects that started is 339 but only 332 reported to ensure consistent reporting with baseline characteristics.

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:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dosereduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on

days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dosereduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

Arm title	Trastuzumab + Vinorelbine (TV)

Arm description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. 169 participants were randomised to the TV arm, however 1 center with 1 participants was excluded from the analysis. Consequently, number of subjects that started is 169 but only 168 reported to ensure consistent reporting with baseline characteristics.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

Number of subjects in period 1[1]	Afatinib + Vinorelbine (AV)	Trastuzumab + Vinorelbine (TV)
Started	332	168
Completed	75	0
Not completed	257	168
Adverse event, non-fatal	24	5
Refused to continue taking medication	24	23
Other than listed above	23	13
Lost to follow-up	-	1
Progressive disease according to RECIST	180	118
Worsening of underlying cancer disease	6	6
Protocol deviation	-	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 dose of the trial medication.

Period 2

Period 2 title	Patients who switched from AV to TV
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open label trial. Blinding was not performed.

Arms

Arm title	AV switched to TV

Arm description:

This group describes participants who discontinued AV treatment and switched to TV, provided they were without disease progression on AV, following data monitoring committee (DMC) recommendation to terminate recruitment on 26 April 2013.

Arm type	Other
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:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dosereduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dosereduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

Number of subjects in period 2	AV switched to TV
Started	75
Completed	2
Not completed	73
Refused to continue taking medication	7
Other than listed above	4
Progressive disease according to RECIST	59
Worsening of underlying cancer disease	3

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib + Vinorelbine (AV)

Reporting group description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine. 339 participants were randomised to the AV arm, however 2 were not treated and 1 center with 5 participants was excluded from the analysis. Consequently, number of subjects that started is 339 but only 332 reported to ensure consistent reporting with baseline characteristics.

Reporting group title	Trastuzumab + Vinorelbine (TV)

Reporting group description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. 169 participants were randomised to the TV arm, however 1 center with 1 participants was excluded from the analysis. Consequently, number of subjects that started is 169 but only 168 reported to ensure consistent reporting with baseline characteristics.

Reporting group values	Afatinib + Vinorelbine (AV)	Trastuzumab + Vinorelbine (TV)	Total
Number of subjects	332	168	500
Age categorical			
Units: Subjects			
Age Continuous			
Treated Set (TS): The TS included all randomised participantsbwho were documented to have taken at least 1 dose of study medication (i.e. afatinib, trastuzumab, or vinorelbine). One centre with 6 subjects was excluded from analysis.			
Units: years			
arithmetic mean	51.8	53.1	
standard deviation	± 11.3	± 12.3	-
Sex: Female, Male			
TS			
Units: Subjects			
Female	332	168	500
Male	0	0	0
Race (NIH/OMB)			
TS. Ethnicity data was not reported for the trial.			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	172	81	253
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	3	9
White	136	72	208
More than one race	0	0	0
Unknown or Not Reported	17	11	28

End points

End points reporting groups

Reporting group title	Afatinib + Vinorelbine (AV)

Reporting group description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine. 339 participants were randomised to the AV arm, however 2 were not treated and 1 center with 5 participants was excluded from the analysis. Consequently, number of subjects that started is 339 but only 332 reported to ensure consistent reporting with baseline characteristics.

Reporting group title	Trastuzumab + Vinorelbine (TV)

Reporting group description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. 169 participants were randomised to the TV arm, however 1 center with 1 participants was excluded from the analysis. Consequently, number of subjects that started is 169 but only 168 reported to ensure consistent reporting with baseline characteristics.

Reporting group title	AV switched to TV

Reporting group description:

This group describes participants who discontinued AV treatment and switched to TV, provided they were without disease progression on AV, following data monitoring committee (DMC) recommendation to terminate recruitment on 26 April 2013.

Subject analysis set title	Afatinib + Vinorelbine (AV)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine. 339 participants were randomised to the AV arm, however 2 were not treated and 1 center with 5 participants was excluded from the analysis. Consequently, number of subjects that started is 339 but only 332 reported to ensure consistent reporting with baseline characteristics.

Subject analysis set title	Trastuzumab + Vinorelbine (TV)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. 169 participants were randomised to the TV arm, however 1 center with 1 participants was excluded from the analysis. Consequently, number of subjects that started is 169 but only 168 reported to ensure consistent reporting with baseline characteristics.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS is defined as time from randomisation to disease progression or death whichever occurs first. Assessed by investigator according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1). RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize") or worsen ("progress") during treatment. Only data collected until the cut-off date for RECIST 1.1 based endpoints (08Jun2013) were considered. Progression of disease was determined if at least 1 of the following criteria applied: - At least a 20% increase in the sum of the diameters (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 1 or more new lesions -

Unequivocal progression of existing non-target lesions. Randomised set (RS): The RS included all participants who were randomised to receive treatment, whether treated or not.

End point type	Primary

End point timeframe:

From randomization (07Sep2010) until disease progression, death or data cut-off (08Jun2013); Up to 34 months

End point values	Afatinib + Vinorelbine (AV)	Trastuzumab + Vinorelbine (TV)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	339[1]	169[2]		
Units: Months				
median (inter-quartile range (Q1-Q3))	5.49 (3.55 to 9.07)	5.55 (3.55 to 10.84)		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Two sided p-value was derived from a log rank test stratified by the setting of prior Trastuzumab failure, hormone receptors status and region of the investigational site.

Comparison groups	Afatinib + Vinorelbine (AV) v Trastuzumab + Vinorelbine (TV)
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.4224 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.41

Notes:

[3] - Hazard ratio is derived from Cox proportional hazard model stratified by prior Trastuzumab failure, hormone receptors status and region of the investigational site.

[4] - Two sided p-value was derived from a log rank test stratified by the setting of prior Trastuzumab failure, hormone receptors status and region of the investigational site.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as time from randomisation to death irrespective of the cause of the death. For patients who had not died up to the cut-off date (03Sep2013), the date they were last known to be alive was derived from the patient status records, the trial completion record, radiological imaging assessments, the study treatment termination record, and the randomisation date.

End point type	Secondary

End point timeframe:

From randomisation (07Sep2010) to database lock (30Jul2018), up to 95 months.

End point values	Afatinib + Vinorelbine (AV)	Trastuzumab + Vinorelbine (TV)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	339[5]	169[6]		
Units: Months				
median (inter-quartile range (Q1-Q3))	20.17 (10.74 to 39.52)	29.60 (13.34 to 43.99)		

Notes:

[5] - RS including participants with available data for OS

[6] - RS including participants with available data for OS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Results of presented analyses are to be seen as exploratory (no confirmatory testing was performed). Two sided p-value from a log rank test stratified by the setting of prior Trastuzumab failure, hormone receptors status and region of the investigational site.

Comparison groups	Afatinib + Vinorelbine (AV) v Trastuzumab + Vinorelbine (TV)
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.024 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.63

Notes:

[7] - Hazard ratio is derived from Cox proportional hazard model stratified by prior Trastuzumab failure, hormone receptors status and region of the investigational site.

[8] - Two sided p-value from a log rank test stratified by the setting of prior Trastuzumab failure, hormone receptors status and region of the investigational site.

Secondary: Best RECIST assessment

End point title	Best RECIST assessment

End point description:

Best RECIST assessment is defined as CR, PR, stable disease (SD), PD or not evaluable by investigator (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 and normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis). PR: At least a 30% decrease in the sum of diameters (SoD) of target lesions taking as reference the baseline sum diameters. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest SoD while on study. PD: At least a 20% increase in the SoD of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). Also, the sum must also demonstrate an absolute increase of a least 5mm. Appearance of one or more new lesions.

End point type	Secondary

End point timeframe:

From randomization (07Sep2010) until disease progression, death or data cut-off (08Jun2013); Up to 34 months

End point values	Afatinib + Vinorelbine (AV)	Trastuzumab + Vinorelbine (TV)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	334[9]	168[10]		
Units: Percentage of participants				
number (not applicable)				
Complete response (CR)	3.3	3.0		
Partial response (PR)	43.1	41.0		
Stable disease (SD)	31.7	26.8		
Progressive Disease (PD)	12.6	17.9		
Missing	9.3	8.3		

Notes:

[9] - RS including participants with available data for best RECIST assessment

[10] - RS including participants with available data for best RECIST assessment

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Results of presented analyses are to be seen as exploratory (no confirmatory testing was performed). Logistic regression stratified by prior Trastuzumab failure, hormone receptors status and region of the investigational site.

Comparison groups	Afatinib + Vinorelbine (AV) v Trastuzumab + Vinorelbine (TV)
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.6431
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.756
upper limit	1.572

Notes:

[11] - The odds ratio for the comparison afatinib + vinorelbine vs. trastuzumab + vinorelbine below 1 favours Afatinib.

Secondary: Objective Response (OR)

End point title	Objective Response (OR)

End point description:

OR is defined as complete response (CR) and partial response (PR). Assessed by investigator according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Complete Response (CR) for target lesions (TL): Disappearance of all target lesions. Complete Response (CR) for non-target lesions (NTL): Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must

be non-pathological in size (<10mm short axis) Partial Response (PR): 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

End point type	Secondary

End point timeframe:

Post baseline tumour-imaging was performed at Week 8, 16, 24, 32, 40, 48, 56 and then every 12 weeks (Until final data-base lock on 30 Jul 2018; Up to 95 months)

End point values	Afatinib + Vinorelbine (AV)	Trastuzumab + Vinorelbine (TV)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	334[12]	168[13]		
Units: Percentage of participants (%)				
number (not applicable)	46.4	47.0		

Notes:

[12] - RS including participants with available data for OR

[13] - RS including participants with available data for OR

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Results of presented analyses are to be seen as exploratory (no confirmatory testing was performed). Logistic regression stratified by prior Trastuzumab failure, hormone receptors status and region of the investigational site.

Comparison groups	Afatinib + Vinorelbine (AV) v Trastuzumab + Vinorelbine (TV)
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.8829
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.707
upper limit	1.496

Notes:

[14] - The odds ratio for the comparison afatinib + vinorelbine vs. trastuzumab + vinorelbine below 1 favours AV.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of treatment within the trial until last administration of treatment within the trial, up to 76 months.

Adverse event reporting additional description:

Treated set was used for reporting the other adverse event and serious adverse event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Afatinib + Vinorelbine (AV)

Reporting group description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

Reporting group title	AV switched to TV

Reporting group description:

This group describes participants who discontinued AV treatment and switched to TV, provided they were without disease progression on AV, following data monitoring committee (DMC) recommendation to terminate recruitment on 26 April 2013.

Reporting group title	Trastuzumab + Vinorelbine (TV)

Reporting group description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

Serious adverse events	Afatinib + Vinorelbine (AV)	AV switched to TV	Trastuzumab + Vinorelbine (TV)
Total subjects affected by serious adverse events			
subjects affected / exposed	123 / 337 (36.50%)	15 / 75 (20.00%)	45 / 169 (26.63%)
number of deaths (all causes)	235	3	111
number of deaths resulting from adverse events	3	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain cancer metastatic			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Brain neoplasm			

subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Breast cancer			
subjects affected / exposed	3 / 337 (0.89%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	2 / 337 (0.59%)	1 / 75 (1.33%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Breast cancer recurrent			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Infected neoplasm			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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	2 / 337 (0.59%)	1 / 75 (1.33%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Metastases to bone			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Metastases to central nervous system			

subjects affected / exposed	10 / 337 (2.97%)	3 / 75 (4.00%)	5 / 169 (2.96%)
occurrences causally related to treatment / all	0 / 10	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 4	0 / 2	0 / 1
Metastases to liver			
subjects affected / exposed	3 / 337 (0.89%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Metastases to meninges			
subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	0 / 169 (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 neoplasm			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Neoplasm progression			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Pericardial effusion malignant			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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 necrosis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Basal cell carcinoma			

subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibroadenoma of breast			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Hypotension			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Phlebitis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Shock			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Thrombosis			

subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Aortic stenosis			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Breast operation			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Central venous catheterisation			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	1 / 169 (0.59%)
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	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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

Condition aggravated			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Disease progression			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Facial pain			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	5 / 337 (1.48%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	15 / 337 (4.45%)	2 / 75 (2.67%)	5 / 169 (2.96%)
occurrences causally related to treatment / all	9 / 16	0 / 2	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site inflammation			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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 thrombosis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast pain			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Pulmonary embolism			
subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	4 / 169 (2.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary fibrosis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung consolidation			
subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	0 / 169 (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
Oropharyngeal pain			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus disorder			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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

Psychiatric disorders			
Mood altered			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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			
Blood creatinine increased			
subjects affected / exposed	3 / 337 (0.89%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood urea increased			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Neutrophil count decreased			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Radius fracture			
subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	0 / 169 (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
Toxicity to various agents			

subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	2 / 169 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Central nervous system lesion			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Depressed level of consciousness			

subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dizziness			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Dysarthria			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Gliosis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Headache			
subjects affected / exposed	2 / 337 (0.59%)	1 / 75 (1.33%)	3 / 169 (1.78%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Intracranial pressure increased			
subjects affected / exposed	1 / 337 (0.30%)	1 / 75 (1.33%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lethargy			

subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Radiculopathy			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	2 / 169 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Anaemia			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	2 / 169 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Febrile neutropenia			
subjects affected / exposed	21 / 337 (6.23%)	2 / 75 (2.67%)	7 / 169 (4.14%)
occurrences causally related to treatment / all	24 / 25	2 / 2	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Neutropenia			
subjects affected / exposed	18 / 337 (5.34%)	2 / 75 (2.67%)	4 / 169 (2.37%)
occurrences causally related to treatment / all	22 / 25	4 / 4	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	2 / 169 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			

subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	0 / 169 (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
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	0 / 169 (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
Keratitis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Abdominal pain			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	2 / 169 (1.18%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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	21 / 337 (6.23%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	20 / 21	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis			

subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Haemorrhagic ascites			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Ileus			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Nausea			
subjects affected / exposed	3 / 337 (0.89%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Stomatitis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Vomiting			

subjects affected / exposed	10 / 337 (2.97%)	0 / 75 (0.00%)	3 / 169 (1.78%)
occurrences causally related to treatment / all	7 / 12	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Hepatic function abnormal			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Neurogenic bladder			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Proteinuria			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Acute kidney injury			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Flank pain			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
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	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Neck pain			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle disorder			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteonecrosis of jaw			
subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Infections and infestations			
Abscess intestinal			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Cardiac infection			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	4 / 337 (1.19%)	0 / 75 (0.00%)	2 / 169 (1.18%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Device related infection			

subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital infection			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Hepatitis B			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Herpes zoster			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Infection			
subjects affected / exposed	2 / 337 (0.59%)	0 / 75 (0.00%)	0 / 169 (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
Influenza			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Lymphangitis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Pharyngitis			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Pneumonia			
subjects affected / exposed	3 / 337 (0.89%)	2 / 75 (2.67%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	1 / 3	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	0 / 169 (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
Sepsis			
subjects affected / exposed	4 / 337 (1.19%)	0 / 75 (0.00%)	2 / 169 (1.18%)
occurrences causally related to treatment / all	2 / 4	0 / 0	2 / 2
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 337 (0.00%)	1 / 75 (1.33%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	3 / 337 (0.89%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viraemia			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Wound infection			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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
Candida infection			
subjects affected / exposed	1 / 337 (0.30%)	0 / 75 (0.00%)	0 / 169 (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			
Dehydration			
subjects affected / exposed	4 / 337 (1.19%)	1 / 75 (1.33%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	4 / 337 (1.19%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 337 (0.00%)	0 / 75 (0.00%)	1 / 169 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Afatinib + Vinorelbine (AV)	AV switched to TV	Trastuzumab + Vinorelbine (TV)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	331 / 337 (98.22%)	64 / 75 (85.33%)	163 / 169 (96.45%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	24 / 337 (7.12%)	7 / 75 (9.33%)	16 / 169 (9.47%)
occurrences (all)	33	11	26
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 337 (6.53%)	8 / 75 (10.67%)	11 / 169 (6.51%)
occurrences (all)	27	9	18
Haemoglobin decreased			
subjects affected / exposed	28 / 337 (8.31%)	5 / 75 (6.67%)	6 / 169 (3.55%)
occurrences (all)	45	6	13
Neutrophil count decreased			
subjects affected / exposed	16 / 337 (4.75%)	6 / 75 (8.00%)	13 / 169 (7.69%)
occurrences (all)	73	18	57
Weight decreased			
subjects affected / exposed	48 / 337 (14.24%)	6 / 75 (8.00%)	10 / 169 (5.92%)
occurrences (all)	55	13	12
White blood cell count decreased			
subjects affected / exposed	23 / 337 (6.82%)	5 / 75 (6.67%)	3 / 169 (1.78%)
occurrences (all)	107	12	33
Nervous system disorders			
Dizziness			
subjects affected / exposed	34 / 337 (10.09%)	5 / 75 (6.67%)	18 / 169 (10.65%)
occurrences (all)	51	5	25
Headache			
subjects affected / exposed	47 / 337 (13.95%)	10 / 75 (13.33%)	25 / 169 (14.79%)
occurrences (all)	73	14	39
Hypoaesthesia			
subjects affected / exposed	9 / 337 (2.67%)	2 / 75 (2.67%)	11 / 169 (6.51%)
occurrences (all)	10	2	12
Neuropathy peripheral			

subjects affected / exposed	15 / 337 (4.45%)	3 / 75 (4.00%)	16 / 169 (9.47%)
occurrences (all)	16	3	18
Peripheral sensory neuropathy			
subjects affected / exposed	15 / 337 (4.45%)	2 / 75 (2.67%)	11 / 169 (6.51%)
occurrences (all)	16	2	13
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	103 / 337 (30.56%)	25 / 75 (33.33%)	62 / 169 (36.69%)
occurrences (all)	206	86	161
Leukopenia			
subjects affected / exposed	115 / 337 (34.12%)	28 / 75 (37.33%)	68 / 169 (40.24%)
occurrences (all)	467	136	401
Neutropenia			
subjects affected / exposed	256 / 337 (75.96%)	46 / 75 (61.33%)	139 / 169 (82.25%)
occurrences (all)	1164	340	1022
Bone marrow failure			
subjects affected / exposed	18 / 337 (5.34%)	5 / 75 (6.67%)	11 / 169 (6.51%)
occurrences (all)	75	22	39
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	63 / 337 (18.69%)	5 / 75 (6.67%)	25 / 169 (14.79%)
occurrences (all)	103	9	38
Fatigue			
subjects affected / exposed	106 / 337 (31.45%)	10 / 75 (13.33%)	51 / 169 (30.18%)
occurrences (all)	197	23	106
Mucosal inflammation			
subjects affected / exposed	82 / 337 (24.33%)	4 / 75 (5.33%)	15 / 169 (8.88%)
occurrences (all)	119	5	27
Oedema peripheral			
subjects affected / exposed	11 / 337 (3.26%)	1 / 75 (1.33%)	11 / 169 (6.51%)
occurrences (all)	12	1	15
Pain			
subjects affected / exposed	23 / 337 (6.82%)	2 / 75 (2.67%)	7 / 169 (4.14%)
occurrences (all)	31	2	8
Pyrexia			

subjects affected / exposed	74 / 337 (21.96%)	11 / 75 (14.67%)	32 / 169 (18.93%)
occurrences (all)	127	21	53
Chills			
subjects affected / exposed	10 / 337 (2.97%)	3 / 75 (4.00%)	9 / 169 (5.33%)
occurrences (all)	10	6	19
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	40 / 337 (11.87%)	1 / 75 (1.33%)	16 / 169 (9.47%)
occurrences (all)	53	4	23
Abdominal pain upper			
subjects affected / exposed	34 / 337 (10.09%)	5 / 75 (6.67%)	14 / 169 (8.28%)
occurrences (all)	37	7	17
Constipation			
subjects affected / exposed	35 / 337 (10.39%)	6 / 75 (8.00%)	27 / 169 (15.98%)
occurrences (all)	50	8	42
Diarrhoea			
subjects affected / exposed	270 / 337 (80.12%)	7 / 75 (9.33%)	45 / 169 (26.63%)
occurrences (all)	786	18	67
Dyspepsia			
subjects affected / exposed	16 / 337 (4.75%)	3 / 75 (4.00%)	12 / 169 (7.10%)
occurrences (all)	18	3	14
Mouth ulceration			
subjects affected / exposed	40 / 337 (11.87%)	1 / 75 (1.33%)	5 / 169 (2.96%)
occurrences (all)	61	1	7
Nausea			
subjects affected / exposed	102 / 337 (30.27%)	6 / 75 (8.00%)	47 / 169 (27.81%)
occurrences (all)	169	14	77
Stomatitis			
subjects affected / exposed	87 / 337 (25.82%)	4 / 75 (5.33%)	19 / 169 (11.24%)
occurrences (all)	136	4	31
Vomiting			
subjects affected / exposed	85 / 337 (25.22%)	5 / 75 (6.67%)	22 / 169 (13.02%)
occurrences (all)	204	9	35
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	39 / 337 (11.57%)	10 / 75 (13.33%)	27 / 169 (15.98%)
occurrences (all)	51	12	36
Dyspnoea			
subjects affected / exposed	27 / 337 (8.01%)	4 / 75 (5.33%)	15 / 169 (8.88%)
occurrences (all)	41	5	23
Epistaxis			
subjects affected / exposed	58 / 337 (17.21%)	3 / 75 (4.00%)	6 / 169 (3.55%)
occurrences (all)	95	5	7
Oropharyngeal pain			
subjects affected / exposed	30 / 337 (8.90%)	5 / 75 (6.67%)	9 / 169 (5.33%)
occurrences (all)	36	6	12
Rhinorrhoea			
subjects affected / exposed	20 / 337 (5.93%)	5 / 75 (6.67%)	10 / 169 (5.92%)
occurrences (all)	24	7	10
Productive cough			
subjects affected / exposed	6 / 337 (1.78%)	4 / 75 (5.33%)	3 / 169 (1.78%)
occurrences (all)	7	7	3
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	22 / 337 (6.53%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences (all)	26	0	0
Alopecia			
subjects affected / exposed	34 / 337 (10.09%)	0 / 75 (0.00%)	13 / 169 (7.69%)
occurrences (all)	34	0	15
Dermatitis acneiform			
subjects affected / exposed	45 / 337 (13.35%)	0 / 75 (0.00%)	0 / 169 (0.00%)
occurrences (all)	59	0	0
Dry skin			
subjects affected / exposed	20 / 337 (5.93%)	1 / 75 (1.33%)	1 / 169 (0.59%)
occurrences (all)	22	1	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	42 / 337 (12.46%)	0 / 75 (0.00%)	2 / 169 (1.18%)
occurrences (all)	55	0	2
Pruritus			

subjects affected / exposed	31 / 337 (9.20%)	2 / 75 (2.67%)	8 / 169 (4.73%)
occurrences (all)	41	2	10
Rash			
subjects affected / exposed	160 / 337 (47.48%)	8 / 75 (10.67%)	19 / 169 (11.24%)
occurrences (all)	213	12	22
Psychiatric disorders			
Insomnia			
subjects affected / exposed	26 / 337 (7.72%)	3 / 75 (4.00%)	28 / 169 (16.57%)
occurrences (all)	34	4	32
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	21 / 337 (6.23%)	1 / 75 (1.33%)	3 / 169 (1.78%)
occurrences (all)	25	1	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 337 (5.34%)	4 / 75 (5.33%)	8 / 169 (4.73%)
occurrences (all)	26	4	10
Back pain			
subjects affected / exposed	24 / 337 (7.12%)	7 / 75 (9.33%)	15 / 169 (8.88%)
occurrences (all)	33	10	25
Muscle spasms			
subjects affected / exposed	27 / 337 (8.01%)	5 / 75 (6.67%)	16 / 169 (9.47%)
occurrences (all)	38	5	21
Musculoskeletal pain			
subjects affected / exposed	12 / 337 (3.56%)	4 / 75 (5.33%)	12 / 169 (7.10%)
occurrences (all)	15	5	14
Myalgia			
subjects affected / exposed	34 / 337 (10.09%)	5 / 75 (6.67%)	18 / 169 (10.65%)
occurrences (all)	39	9	26
Pain in extremity			
subjects affected / exposed	21 / 337 (6.23%)	3 / 75 (4.00%)	20 / 169 (11.83%)
occurrences (all)	27	3	26
Bone pain			
subjects affected / exposed	11 / 337 (3.26%)	0 / 75 (0.00%)	10 / 169 (5.92%)
occurrences (all)	14	0	12
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	30 / 337 (8.90%)	2 / 75 (2.67%)	11 / 169 (6.51%)
occurrences (all)	41	6	17
Paronychia			
subjects affected / exposed	63 / 337 (18.69%)	2 / 75 (2.67%)	2 / 169 (1.18%)
occurrences (all)	81	2	2
Upper respiratory tract infection			
subjects affected / exposed	32 / 337 (9.50%)	8 / 75 (10.67%)	27 / 169 (15.98%)
occurrences (all)	33	21	52
Urinary tract infection			
subjects affected / exposed	35 / 337 (10.39%)	4 / 75 (5.33%)	15 / 169 (8.88%)
occurrences (all)	50	4	25
Conjunctivitis			
subjects affected / exposed	12 / 337 (3.56%)	4 / 75 (5.33%)	4 / 169 (2.37%)
occurrences (all)	13	4	4
Influenza			
subjects affected / exposed	7 / 337 (2.08%)	4 / 75 (5.33%)	0 / 169 (0.00%)
occurrences (all)	10	4	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	98 / 337 (29.08%)	5 / 75 (6.67%)	31 / 169 (18.34%)
occurrences (all)	122	6	51
Hypokalaemia			
subjects affected / exposed	43 / 337 (12.76%)	2 / 75 (2.67%)	7 / 169 (4.14%)
occurrences (all)	53	2	32

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2010	The restricted medications during treatment with afatinib were changed. An additional explanatory paragraph was added that the concomitant use of potent P-glycoprotein (P-gp) inhibitors and inducers was to be avoided during treatment with afatinib. The background was that a trial (1200.79) in healthy volunteers indicated that co-administration of these drugs affected the harmacokinetics of afatinib. Note: This restriction was loosened again with protocol amendment 4.
02 September 2010	Several changes and corrections were introduced with the second amendment to the protocol; major changes are presented below. In line with the requirements by the Health Canada's Food and Drug regulations, the source of trastuzumab for Canada was changed from the EU source to the US source. Statistical information was adjusted regarding the early benefit-risk assessment by the DMC. The ranking of the secondary endpoints was changed to reflect their importance. A reduced timeframe between prior trastuzumab treatment and study entry was allowed (changed from 4 weeks to 3 weeks); this resulted in a modified wording of exclusion criterion 4. The visit and vinorelbine-administration process in case of vinorelbine-related AEs was clarified. Corticosteroids were added to the allowed concomitant medications. Further recommendations regarding interstitial lung disease were added, including instructions for the assessment of pulmonary symptoms and actions to be taken with the study medication. A paragraph about the status of patients after discontinuation of study medication was clarified.
28 October 2011	The third amendment to the protocol again introduced several changes and corrections; major changes are presented below. It was clarified that the left ventricular ejection fraction (LVEF) assessment was not to be repeated at the screening visit if a valid result was available from an assessment performed as part of routine clinical practice within 28 days prior to start of treatment. The dose reduction scheme for afatinib in case of drug-related diarrhoea and the instructions for the treatment of afatinib-related diarrhoea were clarified. The introduction of the requirement for a TMA repository for potential retrospective analyses was added. The definition of the completion of the trial was clarified. New scientific methodologies were implemented to investigate the potential effect of subsequent anti-cancer therapies on OS. The requirements regarding contraception were changed based on new information in the trastuzumab Summary of Product Characteristics (SPC).
12 October 2012	Keratitis and ulcerative keratitis was observed in 0.8% of patients exposed to afatinib and they were reported after treatment with approved epidermal growth factor receptor (EGFR) inhibitors for cancer was added. European Medicines Agency requested a class labelling. Restriction that patients randomised to treatment with afatinib were not to receive treatment with potent P-gp inhibitors or inducers was removed. Based on new data, it was clarified that caution is warranted in concomitant use of P-glycoprotein (P-gp) inhibitors or inducers with afatinib, but their use in patients need such therapies is no longer prohibited. Exclusion criterion 6 was modified. Based on the current SPC for vinorelbine, exclusion criterion 12 was modified. In exclusion criterion 13 the MDRD formula was then accepted for the estimation of the glomerular filtration rate (GFR). Denosumab treatment for patients with bone metastasis was allowed. AE reporting guidance was changed. It was specified that worsening of the underlying disease or of other pre-existing conditions was to be recorded as an (S)AE in the electronic case report form ((e)CRF). Changes in vital signs, electrocardiogram (ECG), physical examination and laboratory test results were to be recorded as an (S)AE in the eCRF, if they were judged clinically relevant by the investigator. Drug-induced liver injury (DILI) was defined as a significant AE and a list of always serious AEs was defined; the reporting obligations of the investigator were specified. Further details about the planned second analysis of overall survival (OS) were added. Several new documents were added to the appendix. The rationale behind this were the modification of exclusion criterion 13.

14 May 2013	An independent DMC monitored the safety of patients who participated in the trial and benefit-risk assessment that was pre-defined in the clinical trial protocol. The DMC concluded that there was a low likelihood of the study meeting the pre-defined criteria for increased efficacy in terms of PFS. In addition, a high rate of treatment discontinuations and dose reductions as well as a higher rate of SAEs and deaths were observed in the afatinib + vinorelbine arm. The DMC recommended stopping recruitment of patients. Further recruitment into this study was therefore stopped as of 26 Apr 2013.
23 August 2013	Amendment 6 specified which procedures were no longer needed due to the premature discontinuation of the trial (e.g. additional FU visits, collection of health-related quality of life questionnaires, information about healthcare-resource use, biomarker sub-study, central independent review of images). In addition, the handling of unscheduled pharmacokinetic samples was specified. In addition, it was clarified that the primary endpoint changed from PFS based on central independent review to PFS based on investigator assessment. A list clearly defining the primary, secondary, and other endpoints of the trial was added. The sections about statistical methods were updated and several analyses were cancelled. Amendment 6 also defined that on trial level, the trial was considered complete when the last patient had completed the EOT visit and the FU visit 28 days after EOT.
12 June 2014	Several clarifications and updated information were introduced with the seventh amendment to the protocol; major changes are presented below. Based on the current SPC for trastuzumab, the instructions for management of trastuzumab cardiotoxicity were modified. Following the request by regulatory authorities, further recommendations for the assessment of keratitis were added to the section about rescue medication, emergency procedures, and additional treatments. The period for the collection of OS data was prolonged to ensure an adequate follow-up of patients and appropriate reporting of OS data: the observation period could have proceeded until at least 50% of patients per arm, or up to 75% of patients overall had died.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The Data Monitoring Committee recommended termination of recruitment due to low likelihood of the study meeting its primary objectives.

Notes: