Clinical trial results:
A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2-Directed Regimens in the Metastatic Setting (NALA)

Summary

EudraCT number	2012-004492-38
Trial protocol	GB DE FI IT BE CZ ES AT SE IE DK PT NL
Global end of trial date	09 December 2019

Results information

Result version number	v1 (current)
This version publication date	13 July 2020
First version publication date	13 July 2020

Trial information

Trial identification

Sponsor protocol code	PUMA-NER-1301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01808573
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Puma Biotechnology, Inc.
Sponsor organisation address	10880 Wilshire Blvd, Suite 2150, Los Angeles, United States, 90024
Public contact	Clinical Trials Information Desk, Puma Biotechnology, Inc., +1 424248 6500, ClinicalTrials@PumaBiotechnology.com
Scientific contact	Clinical Trials Information Desk, Puma Biotechnology, Inc., +1 424248 6500, ClinicalTrials@PumaBiotechnology.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	09 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 September 2018
Global end of trial reached?	Yes
Global end of trial date	09 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The co-primary objectives of this study are to compare independently adjudicated progression free survival (PFS) following treatment with neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive (HER2+) MBC who have received two or more prior HER2- directed regimens in the metastatic setting and compare overall survival (OS) following treatment with neratinib plus capecitabine versus lapatinib plus capecitabine in this population.

Protection of trial subjects:

Study commencement required prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Clinical trial data were monitored at regular intervals by the Sponsor or their representative throughout the study to verify compliance to study protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. Patients were discontinued from investigational product(s) (IP) in the following circumstances: unacceptable toxicity, if patient required more than 2 dose reductions of neratinib, disease progression on combination therapy, initiation of alternative anti-cancer therapy, including chemotherapy, radiotherapy, and cancer-related surgery, pregnancy, or patient request.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2013
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	Argentina: 3
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Brazil: 35
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	United Kingdom: 13

Country: Number of subjects enrolled	Hong Kong: 19
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Israel: 26
Country: Number of subjects enrolled	Italy: 42
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Singapore: 22
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Taiwan: 110
Country: Number of subjects enrolled	United States: 92
Worldwide total number of subjects	621
EEA total number of subjects	195

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)	492
From 65 to 84 years	129
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment starting date is Mar 29, 2013.

Pre-assignment

Screening details:

Screening activities are to be conducted within 21 days prior to randomization. Baseline assessments must be done within 72 hours before randomization. Randomization should occur after all baseline assessments have been completed and the site confirms that the patient still meets all eligibility requirements.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Neratinib Plus Capecitabine

Arm description:

Neratinib 240 mg orally, once daily with food, continuously in 21 day cycles, and capecitabine 1500 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

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

Dosage and administration details:

Neratinib 240 mg orally, once daily with food.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1500 mg/m^2, daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, 14 of each 21 day cycle.

Arm title	Lapatinib Plus Capecitabine

Arm description:

Lapatinib 1250 mg orally, once daily, continuously in 21 day cycles, and capecitabine 2000 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

Arm type	Active comparator

Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lapatinib 1250 mg orally, once daily, continuously in 21 day cycles.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 2000 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

Number of subjects in period 1	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine
Started	307	314
Completed	0	0
Not completed	307	314
Randomized in error	1	-
Consent withdrawn by subject	12	10
Death	212	240
Discontinuation of study by sponsor	79	64
Lost to follow-up	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Neratinib Plus Capecitabine

Reporting group description:

Neratinib 240 mg orally, once daily with food, continuously in 21 day cycles, and capecitabine 1500 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

Reporting group title	Lapatinib Plus Capecitabine

Reporting group description:

Lapatinib 1250 mg orally, once daily, continuously in 21 day cycles, and capecitabine 2000 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

Reporting group values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine	Total
Number of subjects	307	314	621
Age categorical Units: Subjects			
<65 years	244	248	492
>=65 years	63	66	129
Age continuous Units: years			
arithmetic mean	55.04	54.32	
standard deviation	± 11.37	± 11.36	-
Gender categorical Units: Subjects			
Female	307	311	618
Male	0	3	3
Previous HER2 Regimens Units: Subjects			
3 or more lines	92	99	191
2 lines	215	215	430
Disease Location Units: Subjects			
Non Visceral	60	61	121
Visceral	247	253	500
Hormone Receptor Status Units: Subjects			
Negative	126	128	254
Positive	181	186	367
Geographic Region Units: Subjects			
Europe	121	123	244
North America	59	65	124
Rest of World	127	126	253

Subject analysis sets

Subject analysis set title	Intent to treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent to treat population is defined as all patients who are randomized into the study. Patients will be analyzed in the treatment arm to which they were randomly assigned regardless of which treatment they received.

Reporting group values	Intent to treat population		
Number of subjects	621		
Age categorical Units: Subjects			
<65 years	492		
>=65 years	129		
Age continuous Units: years			
arithmetic mean	54.67		
standard deviation	± 11.36		
Gender categorical Units: Subjects			
Female	618		
Male	3		
Previous HER2 Regimens Units: Subjects			
3 or more lines	191		
2 lines	430		
Disease Location Units: Subjects			
Non Visceral	121		
Visceral	500		
Hormone Receptor Status Units: Subjects			
Negative	254		
Positive	367		
Geographic Region Units: Subjects			
Europe	244		
North America	124		
Rest of World	253		

End points

End points reporting groups

Reporting group title	Neratinib Plus Capecitabine

Reporting group description:

Neratinib 240 mg orally, once daily with food, continuously in 21 day cycles, and capecitabine 1500 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

Reporting group title	Lapatinib Plus Capecitabine

Reporting group description:

Lapatinib 1250 mg orally, once daily, continuously in 21 day cycles, and capecitabine 2000 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

Subject analysis set title	Intent to treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent to treat population is defined as all patients who are randomized into the study. Patients will be analyzed in the treatment arm to which they were randomly assigned regardless of which treatment they received.

Primary: Centrally Assessed Progression Free Survival

End point title	Centrally Assessed Progression Free Survival

End point description:

Progression Free Survival (PFS), Measured in Months, for Randomized Subjects of the Central Assessment. The time interval from the date of randomization until the first date on which recurrence, progression (per Response Evaluation Criteria in Solid Tumors Criteria (RECIST) v1.1), or death due to any cause, is documented. For subjects without recurrence, progression or death, it is censored at the last valid tumor assessment. Progression is defined using Response Evaluation Criteria in Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions. Here, the time to event was reported as the restricted mean survival time. The restricted mean survival time was defined as the area under the curve of the survival function up to 24 months.

End point type	Primary

End point timeframe:

From randomization date to recurrence, progression or death, assessed up to 38 months. The result is based on primary analysis data cut on 28Sep2018.

End point values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	314		
Units: months				
number (confidence interval 95%)	8.8 (7.8 to 9.8)	6.6 (5.9 to 7.4)		

Statistical analyses

Statistical analysis title	PFS (LogRank Pvalue and Hazard Ratio)

Statistical analysis description:

Lapatinib Plus Capecitabine is the reference. LogRank P-value and Hazard Ratio are stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, and visceral disease vs. non-visceral.

Comparison groups	Neratinib Plus Capecitabine v Lapatinib Plus Capecitabine
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0059
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.762
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.626
upper limit	0.926

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) is defined as the time from randomization to death due to any cause, censored at the last date known alive on or prior to the data cutoff employed for the analysis, whichever was earlier. Here, the time to event was reported as the restricted mean survival time. The restricted mean survival time was defined as the area under the curve of the survival function up to 48 months.

End point type	Primary

End point timeframe:

From randomization date to death, assessed up to 59 months. The result is based on primary analysis data cut on 28Sep2018.

End point values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	314		
Units: months				
number (confidence interval 95%)	24.0 (22.1 to 25.9)	22.2 (20.4 to 24.0)		

Statistical analyses

Statistical analysis title	Overall Survival (LogRank Pvalue and Hazard Ratio)

Statistical analysis description:

Lapatinib Plus Capecitabine is the reference. LogRank P-value and Hazard Ratio are stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, and visceral disease vs. non-visceral.

Comparison groups	Neratinib Plus Capecitabine v Lapatinib Plus Capecitabine

Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2086
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.881
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.723
upper limit	1.073

Secondary: Intervention for Symptomatic Metastatic Central Nervous System Disease

End point title	Intervention for Symptomatic Metastatic Central Nervous System Disease

End point description:

Intervention for symptomatic metastatic central nervous system disease is defined as the time from randomization to the first start date of an intervention for symptomatic metastatic CNS disease. Subjects that do not have an intervention for symptomatic metastatic CNS and do not die will be censored at the last date known alive on or prior to the data cutoff. Deaths are treated as competing events. Percentage of participants with intervention for CNS, estimated by cumulative incidence methods. Cumulative incidence methods are the standard way to estimate incidence of an endpoint in the presence of competing risks and censoring.

End point type	Secondary

End point timeframe:

From randomization date to first intervention for symptomatic metastatic CNS disease, assessed up to 59 months. The result is based on primary analysis data cut on 28Sep2018.

End point values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	314		
Units: percentage of participants				
number (confidence interval 95%)	22.76 (15.48 to 30.91)	29.19 (22.54 to 36.14)		

Statistical analyses

Statistical analysis title	Gray's Test: Intervention for Symptomatic CNS

Statistical analysis description:

Stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting and visceral disease vs. non-visceral disease.

Comparison groups	Neratinib Plus Capecitabine v Lapatinib Plus Capecitabine

Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	Gray's Test

Secondary: Objective Response Rate (ORR) - Central Assessment (ITT Population With Measurable Disease at Screening)

End point title	Objective Response Rate (ORR) - Central Assessment (ITT Population With Measurable Disease at Screening)

End point description:

Objective response rate is defined as the percentage of participants demonstrating an objective response during the study. Objective response includes confirmed complete responses (CR) and partial responses (PR) as defined in the RECIST criteria included in the study protocol. The ORR is for Central Assessment for subjects that had measurable disease at screening. Per Response Evaluation Criteria in Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

From randomization date to first confirmed Complete or Partial Response, whichever came earlier, up to 42 months. The result is based on primary analysis data cut on 28Sep2018.

End point values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	270		
Units: percentage of participants				
number (confidence interval 95%)	32.8 (27.1 to 38.9)	26.7 (21.5 to 32.4)		

Statistical analyses

Statistical analysis title	Objective Response Rate: CMH and Rate Difference

Statistical analysis description:

Stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting and visceral disease vs. non-visceral.

Comparison groups	Neratinib Plus Capecitabine v Lapatinib Plus Capecitabine
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1201
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in rate (or proportions)
Point estimate	6.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	14.64

Secondary: Clinical Benefit Rate (CBR) - Central Assessment (ITT Population With Measurable Disease at Screening)

End point title	Clinical Benefit Rate (CBR) - Central Assessment (ITT Population With Measurable Disease at Screening)

End point description:

Clinical benefit rate is the percentage of participants who achieve overall tumor response (confirmed CR or PR) or stable disease (SD) lasting for at least 24 weeks from randomization. The CBR was for Central Assessment for subjects who had Measurable Disease at Screening.

End point type	Secondary

End point timeframe:

From randomization date to either first confirmed CR or PR or Stable Disease, whichever came earlier, up to 42 months. The result is based on primary analysis data cut on 28Sep2018.

End point values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	270		
Units: percentage of participants				
number (confidence interval 95%)	44.5 (38.3 to 50.8)	35.6 (29.8 to 41.6)		

Statistical analyses

Statistical analysis title	Clinical Benefit Rate: CMH and Rate Difference

Statistical analysis description:

Stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting and visceral disease vs. non-visceral.

Comparison groups	Lapatinib Plus Capecitabine v Neratinib Plus Capecitabine
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0328
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in rate (or proportions)
Point estimate	8.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	17.43

Secondary: Duration of Response (DOR) - Central Assessment (Population that Had a Response With Measurable Disease at Screening)

End point title	Duration of Response (DOR) - Central Assessment (Population that Had a Response With Measurable Disease at Screening)

End point description:

The Duration of Response (DOR) is for Central Assessment for the Population that Had a Response with Measurable Disease at Screening. Duration of response is measured from the time at which measurement criteria are first met for CR or PR (whichever status is recorded first) until the first date of recurrence or progressive disease (PD) or death is objectively documented, taking as a reference for PD the smallest measurements recorded since enrollment, per RECIST v1.1. This value is censored at the last valid tumor assessment if PD or death has not been documented

End point type	Secondary

End point timeframe:

From start date of response after randomization to first PD, up to 33 months. The result is based on primary analysis data cut on 28Sep2018.

End point values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	72		
Units: months				
median (confidence interval 95%)	8.54 (5.62 to 11.17)	5.55 (4.21 to 6.41)		

Statistical analyses

Statistical analysis title	Duration of Response: LogRank Pvalue and HR

Statistical analysis description:

Lapatanib Plus Capecitabine is the reference.

Comparison groups	Neratinib Plus Capecitabine v Lapatinib Plus Capecitabine
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.495
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.332
upper limit	0.736

Secondary: Percentage of Participants With Any Treatment-Emergent Adverse Events (Safety Population)

End point title	Percentage of Participants With Any Treatment-Emergent Adverse Events (Safety Population)

End point description:

Adverse Events to be measured are Any Treatment-Emergent Adverse Events that occurred on or after first dose of investigational product and up to 28 days after the last dose. Safety population: Participants receiving at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

From time of first dose, through 28 days after last dose, assessed up to 41 months. The result is based on the final data cut of 18Dec2019. Last patient last visit (LPLV) is 9Dec2019.

End point values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	311		
Units: percentage of participants				
number (not applicable)	99.7	99.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serious Treatment-Emergent Adverse Events (Safety Population)

End point title	Percentage of Participants With Serious Treatment-Emergent Adverse Events (Safety Population)

End point description:

Adverse Events to be measured are Serious Treatment-Emergent AEs that occurred on or after first dose of investigational product and up to 28 days after the last dose. Safety population: Participants receiving at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

From first dose through last dose + 28 days, up to 41 months. The result is based on final data cut on 18Dec2019. Last patient last visit (LPLV) is 9Dec2019.

End point values	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	311		
Units: percentage of participants				
number (not applicable)	34.0	29.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose through last dose + 28 days, up to 41 months. The result is based on final data cut.

Adverse event reporting additional description:

Safety population: Participants receiving at least 1 dose of investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Neratinib Plus Capecitabine

Reporting group description:

Neratinib 240 mg orally, once daily with food, continuously in 21 day cycles, and capecitabine 1500 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

Reporting group title	Lapatinib Plus Capecitabine

Reporting group description:

Lapatinib 1250 mg orally, once daily, continuously in 21 day cycles, and capecitabine 2000 mg/m^2 daily in 2 evenly divided doses, orally with water within 30 minutes after a meal, taken on days 1 to 14 of each 21 day cycle.

Serious adverse events	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 303 (33.99%)	93 / 311 (29.90%)	
number of deaths (all causes)	216	240	
number of deaths resulting from adverse events	8	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			

subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	6 / 303 (1.98%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis malignant			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour compression			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	2 / 303 (0.66%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 303 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Abasia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 303 (0.33%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (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	2 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	1 / 303 (0.33%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Malaise			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 303 (0.33%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suprapubic pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 303 (0.99%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 303 (0.66%)	3 / 311 (0.96%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 303 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	10 / 303 (3.30%)	11 / 311 (3.54%)	
occurrences causally related to treatment / all	0 / 11	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia aspiration			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 303 (0.66%)	7 / 311 (2.25%)	
occurrences causally related to treatment / all	2 / 2	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood potassium increased			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 303 (0.00%)	3 / 311 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
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 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 303 (0.66%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip fracture			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac tamponade			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	2 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 303 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 303 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar syndrome			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 303 (0.33%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 303 (0.33%)	6 / 311 (1.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			

subjects affected / exposed	2 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lethargy			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	4 / 303 (1.32%)	3 / 311 (0.96%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord oedema			

subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic convulsion			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 303 (0.33%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 303 (0.33%)	3 / 311 (0.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Chorioretinopathy			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 303 (0.33%)	5 / 311 (1.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 303 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 303 (0.99%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	22 / 303 (7.26%)	13 / 311 (4.18%)	
occurrences causally related to treatment / all	31 / 32	15 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	2 / 303 (0.66%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	7 / 303 (2.31%)	6 / 311 (1.93%)	
occurrences causally related to treatment / all	11 / 11	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	9 / 303 (2.97%)	6 / 311 (1.93%)	
occurrences causally related to treatment / all	7 / 9	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			

subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bile duct obstruction			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis fulminant			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Jaundice			
subjects affected / exposed	0 / 303 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	7 / 303 (2.31%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	4 / 9	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (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			
Back pain			
subjects affected / exposed	1 / 303 (0.33%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
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	1 / 303 (0.33%)	4 / 311 (1.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	4 / 303 (1.32%)	5 / 311 (1.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 303 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Paronychia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 303 (1.98%)	5 / 311 (1.61%)	
occurrences causally related to treatment / all	1 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 303 (0.33%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 303 (0.33%)	4 / 311 (1.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 303 (0.66%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 303 (0.99%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 311 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 303 (1.32%)	5 / 311 (1.61%)	
occurrences causally related to treatment / all	3 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 303 (0.66%)	4 / 311 (1.29%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 311 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	0 / 303 (0.00%)	2 / 311 (0.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Neratinib Plus Capecitabine	Lapatinib Plus Capecitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	301 / 303 (99.34%)	309 / 311 (99.36%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	27 / 303 (8.91%)	22 / 311 (7.07%)	
occurrences (all)	39	35	
Aspartate aminotransferase increased			
subjects affected / exposed	29 / 303 (9.57%)	28 / 311 (9.00%)	
occurrences (all)	42	42	
Blood bilirubin increased			
subjects affected / exposed	18 / 303 (5.94%)	34 / 311 (10.93%)	
occurrences (all)	36	97	
Weight decreased			
subjects affected / exposed	60 / 303 (19.80%)	41 / 311 (13.18%)	
occurrences (all)	101	60	
Nervous system disorders			
Dizziness			
subjects affected / exposed	43 / 303 (14.19%)	30 / 311 (9.65%)	
occurrences (all)	52	34	
Dysgeusia			
subjects affected / exposed	17 / 303 (5.61%)	13 / 311 (4.18%)	
occurrences (all)	18	16	
Headache			
subjects affected / exposed	32 / 303 (10.56%)	50 / 311 (16.08%)	
occurrences (all)	34	62	
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	23 / 303 (7.59%)	16 / 311 (5.14%)	
occurrences (all)	55	43	
Anaemia			
subjects affected / exposed	45 / 303 (14.85%)	50 / 311 (16.08%)	
occurrences (all)	76	105	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	36 / 303 (11.88%)	34 / 311 (10.93%)	
occurrences (all)	86	56	
Fatigue			
subjects affected / exposed	102 / 303 (33.66%)	97 / 311 (31.19%)	
occurrences (all)	149	140	
Oedema peripheral			
subjects affected / exposed	16 / 303 (5.28%)	21 / 311 (6.75%)	
occurrences (all)	22	23	
Pyrexia			
subjects affected / exposed	32 / 303 (10.56%)	32 / 311 (10.29%)	
occurrences (all)	37	40	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	37 / 303 (12.21%)	42 / 311 (13.50%)	
occurrences (all)	60	53	
Abdominal distension			
subjects affected / exposed	25 / 303 (8.25%)	9 / 311 (2.89%)	
occurrences (all)	31	11	
Abdominal pain upper			
subjects affected / exposed	18 / 303 (5.94%)	28 / 311 (9.00%)	
occurrences (all)	23	36	
Constipation			
subjects affected / exposed	95 / 303 (31.35%)	40 / 311 (12.86%)	
occurrences (all)	142	45	
Diarrhoea			
subjects affected / exposed	248 / 303 (81.85%)	205 / 311 (65.92%)	
occurrences (all)	1260	629	
Dry mouth			

subjects affected / exposed	15 / 303 (4.95%)	18 / 311 (5.79%)	
occurrences (all)	15	18	
Dyspepsia			
subjects affected / exposed	20 / 303 (6.60%)	29 / 311 (9.32%)	
occurrences (all)	23	30	
Nausea			
subjects affected / exposed	161 / 303 (53.14%)	130 / 311 (41.80%)	
occurrences (all)	280	206	
Stomatitis			
subjects affected / exposed	63 / 303 (20.79%)	83 / 311 (26.69%)	
occurrences (all)	104	127	
Vomiting			
subjects affected / exposed	138 / 303 (45.54%)	95 / 311 (30.55%)	
occurrences (all)	256	163	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	13 / 303 (4.29%)	20 / 311 (6.43%)	
occurrences (all)	14	21	
Dyspnoea			
subjects affected / exposed	19 / 303 (6.27%)	26 / 311 (8.36%)	
occurrences (all)	27	34	
Cough			
subjects affected / exposed	41 / 303 (13.53%)	34 / 311 (10.93%)	
occurrences (all)	47	36	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	13 / 303 (4.29%)	23 / 311 (7.40%)	
occurrences (all)	14	26	
Dry skin			
subjects affected / exposed	20 / 303 (6.60%)	15 / 311 (4.82%)	
occurrences (all)	25	15	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	139 / 303 (45.87%)	175 / 311 (56.27%)	
occurrences (all)	397	468	
Rash			

subjects affected / exposed	31 / 303 (10.23%)	69 / 311 (22.19%)	
occurrences (all)	37	95	
Skin fissures			
subjects affected / exposed	9 / 303 (2.97%)	19 / 311 (6.11%)	
occurrences (all)	13	33	
Pruritus			
subjects affected / exposed	26 / 303 (8.58%)	25 / 311 (8.04%)	
occurrences (all)	31	26	
Skin hyperpigmentation			
subjects affected / exposed	7 / 303 (2.31%)	17 / 311 (5.47%)	
occurrences (all)	7	17	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	20 / 303 (6.60%)	23 / 311 (7.40%)	
occurrences (all)	22	25	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 303 (9.57%)	20 / 311 (6.43%)	
occurrences (all)	36	29	
Back pain			
subjects affected / exposed	30 / 303 (9.90%)	22 / 311 (7.07%)	
occurrences (all)	38	32	
Musculoskeletal pain			
subjects affected / exposed	19 / 303 (6.27%)	14 / 311 (4.50%)	
occurrences (all)	24	14	
Pain in extremity			
subjects affected / exposed	25 / 303 (8.25%)	21 / 311 (6.75%)	
occurrences (all)	28	29	
Infections and infestations			
Paronychia			
subjects affected / exposed	35 / 303 (11.55%)	49 / 311 (15.76%)	
occurrences (all)	71	95	
Urinary tract infection			
subjects affected / exposed	27 / 303 (8.91%)	12 / 311 (3.86%)	
occurrences (all)	36	12	
Upper respiratory tract infection			

subjects affected / exposed	26 / 303 (8.58%)	14 / 311 (4.50%)	
occurrences (all)	33	21	
Viral upper respiratory tract infection			
subjects affected / exposed	20 / 303 (6.60%)	23 / 311 (7.40%)	
occurrences (all)	23	26	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	107 / 303 (35.31%)	67 / 311 (21.54%)	
occurrences (all)	153	88	
Dehydration			
subjects affected / exposed	14 / 303 (4.62%)	16 / 311 (5.14%)	
occurrences (all)	31	18	
Hypokalaemia			
subjects affected / exposed	35 / 303 (11.55%)	41 / 311 (13.18%)	
occurrences (all)	51	71	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2013	The purpose of this amendment is to address the comments resulting from the SPA review by FDA of Amendment 2 dated 8 July, 2013, regarding the timing of start of first dose of study drug after randomization; Correct the trade name of the fluorescence in situ hybridization kit used for identifying HER2 mutations; Revise/correct dose adjustment Tables A2.7, A2.8, and A2.9 in Appendix 2; Perform an administrative text change in footnote "a" of Table A1.1 and in Appendix 7 regarding the timing of the baseline tumor assessments relative to randomization and treatment to be aligned with the previously agreed changes in Section 8.1.2.1.; Make other minor administrative/typographic changes where applicable.
13 February 2014	The purpose of this amendment is to increase the number of study sites; Adjust the prior cumulative anthracycline dose that a patient could have received; Reduce the time interval between the end of a prior therapy and initiation of study therapy from ≥28 days to ≥21 days; Change the time between completion of baseline assessments and randomization; Change the acceptable type of tumor tissue specimen that can be submitted for HER2 and ER/PR testing and the stage of disease at which it was obtained during a patient's cancer history; Clarify that patients who discontinue study therapy and have not progressed will continue tumor assessments per protocol until disease progression and are followed up for survival; Clarify the frequency of tumor scans after a patient has a confirmed complete response; Make other minor typographic, grammatical, and administrative changes as necessary.

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 reported efficacy results include data collected up to the clinical data cut-off date of 28 Sep 2018. The safety results include all data up to study close on 9 Dec 2019.

Notes: