Clinical trial results:
An Open-Label, Phase 2 Basket Study of Neratinib in Patients with Solid Tumors with Somatic Activating HER Mutations

Summary

EudraCT number	2013-002872-42
Trial protocol	ES IT FI GB DK BE FR IE
Global end of trial date	02 January 2023

Results information

Result version number	v1
This version publication date	06 January 2024
First version publication date	06 January 2024

Trial information

Trial identification

Sponsor protocol code	PUMA-NER-5201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01953926
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 4242486500, clinicaltrials@pumabiotechnology.com
Scientific contact	Clinical Trials Information Desk, Puma Biotechnology, Inc., 1 4242486500, 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	02 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the objective response rate at 8 weeks (ORR8) following treatment with neratinib in patients with solid tumors that test positive for somatic human epidermal growth factor receptor mutations in the ERBB gene family (EGFR, HER2, and/or HER3) or EGFR gene amplification.

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) prior to study closure in the following circumstances: disease progression, unacceptable toxicity, and withdrawal of consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 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	Australia: 10
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	United States: 346
Country: Number of subjects enrolled	Spain: 113
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	582
EEA total number of subjects	186

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)	359
From 65 to 84 years	216
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients will be assigned to cohorts based on tumors harboring somatic mutations in EGFR or HER2 identified through previously documented mutation testing performed prior to screening and by the tumor type. If a tumor harbors more than one qualifying aberration/mutation, then the patient will be assigned to the appropriate tumor-specific cohort.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Neratinib

Arm description:

Neratinib 240 mg PO QD

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:

240 mg PO QD

Arm title	Neratinib + Fulvestrant

Arm description:

Neratinib 240 mg PO QD + Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg IM on Days 1, 15, 29, then once every 28 days thereafter.

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

Dosage and administration details:

240 mg PO QD

Arm title	Neratinib + Paclitaxel

Arm description:

Neratinib 240 mg PO QD + Paclitaxel 80 mg/m^2 on Days 1, 8, 15 of every 4-week cycle

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

80 mg/m^2 on Days 1, 8, 15 of every 4-week cycle

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

Dosage and administration details:

240 mg PO QD

Arm title	Neratinib + Trastuzumab

Arm description:

Neratinib 240 mg PO QD + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks.

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

Dosage and administration details:

8 mg/kg once then 6 mg/kg every 3 weeks

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

Dosage and administration details:

240 mg PO QD

Arm title	Neratinib + Fulvestrant + Trastuzumab

Arm description:

Neratinib 240 mg PO QD + Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks

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:

240 mg PO QD

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

Dosage and administration details: 8 mg/kg once then 6 mg/kg every 3 weeks	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: 500 mg IM on Days 1, 15, 29, then once every 28 days thereafter.	
Arm title	Fulvestrant
Arm description: Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days	
Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: 500 mg IM on Days 1, 15, 29, then once every 28 days thereafter.	
Arm title	Fulvestrant + Trastuzumab
Arm description: Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks	
Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 8 mg/kg once then 6 mg/kg every 3 weeks	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: 500 mg IM on Days 1, 15, 29, then once every 28 days thereafter.	
Arm title	Not treated
Arm description: Subjects who were assigned a cohort but not treated	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Neratinib	Neratinib + Fulvestrant	Neratinib + Paclitaxel
Started	317	45	22
Treated	317	45	22
Completed	231	31	14
Not completed	86	14	8
Consent withdrawn by subject	23	3	3
Physician decision	1	-	-
Never received study drug	-	-	-
Discontinuation of study by sponsor	41	7	5
Lost to follow-up	18	3	-
Disease Progression	2	1	-
Protocol deviation	1	-	-

Number of subjects in period 1	Neratinib + Trastuzumab	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant
Started	92	90	7
Treated	92	90	7
Completed	70	32	2
Not completed	22	58	5
Consent withdrawn by subject	5	6	-
Physician decision	-	2	-
Never received study drug	-	-	-
Discontinuation of study by sponsor	12	46	5
Lost to follow-up	5	3	-
Disease Progression	-	1	-
Protocol deviation	-	-	-

Number of subjects in period 1	Fulvestrant + Trastuzumab	Not treated
Started	7	2
Treated	7	0
Completed	0	0
Not completed	7	2
Consent withdrawn by subject	1	-
Physician decision	-	-
Never received study drug	-	2
Discontinuation of study by sponsor	6	-
Lost to follow-up	-	-
Disease Progression	-	-
Protocol deviation	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Neratinib
Reporting group description:	
Neratinib 240 mg PO QD	
Reporting group title	Neratinib + Fulvestrant
Reporting group description:	
Neratinib 240 mg PO QD + Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days	
Reporting group title	Neratinib + Paclitaxel
Reporting group description:	
Neratinib 240 mg PO QD + Paclitaxel 80 mg/m^2 on Days 1, 8, 15 of every 4-week cycle	
Reporting group title	Neratinib + Trastuzumab
Reporting group description:	
Neratinib 240 mg PO QD + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks.	
Reporting group title	Neratinib + Fulvestrant + Trastuzumab
Reporting group description:	
Neratinib 240 mg PO QD + Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks	
Reporting group title	Fulvestrant
Reporting group description:	
Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days	
Reporting group title	Fulvestrant + Trastuzumab
Reporting group description:	
Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks	
Reporting group title	Not treated
Reporting group description:	
Subjects who were assigned a cohort but not treated	

Reporting group values	Neratinib	Neratinib + Fulvestrant	Neratinib + Paclitaxel
Number of subjects	317	45	22
Age categorical Units: Subjects			
Adults (18-64 years)	201	28	4
From 65-84 years	112	15	17
85 years and over	4	2	1
Age continuous Units: years			
arithmetic mean	59.4	60.6	69.4
standard deviation	± 13.1	± 11.5	± 9.4
Gender categorical Units: Subjects			
Female	188	45	5
Male	129	0	17

Reporting group values	Neratinib + Trastuzumab	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant
Number of subjects	92	90	7

Age categorical Units: Subjects			
Adults (18-64 years)	57	59	6
From 65-84 years	35	31	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60.4	59.2	58.3
standard deviation	± 11.1	± 11.6	± 11.2
Gender categorical Units: Subjects			
Female	58	89	7
Male	34	1	0

Reporting group values	Fulvestrant + Trastuzumab	Not treated	Total
Number of subjects	7	2	582
Age categorical Units: Subjects			
Adults (18-64 years)	3	1	359
From 65-84 years	4	1	216
85 years and over	0	0	7
Age continuous Units: years			
arithmetic mean	62.0	63.5	
standard deviation	± 12.4	± 4.9	-
Gender categorical Units: Subjects			
Female	7	1	400
Male	0	1	182

End points

End points reporting groups

Reporting group title	Neratinib
Reporting group description:	
Neratinib 240 mg PO QD	
Reporting group title	Neratinib + Fulvestrant
Reporting group description:	
Neratinib 240 mg PO QD + Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days	
Reporting group title	Neratinib + Paclitaxel
Reporting group description:	
Neratinib 240 mg PO QD + Paclitaxel 80 mg/m^2 on Days 1, 8, 15 of every 4-week cycle	
Reporting group title	Neratinib + Trastuzumab
Reporting group description:	
Neratinib 240 mg PO QD + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks.	
Reporting group title	Neratinib + Fulvestrant + Trastuzumab
Reporting group description:	
Neratinib 240 mg PO QD + Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks	
Reporting group title	Fulvestrant
Reporting group description:	
Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days	
Reporting group title	Fulvestrant + Trastuzumab
Reporting group description:	
Fulvestrant 500 mg IM on days 1, 15, 29, then every 28 days + Trastuzumab 8 mg/kg once then 6 mg/kg every 3 weeks	
Reporting group title	Not treated
Reporting group description:	
Subjects who were assigned a cohort but not treated	

Primary: Confirmed Objective Response Rate (ORR) Central Assessment (Breast Cancer With Prior CDK46i Cohort)

End point title	Confirmed Objective Response Rate (ORR) Central Assessment (Breast Cancer With Prior CDK46i Cohort)[1][2]
End point description:	
Percentage of participants who are confirmed by independent central review to have achieved complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.	
End point type	Primary
End point timeframe:	
From enrollment until PD or death due to any cause, assessed up to 58 months.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal comparisons between treatment groups were specified by the protocol. Descriptive statistics only are provided.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant	Fulvestrant + Trastuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	7	7	
Units: Percent				
number (confidence interval 95%)				
ORR by central assessment	40.7 (28.1 to 54.3)	0 (0.0 to 41)	14.3 (0.4 to 57.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Confirmed Objective Response Rate (ORR) Cervical Cohort

End point title	Confirmed Objective Response Rate (ORR) Cervical Cohort[3][4]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Primary

End point timeframe:

From first treatment date until PD or death due to any cause, assessed up to 58 months.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal comparisons between treatment groups were specified by the protocol. Descriptive statistics only are provided.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: percent				
number (confidence interval 95%)	18.2 (5.2 to 40.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Lung HER2-mutant Cohort

End point title	ORR at Week 8 Lung HER2-mutant Cohort[5]

End point description:

Percentage of participants who achieve CR or PR per Response Evaluation Criteria in Sold Tumors Criteria (RECIST) v1.1, or other defined response criteria, at the first scheduled tumor assessment, per RECIST or PERCIST, taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks or 9 weeks.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	52		
Units: percent				
number (confidence interval 95%)				
Objective Response Rate (ORR) at week 8	3.8 (0.1 to 19.6)	15.4 (6.9 to 28.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) at Week 8 (Other Breast Cancer Cohorts)

End point title	Objective Response Rate (ORR) at Week 8 (Other Breast Cancer Cohorts)[6]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks or 9 weeks.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Fulvestrant	Neratinib + Trastuzumab	Neratinib + Fulvestrant + Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	45	21	31
Units: Percent				
number (confidence interval 95%)	36.1 (20.8 to 53.8)	42.2 (27.7 to 57.8)	33.3 (14.6 to 57.0)	48.4 (30.2 to 66.9)

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Lung EGFR-mutant Cohort

End point title	ORR at Week 8 Lung EGFR-mutant Cohort[7]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: percentage				
number (confidence interval 95%)	19.4 (7.5 to 37.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Biliary tract Cohort

End point title	ORR at Week 8 Biliary tract Cohort[8]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percent				
number (confidence interval 95%)	12.0 (2.5 to 31.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 4 Brain Cohort

End point title	ORR at Week 4 Brain Cohort[9]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 4 weeks of study therapy, which corresponds to the first scheduled tumor assessment according to Macdonald Criteria.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 4 weeks.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percent				
number (confidence interval 95%)	0 (0.0 to 9.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Colorectal Cohort

End point title	ORR at Week 8 Colorectal Cohort[10]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks or 9 weeks.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	19		
Units: percent				
number (confidence interval 95%)	0.0 (0.0 to 26.5)	5.3 (0.1 to 26.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Bladder/Urinary tract Cohort

End point title	ORR at Week 8 Bladder/Urinary tract Cohort[11]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: percent				
number (confidence interval 95%)	0.0 (0.0 to 20.6)	13.6 (2.9 to 34.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Salivary gland Cohort

End point title	ORR at Week 8 Salivary gland Cohort[12]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent				
number (confidence interval 95%)	36.4 (10.9 to 69.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Ovarian Cohort

End point title	ORR at Week 8 Ovarian Cohort[13]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percent				
number (confidence interval 95%)	0 (0.0 to 30.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Fibrolamellar carcinoma (FLC) Cohort

End point title	ORR at Week 8 Fibrolamellar carcinoma (FLC) Cohort[14]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent				
number (confidence interval 95%)	0 (0.0 to 21.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Gastroesophageal Cohort

End point title	ORR at Week 8 Gastroesophageal Cohort[15]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
number (confidence interval 95%)	0 (0.0 to 41.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 Endometrial Cohort

End point title	ORR at Week 8 Endometrial Cohort[16]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
number (confidence interval 95%)	0 (0.0 to 41.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 HER3 NOS Cohort

End point title	ORR at Week 8 HER3 NOS Cohort[17]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percent				
number (confidence interval 95%)	0.0 (0.0 to 20.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 HER4 NOS Cohort

End point title	ORR at Week 8 HER4 NOS Cohort[18]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percent				
number (confidence interval 95%)	0.0 (0.0 to 70.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed Objective Response Rate (ORR) (Breast Cancer With Prior CDK46i Cohort)

End point title	Confirmed Objective Response Rate (ORR) (Breast Cancer With Prior CDK46i Cohort)[19]

End point description:

Percentage of participants who are confirmed by Investigator assessment to have achieved complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

End point type	Secondary

End point timeframe:

From enrollment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant	Fulvestrant + Trastuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	7	7	
Units: percent				
number (confidence interval 95%)	39.0 (26.5 to 52.6)	0 (0 to 41.0)	0 (0 to 41.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: ORR at Week 8 HER2 NOS Cohort

End point title	ORR at Week 8 HER2 NOS Cohort[20]

End point description:

First Objective response is defined as complete responses (CR) or partial responses (PR) at 8 weeks or 9 weeks of study therapy, which corresponds to the first scheduled tumor assessment; taking better results from RECIST or PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date to Complete or Partial Response, up to 8 weeks.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: percent				
number (confidence interval 95%)	4.8 (0.6 to 16.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR (Other Breast Cancer Cohorts)

End point title	Confirmed ORR (Other Breast Cancer Cohorts)[21]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Fulvestrant	Neratinib + Trastuzumab	Neratinib + Fulvestrant + Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	45	21	31
Units: percent				
number (confidence interval 95%)	25.0 (12.1 to 42.2)	28.9 (16.4 to 44.3)	33.3 (14.6 to 57.0)	35.5 (19.2 to 54.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Lung HER2-mutant Cohort

End point title	Confirmed ORR Lung HER2-mutant Cohort[22]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	52		
Units: percent				
number (confidence interval 95%)	3.8 (0.1 to 19.6)	9.6 (3.2 to 21.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Lung EGFR-mutant Cohort

End point title	Confirmed ORR Lung EGFR-mutant Cohort[23]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: percent				
number (confidence interval 95%)	32.3 (16.7 to 51.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Biliary tract Cohort

End point title	Confirmed ORR Biliary tract Cohort[24]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: percent				
number (confidence interval 95%)	16.0 (4.5 to 36.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Bladder/Urinary tract Cohort

End point title	Confirmed ORR Bladder/Urinary tract Cohort[25]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: percent				
number (confidence interval 95%)	0 (0 to 20.6)	13.6 (2.9 to 34.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Brain Cohort

End point title	Confirmed ORR Brain Cohort[26]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met. Brain tumor assessment is based on Macdonald Criteria.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: percent				
number (confidence interval 95%)	2.6 (0.1 to 13.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Colorectal Cohort

End point title	Confirmed ORR Colorectal Cohort[27]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking

results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	19		
Units: percent				
number (confidence interval 95%)	0 (0 to 26.5)	5.3 (0.1 to 26.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Ovarian Cohort

End point title	Confirmed ORR Ovarian Cohort[28]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percent				
number (confidence interval 95%)	0 (0 to 30.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Fibrolamellar carcinoma (FLC) Cohort

End point title	Confirmed ORR Fibrolamellar carcinoma (FLC) Cohort[29]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percent				
number (confidence interval 95%)	0 (0 to 21.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Gastroesophageal Cohort

End point title	Confirmed ORR Gastroesophageal Cohort[30]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
number (confidence interval 95%)	0 (0 to 41.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Salivary gland Cohort

End point title	Confirmed ORR Salivary gland Cohort[31]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent				
number (confidence interval 95%)	9.1 (0.2 to 41.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR Endometrial Cohort

End point title	Confirmed ORR Endometrial Cohort[32]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
number (confidence interval 95%)	0 (0 to 41.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR HER2 NOS Cohort

End point title	Confirmed ORR HER2 NOS Cohort[33]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: percent				
number (confidence interval 95%)	2.4 (0.1 to 12.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR HER3 NOS Cohort

End point title	Confirmed ORR HER3 NOS Cohort[34]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percent				
number (confidence interval 95%)	0 (0 to 20.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed ORR HER4 NOS Cohort

End point title	Confirmed ORR HER4 NOS Cohort[35]

End point description:

Overall objective response is defined as either a complete or partial response. A complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percent				
number (confidence interval 95%)	0 (0 to 70.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Central Assessment (Breast Cancer With Prior CDK46i Cohort)

End point title	Duration of Response (DOR) Central Assessment (Breast Cancer With Prior CDK46i Cohort)[36]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD

or date of death, whichever occurred first. PD was assessed as per RECIST version 1.1.

End point type	Secondary

End point timeframe:

From enrollment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant	Fulvestrant + Trastuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	0[37]	1	
Units: month				
median (full range (min-max))	13.14 (2.3 to 23.7)	(to)	1.4 (1.4 to 1.4)	

Notes:

[37] - There were no responders in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Investigator Assessment (Breast Cancer With Prior CDK46i Cohort)

End point title	Duration of Response (DOR) Investigator Assessment (Breast Cancer With Prior CDK46i Cohort)[38]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression was assessed as per RECIST version 1.1.

End point type	Secondary

End point timeframe:

From enrollment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant	Fulvestrant + Trastuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	0[39]	0[40]	
Units: month				
median (full range (min-max))	14.4 (2.1 to 31.4)	(to)	(to)	

Notes:

[39] - There were no responders in this arm.

[40] - There were no responders in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Cervical Cohort

End point title	Duration of Response (DOR) Cervical Cohort[41]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: month				
median (full range (min-max))	7.62 (5.6 to 12.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) (Other Breast Cancer Cohorts)

End point title	Duration of Response (DOR) (Other Breast Cancer Cohorts)[42]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Fulvestrant	Neratinib + Trastuzumab	Neratinib + Fulvestrant + Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	13	7	11
Units: month				
median (full range (min-max))	4.76 (1.9 to 16.6)	9.23 (3.9 to 55.0)	7.28 (1.9 to 14.5)	9.17 (4.0 to 55.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Lung HER2-mutant Cohort

End point title	Duration of Response (DOR) Lung HER2-mutant Cohort[43]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	5		
Units: month				
median (full range (min-max))	9.23 (9.2 to 9.23)	6.80 (4.2 to 47.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Lung EGFR-mutant Cohort

End point title	Duration of Response (DOR) Lung EGFR-mutant Cohort[44]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: month				
median (full range (min-max))	22.24 (4.0 to 30.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Biliary tract Cohort

End point title	Duration of Response (DOR) Biliary tract Cohort[45]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: month				
median (full range (min-max))	3.75 (3.0 to 4.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Bladder/Urinary tract Cohort

End point title	Duration of Response (DOR) Bladder/Urinary tract Cohort[46]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[47]	3		
Units: month				
median (full range (min-max))	(to)	7.20 (2.8 to 7.6)		

Notes:

[47] - There were no responders in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Brain Cohort

End point title	Duration of Response (DOR) Brain Cohort[48]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: month				
median (full range (min-max))	19.94 (19.9 to 19.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Colorectal Cohort

End point title	Duration of Response (DOR) Colorectal Cohort[49]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[50]	1		
Units: month				
median (full range (min-max))	(to)	12.19 (12.19 to 12.2)		

Notes:

[50] - There were no responders in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Salivary gland Cohort

End point title	Duration of Response (DOR) Salivary gland Cohort[51]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: month				
median (full range (min-max))	5.4 (5.4 to 5.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) HER2 NOS Cohort

End point title	Duration of Response (DOR) HER2 NOS Cohort[52]

End point description:

Duration of response was defined as the time (in months) from the date of the first documented objective response of CR or PR, confirmed at least 4 weeks later to the date of the first documented PD or date of death, whichever occurred first. Disease progression assessed by RECIST criteria, or for PERCIST for those participants who did not have RECIST performed.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: month				
median (full range (min-max))	3.71 (3.7 to 3.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Central Assessment (Breast Cancer With Prior CDK46i Cohort)

End point title	Clinical Benefit Rate (CBR) Central Assessment (Breast Cancer With Prior CDK46i Cohort)[53]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment based on RECIST version 1.1.

End point type	Secondary

End point timeframe:

From enrollment until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant	Fulvestrant + Trastuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	7	7	
Units: month				
number (confidence interval 95%)	49.2 (35.9 to 62.5)	0 (0 to 41.0)	14.3 (0.4 to 57.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Investigator Assessment (Breast Cancer With Prior CDK46i Cohort)

End point title	Clinical Benefit Rate (CBR) Investigator Assessment (Breast Cancer With Prior CDK46i Cohort)[54]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment based on RECIST version 1.1.

End point type	Secondary

End point timeframe:

From enrollment until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant	Fulvestrant + Trastuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	7	7	
Units: month				
number (confidence interval 95%)	54.2 (40.8 to 67.3)	0 (0 to 41.0)	0 (0 to 41.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Cervical Cohort

End point title	Clinical Benefit Rate (CBR) Cervical Cohort[55]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: month				
number (confidence interval 95%)	45.5 (24.4 to 67.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) (Other Breast Cancer Cohorts)

End point title	Clinical Benefit Rate (CBR) (Other Breast Cancer Cohorts)[56]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Fulvestrant	Neratinib + Trastuzumab	Neratinib + Fulvestrant + Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	45	21	31
Units: month				
number (confidence interval 95%)	33.3 (18.6 to 51.0)	42.2 (27.7 to 57.8)	42.9 (21.8 to 66.0)	54.8 (36.0 to 72.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Lung HER2-mutant Cohort

End point title	Clinical Benefit Rate (CBR) Lung HER2-mutant Cohort[57]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	52		
Units: month				
number (confidence interval 95%)	38.5 (20.2 to 59.4)	30.8 (18.7 to 45.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Lung EGFR-mutant Cohort

End point title	Clinical Benefit Rate (CBR) Lung EGFR-mutant Cohort[58]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: month				
number (confidence interval 95%)	48.4 (30.2 to 66.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Biliary tract Cohort

End point title	Clinical Benefit Rate (CBR) Biliary tract Cohort[59]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: month				
number (confidence interval 95%)	24.0 (9.4 to 45.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Bladder/Urinary tract Cohort

End point title	Clinical Benefit Rate (CBR) Bladder/Urinary tract Cohort[60]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor

assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: month				
number (confidence interval 95%)	18.8 (4.0 to 45.6)	31.8 (13.9 to 54.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Brain Cohort

End point title	Clinical Benefit Rate (CBR) Brain Cohort[61]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor was assessed per Macdonald Criteria.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: month				
number (confidence interval 95%)	10.5 (2.9 to 24.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Colorectal Cohort

End point title	Clinical Benefit Rate (CBR) Colorectal Cohort[62]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	19		
Units: month				
number (confidence interval 95%)	8.3 (0.2 to 38.5)	21.1 (6.1 to 45.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Ovarian Cohort

End point title	Clinical Benefit Rate (CBR) Ovarian Cohort[63]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: month				
number (confidence interval 95%)	20.0 (2.5 to 55.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Fibrolamellar carcinoma (FLC) Cohort

End point title	Clinical Benefit Rate (CBR) Fibrolamellar carcinoma (FLC) Cohort[64]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: month				
number (confidence interval 95%)	13.3 (1.7 to 40.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Gastroesophageal Cohort

End point title	Clinical Benefit Rate (CBR) Gastroesophageal Cohort[65]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: month				
number (confidence interval 95%)	0 (0 to 41.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Salivary gland Cohort

End point title	Clinical Benefit Rate (CBR) Salivary gland Cohort[66]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: month				
number (confidence interval 95%)	54.5 (23.4 to 83.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) Endometrial Cohort

End point title	Clinical Benefit Rate (CBR) Endometrial Cohort[67]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: month				
number (confidence interval 95%)	14.3 (0.4 to 57.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) HER2 NOS Cohort

End point title	Clinical Benefit Rate (CBR) HER2 NOS Cohort[68]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: month				
number (confidence interval 95%)	19.0 (8.6 to 34.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) HER3 NOS Cohort

End point title	Clinical Benefit Rate (CBR) HER3 NOS Cohort[69]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[69] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: month				
number (confidence interval 95%)	6.3 (0.2 to 30.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) HER4 NOS Cohort

End point title	Clinical Benefit Rate (CBR) HER4 NOS Cohort[70]

End point description:

The Clinical Benefit Rate (CBR) is defined as the percent of patients who achieve overall tumor response (CR or PR) or SD for at least 16 weeks (at least 24 weeks for the breast cancer cohorts). Tumor assessment taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: month				
number (confidence interval 95%)	0 (0 to 70.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Central Assessment (Breast Cancer With Prior CDK46i Cohort)

End point title	Progression-Free Survival (PFS) Central Assessment (Breast Cancer With Prior CDK46i Cohort)[71]

End point description:

PFS was defined as the time (in months) from enrollment to the earlier date of the documented PD or death due to any cause. PD was assessed based on RECIST version 1.1.

End point type	Secondary

End point timeframe:

From enrollment until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[71] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant	Fulvestrant + Trastuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	7	7	
Units: month				
number (confidence interval 95%)	8.11 (6.01 to 16.39)	2.27 (1.61 to 2.7)	4.11 (1.87 to 4.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Investigator Assessment (Breast Cancer With Prior CDK46i Cohort)

End point title	Progression-Free Survival (PFS) Investigator Assessment (Breast Cancer With Prior CDK46i Cohort)[72]

End point description:

PFS was defined as the time (in months) from enrollment to the earlier date of the documented PD or death due to any cause. PD was assessed based on RECIST version 1.1.

End point type	Secondary

End point timeframe:

From enrollment until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib + Fulvestrant + Trastuzumab	Fulvestrant	Fulvestrant + Trastuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	7	7	
Units: month				
number (confidence interval 95%)	8.3 (6.0 to 12.7)	4.1 (1.6 to 4.1)	3.9 (1.9 to 4.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Cervical Cohort

End point title	Progression-Free Survival (PFS) Cervical Cohort[73]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[73] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: month				
number (confidence interval 95%)	5.09 (1.74 to 7.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) (Other Breast Cancer Cohorts)

End point title	Progression-Free Survival (PFS) (Other Breast Cancer

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Fulvestrant	Neratinib + Trastuzumab	Neratinib + Fulvestrant + Trastuzumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	45	21	31
Units: month				
number (confidence interval 95%)	3.48 (1.94 to 3.88)	5.36 (3.71 to 9.23)	6.24 (2.10 to 10.25)	8.21 (4.07 to 11.01)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Lung HER2-mutant Cohort

End point title	Progression-Free Survival (PFS) Lung HER2-mutant Cohort[75]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	52		
Units: month				
number (confidence interval 95%)	4.17 (1.87 to 8.80)	4.01 (2.10 to 4.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Lung EGFR-mutant Cohort

End point title	Progression-Free Survival (PFS) Lung EGFR-mutant Cohort[76]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the

documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: month				
number (confidence interval 95%)	5.75 (2.27 to 9.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Biliary tract Cohort

End point title	Progression-Free Survival (PFS) Biliary tract Cohort[77]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: month				
number (confidence interval 95%)	2.76 (1.05 to 3.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Bladder/Urinary tract Cohort

End point title	Progression-Free Survival (PFS) Bladder/Urinary tract Cohort[78]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[78] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	22		
Units: month				
number (confidence interval 95%)	1.77 (1.68 to 3.55)	3.75 (1.87 to 5.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Brain Cohort

End point title	Progression-Free Survival (PFS) Brain Cohort[79]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed per Macdonald Criteria.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[79] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: month				
number (confidence interval 95%)	1.81 (1.02 to 2.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Colorectal Cohort

End point title	Progression-Free Survival (PFS) Colorectal Cohort[80]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[80] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib	Neratinib + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	19		
Units: month				
number (confidence interval 95%)	1.71 (1.45 to 1.87)	2.04 (1.81 to 3.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Ovarian Cohort

End point title	Progression-Free Survival (PFS) Ovarian Cohort[81]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[81] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: month				
number (confidence interval 95%)	2.37 (1.48 to 7.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Fibrolamellar carcinoma (FLC) Cohort

End point title	Progression-Free Survival (PFS) Fibrolamellar carcinoma (FLC) Cohort[82]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[82] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: month				
number (confidence interval 95%)	3.58 (1.84 to 3.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Gastroesophageal Cohort

End point title	Progression-Free Survival (PFS) Gastroesophageal Cohort[83]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[83] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: month				
number (confidence interval 95%)	1.74 (0.82 to 2.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Salivary gland Cohort

End point title	Progression-Free Survival (PFS) Salivary gland Cohort[84]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[84] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: month				
number (confidence interval 95%)	5.32 (1.81 to 9.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Endometrial Cohort

End point title	Progression-Free Survival (PFS) Endometrial Cohort[85]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[85] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: month				
number (confidence interval 95%)	1.87 (1.61 to 6.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) HER2 NOS Cohort

End point title	Progression-Free Survival (PFS) HER2 NOS Cohort[86]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[86] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: month				
number (confidence interval 95%)	1.84 (1.74 to 2.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) HER3 NOS Cohort

End point title	Progression-Free Survival (PFS) HER3 NOS Cohort[87]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[87] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: month				
number (confidence interval 95%)	1.69 (1.41 to 2.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) HER4 NOS Cohort

End point title	Progression-Free Survival (PFS) HER4 NOS Cohort[88]

End point description:

PFS was defined as the time (in months) from the first treatment date to the earlier date of the documented PD or death due to any cause. PD was assessed taking results from RECIST over PERCIST.

End point type	Secondary

End point timeframe:

From first treatment date until disease progression or death due to any cause, assessed up to 58 months.

Notes:

[88] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arms represented here were treated in this cohort of patients.

End point values	Neratinib			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: month				
number (confidence interval 95%)	1.71 (1.12 to 1.74)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 1st dose through 28 days after last dose	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1
Reporting groups	
Reporting group title	Neratinib Monotherapy
Reporting group description: Neratinib Monotherapy	
Reporting group title	Neratinib + Fulvestrant + Trastuzumab
Reporting group description: Neratinib + Fulvestrant + Trastuzumab	
Reporting group title	Neratinib + Paclitaxel
Reporting group description: Neratinib + Paclitaxel	
Reporting group title	Fulvestrant + Trastuzumab
Reporting group description: Fulvestrant + Trastuzumab	
Reporting group title	Fulvestrant Monotherapy
Reporting group description: Fulvestrant Monotherapy	
Reporting group title	Neratinib + Fulvestrant
Reporting group description: Neratinib + Fulvestrant	
Reporting group title	Neratinib + Trastuzumab
Reporting group description: Neratinib + Trastuzumab	

Serious adverse events	Neratinib Monotherapy	Neratinib + Fulvestrant + Trastuzumab	Neratinib + Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	144 / 317 (45.43%)	28 / 90 (31.11%)	13 / 22 (59.09%)
number of deaths (all causes)	231	32	14
number of deaths resulting from adverse events	16	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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 associated fever			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Cancer pain			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (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
Tumour pain			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	3 / 317 (0.95%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic thrombosis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Deep vein thrombosis			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain management			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Pain			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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

Oedema peripheral			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Asthenia			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
General physical health deterioration			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Pyrexia			
subjects affected / exposed	7 / 317 (2.21%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Pelvic pain			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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			
Aspiration			

subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Acute respiratory failure			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	8 / 317 (2.52%)	3 / 90 (3.33%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 8	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Productive cough			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Lung disorder			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Pneumothorax			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug abuse			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Confusional state			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Agitation			

subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Product issues			
Device malfunction			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 317 (1.26%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
International normalised ratio increased			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Ejection fraction decreased			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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

Blood creatinine increased			
subjects affected / exposed	4 / 317 (1.26%)	2 / 90 (2.22%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	2 / 5	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	2 / 317 (0.63%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Neutrophil count decreased			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Overdose			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural bile leak			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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 disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Aphasia			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			

subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Cerebrovascular accident			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Coma			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (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
Hypoaesthesia			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Partial seizures			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Neurological decompensation			

subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Syncope			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Nervous system disorder			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	1 / 22 (4.55%)
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	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Epilepsy			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Neutropenia			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Diplopia			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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 pain upper			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Abdominal pain			
subjects affected / exposed	17 / 317 (5.36%)	0 / 90 (0.00%)	3 / 22 (13.64%)
occurrences causally related to treatment / all	2 / 20	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	4 / 317 (1.26%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	4 / 317 (1.26%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Diarrhoea			
subjects affected / exposed	30 / 317 (9.46%)	6 / 90 (6.67%)	6 / 22 (27.27%)
occurrences causally related to treatment / all	34 / 35	7 / 7	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (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
Ileus			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Intestinal obstruction			
subjects affected / exposed	2 / 317 (0.63%)	2 / 90 (2.22%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Intestinal perforation			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Pancreatitis			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	9 / 317 (2.84%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	5 / 9	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			

subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Large intestinal obstruction			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Vomiting			
subjects affected / exposed	14 / 317 (4.42%)	3 / 90 (3.33%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	10 / 16	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Small intestinal obstruction			
subjects affected / exposed	4 / 317 (1.26%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Bile duct stone			

subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Acute hepatic failure			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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 biliary obstruction			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Gallbladder obstruction			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Cholecystitis acute			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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			
Drug eruption			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Hydronephrosis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	5 / 317 (1.58%)	4 / 90 (4.44%)	4 / 22 (18.18%)
occurrences causally related to treatment / all	3 / 7	3 / 5	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 317 (0.32%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 317 (0.32%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 317 (1.26%)	0 / 90 (0.00%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Flank pain			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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

Muscular weakness			
subjects affected / exposed	1 / 317 (0.32%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 317 (0.32%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Sacral pain			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Bone pain			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (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
Abdominal infection			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Bacteraemia			

subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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 infection			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Cystitis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Clostridium difficile infection			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Influenza			
subjects affected / exposed	1 / 317 (0.32%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Lymphangitis			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Perirectal abscess			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Herpes zoster			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Liver abscess			

subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 317 (0.95%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	6 / 317 (1.89%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Urinary tract infection			

subjects affected / exposed	8 / 317 (2.52%)	3 / 90 (3.33%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 10	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (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
Hypoalbuminaemia			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	0 / 317 (0.00%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Dehydration			
subjects affected / exposed	10 / 317 (3.15%)	3 / 90 (3.33%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	5 / 10	1 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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
Hyperkalaemia			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Hyponatraemia			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (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
Malnutrition			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (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

Serious adverse events	Fulvestrant + Trastuzumab	Fulvestrant Monotherapy	Neratinib + Fulvestrant
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	5 / 7 (71.43%)	12 / 45 (26.67%)
number of deaths (all causes)	0	2	31
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tumour associated fever			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cancer pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Mammoplasty			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain management			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (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
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug abuse			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural bile leak			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (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
Brain oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (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
Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute hepatic failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant biliary obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sacral pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Neratinib + Trastuzumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 92 (48.91%)		
number of deaths (all causes)	71		
number of deaths resulting from adverse events	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm malignant			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Tumour pain				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Embolism				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aortic thrombosis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic stenosis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Mammoplasty				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain management				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Pyrexia				
subjects affected / exposed	3 / 92 (3.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Testicular pain				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic pain				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Aspiration				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Productive cough				

subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary embolism				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Disorientation				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug abuse				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Agitation				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device malfunction				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphocyte count decreased				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Troponin I increased				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood lactate dehydrogenase increased				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural bile leak				

subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular arrhythmia			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Cardiac tamponade				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aphasia				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coma				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neurological decompensation				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Epilepsy				

subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	3 / 92 (3.26%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Constipation				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	12 / 92 (13.04%)			
occurrences causally related to treatment / all	15 / 16			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 92 (2.17%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Obstruction gastric				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	6 / 92 (6.52%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis acute				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary obstruction				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct stone				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute hepatic failure				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant biliary obstruction				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gallbladder obstruction				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Drug eruption				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Hydronephrosis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	6 / 92 (6.52%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				

subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sacral pain			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone pain			

subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Arthritis bacterial				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal infection				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Kidney infection				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphangitis				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver abscess				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 92 (4.35%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Pseudomonal sepsis				

subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 92 (1.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Failure to thrive				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 92 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cachexia				

subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Neratinib Monotherapy	Neratinib + Fulvestrant + Trastuzumab	Neratinib + Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	304 / 317 (95.90%)	89 / 90 (98.89%)	20 / 22 (90.91%)
Vascular disorders			
Lymphoedema			
subjects affected / exposed	3 / 317 (0.95%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences (all)	3	1	0
Hot flush			
subjects affected / exposed	4 / 317 (1.26%)	8 / 90 (8.89%)	0 / 22 (0.00%)
occurrences (all)	4	10	0
Hypertension			
subjects affected / exposed	19 / 317 (5.99%)	10 / 90 (11.11%)	1 / 22 (4.55%)
occurrences (all)	23	24	1
Haematoma			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	98 / 317 (30.91%)	33 / 90 (36.67%)	10 / 22 (45.45%)
occurrences (all)	122	61	25
Chills			
subjects affected / exposed	10 / 317 (3.15%)	9 / 90 (10.00%)	2 / 22 (9.09%)
occurrences (all)	11	9	2
Asthenia			
subjects affected / exposed	26 / 317 (8.20%)	17 / 90 (18.89%)	4 / 22 (18.18%)
occurrences (all)	35	32	6
Mass			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Induration			

subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	21 / 317 (6.62%)	10 / 90 (11.11%)	1 / 22 (4.55%)
occurrences (all)	23	13	2
Pyrexia			
subjects affected / exposed	27 / 317 (8.52%)	7 / 90 (7.78%)	3 / 22 (13.64%)
occurrences (all)	33	9	4
Pain			
subjects affected / exposed	10 / 317 (3.15%)	5 / 90 (5.56%)	2 / 22 (9.09%)
occurrences (all)	18	5	2
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	24 / 317 (7.57%)	8 / 90 (8.89%)	3 / 22 (13.64%)
occurrences (all)	30	11	3
Nasal congestion			
subjects affected / exposed	8 / 317 (2.52%)	4 / 90 (4.44%)	0 / 22 (0.00%)
occurrences (all)	8	4	0
Epistaxis			
subjects affected / exposed	9 / 317 (2.84%)	6 / 90 (6.67%)	2 / 22 (9.09%)
occurrences (all)	9	6	4
Cough			
subjects affected / exposed	20 / 317 (6.31%)	8 / 90 (8.89%)	2 / 22 (9.09%)
occurrences (all)	25	10	2
Hiccups			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Disorientation			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	13 / 317 (4.10%)	4 / 90 (4.44%)	1 / 22 (4.55%)
occurrences (all)	14	5	1
Insomnia			
subjects affected / exposed	12 / 317 (3.79%)	5 / 90 (5.56%)	3 / 22 (13.64%)
occurrences (all)	12	5	3
Depression			
subjects affected / exposed	7 / 317 (2.21%)	5 / 90 (5.56%)	2 / 22 (9.09%)
occurrences (all)	9	6	2
Daydreaming			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	27 / 317 (8.52%)	5 / 90 (5.56%)	1 / 22 (4.55%)
occurrences (all)	40	7	2
Blood creatinine increased			
subjects affected / exposed	14 / 317 (4.42%)	9 / 90 (10.00%)	6 / 22 (27.27%)
occurrences (all)	32	18	11
Ejection fraction decreased			
subjects affected / exposed	0 / 317 (0.00%)	6 / 90 (6.67%)	0 / 22 (0.00%)
occurrences (all)	0	6	0
Aspartate aminotransferase increased			
subjects affected / exposed	31 / 317 (9.78%)	8 / 90 (8.89%)	2 / 22 (9.09%)
occurrences (all)	45	13	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 317 (0.32%)	2 / 90 (2.22%)	1 / 22 (4.55%)
occurrences (all)	1	2	1
Neutrophil count decreased			

subjects affected / exposed	5 / 317 (1.58%)	2 / 90 (2.22%)	2 / 22 (9.09%)
occurrences (all)	5	4	4
Blood alkaline phosphatase increased			
subjects affected / exposed	19 / 317 (5.99%)	4 / 90 (4.44%)	2 / 22 (9.09%)
occurrences (all)	27	6	4
Lymphocyte count decreased			
subjects affected / exposed	7 / 317 (2.21%)	2 / 90 (2.22%)	1 / 22 (4.55%)
occurrences (all)	15	7	1
Weight decreased			
subjects affected / exposed	34 / 317 (10.73%)	14 / 90 (15.56%)	1 / 22 (4.55%)
occurrences (all)	50	16	2
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 317 (0.00%)	5 / 90 (5.56%)	1 / 22 (4.55%)
occurrences (all)	0	5	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	4 / 317 (1.26%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences (all)	4	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 317 (6.62%)	6 / 90 (6.67%)	4 / 22 (18.18%)
occurrences (all)	25	8	8
Headache			
subjects affected / exposed	30 / 317 (9.46%)	17 / 90 (18.89%)	0 / 22 (0.00%)
occurrences (all)	32	20	0
Paraesthesia			
subjects affected / exposed	4 / 317 (1.26%)	5 / 90 (5.56%)	1 / 22 (4.55%)
occurrences (all)	4	7	1
Dysmetria			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	5 / 317 (1.58%)	4 / 90 (4.44%)	5 / 22 (22.73%)
occurrences (all)	5	5	10
Dysgeusia			

subjects affected / exposed	18 / 317 (5.68%)	9 / 90 (10.00%)	4 / 22 (18.18%)
occurrences (all)	18	10	5
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	3 / 317 (0.95%)	0 / 90 (0.00%)	2 / 22 (9.09%)
occurrences (all)	8	0	2
Anaemia			
subjects affected / exposed	44 / 317 (13.88%)	13 / 90 (14.44%)	4 / 22 (18.18%)
occurrences (all)	77	30	12
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	2 / 317 (0.63%)	5 / 90 (5.56%)	0 / 22 (0.00%)
occurrences (all)	2	6	0
Retinal detachment			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 317 (0.32%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Constipation			
subjects affected / exposed	111 / 317 (35.02%)	34 / 90 (37.78%)	7 / 22 (31.82%)
occurrences (all)	157	64	12
Abdominal distension			
subjects affected / exposed	13 / 317 (4.10%)	9 / 90 (10.00%)	1 / 22 (4.55%)
occurrences (all)	14	12	1
Abdominal pain			
subjects affected / exposed	60 / 317 (18.93%)	26 / 90 (28.89%)	5 / 22 (22.73%)
occurrences (all)	83	35	6
Abdominal pain lower			

subjects affected / exposed	5 / 317 (1.58%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	5	0	0
Abdominal pain upper			
subjects affected / exposed	9 / 317 (2.84%)	8 / 90 (8.89%)	0 / 22 (0.00%)
occurrences (all)	9	9	0
Diarrhoea			
subjects affected / exposed	211 / 317 (66.56%)	82 / 90 (91.11%)	16 / 22 (72.73%)
occurrences (all)	1225	1068	61
Dry mouth			
subjects affected / exposed	16 / 317 (5.05%)	6 / 90 (6.67%)	2 / 22 (9.09%)
occurrences (all)	18	6	2
Dysphagia			
subjects affected / exposed	8 / 317 (2.52%)	5 / 90 (5.56%)	0 / 22 (0.00%)
occurrences (all)	8	6	0
Gastrointestinal disorder			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	133 / 317 (41.96%)	59 / 90 (65.56%)	11 / 22 (50.00%)
occurrences (all)	181	106	24
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 317 (2.84%)	5 / 90 (5.56%)	2 / 22 (9.09%)
occurrences (all)	9	5	2
Vomiting			
subjects affected / exposed	105 / 317 (33.12%)	44 / 90 (48.89%)	10 / 22 (45.45%)
occurrences (all)	164	83	22
Stomatitis			
subjects affected / exposed	16 / 317 (5.05%)	13 / 90 (14.44%)	0 / 22 (0.00%)
occurrences (all)	19	16	0
Dyspepsia			
subjects affected / exposed	14 / 317 (4.42%)	10 / 90 (11.11%)	3 / 22 (13.64%)
occurrences (all)	14	19	3
Flatulence			
subjects affected / exposed	4 / 317 (1.26%)	4 / 90 (4.44%)	0 / 22 (0.00%)
occurrences (all)	4	4	0
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	7 / 317 (2.21%)	4 / 90 (4.44%)	2 / 22 (9.09%)
occurrences (all)	8	4	2
Onychoclasis			
subjects affected / exposed	3 / 317 (0.95%)	6 / 90 (6.67%)	0 / 22 (0.00%)
occurrences (all)	3	7	0
Rash			
subjects affected / exposed	26 / 317 (8.20%)	13 / 90 (14.44%)	4 / 22 (18.18%)
occurrences (all)	29	16	6
Rash maculo-papular			
subjects affected / exposed	11 / 317 (3.47%)	6 / 90 (6.67%)	0 / 22 (0.00%)
occurrences (all)	13	8	0
Nail disorder			
subjects affected / exposed	1 / 317 (0.32%)	4 / 90 (4.44%)	3 / 22 (13.64%)
occurrences (all)	1	4	3
Pruritus			
subjects affected / exposed	18 / 317 (5.68%)	8 / 90 (8.89%)	1 / 22 (4.55%)
occurrences (all)	20	9	1
Nail ridging			
subjects affected / exposed	1 / 317 (0.32%)	2 / 90 (2.22%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Dry skin			
subjects affected / exposed	20 / 317 (6.31%)	9 / 90 (10.00%)	1 / 22 (4.55%)
occurrences (all)	20	10	1
Dermatitis acneiform			
subjects affected / exposed	11 / 317 (3.47%)	5 / 90 (5.56%)	3 / 22 (13.64%)
occurrences (all)	11	8	3
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Urinary tract obstruction			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	2 / 22 (9.09%)
occurrences (all)	1	0	2
Pollakiuria			

subjects affected / exposed	3 / 317 (0.95%)	3 / 90 (3.33%)	2 / 22 (9.09%)
occurrences (all)	3	5	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	14 / 317 (4.42%)	12 / 90 (13.33%)	2 / 22 (9.09%)
occurrences (all)	16	18	2
Back pain			
subjects affected / exposed	28 / 317 (8.83%)	7 / 90 (7.78%)	3 / 22 (13.64%)
occurrences (all)	32	7	3
Arthralgia			
subjects affected / exposed	23 / 317 (7.26%)	11 / 90 (12.22%)	5 / 22 (22.73%)
occurrences (all)	23	15	6
Spinal disorder			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	8 / 317 (2.52%)	6 / 90 (6.67%)	0 / 22 (0.00%)
occurrences (all)	9	8	0
Musculoskeletal chest pain			
subjects affected / exposed	12 / 317 (3.79%)	4 / 90 (4.44%)	1 / 22 (4.55%)
occurrences (all)	13	6	1
Muscle spasms			
subjects affected / exposed	13 / 317 (4.10%)	15 / 90 (16.67%)	0 / 22 (0.00%)
occurrences (all)	18	15	0
Musculoskeletal pain			
subjects affected / exposed	4 / 317 (1.26%)	4 / 90 (4.44%)	0 / 22 (0.00%)
occurrences (all)	4	5	0
Flank pain			

subjects affected / exposed	2 / 317 (0.63%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Bone pain			
subjects affected / exposed	3 / 317 (0.95%)	4 / 90 (4.44%)	0 / 22 (0.00%)
occurrences (all)	5	5	0
Muscular weakness			
subjects affected / exposed	8 / 317 (2.52%)	5 / 90 (5.56%)	2 / 22 (9.09%)
occurrences (all)	10	6	2
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 317 (0.63%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Infection			
subjects affected / exposed	0 / 317 (0.00%)	0 / 90 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	3 / 317 (0.95%)	7 / 90 (7.78%)	0 / 22 (0.00%)
occurrences (all)	4	7	0
Urinary tract infection			
subjects affected / exposed	21 / 317 (6.62%)	12 / 90 (13.33%)	3 / 22 (13.64%)
occurrences (all)	33	17	5
Respiratory tract infection			
subjects affected / exposed	1 / 317 (0.32%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	7 / 317 (2.21%)	8 / 90 (8.89%)	0 / 22 (0.00%)
occurrences (all)	7	12	0
Upper respiratory tract infection			
subjects affected / exposed	8 / 317 (2.52%)	0 / 90 (0.00%)	0 / 22 (0.00%)
occurrences (all)	9	0	0
Localised infection			
subjects affected / exposed	1 / 317 (0.32%)	1 / 90 (1.11%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	84 / 317 (26.50%)	34 / 90 (37.78%)	6 / 22 (27.27%)
occurrences (all)	99	49	12
Hyperglycaemia			
subjects affected / exposed	9 / 317 (2.84%)	3 / 90 (3.33%)	0 / 22 (0.00%)
occurrences (all)	10	7	0
Dehydration			
subjects affected / exposed	20 / 317 (6.31%)	7 / 90 (7.78%)	4 / 22 (18.18%)
occurrences (all)	33	9	5
Hyperkalaemia			
subjects affected / exposed	8 / 317 (2.52%)	2 / 90 (2.22%)	2 / 22 (9.09%)
occurrences (all)	10	5	2
Hypomagnesaemia			
subjects affected / exposed	11 / 317 (3.47%)	7 / 90 (7.78%)	0 / 22 (0.00%)
occurrences (all)	13	7	0
Hyponatraemia			
subjects affected / exposed	9 / 317 (2.84%)	4 / 90 (4.44%)	2 / 22 (9.09%)
occurrences (all)	12	9	2
Hypoalbuminaemia			
subjects affected / exposed	7 / 317 (2.21%)	4 / 90 (4.44%)	1 / 22 (4.55%)
occurrences (all)	13	8	1
Hypocalcaemia			
subjects affected / exposed	6 / 317 (1.89%)	5 / 90 (5.56%)	1 / 22 (4.55%)
occurrences (all)	7	11	1
Hypophosphataemia			
subjects affected / exposed	11 / 317 (3.47%)	7 / 90 (7.78%)	1 / 22 (4.55%)
occurrences (all)	13	15	2
Hypokalaemia			
subjects affected / exposed	15 / 317 (4.73%)	12 / 90 (13.33%)	1 / 22 (4.55%)
occurrences (all)	17	14	1

Non-serious adverse events	Fulvestrant + Trastuzumab	Fulvestrant Monotherapy	Neratinib + Fulvestrant
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	7 / 7 (100.00%)	45 / 45 (100.00%)
Vascular disorders			
Lymphoedema			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	3 / 45 (6.67%)
occurrences (all)	0	1	3
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	5 / 45 (11.11%)
occurrences (all)	0	1	5
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	3 / 45 (6.67%)
occurrences (all)	4	0	3
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	12 / 45 (26.67%)
occurrences (all)	1	5	20
Chills			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	4 / 45 (8.89%)
occurrences (all)	0	1	8
Mass			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Injection site pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Induration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	8 / 45 (17.78%)
occurrences (all)	0	0	10
Pyrexia			

subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	5 / 45 (11.11%)
occurrences (all)	2	1	5
Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	7 / 45 (15.56%)
occurrences (all)	1	0	7
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	4 / 45 (8.89%)
occurrences (all)	0	0	4
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	2
Cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	4 / 45 (8.89%)
occurrences (all)	0	0	5
Hiccups			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0

Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	6 / 45 (13.33%)
occurrences (all)	0	2	9
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Daydreaming			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	3
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	4 / 45 (8.89%)
occurrences (all)	0	1	4
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	3	0	1
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	5 / 45 (11.11%)
occurrences (all)	2	0	7
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	4 / 45 (8.89%)
occurrences (all)	0	2	4
Headache			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	8 / 45 (17.78%)
occurrences (all)	1	2	10
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	3 / 45 (6.67%)
occurrences (all)	0	1	3
Dysmetria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences (all)	1	0	2
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	4

Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	7 / 45 (15.56%)
occurrences (all)	1	1	16
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Retinal detachment			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	17 / 45 (37.78%)
occurrences (all)	4	3	21
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	8 / 45 (17.78%)
occurrences (all)	1	0	8
Abdominal pain lower			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	3 / 45 (6.67%)
occurrences (all)	0	1	4
Diarrhoea			

subjects affected / exposed	6 / 7 (85.71%)	6 / 7 (85.71%)	39 / 45 (86.67%)
occurrences (all)	8	107	421
Dry mouth			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 45 (6.67%)
occurrences (all)	1	1	4
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Gastrointestinal disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	3 / 7 (42.86%)	3 / 7 (42.86%)	19 / 45 (42.22%)
occurrences (all)	3	5	29
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	3
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	10 / 45 (22.22%)
occurrences (all)	2	1	16
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	4 / 45 (8.89%)
occurrences (all)	0	1	7
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	4 / 45 (8.89%)
occurrences (all)	0	1	4
Flatulence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	3
Onychoclasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0

Rash			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	7 / 45 (15.56%)
occurrences (all)	2	0	8
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	5 / 45 (11.11%)
occurrences (all)	0	0	6
Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	4 / 45 (8.89%)
occurrences (all)	0	0	4
Nail ridging			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	8 / 45 (17.78%)
occurrences (all)	1	0	9
Dermatitis acneiform			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	2	1
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Urinary tract obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	5 / 45 (11.11%)
occurrences (all)	0	1	5
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	8 / 45 (17.78%)
occurrences (all)	0	0	9
Arthralgia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	7 / 45 (15.56%)
occurrences (all)	2	1	10
Spinal disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	6 / 45 (13.33%)
occurrences (all)	0	1	8
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 45 (6.67%)
occurrences (all)	1	1	3
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	3
Musculoskeletal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	1	0	1
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 45 (4.44%)
occurrences (all)	0	1	3
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	1	1

Infections and infestations			
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	3
Respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	4 / 45 (8.89%)
occurrences (all)	0	0	4
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	5 / 45 (11.11%)
occurrences (all)	0	0	5
Localised infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	13 / 45 (28.89%)
occurrences (all)	1	4	16
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	9
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	3
Hyperkalaemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	3 / 45 (6.67%)
occurrences (all)	1	0	9
Hyponatraemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	2 / 45 (4.44%)
occurrences (all)	2	0	4
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	1	0	2
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	4 / 45 (8.89%)
occurrences (all)	0	0	8
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	3

Non-serious adverse events	Neratinib + Trastuzumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 92 (100.00%)		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	10		
Haematoma			

subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	33 / 92 (35.87%)		
occurrences (all)	52		
Chills			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	7		
Asthenia			
subjects affected / exposed	11 / 92 (11.96%)		
occurrences (all)	18		
Mass			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Injection site pruritus			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Induration			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	15 / 92 (16.30%)		
occurrences (all)	22		
Pain			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	3		
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			

Breast mass			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	12 / 92 (13.04%)		
occurrences (all)	14		
Nasal congestion			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	7		
Cough			
subjects affected / exposed	10 / 92 (10.87%)		
occurrences (all)	11		
Hiccups			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	4 / 92 (4.35%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Depression			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	2		
Daydreaming			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Mood swings			

subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	7		
Blood creatinine increased			
subjects affected / exposed	6 / 92 (6.52%)		
occurrences (all)	7		
Ejection fraction decreased			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 92 (4.35%)		
occurrences (all)	5		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	3		
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 92 (4.35%)		
occurrences (all)	4		
Lymphocyte count decreased			
subjects affected / exposed	3 / 92 (3.26%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	15 / 92 (16.30%)		
occurrences (all)	16		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	2		
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	0 / 92 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Dysmetria subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all)	 9 / 92 (9.78%) 10 6 / 92 (6.52%) 7 1 / 92 (1.09%) 1 0 / 92 (0.00%) 0 0 / 92 (0.00%) 0 5 / 92 (5.43%) 5		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	 1 / 92 (1.09%) 1 17 / 92 (18.48%) 29		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	 1 / 92 (1.09%) 1		
Eye disorders Visual acuity reduced subjects affected / exposed occurrences (all)	 0 / 92 (0.00%) 0		

Dry eye			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Retinal detachment			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	28 / 92 (30.43%)		
occurrences (all)	41		
Abdominal distension			
subjects affected / exposed	4 / 92 (4.35%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	12 / 92 (13.04%)		
occurrences (all)	15		
Abdominal pain lower			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	7 / 92 (7.61%)		
occurrences (all)	10		
Diarrhoea			
subjects affected / exposed	74 / 92 (80.43%)		
occurrences (all)	388		
Dry mouth			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	3		
Gastrointestinal disorder			

subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	43 / 92 (46.74%)		
occurrences (all)	66		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	42 / 92 (45.65%)		
occurrences (all)	74		
Stomatitis			
subjects affected / exposed	12 / 92 (13.04%)		
occurrences (all)	19		
Dyspepsia			
subjects affected / exposed	8 / 92 (8.70%)		
occurrences (all)	9		
Flatulence			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 92 (3.26%)		
occurrences (all)	3		
Onychoclasis			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	12 / 92 (13.04%)		
occurrences (all)	17		
Rash maculo-papular			
subjects affected / exposed	4 / 92 (4.35%)		
occurrences (all)	9		
Nail disorder			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		

Pruritus subjects affected / exposed occurrences (all) Nail ridging subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Dermatitis acneiform subjects affected / exposed occurrences (all)	3 / 92 (3.26%) 4 1 / 92 (1.09%) 1 4 / 92 (4.35%) 4 11 / 92 (11.96%) 15		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) Urinary tract obstruction subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all)	2 / 92 (2.17%) 3 0 / 92 (0.00%) 0 0 / 92 (0.00%) 0		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 92 (0.00%) 0		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	2 / 92 (2.17%) 2 11 / 92 (11.96%) 14 12 / 92 (13.04%) 13		

Spinal disorder subjects affected / exposed occurrences (all)	0 / 92 (0.00%) 0		
Spinal pain subjects affected / exposed occurrences (all)	0 / 92 (0.00%) 0		
Pain in extremity subjects affected / exposed occurrences (all)	8 / 92 (8.70%) 9		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	3 / 92 (3.26%) 3		
Muscle spasms subjects affected / exposed occurrences (all)	5 / 92 (5.43%) 5		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 92 (2.17%) 2		
Flank pain subjects affected / exposed occurrences (all)	4 / 92 (4.35%) 6		
Bone pain subjects affected / exposed occurrences (all)	2 / 92 (2.17%) 2		
Muscular weakness subjects affected / exposed occurrences (all)	2 / 92 (2.17%) 2		
Infections and infestations Influenza subjects affected / exposed occurrences (all)	0 / 92 (0.00%) 0		
Infection subjects affected / exposed occurrences (all)	0 / 92 (0.00%) 0		
Nasopharyngitis			

subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Respiratory tract infection			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Paronychia			
subjects affected / exposed	7 / 92 (7.61%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	25 / 92 (27.17%)		
occurrences (all)	33		
Hyperglycaemia			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	5		
Dehydration			
subjects affected / exposed	3 / 92 (3.26%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	5 / 92 (5.43%)		
occurrences (all)	7		
Hyponatraemia			
subjects affected / exposed	4 / 92 (4.35%)		
occurrences (all)	5		

Hypoalbuminaemia subjects affected / exposed occurrences (all)	6 / 92 (6.52%) 6		
Hypocalcaemia subjects affected / exposed occurrences (all)	5 / 92 (5.43%) 7		
Hypophosphataemia subjects affected / exposed occurrences (all)	2 / 92 (2.17%) 2		
Hypokalaemia subjects affected / exposed occurrences (all)	7 / 92 (7.61%) 15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2013	Amendment 1 key changes included primary and secondary objectives, including the primary objective was changed from "HER2-mutation positive solid tumors" to "solid tumors that test positive for somatic human epidermal growth factor receptor mutations in the ERBB gene family (EGFR, HER2, and/or HER3) or EGFR gene amplification", secondary objective #1 was revised from "HER2-mutation positive solid tumors" to "tumors that test positive for somatic human epidermal growth factor receptor mutations (EGFR, HER2, HER3) in the ERBB gene family (EGFR, HER2, and/or HER3) or EGFR gene amplification", secondary objective #2 changed the clinical benefit rate starting from "date of enrollment" to "C1D1". Changes were made to the exploratory objectives. In study design, the safety follow up was revised from "28 to 35 days" to "28 days (+14 days)", two new cohorts of patients with solid tumors were added, for a total of 8 cohorts of patients organized in two groups (HER2 mutation positive and HER3 mutation positive). Additional changes included inclusion and exclusion criteria, study assessments, and clarifications to the study analysis plan.
02 April 2014	Amendment 2 key changes included the addition of a HER2-mutant breast cancer cohort, for a total of nine cohorts organized in two groups (HER2 mutation and HER3 mutation). The number of patients and study centers was increased. Modified PERCIST (mPERCIST) was included with clarification of resistance mechanism to drug and exploratory objectives. The Primary Efficacy Endpoint (Objective Response Rate at 8 weeks) was defined as the proportion of patients who achieved confirmed Complete Response or Partial Response per RECIST version 1.1 or other defined response criteria. Additional changes were made to the study analysis section and known HER2 mutations.
17 March 2015	Amendment 3 key changes included increase in number of patients and study duration, and the addition of five new cohorts, for a total of 14 cohorts organized by mutations (ERBB2, EGFR, and ERBB3), clarified that mutation testing will be centrally evaluated retrospectively, clarifications to the primary and secondary endpoints, addition of new inclusion and exclusion criteria, secondary endpoints, exploratory objectives and clarifications to study analysis methods and treatment timelines. Additional changes to study design included the addition of new combination of regimens, concomitant medications and study assessments.
20 May 2016	Amendment 4 key changes included an increase in the number of centers and study duration, clarifications to the primary objective of the study, introduction of a new treatment cohort with combination treatment of neratinib with paclitaxel in bladder/urinary tract cancer. The following cohorts were closed to enrollment: bladder/urinary tract monotherapy, colorectal monotherapy, breast HR positive monotherapy, lung (NSCLC) monotherapy, primary brain monotherapy, and solid tumors (NOS) ERBB3-mutant monotherapy cohorts. Additional changes included inclusion and exclusion criteria, study assessments, study analysis, and instructions on combination treatment dosing administration and concomitant medications.

04 October 2017	Amendment 5 key changes included an increase in the number of centers, number of patients, and study duration. The primary objective of the study was clarified. A new treatment cohort was added: patients with ERBB2-mutant cervical cancer treated with neratinib monotherapy; patients with ERBB4-mutant solid tumors treated with neratinib monotherapy; patients with EGFR exon 18 mutant lung cancer treated with neratinib monotherapy; and patients with ERBB2-mutant breast, lung, or colorectal cancer treated with neratinib + trastuzumab ± fulvestrant combination therapy. The following cohorts were closed to enrollment: ERBB2-mutant bladder/urinary tract monotherapy, ERBB2-mutant HR positive breast monotherapy, ERBB2-mutant HR positive breast combination with fulvestrant, ERBB2-mutant HR negative breast monotherapy, ERBB2-mutant colorectal monotherapy, ERBB2-mutant endometrial monotherapy, ERBB2-mutant lung monotherapy, EGFR-mutant or amplified primary brain monotherapy, and ERBB3-mutant solid tumor (NOS) monotherapy cohorts. Additional changes included inclusion and exclusion criteria, study assessments, study analysis, and instructions on dose adjustment due to toxicity and combination treatment regimens.
21 January 2020	Amendment 6 key changes included an increase in the number of centers, number of patients, and study duration, and updates to primary, secondary and exploratory objectives of the study. The following cohorts were closed to enrollment: colorectal cancer combination therapy with neratinib + trastuzumab, lung cancer HER2-mutant combination therapy with neratinib + trastuzumab, esophageal cancer monotherapy, biliary cancer monotherapy, ovarian cancer monotherapy, solid tumors (not otherwise specified) HER4-mutant, and fibrolamellar carcinoma. The overall design and plan of the study was revised to accommodate changes to procedures and schedule of events specific to hormone receptor positive, HER2 negative metastatic breast cancer and metastatic cervical cancer cohort and by removal of information applicable to discontinued cohorts. Randomization procedures were added for patients in the HER2-negative, HER2-mutant, HR positive breast cancer cohort with RECIST measurable tumors who were previously treated with CDK4/6 inhibitors. Additional changes included inclusion and exclusion criteria, study assessments, study analysis, and instructions on combination treatment regimens and concomitant therapies.
03 February 2021	Amendment 7 key changes included increase in study duration and exploratory objectives. The following cohorts were closed to enrollment: solid tumors (NOS) HER2-mutant monotherapy and bladder/urinary HER2-mutant combination therapy of neratinib + paclitaxel, clarifications related to these closures were included. Additional changes included inclusion and exclusion criteria and study assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29420467

http://www.ncbi.nlm.nih.gov/pubmed/31806627