Clinical trial results:
A Double-Blind, Placebo-Controlled, Randomized, Multicenter Phase III Study Evaluating the Efficacy and Safety of Pertuzumab in Combination With Trastuzumab and Chemotherapy in Patients With HER2-Positive Metastatic Gastroesophageal Junction and Gastric Cancer

Summary

EudraCT number	2012-003554-83
Trial protocol	ES AT DE FI NL IT BE HU BG PL
Global end of trial date	

Results information

Result version number	v1
This version publication date	24 December 2017
First version publication date	24 December 2017

Trial information

Trial identification

Sponsor protocol code	BO25114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01774786
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, CH, Basel, Switzerland, CH-4070
Public contact	Medical Communications, Hoffmann-La Roche, 41 8008218590, genentech@druginfo.com
Scientific contact	Medical Communications, Hoffmann-La Roche, 41 8008218590, genentech@druginfo.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	Interim
Date of interim/final analysis	09 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare overall survival in subjects treated with pertuzumab in addition to trastuzumab, fluoropyrimidine and cisplatin (TFP) versus subjects treated with placebo in addition to TFP.

Protection of trial subjects:

All subjects (or authorized representatives) signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 163
Country: Number of subjects enrolled	Kazakhstan: 2
Country: Number of subjects enrolled	Korea, Republic of: 94
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	Japan: 80
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Spain: 51
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Turkey: 57
Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	Bulgaria: 6

Country: Number of subjects enrolled	Brazil: 22
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 10
Country: Number of subjects enrolled	Panama: 2
Country: Number of subjects enrolled	Peru: 14
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 21
Worldwide total number of subjects	780
EEA total number of subjects	221

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)	475
From 65 to 84 years	304
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The analysis included data up to a clinical data cut-off date of 9 December 2016.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Pertuzumab + Trastuzumab + Chemotherapy

Arm description:

Subjects will receive pertuzumab in combination with trastuzumab and chemotherapy (cisplatin and fluoropyrimidine [capecitabine or 5-fluorouracil]) for the first 6 treatment cycles (cycle length = 21 days). Subjects will continue to receive pertuzumab and trastuzumab until disease progression occurrence of unacceptable toxicity or withdrawal from the study for another reason.

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

Dosage and administration details:

Subjects will receive pertuzumab 840 milligrams (mg) intravenously (IV) every 3 weeks (q3w) until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

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

Dosage and administration details:

Subjects will receive 8 milligrams per kilogram (mg/kg) IV initial dose on Day 1, followed by 6 mg/kg IV q3w until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will receive 5-fluorouracil 800 milligrams per meter square (mg/m^2)/24 hour IV infusion for 120 hours (Days 1-5) q3w for 6 cycles.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects will receive capecitabine 1000 mg/m^2 orally twice daily, evening of Day 1 to morning of Day 15 (28 doses) q3w for 6 cycles.

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

Dosage and administration details:

Subjects will receive cisplatin 80 mg/m^2 IV q3w for 6 cycles.

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

Dosage and administration details:

Subjects will receive pertuzumab placebo IV q3w until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

Arm title	Placebo + Trastuzumab + Chemotherapy

Arm description:

Subjects will receive pertuzumab placebo in combination with trastuzumab and chemotherapy (cisplatin and fluoropyrimidine [capecitabine or 5-fluorouracil]) for the first 6 treatment cycles (cycle length = 21 days). Subjects will continue to receive pertuzumab placebo and trastuzumab until disease progression occurrence of unacceptable toxicity or withdrawal from the study for another reason.

Arm type	Placebo
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will receive pertuzumab 840 mg intravenously (IV) every 3 weeks (q3w) until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

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

Dosage and administration details:

Subjects will receive 8 mg/kg IV initial dose on Day 1, followed by 6 mg/kg IV q3w until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

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

Dosage and administration details:

Subjects will receive capecitabine 1000 mg/m^2 orally twice daily, evening of Day 1 to morning of Day 15 (28 doses) q3w for 6 cycles.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will receive 5-fluorouracil 800 milligrams per meter square (mg/m^2)/24 hour IV infusion for 120 hours (Days 1-5) q3w for 6 cycles.

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

Dosage and administration details:

Subjects will receive pertuzumab placebo IV q3w until disease progression, occurrence of unacceptable toxicity, or withdrawal from the study for another reason.

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

Dosage and administration details:

Subjects will receive cisplatin 80 mg/m^2 IV q3w for 6 cycles.

Number of subjects in period 1	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy
Started	388	392
Did Not Receive Study Drug	4	3
Received One Dose of Pertuzumab by Error	0	1
Received at Least One Dose of Study Drug	385	388
Completed	0	0
Not completed	388	392
Between Treatment and Follow-up	6	2
Ineligible for Study	1	3
On Treatment	55	47
Consent withdrawn by subject	15	12
Physician decision	1	-
Death	242	262
Lost to follow-up	3	4
In Follow-up	65	62

Baseline characteristics

Reporting groups	
Reporting group title	Pertuzumab + Trastuzumab + Chemotherapy
Reporting group description:	
Subjects will receive pertuzumab in combination with trastuzumab and chemotherapy (cisplatin and fluoropyrimidine [capecitabine or 5-fluorouracil]) for the first 6 treatment cycles (cycle length = 21 days). Subjects will continue to receive pertuzumab and trastuzumab until disease progression occurrence of unacceptable toxicity or withdrawal from the study for another reason.	
Reporting group title	Placebo + Trastuzumab + Chemotherapy
Reporting group description:	
Subjects will receive pertuzumab placebo in combination with trastuzumab and chemotherapy (cisplatin and fluoropyrimidine [capecitabine or 5-fluorouracil]) for the first 6 treatment cycles (cycle length = 21 days). Subjects will continue to receive pertuzumab placebo and trastuzumab until disease progression occurrence of unacceptable toxicity or withdrawal from the study for another reason.	

Reporting group values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy	Total
Number of subjects	388	392	780
Age categorical Units: Subjects			
Adults (18-64 years)	228	247	475
From 65-84 years	159	145	304
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	60.9	60.1	
standard deviation	± 11.3	± 10.7	-
Sex: Female, Male Units: Subjects			
Female	94	69	163
Male	294	323	617
EORTC QLQ-C30 Scores at Baseline - Appetite Loss			
European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30) Appetite Loss Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	26.68	27.59	
standard deviation	± 28.65	± 29.96	-
EORTC QLQ-C30 Scores at Baseline - Cognitive Functional Scale			
EORTC QLQ-C30 Cognitive Functional Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	87.95	88.22	
standard deviation	± 17.32	± 16.18	-
EORTC QLQ-C30 Scores at Baseline - Constipation Symptom Scale			
EORTC QLQ-C30 Constipation Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	20.43	18.41	
standard deviation	± 28.45	± 27.13	-
EORTC QLQ-C30 Scores at Baseline -			

Diarrhea Symptom Scale			
EORTC QLQ-C30 Diarrhea Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	8.87	9.16	
standard deviation	± 17.70	± 18.87	-
EORTC QLQ-C30 Scores at Baseline - Dyspnoea Symptom Scale			
EORTC QLQ-C30 Dyspnoea Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	12.07	12.65	
standard deviation	± 17.99	± 20.20	-
EORTC QLQ-C30 Scores at Baseline - Emotional Functional Scale			
EORTC QLQ-C30 Emotional Functional Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	76.90	76.56	
standard deviation	± 20.21	± 19.84	-
EORTC QLQ-C30 Scores at Baseline - Fatigue Symptom Scale			
EORTC QLQ-C30 Fatigue Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	31.96	32.27	
standard deviation	± 23.46	± 21.92	-
EORTC QLQ-C30 Scores at Baseline - Financial Difficulties Symptom Scale			
EORTC QLQ-C30 Financial Difficulties Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	26.67	26.21	
standard deviation	± 30.32	± 29.78	-
EORTC QLQ-C30 Scores at Baseline - Nausea and Vomiting Symptom Scale			
EORTC QLQ-C30 Nausea and Vomiting Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	11.14	11.92	
standard deviation	± 19.11	± 18.76	-
EORTC QLQ-C30 Scores at Baseline - Pain Symptom Scale			
EORTC QLQ-C30 Pain Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	23.92	23.72	
standard deviation	± 25.92	± 24.82	-
EORTC QLQ-C30 Scores at Baseline - Physical Functional Scale			
EORTC QLQ-C30 Physical Functional Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	80.86	82.05	
standard deviation	± 19.53	± 18.32	-
EORTC QLQ-C30 Scores at Baseline - Global Health Status Scale			
EORTC QLQ-C30 Global Health Status Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	59.77	59.90	
standard deviation	± 22.88	± 22.11	-
EORTC QLQ-C30 Scores at Baseline - Role Functional Scale			

EORTC QLQ-C30 Role Functional Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	77.06	79.33	
standard deviation	± 27.02	± 25.12	-
EORTC QLQ-C30 Scores at Baseline - Social Functional Scale			
EORTC QLQ-C30 Social Functional Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	77.96	75.90	
standard deviation	± 24.09	± 24.69	-
EORTC QLQ-C30 Scores at Baseline - Insomnia Symptom Scale			
EORTC QLQ-C30 Insomnia Symptom Scale score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	22.94	25.41	
standard deviation	± 28.00	± 28.81	-
EORTC QLQ-STO22 Scores at Baseline - Anxiety			
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer Module (EORTC QLQ-STO22) Anxiety score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	40.10	40.48	
standard deviation	± 25.85	± 25.32	-
EORTC QLQ-STO22 Scores at Baseline - Body Image			
EORTC QLQ-STO22 Body Image score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	23.53	23.68	
standard deviation	± 28.40	± 27.47	-
EORTC QLQ-STO22 Scores at Baseline - Dry Mouth			
EORTC QLQ-STO22 Dry Mouth score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	21.80	23.32	
standard deviation	± 25.07	± 26.79	-
EORTC QLQ-STO22 Scores at Baseline - Dysphagia			
EORTC QLQ-STO22 Dysphagia score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	16.29	14.15	
standard deviation	± 21.46	± 18.93	-
EORTC QLQ-STO22 Scores at Baseline - Eating Restrictions			
EORTC QLQ-STO22 Eating Restrictions score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	23.26	22.33	
standard deviation	± 21.78	± 20.22	-
EORTC QLQ-STO22 Scores at Baseline - Hair Loss			
EORTC QLQ-STO22 Hair Loss score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	4.73	4.04	
standard deviation	± 13.28	± 13.20	-
EORTC QLQ-STO22 Scores at Baseline - Pain			

EORTC QLQ-STO22 Pain score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	26.48	26.47	
standard deviation	± 21.34	± 20.70	-
EORTC QLQ-STO22 Scores at Baseline - Reflux Symptoms			
EORTC QLQ-STO22 Reflux Symptoms score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	16.68	17.34	
standard deviation	± 19.03	± 18.31	-
EORTC QLQ-STO22 Scores at Baseline - Taste			
EORTC QLQ-STO22 Taste score at baseline (Cycle 1, Day 1)			
Units: score on a scale			
arithmetic mean	13.79	16.22	
standard deviation	± 23.99	± 25.49	-

End points

End points reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Chemotherapy

Reporting group description:

Subjects will receive pertuzumab in combination with trastuzumab and chemotherapy (cisplatin and fluoropyrimidine [capecitabine or 5-fluorouracil]) for the first 6 treatment cycles (cycle length = 21 days). Subjects will continue to receive pertuzumab and trastuzumab until disease progression occurrence of unacceptable toxicity or withdrawal from the study for another reason.

Reporting group title	Placebo + Trastuzumab + Chemotherapy

Reporting group description:

Subjects will receive pertuzumab placebo in combination with trastuzumab and chemotherapy (cisplatin and fluoropyrimidine [capecitabine or 5-fluorouracil]) for the first 6 treatment cycles (cycle length = 21 days). Subjects will continue to receive pertuzumab placebo and trastuzumab until disease progression occurrence of unacceptable toxicity or withdrawal from the study for another reason.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the time from randomization to death from any cause. The intent-to-treat (ITT) population included all randomized subjects, regardless of whether study medication was received.

End point type	Primary

End point timeframe:

Baseline up to death (up to the 09 Dec 2016 data cutoff, approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	392		
Units: Months				
median (confidence interval 95%)	17.5 (16.2 to 19.3)	14.2 (12.9 to 15.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

The null hypothesis is that the survival distribution of OS is the same in the two treatment arms.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy

Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0565 [2]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1

Notes:

[1] - The study was designed to have 80% power to show a significant difference with respect to the primary endpoint.
[2] - The actual p-value significance threshold required for OS was 0.0452, after alpha spent at the interim analysis was taken into account.

Secondary: Progression-Free Survival, as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Criteria

End point title	Progression-Free Survival, as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Criteria

End point description:

Progression-free survival (PFS) is defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause. Disease progression: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 millimeters (mm) in the sum of diameters of target lesions; the appearance of one or more new lesions. The intent-to-treat (ITT) population included all randomized subjects, regardless of whether study medication was received.

End point type	Secondary

End point timeframe:

Baseline up to death or disease progression, whichever occurs first (up to the 09 Dec 2016 data cutoff, approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	392		
Units: months				
median (confidence interval 95%)	8.5 (8.2 to 9.7)	7.0 (6.4 to 8.2)		

Statistical analyses

Statistical analysis title	Stratified Cox Regression
Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy

Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.86

Notes:

[3] - Given the hierarchical testing procedure and non-statistical significant OS result, confirmatory statistical significance of PFS based on the Log-Rank test p-value cannot be concluded.

Secondary: Percentage of Subjects With Overall Objective Response, as Determined by the Investigator According to RECIST v1.1 Criteria

End point title	Percentage of Subjects With Overall Objective Response, as Determined by the Investigator According to RECIST v1.1 Criteria

End point description:

Overall objective response (partial response [PR] or complete response [CR]) occurring on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator using RECIST v1.1. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. CR: disappearance of all target lesions. Measurable disease is defined as tumor lesions measured in at least one dimension (longest diameter in plane of measurement) with a minimum size of: 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan; 10 mm caliper measurement by clinical examination; 20 mm by chest X-ray. For a malignant lymph node to be considered pathologically enlarged and measurable, it must be greater than or equal to (≥) 15 mm in short axis when assessed by CT scan. The analysis population included subjects with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Baseline up to death or disease progression, whichever occurs first (up to the 09 Dec 2016 data cutoff, approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	352		
Units: Percentage of subjects				
number (not applicable)	56.7	48.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response, as Determined by Investigator According to RECIST v1.1 Criteria

End point title	Duration of Objective Response, as Determined by Investigator According to RECIST v1.1 Criteria

End point description:

Duration of objective response is defined as the time from the first occurrence of a documented objective response to documented disease progression, as determined by the investigator using RECIST v1.1, or death from any cause during the study. Overall objective response: PR or CR occurring on two consecutive occasions ≥ 4 weeks apart. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. CR: disappearance of all target lesions. Disease progression: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; the appearance of one or more new lesions. Data are reported for subjects with measurable disease at baseline who achieved a documented objective response.

End point type	Secondary

End point timeframe:

Baseline up to death or disease progression, whichever occurs first (up to the 09 Dec 2016 data cutoff, approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	170		
Units: months				
median (confidence interval 95%)	10.2 (8.4 to 10.7)	8.4 (6.8 to 8.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Benefit, as Determined by the Investigator According to RECIST v1.1 Criteria

End point title	Percentage of Subjects With Clinical Benefit, as Determined by the Investigator According to RECIST v1.1 Criteria

End point description:

Clinical benefit rate is defined as best response of CR or PR or stable disease for 6 weeks or longer, as determined by the investigator using RECIST v1.1. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Stable Disease: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression, taking as reference the smallest sum diameters while on study. The analysis population included subjects with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Baseline up to death or disease progression, whichever occurs first (up to the 09 Dec 2016 data cutoff, approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	352		
Units: percentage of subjects				
number (not applicable)	84.6	81.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events

End point title	Percentage of Subjects With Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The safety population included all subjects who received any amount of any study medication.

End point type	Secondary

End point timeframe:

Baseline up to the 09 Dec 2016 data cutoff, approximately 3.5 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	388		
Units: percentage of subjects				
number (not applicable)	99.0	99.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Left Ventricular Systolic Dysfunction (LVSD, Symptomatic or Asymptomatic)

End point title	Percentage of Subjects With Left Ventricular Systolic Dysfunction (LVSD, Symptomatic or Asymptomatic)

End point description:

Left ventricular systolic dysfunction may either be asymptomatic or have symptoms of heart failure. It is characterized by dilation of the left ventricle and vasoconstriction. The safety population included all subjects who received any amount of any study medication.

End point type	Secondary

End point timeframe:

Baseline up to the 09 Dec 2016 data cutoff, approximately 3.5 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	388		
Units: percentage of subjects				
number (not applicable)				
Symptomatic LVSD	0.5	0.3		
Asymptomatic LVSD	4.7	4.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Score

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Score

End point description:

The EORTC QLQ-C30 included global health status, functional scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain) and single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Most questions used a 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale [1 'very poor' to 7 'Excellent']). Scores were averaged and transformed to 0 - 100 scale, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 5 - 10 points considered to be a minimally important difference to participants. A positive value means an increase, while a negative value means a decrease, in score at the indicated time-point relative to the score at baseline (Cycle 1, Day 1). Subjects in ITT population with both a baseline and at least 1 post-treatment assessment are included.

End point type	Secondary

End point timeframe:

Day 1 of each 21-day treatment cycle up to 28 and 60-90 days after Day 1 of last treatment cycle (up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	392		
Units: score on a scale				
arithmetic mean (standard deviation)				
Appetite Loss: Cycle 2	6.57 (± 33.18)	0.97 (± 35.86)		
Appetite Loss: Cycle 3	3.63 (± 36.19)	3.81 (± 36.76)		
Appetite Loss: Cycle 4	5.24 (± 34.20)	0.79 (± 34.33)		
Appetite Loss: Cycle 5	4.55 (± 36.50)	2.90 (± 35.85)		

Appetite Loss: Cycle 6	3.94 (± 36.07)	-0.39 (± 36.86)		
Appetite Loss: Cycle 7	2.07 (± 38.05)	1.61 (± 35.98)		
Appetite Loss: Cycle 8	-2.42 (± 33.81)	-3.69 (± 34.20)		
Appetite Loss: Cycle 9	-6.67 (± 31.92)	-4.76 (± 31.67)		
Appetite Loss: Cycle 10	-8.06 (± 32.52)	-6.63 (± 28.48)		
Appetite Loss: Cycle 11	-9.36 (± 33.19)	-9.68 (± 27.38)		
Appetite Loss: Cycle 12	-9.22 (± 33.73)	-9.05 (± 28.51)		
Appetite Loss: Cycle 13	-10.17 (± 31.10)	-10.81 (± 29.18)		
Appetite Loss: Cycle 14	-12.10 (± 31.96)	-12.09 (± 30.32)		
Appetite Loss: Cycle 15	-8.21 (± 32.96)	-9.18 (± 29.81)		
Appetite Loss: Cycle 16	-6.03 (± 33.07)	-10.59 (± 28.74)		
Appetite Loss: Cycle 17	-6.55 (± 29.29)	-9.91 (± 29.05)		
Appetite Loss: Cycle 18	-4.90 (± 31.25)	-14.08 (± 27.98)		
Appetite Loss: Cycle 19	-8.33 (± 31.34)	-13.13 (± 28.57)		
Appetite Loss: Cycle 20	-3.97 (± 31.65)	-13.23 (± 29.66)		
Appetite Loss: Cycle 21	-5.91 (± 31.01)	-14.20 (± 32.76)		
Appetite Loss: Cycle 22	-4.98 (± 34.45)	-16.31 (± 29.38)		
Appetite Loss: Cycle 23	-6.35 (± 36.84)	-11.36 (± 35.90)		
Appetite Loss: Cycle 24	-7.78 (± 33.82)	-13.33 (± 30.00)		
Appetite Loss: Cycle 25	-7.05 (± 35.14)	-12.04 (± 31.02)		
Appetite Loss: Cycle 26	-7.48 (± 34.87)	-12.50 (± 32.52)		
Appetite Loss: Cycle 27	-10.08 (± 33.76)	-9.20 (± 28.03)		
Appetite Loss: Cycle 28	-10.00 (± 32.20)	-11.54 (± 29.73)		
Appetite Loss: Post-treatment Visit 1	7.30 (± 36.86)	2.64 (± 33.14)		
Appetite Loss: Post-treatment Visit 2	-0.33 (± 33.83)	4.55 (± 34.53)		
Cognitive Functional Scale: Cycle 2	-1.90 (± 17.82)	-1.81 (± 16.93)		
Cognitive Functional Scale: Cycle 3	-0.83 (± 17.11)	-3.17 (± 18.30)		
Cognitive Functional Scale: Cycle 4	-2.04 (± 17.78)	-2.99 (± 19.28)		
Cognitive Functional Scale: Cycle 5	-3.04 (± 19.09)	-4.59 (± 19.59)		
Cognitive Functional Scale: Cycle 6	-5.10 (± 19.23)	-3.84 (± 19.00)		
Cognitive Functional Scale: Cycle 7	-4.34 (± 19.52)	-4.31 (± 19.09)		
Cognitive Functional Scale: Cycle 8	-3.15 (± 17.90)	-3.30 (± 17.59)		

Cognitive Functional Scale: Cycle 9	-2.22 (± 18.53)	-4.59 (± 18.53)		
Cognitive Functional Scale: Cycle 10	-3.32 (± 19.44)	-3.11 (± 18.50)		
Cognitive Functional Scale: Cycle 11	-2.83 (± 18.44)	-3.44 (± 17.06)		
Cognitive Functional Scale: Cycle 12	-3.35 (± 20.00)	-2.52 (± 18.16)		
Cognitive Functional Scale: Cycle 13	-1.79 (± 19.04)	-3.60 (± 17.89)		
Cognitive Functional Scale: Cycle 14	-1.98 (± 19.00)	-2.29 (± 17.56)		
Cognitive Functional Scale: Cycle 15	-1.15 (± 18.47)	-2.38 (± 16.05)		
Cognitive Functional Scale: Cycle 16	-2.73 (± 17.16)	-2.55 (± 17.16)		
Cognitive Functional Scale: Cycle 17	-2.53 (± 17.21)	-1.13 (± 15.44)		
Cognitive Functional Scale: Cycle 18	-2.78 (± 18.18)	0.47 (± 16.42)		
Cognitive Functional Scale: Cycle 19	-1.04 (± 18.07)	0.00 (± 14.62)		
Cognitive Functional Scale: Cycle 20	-2.18 (± 19.67)	0.79 (± 15.68)		
Cognitive Functional Scale: Cycle 21	-2.11 (± 20.56)	0.62 (± 16.50)		
Cognitive Functional Scale: Cycle 22	-4.73 (± 18.98)	-0.71 (± 18.04)		
Cognitive Functional Scale: Cycle 23	-2.38 (± 19.60)	1.14 (± 17.75)		
Cognitive Functional Scale: Cycle 24	-2.78 (± 19.69)	1.25 (± 16.18)		
Cognitive Functional Scale: Cycle 25	-5.45 (± 16.41)	-0.93 (± 18.66)		
Cognitive Functional Scale: Cycle 26	-2.38 (± 16.32)	-1.56 (± 18.63)		
Cognitive Functional Scale: Cycle 27	-3.88 (± 18.84)	-1.15 (± 18.33)		
Cognitive Functional Scale: Cycle 28	-3.75 (± 15.78)	0.00 (± 20.00)		
Cognitive Functional Scale: Post-treatment Visit 1	-9.13 (± 21.90)	-9.16 (± 20.02)		
Cognitive Functional Scale: Post-treatment Visit 2	-8.42 (± 20.22)	-11.21 (± 22.48)		
Constipation Symptom Scale: Cycle 2	-5.39 (± 27.05)	0.29 (± 27.23)		
Constipation Symptom Scale: Cycle 3	-7.48 (± 28.98)	-2.11 (± 27.65)		
Constipation Symptom Scale: Cycle 4	-5.32 (± 29.21)	-3.73 (± 28.26)		
Constipation Symptom Scale: Cycle 5	-5.94 (± 29.15)	-1.28 (± 27.64)		
Constipation Symptom Scale: Cycle 6	-7.13 (± 29.65)	-2.33 (± 30.24)		
Constipation Symptom Scale: Cycle 7	-8.13 (± 30.11)	-4.09 (± 29.06)		
Constipation Symptom Scale: Cycle 8	-8.05 (± 30.90)	-4.45 (± 27.32)		
Constipation Symptom Scale: Cycle 9	-10.00 (± 27.10)	-5.61 (± 26.74)		
Constipation Symptom Scale: Cycle 10	-9.32 (± 29.56)	-7.43 (± 26.81)		

Constipation Symptom Scale: Cycle 11	-9.16 (± 29.60)	-6.88 (± 27.84)		
Constipation Symptom Scale: Cycle 12	-10.27 (± 29.04)	-7.25 (± 25.39)		
Constipation Symptom Scale: Cycle 13	-11.19 (± 29.55)	-5.76 (± 26.27)		
Constipation Symptom Scale: Cycle 14	-11.60 (± 27.11)	-6.21 (± 26.00)		
Constipation Symptom Scale: Cycle 15	-10.51 (± 26.59)	-7.14 (± 24.52)		
Constipation Symptom Scale: Cycle 16	-8.62 (± 24.91)	-7.45 (± 25.39)		
Constipation Symptom Scale: Cycle 17	-8.33 (± 24.30)	-5.86 (± 18.59)		
Constipation Symptom Scale: Cycle 18	-7.52 (± 22.93)	-6.57 (± 26.20)		
Constipation Symptom Scale: Cycle 19	-3.47 (± 25.81)	-3.03 (± 25.97)		
Constipation Symptom Scale: Cycle 20	-3.97 (± 26.08)	-4.76 (± 26.68)		
Constipation Symptom Scale: Cycle 21	-3.80 (± 29.23)	-9.26 (± 25.42)		
Constipation Symptom Scale: Cycle 22	-4.98 (± 28.58)	-8.51 (± 27.34)		
Constipation Symptom Scale: Cycle 23	-6.35 (± 28.62)	-8.33 (± 26.04)		
Constipation Symptom Scale: Cycle 24	-7.78 (± 27.01)	-10.00 (± 26.37)		
Constipation Symptom Scale: Cycle 25	-7.05 (± 29.77)	-9.26 (± 28.30)		
Constipation Symptom Scale: Cycle 26	-6.12 (± 30.94)	-6.25 (± 23.09)		
Constipation Symptom Scale: Cycle 27	-7.75 (± 28.95)	-10.34 (± 26.88)		
Constipation Symptom Scale: Cycle 28	-6.67 (± 26.37)	-6.41 (± 21.12)		
Constipation Symptom Scale: Post-treatment Visit 1	-6.78 (± 31.45)	-4.62 (± 26.19)		
Constipation Symptom Scale: Post-treatment Visit 2	-6.93 (± 28.41)	-0.91 (± 31.11)		
Diarrhea Symptom Scale: Cycle 2	15.12 (± 30.42)	5.20 (± 23.79)		
Diarrhea Symptom Scale: Cycle 3	14.64 (± 27.71)	4.99 (± 26.10)		
Diarrhea Symptom Scale: Cycle 4	14.13 (± 27.15)	4.63 (± 24.07)		
Diarrhea Symptom Scale: Cycle 5	13.17 (± 25.47)	4.99 (± 23.70)		
Diarrhea Symptom Scale: Cycle 6	14.81 (± 27.01)	2.47 (± 23.76)		
Diarrhea Symptom Scale: Cycle 7	12.26 (± 23.74)	2.92 (± 23.44)		
Diarrhea Symptom Scale: Cycle 8	8.91 (± 23.56)	2.61 (± 23.53)		
Diarrhea Symptom Scale: Cycle 9	6.83 (± 23.76)	2.04 (± 21.25)		
Diarrhea Symptom Scale: Cycle 10	6.63 (± 23.97)	0.60 (± 20.91)		
Diarrhea Symptom Scale: Cycle 11	5.26 (± 21.80)	2.60 (± 20.36)		
Diarrhea Symptom Scale: Cycle 12	3.98 (± 22.30)	1.92 (± 19.97)		
Diarrhea Symptom Scale: Cycle 13	4.29 (± 24.27)	1.50 (± 19.27)		
Diarrhea Symptom Scale: Cycle 14	3.95 (± 24.45)	0.98 (± 20.15)		
Diarrhea Symptom Scale: Cycle 15	3.33 (± 23.79)	1.02 (± 19.42)		

Diarrhea Symptom Scale: Cycle 16	5.46 (± 21.06)	3.14 (± 15.10)		
Diarrhea Symptom Scale: Cycle 17	2.68 (± 21.05)	2.25 (± 14.94)		
Diarrhea Symptom Scale: Cycle 18	3.59 (± 21.95)	3.29 (± 17.95)		
Diarrhea Symptom Scale: Cycle 19	3.82 (± 19.86)	2.02 (± 16.41)		
Diarrhea Symptom Scale: Cycle 20	5.95 (± 19.47)	3.70 (± 17.05)		
Diarrhea Symptom Scale: Cycle 21	3.80 (± 23.26)	1.85 (± 16.40)		
Diarrhea Symptom Scale: Cycle 22	6.97 (± 24.98)	4.26 (± 17.88)		
Diarrhea Symptom Scale: Cycle 23	6.88 (± 21.72)	8.33 (± 20.49)		
Diarrhea Symptom Scale: Cycle 24	7.22 (± 22.21)	3.33 (± 16.54)		
Diarrhea Symptom Scale: Cycle 25	8.97 (± 23.91)	2.78 (± 14.64)		
Diarrhea Symptom Scale: Cycle 26	5.44 (± 21.89)	5.21 (± 20.93)		
Diarrhea Symptom Scale: Cycle 27	3.88 (± 22.07)	3.45 (± 16.29)		
Diarrhea Symptom Scale: Cycle 28	7.50 (± 27.72)	2.56 (± 16.12)		
Diarrhea Symptom Scale: Post-treatment Visit 1	8.14 (± 26.00)	1.98 (± 24.35)		
Diarrhea Symptom Scale: Post-treatment Visit 2	7.26 (± 25.65)	4.24 (± 29.65)		
Dyspnoea Symptom Scale: Cycle 2	-0.50 (± 19.04)	0.29 (± 19.72)		
Dyspnoea Symptom Scale: Cycle 3	-0.31 (± 20.18)	-0.32 (± 20.38)		
Dyspnoea Symptom Scale: Cycle 4	1.23 (± 20.31)	1.81 (± 21.08)		
Dyspnoea Symptom Scale: Cycle 5	2.58 (± 20.62)	1.39 (± 21.18)		
Dyspnoea Symptom Scale: Cycle 6	3.20 (± 23.79)	0.39 (± 20.55)		
Dyspnoea Symptom Scale: Cycle 7	0.00 (± 21.94)	0.59 (± 20.07)		
Dyspnoea Symptom Scale: Cycle 8	-0.14 (± 21.99)	0.93 (± 20.56)		
Dyspnoea Symptom Scale: Cycle 9	-1.12 (± 20.51)	0.17 (± 18.95)		
Dyspnoea Symptom Scale: Cycle 10	-0.54 (± 21.56)	1.00 (± 16.99)		
Dyspnoea Symptom Scale: Cycle 11	-2.16 (± 19.58)	-1.29 (± 17.77)		
Dyspnoea Symptom Scale: Cycle 12	-2.53 (± 19.75)	-0.71 (± 18.95)		
Dyspnoea Symptom Scale: Cycle 13	-1.43 (± 20.34)	-1.20 (± 16.77)		
Dyspnoea Symptom Scale: Cycle 14	-1.98 (± 19.00)	-2.61 (± 17.98)		
Dyspnoea Symptom Scale: Cycle 15	-2.84 (± 21.26)	2.72 (± 18.95)		
Dyspnoea Symptom Scale: Cycle 16	-1.45 (± 20.42)	1.18 (± 18.86)		
Dyspnoea Symptom Scale: Cycle 17	-1.82 (± 20.61)	0.90 (± 19.87)		
Dyspnoea Symptom Scale: Cycle 18	-0.98 (± 20.15)	-2.35 (± 18.10)		
Dyspnoea Symptom Scale: Cycle 19	-1.74 (± 20.73)	0.51 (± 18.15)		
Dyspnoea Symptom Scale: Cycle 20	-1.19 (± 20.98)	-1.06 (± 16.90)		
Dyspnoea Symptom Scale: Cycle 21	1.27 (± 22.29)	-0.62 (± 19.95)		
Dyspnoea Symptom Scale: Cycle 22	-1.99 (± 22.38)	0.71 (± 14.73)		
Dyspnoea Symptom Scale: Cycle 23	-1.59 (± 21.94)	1.52 (± 14.30)		
Dyspnoea Symptom Scale: Cycle 24	1.11 (± 22.10)	-1.67 (± 12.96)		

Dyspnoea Symptom Scale: Cycle 25	0.64 (± 21.38)	-3.70 (± 15.49)		
Dyspnoea Symptom Scale: Cycle 26	0.00 (± 22.57)	1.04 (± 23.16)		
Dyspnoea Symptom Scale: Cycle 27	0.78 (± 21.19)	3.45 (± 22.44)		
Dyspnoea Symptom Scale: Cycle 28	1.67 (± 21.28)	3.85 (± 17.20)		
Dyspnoea Symptom Scale: Post-treatment Visit 1	6.97 (± 26.98)	6.77 (± 23.82)		
Dyspnoea Symptom Scale: Post-treatment Visit 2	3.30 (± 23.81)	9.39 (± 26.76)		
Emotional Functional Scale: Cycle 2	3.53 (± 16.84)	3.05 (± 18.49)		
Emotional Functional Scale: Cycle 3	2.65 (± 18.63)	3.96 (± 19.95)		
Emotional Functional Scale: Cycle 4	3.10 (± 21.11)	3.67 (± 20.44)		
Emotional Functional Scale: Cycle 5	2.62 (± 19.97)	2.74 (± 21.72)		
Emotional Functional Scale: Cycle 6	1.01 (± 19.64)	4.93 (± 21.00)		
Emotional Functional Scale: Cycle 7	1.72 (± 21.09)	4.41 (± 20.18)		
Emotional Functional Scale: Cycle:8	3.43 (± 20.66)	5.66 (± 19.63)		
Emotional Functional Scale: Cycle 9	4.72 (± 20.10)	4.78 (± 19.45)		
Emotional Functional Scale: Cycle 10	3.72 (± 21.76)	6.74 (± 18.13)		
Emotional Functional Scale: Cycle 11	5.85 (± 19.64)	4.96 (± 19.21)		
Emotional Functional Scale: Cycle 12	4.93 (± 21.38)	5.24 (± 19.14)		
Emotional Functional Scale: Cycle 13	5.00 (± 23.07)	5.18 (± 17.95)		
Emotional Functional Scale: Cycle 14	5.93 (± 22.90)	6.29 (± 19.03)		
Emotional Functional Scale: Cycle 15	6.03 (± 22.13)	5.19 (± 19.61)		
Emotional Functional Scale: Cycle 16	5.17 (± 23.20)	5.29 (± 20.81)		
Emotional Functional Scale: Cycle 17	6.01 (± 23.55)	6.31 (± 18.70)		
Emotional Functional Scale: Cycle 18	3.68 (± 24.11)	5.87 (± 19.39)		
Emotional Functional Scale: Cycle 19	4.69 (± 26.01)	5.56 (± 18.68)		
Emotional Functional Scale: Cycle 20	3.47 (± 26.92)	5.42 (± 17.91)		
Emotional Functional Scale: Cycle 21	4.54 (± 26.55)	6.48 (± 22.00)		
Emotional Functional Scale: Cycle 22	5.35 (± 28.67)	6.91 (± 18.66)		
Emotional Functional Scale: Cycle 23	5.82 (± 28.42)	6.63 (± 21.00)		
Emotional Functional Scale: Cycle 24	5.28 (± 26.22)	8.54 (± 19.57)		
Emotional Functional Scale: Cycle 25	5.93 (± 25.48)	8.80 (± 20.89)		
Emotional Functional Scale: Cycle 26	5.44 (± 27.77)	5.99 (± 16.15)		
Emotional Functional Scale: Cycle 27	7.56 (± 28.34)	5.75 (± 18.51)		
Emotional Functional Scale: Cycle 28	7.08 (± 25.43)	7.05 (± 18.96)		
Emotional Functional Scale: Post-treatment Visit 1	-5.48 (± 23.16)	-3.92 (± 23.28)		
Emotional Functional Scale: Post-treatment Visit 2	-2.64 (± 23.33)	-4.47 (± 23.34)		
Fatigue Symptom Scale: Cycle 2	3.13 (± 19.80)	2.32 (± 21.57)		
Fatigue Symptom Scale: Cycle 3	1.41 (± 22.65)	3.19 (± 22.97)		
Fatigue Symptom Scale: Cycle 4	2.77 (± 23.14)	1.58 (± 24.04)		
Fatigue Symptom Scale: Cycle 5	3.87 (± 25.75)	3.05 (± 24.29)		
Fatigue Symptom Scale: Cycle 6	4.37 (± 25.64)	2.62 (± 23.68)		
Fatigue Symptom Scale: Cycle 7	2.36 (± 26.79)	0.97 (± 23.44)		
Fatigue Symptom Scale: Cycle 8	-0.19 (± 25.00)	-1.18 (± 22.74)		
Fatigue Symptom Scale: Cycle 9	-2.38 (± 22.69)	-2.01 (± 22.84)		
Fatigue Symptom Scale: Cycle 10	-3.41 (± 24.69)	-3.08 (± 22.41)		
Fatigue Symptom Scale: Cycle 11	-4.35 (± 22.66)	-3.44 (± 21.21)		

Fatigue Symptom Scale: Cycle 12	-3.14 (± 24.56)	-4.60 (± 24.39)		
Fatigue Symptom Scale: Cycle 13	-4.57 (± 23.31)	-4.50 (± 21.47)		
Fatigue Symptom Scale: Cycle 14	-6.75 (± 24.32)	-6.54 (± 22.89)		
Fatigue Symptom Scale: Cycle 15	-5.47 (± 24.68)	-4.99 (± 22.40)		
Fatigue Symptom Scale: Cycle 16	-3.54 (± 24.81)	-6.93 (± 21.89)		
Fatigue Symptom Scale: Cycle 17	-4.27 (± 25.50)	-3.45 (± 21.91)		
Fatigue Symptom Scale: Cycle 18	-4.14 (± 24.42)	-8.92 (± 20.54)		
Fatigue Symptom Scale: Cycle 19	-5.32 (± 27.83)	-9.01 (± 20.71)		
Fatigue Symptom Scale: Cycle 20	-5.56 (± 26.64)	-6.53 (± 21.83)		
Fatigue Symptom Scale: Cycle 21	-3.94 (± 25.97)	-7.41 (± 23.45)		
Fatigue Symptom Scale: Cycle 22	-1.49 (± 25.58)	-10.64 (± 22.22)		
Fatigue Symptom Scale: Cycle 23	-5.82 (± 25.23)	-9.60 (± 28.01)		
Fatigue Symptom Scale: Cycle 24	-1.67 (± 27.05)	-12.50 (± 24.29)		
Fatigue Symptom Scale: Cycle 25	-4.70 (± 26.16)	-12.35 (± 22.03)		
Fatigue Symptom Scale: Cycle 26	-4.99 (± 24.85)	-11.46 (± 22.84)		
Fatigue Symptom Scale: Cycle 27	-6.98 (± 23.76)	-5.36 (± 23.87)		
Fatigue Symptom Scale: Cycle 28	-6.39 (± 18.98)	-4.70 (± 26.14)		
Fatigue Symptom Scale: Post-treatment Visit 1	10.02 (± 28.48)	5.25 (± 24.00)		
Fatigue Symptom Scale: Post-treatment Visit 2	7.70 (± 27.65)	9.70 (± 25.01)		
Financial Difficulties Symptom Scale: Cycle 2	-0.90 (± 26.85)	-2.46 (± 25.46)		
Financial Difficulties Symptom Scale: Cycle 3	0.31 (± 27.62)	0.00 (± 26.33)		
Financial Difficulties Symptom Scale: Cycle 4	0.89 (± 25.95)	0.11 (± 25.10)		
Financial Difficulties Symptom Scale: Cycle 5	1.75 (± 27.71)	2.58 (± 26.46)		
Financial Difficulties Symptom Scale: Cycle 6	1.11 (± 27.62)	0.92 (± 26.36)		
Financial Difficulties Symptom Scale: Cycle 7	1.11 (± 31.08)	0.30 (± 26.41)		
Financial Difficulties Symptom Scale: Cycle 8	1.15 (± 30.21)	0.47 (± 25.27)		
Financial Difficulties Symptom Scale: Cycle 9	1.11 (± 29.78)	-0.51 (± 24.75)		
Financial Difficulties Symptom Scale: Cycle 10	0.90 (± 30.10)	-2.42 (± 24.30)		
Financial Difficulties Symptom Scale: Cycle 11	0.39 (± 29.37)	-0.22 (± 24.84)		
Financial Difficulties Symptom Scale: Cycle 12	-1.05 (± 28.91)	-0.97 (± 26.39)		
Financial Difficulties Symptom Scale: Cycle 13	-0.95 (± 28.82)	0.30 (± 24.82)		

Financial Difficulties Symptom Scale: Cycle 14	-1.73 (± 29.74)	-0.98 (± 25.02)		
Financial Difficulties Symptom Scale: Cycle 15	-1.81 (± 28.96)	1.36 (± 26.18)		
Financial Difficulties Symptom Scale: Cycle 16	-3.16 (± 30.13)	0.39 (± 25.97)		
Financial Difficulties Symptom Scale: Cycle 17	-3.87 (± 29.59)	1.35 (± 27.28)		
Financial Difficulties Symptom Scale: Cycle 18	-2.29 (± 27.46)	2.35 (± 26.02)		
Financial Difficulties Symptom Scale: Cycle 19	-0.35 (± 28.41)	-0.51 (± 27.73)		
Financial Difficulties Symptom Scale: Cycle 20	1.19 (± 29.47)	1.59 (± 27.71)		
Financial Difficulties Symptom Scale: Cycle 21	1.27 (± 28.96)	-4.94 (± 27.78)		
Financial Difficulties Symptom Scale: Cycle 22	2.49 (± 26.79)	-4.26 (± 23.69)		
Financial Difficulties Symptom Scale: Cycle 23	-0.53 (± 26.43)	-2.27 (± 29.11)		
Financial Difficulties Symptom Scale: Cycle 24	1.11 (± 24.52)	-5.83 (± 26.03)		
Financial Difficulties Symptom Scale: Cycle 25	3.21 (± 27.42)	-4.63 (± 25.39)		
Financial Difficulties Symptom Scale: Cycle 26	2.72 (± 28.74)	-2.22 (± 26.16)		
Financial Difficulties Symptom Scale: Cycle 27	-3.10 (± 23.92)	1.15 (± 24.37)		
Financial Difficulties Symptom Scale: Cycle 28	-1.67 (± 23.81)	-1.28 (± 24.00)		
Financial Difficulties: Post-treatment Visit 1	1.70 (± 29.66)	1.33 (± 26.21)		
Financial Difficulties: Post-treatment Visit 2	1.98 (± 26.17)	4.24 (± 31.32)		
Nausea And Vomiting Symptom Scale: Cycle 2	5.85 (± 22.65)	4.08 (± 22.25)		
Nausea And Vomiting Symptom Scale: Cycle 3	5.12 (± 23.62)	5.06 (± 21.14)		
Nausea And Vomiting Symptom Scale: Cycle 4	4.10 (± 21.85)	3.56 (± 23.76)		
Nausea And Vomiting Symptom Scale: Cycle 5	5.13 (± 22.58)	5.15 (± 23.81)		
Nausea And Vomiting Symptom Scale: Cycle 6	4.11 (± 23.36)	2.59 (± 21.24)		
Nausea And Vomiting Symptom Scale: Cycle 7	2.07 (± 23.58)	2.49 (± 22.31)		
Nausea And Vomiting Symptom Scale: Cycle 8	-0.86 (± 20.80)	-0.77 (± 20.21)		
Nausea And Vomiting Symptom Scale: Cycle 9	-2.54 (± 20.85)	-2.98 (± 19.78)		
Nausea And Vomiting Symptom Scale: Cycle 10	-4.30 (± 18.81)	-2.81 (± 20.57)		
Nausea And Vomiting Symptom Scale: Cycle 11	-3.51 (± 18.01)	-3.66 (± 20.04)		
Nausea And Vomiting Symptom Scale: Cycle 12	-3.04 (± 18.07)	-3.45 (± 20.34)		
Nausea And Vomiting Symptom Scale: Cycle 13	-4.02 (± 16.29)	-3.60 (± 19.25)		
Nausea And Vomiting Symptom Scale: Cycle 14	-3.46 (± 19.54)	-5.72 (± 18.54)		
Nausea And Vomiting Symptom Scale: Cycle 15	-3.59 (± 16.34)	-3.91 (± 16.55)		

Nausea And Vomiting Symptom Scale: Cycle 16	-0.43 (± 20.32)	-2.55 (± 20.00)		
Nausea And Vomiting Symptom Scale: Cycle 17	-0.60 (± 17.46)	-3.15 (± 16.48)		
Nausea And Vomiting Symptom Scale: Cycle 18	-0.65 (± 16.90)	-3.52 (± 18.24)		
Nausea And Vomiting Symptom Scale: Cycle 19	-0.87 (± 18.32)	-4.04 (± 19.62)		
Nausea And Vomiting Symptom Scale: Cycle 20	-1.79 (± 18.48)	-3.97 (± 17.89)		
Nausea And Vomiting Symptom Scale: Cycle 21	-1.05 (± 20.03)	-6.48 (± 19.80)		
Nausea And Vomiting Symptom Scale: Cycle 22	-3.48 (± 19.14)	-8.16 (± 18.99)		
Nausea And Vomiting Symptom Scale: Cycle 23	-4.23 (± 17.70)	-6.44 (± 24.70)		
Nausea And Vomiting Symptom Scale: Cycle 24	-4.72 (± 16.26)	-7.92 (± 17.70)		
Nausea And Vomiting Symptom Scale: Cycle 25	-4.17 (± 20.84)	-7.41 (± 19.29)		
Nausea And Vomiting Symptom Scale: Cycle 26	-3.40 (± 24.29)	-9.38 (± 19.37)		
Nausea And Vomiting Symptom Scale: Cycle 27	-5.04 (± 22.58)	-7.47 (± 20.70)		
Nausea And Vomiting Symptom Scale: Cycle 28	-1.25 (± 20.11)	-6.41 (± 17.69)		
Nausea/Vomiting Scale: Post-treatment Visit 1	4.68 (± 22.20)	4.13 (± 23.91)		
Nausea/Vomiting Scale: Post-treatment Visit 2	4.29 (± 23.05)	2.73 (± 21.60)		
Pain Symptom Scale: Cycle 2	-6.80 (± 24.69)	-6.38 (± 23.58)		
Pain Symptom Scale: Cycle 3	-9.89 (± 25.16)	-7.23 (± 25.78)		
Pain Symptom Scale: Cycle 4	-10.26 (± 24.78)	-7.46 (± 26.06)		
Pain Symptom Scale: Cycle 5	-8.86 (± 25.88)	-6.25 (± 25.42)		
Pain Symptom Scale: Cycle 6	-8.95 (± 25.73)	-7.33 (± 24.85)		
Pain Symptom Scale: Cycle 7	-10.95 (± 26.13)	-7.46 (± 24.79)		
Pain Symptom Scale: Cycle 8	-9.97 (± 25.80)	-8.53 (± 22.86)		
Pain Symptom Scale: Cycle 9	-9.29 (± 24.83)	-7.82 (± 22.98)		
Pain Symptom Scale: Cycle 10	-9.41 (± 26.10)	-8.13 (± 22.75)		
Pain Symptom Scale: Cycle 11	-10.33 (± 25.77)	-6.34 (± 22.97)		
Pain Symptom Scale: Cycle 12	-10.27 (± 23.10)	-5.24 (± 25.29)		
Pain Symptom Scale: Cycle 13	-10.28 (± 25.79)	-4.80 (± 20.27)		
Pain Symptom Scale: Cycle 14	-10.49 (± 25.49)	-5.56 (± 23.37)		
Pain Symptom Scale: Cycle 15	-11.15 (± 22.86)	-3.74 (± 22.77)		
Pain Symptom Scale: Cycle 16	-9.91 (± 22.94)	-4.71 (± 23.66)		
Pain Symptom Scale: Cycle 17	-7.59 (± 25.00)	-5.63 (± 22.63)		

Pain Symptom Scale: Cycle 18	-8.82 (± 23.42)	-8.22 (± 20.68)		
Pain Symptom Scale: Cycle 19	-8.16 (± 25.13)	-5.05 (± 21.48)		
Pain Symptom Scale: Cycle 20	-6.94 (± 25.90)	-6.08 (± 19.24)		
Pain Symptom Scale: Cycle 21	-9.92 (± 27.15)	-6.48 (± 23.44)		
Pain Symptom Scale: Cycle 22	-7.71 (± 26.96)	-8.51 (± 19.62)		
Pain Symptom Scale: Cycle 23	-10.85 (± 22.03)	-7.95 (± 26.29)		
Pain Symptom Scale: Cycle 24	-10.00 (± 24.39)	-10.00 (± 17.21)		
Pain Symptom Scale: Cycle 25	-9.94 (± 24.09)	-12.96 (± 19.96)		
Pain Symptom Scale: Cycle 26	-10.54 (± 22.49)	-8.33 (± 18.45)		
Pain Symptom Scale: Cycle 27	-11.24 (± 22.34)	-5.75 (± 21.95)		
Pain Symptom Scale: Cycle 28	-10.42 (± 27.91)	-9.62 (± 19.54)		
Pain Symptom Scale: Post-treatment Visit 1	1.13 (± 27.27)	2.06 (± 28.70)		
Pain Symptom Scale: Post-treatment Visit 2	-1.49 (± 28.39)	5.45 (± 29.96)		
Physical Functional Scale: Cycle 2	-3.58 (± 14.56)	-3.01 (± 15.34)		
Physical Functional Scale: Cycle 3	-2.99 (± 17.19)	-3.92 (± 17.03)		
Physical Functional Scale: Cycle 4	-3.28 (± 18.87)	-3.50 (± 17.99)		
Physical Functional Scale: Cycle 5	-3.10 (± 19.35)	-4.62 (± 17.62)		
Physical Functional Scale: Cycle 6	-5.00 (± 20.30)	-3.84 (± 18.65)		
Physical Functional Scale: Cycle 7	-3.66 (± 20.75)	-3.79 (± 19.82)		
Physical Functional Scale: Cycle 8	-2.24 (± 21.14)	-1.56 (± 18.55)		
Physical Functional Scale: Cycle 9	-1.59 (± 20.21)	-0.75 (± 18.44)		
Physical Functional Scale: Cycle 10	0.11 (± 19.93)	-0.27 (± 17.16)		
Physical Functional Scale: Cycle 11	0.35 (± 19.43)	0.27 (± 17.09)		
Physical Functional Scale: Cycle 12	-1.05 (± 20.06)	0.89 (± 16.35)		
Physical Functional Scale: Cycle 13	-0.80 (± 20.65)	0.27 (± 17.41)		
Physical Functional Scale: Cycle 14	-0.02 (± 20.14)	1.70 (± 18.09)		
Physical Functional Scale: Cycle 15	0.41 (± 18.91)	-0.95 (± 17.99)		
Physical Functional Scale: Cycle 16	-1.08 (± 19.85)	-0.08 (± 18.18)		
Physical Functional Scale: Cycle 17	-0.46 (± 19.43)	-0.81 (± 17.55)		
Physical Functional Scale: Cycle 18	0.13 (± 19.74)	0.75 (± 16.85)		
Physical Functional Scale: Cycle 19	1.39 (± 19.82)	1.31 (± 14.38)		
Physical Functional Scale: Cycle 20	0.71 (± 21.08)	0.85 (± 16.74)		
Physical Functional Scale: Cycle 21	0.42 (± 22.20)	0.25 (± 18.18)		

Physical Functional Scale: Cycle 22	-2.79 (± 21.90)	1.42 (± 16.79)		
Physical Functional Scale: Cycle 23	-1.48 (± 21.47)	0.61 (± 19.60)		
Physical Functional Scale: Cycle 24	-2.67 (± 22.27)	3.00 (± 16.47)		
Physical Functional Scale: Cycle 25	-2.18 (± 20.61)	4.81 (± 15.91)		
Physical Functional Scale: Cycle 26	-1.90 (± 20.09)	-1.88 (± 20.69)		
Physical Functional Scale: Cycle 27	0.16 (± 18.66)	-3.68 (± 19.40)		
Physical Functional Scale: Cycle 28	-1.17 (± 17.79)	-2.82 (± 18.97)		
Physical Functional Scale: Post-treatment Visit 1	-11.37 (± 23.67)	-7.51 (± 20.53)		
Physical Functional Scale: Post-treatment Visit 2	-11.49 (± 24.31)	-11.82 (± 20.27)		
Global Health Status Scale: Cycle 2	1.81 (± 23.35)	4.29 (± 23.42)		
Global Health Status Scale: Cycle 3	1.56 (± 25.05)	2.86 (± 25.03)		
Global Health Status Scale: Cycle 4	1.39 (± 25.26)	4.15 (± 23.79)		
Global Health Status Scale: Cycle 5	1.17 (± 25.70)	3.92 (± 23.05)		
Global Health Status Scale: Cycle 6	0.68 (± 27.89)	3.61 (± 23.13)		
Global Health Status Scale: Cycle 7	1.83 (± 27.81)	3.33 (± 22.77)		
Global Health Status Scale: Cycle 8	3.06 (± 27.09)	5.18 (± 23.18)		
Global Health Status Scale: Cycle 9	4.39 (± 26.25)	4.68 (± 22.99)		
Global Health Status Scale: Cycle 10	4.80 (± 25.35)	5.07 (± 22.77)		
Global Health Status Scale: Cycle 11	5.78 (± 26.62)	3.82 (± 23.75)		
Global Health Status Scale: Cycle 12	3.11 (± 24.89)	5.34 (± 24.47)		
Global Health Status Scale: Cycle 13	3.51 (± 23.82)	3.83 (± 23.78)		
Global Health Status Scale: Cycle 14	5.97 (± 23.09)	4.82 (± 24.86)		
Global Health Status Scale: Cycle 15	4.26 (± 25.98)	1.70 (± 24.46)		
Global Health Status Scale: Cycle 16	3.12 (± 25.16)	3.04 (± 23.77)		
Global Health Status Scale: Cycle 17	2.93 (± 24.84)	3.83 (± 24.84)		
Global Health Status Scale: Cycle 18	3.02 (± 23.88)	2.58 (± 27.08)		
Global Health Status Scale: Cycle 19	3.25 (± 26.39)	3.97 (± 25.43)		
Global Health Status Scale: Cycle 20	5.12 (± 24.20)	4.89 (± 25.69)		
Global Health Status Scale: Cycle 21	5.38 (± 23.87)	5.40 (± 24.72)		
Global Health Status Scale: Cycle 22	3.79 (± 22.56)	3.19 (± 25.57)		
Global Health Status Scale: Cycle 23	4.03 (± 23.85)	4.07 (± 27.18)		
Global Health Status Scale: Cycle 24	4.24 (± 22.66)	2.92 (± 30.58)		
Global Health Status Scale: Cycle 25	3.59 (± 22.38)	8.10 (± 25.39)		
Global Health Status Scale: Cycle 26	7.27 (± 24.55)	5.47 (± 26.91)		
Global Health Status Scale: Cycle 27	7.54 (± 23.19)	1.72 (± 28.38)		
Global Health Status Scale: Cycle 28	4.49 (± 22.69)	4.81 (± 28.98)		
Global Health Status Scale: Post-treatment Visit 1	-7.24 (± 27.24)	-6.14 (± 24.97)		
Global Health Status Scale: Post-treatment Visit 2	-2.72 (± 27.46)	-5.68 (± 26.57)		
Role Functional Scale: Cycle 2	-3.78 (± 24.99)	-2.82 (± 24.35)		
Role Functional Scale: Cycle 3	-3.62 (± 25.96)	-4.55 (± 28.00)		
Role Functional Scale: Cycle 4	-4.64 (± 27.69)	-5.99 (± 26.87)		
Role Functional Scale: Cycle 5	-4.72 (± 27.68)	-7.41 (± 27.25)		

Role Functional Scale: Cycle 6	-6.13 (± 28.94)	-6.03 (± 28.51)		
Role Functional Scale: Cycle 7	-4.82 (± 29.75)	-5.34 (± 26.31)		
Role Functional Scale: Cycle 8	-1.85 (± 28.87)	-2.38 (± 26.41)		
Role Functional Scale: Cycle 9	-1.19 (± 28.57)	-2.47 (± 27.29)		
Role Functional Scale: Cycle 10	-1.79 (± 28.10)	0.90 (± 25.97)		
Role Functional Scale: Cycle 11	-0.78 (± 28.34)	-2.69 (± 24.94)		
Role Functional Scale: Cycle 12	-1.05 (± 27.28)	0.24 (± 24.07)		
Role Functional Scale: Cycle 13	-2.01 (± 26.61)	-2.40 (± 24.91)		
Role Functional Scale: Cycle 14	-0.86 (± 27.27)	-1.31 (± 25.66)		
Role Functional Scale: Cycle 15	-1.03 (± 27.51)	-3.23 (± 25.40)		
Role Functional Scale: Cycle 16	-3.16 (± 28.73)	-2.35 (± 25.48)		
Role Functional Scale: Cycle 17	-1.04 (± 26.69)	-3.38 (± 25.88)		
Role Functional Scale: Cycle 18	-0.16 (± 27.10)	0.23 (± 26.05)		
Role Functional Scale: Cycle 19	1.04 (± 27.55)	-0.25 (± 23.48)		
Role Functional Scale: Cycle 20	-1.19 (± 30.04)	0.79 (± 23.46)		
Role Functional Scale: Cycle 21	-0.84 (± 28.98)	0.00 (± 27.47)		
Role Functional Scale: Cycle 22	-2.24 (± 27.96)	1.06 (± 22.63)		
Role Functional Scale: Cycle 23	-3.44 (± 30.11)	1.14 (± 25.01)		
Role Functional Scale: Cycle 24	-4.44 (± 29.73)	2.08 (± 24.22)		
Role Functional Scale: Cycle 25	-3.53 (± 29.21)	4.63 (± 26.91)		
Role Functional Scale: Cycle 26	-1.36 (± 28.02)	0.52 (± 26.60)		
Role Functional Scale: Cycle 27	-1.55 (± 30.82)	-4.02 (± 29.77)		
Role Functional Scale: Cycle 28	-0.42 (± 27.86)	-3.85 (± 29.56)		
Role Functional Scale: Post-Treatment Visit 1	-14.61 (± 30.41)	-9.49 (± 28.64)		
Role Functional Scale: Post-Treatment Visit 2	-10.73 (± 31.94)	-15.45 (± 31.82)		
Social Functional Scale: Cycle 2	-3.45 (± 24.07)	-0.44 (± 23.09)		
Social Functional Scale: Cycle 3	-4.62 (± 25.25)	-2.07 (± 25.35)		
Social Functional Scale: Cycle 4	-2.59 (± 25.08)	-1.70 (± 26.58)		
Social Functional Scale: Cycle 5	-5.54 (± 27.03)	-3.26 (± 27.24)		
Social Functional Scale: Cycle 6	-5.72 (± 27.87)	-1.04 (± 27.20)		
Social Functional Scale: Cycle 7	-2.69 (± 27.13)	-0.15 (± 26.00)		

Social Functional Scale: Cycle 8	-1.72 (± 26.93)	1.08 (± 26.49)		
Social Functional Scale: Cycle 9	0.56 (± 27.59)	0.77 (± 25.11)		
Social Functional Scale: Cycle 10	-0.81 (± 27.31)	2.31 (± 25.75)		
Social Functional Scale: Cycle 11	0.58 (± 27.35)	1.94 (± 24.39)		
Social Functional Scale: Cycle 12	0.52 (± 28.59)	2.40 (± 24.70)		
Social Functional Scale: Cycle 13	0.83 (± 25.31)	2.10 (± 25.73)		
Social Functional Scale: Cycle 14	1.98 (± 26.71)	2.12 (± 24.89)		
Social Functional Scale: Cycle 15	1.79 (± 27.24)	0.00 (± 27.08)		
Social Functional Scale: Cycle 16	-0.72 (± 25.76)	0.39 (± 25.84)		
Social Functional Scale: Cycle 17	-0.45 (± 26.51)	1.58 (± 24.39)		
Social Functional Scale: Cycle 18	-0.98 (± 25.99)	2.11 (± 26.42)		
Social Functional Scale: Cycle 19	2.26 (± 26.56)	3.28 (± 21.53)		
Social Functional Scale: Cycle 20	1.59 (± 27.09)	0.79 (± 22.88)		
Social Functional Scale: Cycle 21	1.27 (± 28.09)	5.86 (± 22.00)		
Social Functional Scale: Cycle 22	1.24 (± 27.72)	2.84 (± 24.16)		
Social Functional Scale: Cycle 23	6.08 (± 27.32)	1.89 (± 22.51)		
Social Functional Scale: Cycle 24	5.83 (± 25.64)	4.17 (± 24.39)		
Social Functional Scale: Cycle 25	1.60 (± 27.27)	2.78 (± 23.40)		
Social Functional Scale: Cycle 26	3.74 (± 26.19)	1.56 (± 24.45)		
Social Functional Scale: Cycle 27	5.81 (± 24.37)	-1.72 (± 26.85)		
Social Functional Scale: Cycle 28	6.25 (± 23.48)	-0.64 (± 24.26)		
Social Functional Scale: Post-Treatment Visit 1	-9.13 (± 26.47)	-3.80 (± 28.74)		
Social Functional Scale: Post-Treatment Visit 2	-5.45 (± 28.49)	-8.48 (± 28.98)		
Insomnia Symptom Scale: Cycle 2	-0.69 (± 26.82)	-0.39 (± 28.27)		
Insomnia Symptom Scale: Cycle 3	-3.53 (± 27.03)	-3.48 (± 30.14)		
Insomnia Symptom Scale: Cycle 4	-2.88 (± 28.14)	-3.62 (± 30.40)		
Insomnia Symptom Scale: Cycle 5	-2.21 (± 29.27)	-2.66 (± 30.17)		
Insomnia Symptom Scale: Cycle 6	-2.94 (± 28.63)	-5.58 (± 32.53)		
Insomnia Symptom Scale: Cycle 7	-4.56 (± 28.42)	-4.82 (± 32.98)		
Insomnia Symptom Scale: Cycle 8	-6.13 (± 27.72)	-6.45 (± 30.75)		
Insomnia Symptom Scale: Cycle 9	-8.97 (± 25.69)	-6.12 (± 30.32)		
Insomnia Symptom Scale: Cycle 10	-8.24 (± 26.69)	-4.42 (± 28.79)		
Insomnia Symptom Scale: Cycle 11	-8.97 (± 28.19)	-5.81 (± 27.69)		
Insomnia Symptom Scale: Cycle 12	-8.81 (± 27.67)	-6.43 (± 26.49)		
Insomnia Symptom Scale: Cycle 13	-10.17 (± 26.71)	-5.11 (± 24.29)		
Insomnia Symptom Scale: Cycle 14	-9.14 (± 26.84)	-7.84 (± 24.45)		

Insomnia Symptom Scale: Cycle 15	-9.74 (± 28.89)	-5.10 (± 21.59)		
Insomnia Symptom Scale: Cycle 16	-8.91 (± 26.14)	-4.31 (± 26.62)		
Insomnia Symptom Scale: Cycle 17	-11.01 (± 26.62)	-5.41 (± 26.48)		
Insomnia Symptom Scale: Cycle 18	-8.82 (± 28.12)	-8.45 (± 20.09)		
Insomnia Symptom Scale: Cycle 19	-11.46 (± 29.35)	-7.58 (± 22.49)		
Insomnia Symptom Scale: Cycle 20	-10.32 (± 27.37)	-5.29 (± 25.55)		
Insomnia Symptom Scale: Cycle 21	-11.81 (± 27.24)	-4.94 (± 27.02)		
Insomnia Symptom Scale: Cycle 22	-10.95 (± 31.46)	-7.80 (± 19.92)		
Insomnia Symptom Scale: Cycle 23	-10.58 (± 34.82)	-6.06 (± 23.04)		
Insomnia Symptom Scale: Cycle 24	-9.44 (± 31.94)	-7.50 (± 21.99)		
Insomnia Symptom Scale: Cycle 25	-10.26 (± 28.42)	-8.33 (± 26.87)		
Insomnia Symptom Scale: Cycle 26	-9.52 (± 32.63)	-4.17 (± 20.30)		
Insomnia Symptom Scale: Cycle 27	-13.18 (± 30.11)	-4.60 (± 19.36)		
Insomnia Symptom Scale: Cycle 28	-11.67 (± 31.62)	-1.28 (± 22.07)		
Insomnia Symptom Scale: Post-Treatment Visit 1	2.81 (± 29.19)	-1.32 (± 30.81)		
Insomnia Symptom Scale: Post-Treatment Visit 2	5.67 (± 29.23)	3.03 (± 31.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EORTC QLQ-Gastric Cancer Module (EORTC QLQ-STO22) Questionnaire Score

End point title	Change from Baseline in EORTC QLQ-Gastric Cancer Module (EORTC QLQ-STO22) Questionnaire Score

End point description:

The EORTC QLQ-STO22 is a gastric cancer quality of life questionnaire. There are 22 questions concerning disease, treatment related symptoms, side effects, dysphagia, nutritional aspects, and questions about the emotional problems of gastric cancer (dysphagia, pain, reflux, eating restrictions, anxiety, dry mouth, body image, and hair loss). The questions are grouped into five scales and 4 single items which are related to the symptoms of the disease. Most questions used 4-point scale (1 'Not at all' to 4 'Very much'; 1 question was a yes or no answer). A linear transformation was used to standardize all scores and single-items to a scale of 0 to 100; higher score=better level of functioning or greater degree of symptoms. Positive value means increase, while negative value means decrease, in score at indicated time-point relative to score at baseline (Cycle 1, Day 1). Subjects in ITT population with both a baseline and at least 1 post-treatment assessment are included.

End point type	Secondary

End point timeframe:

Day 1 of each 21-day treatment cycle up to 28 and 60-90 days after Day 1 of last treatment cycle (up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	392		
Units: score on a scale				
arithmetic mean (standard deviation)				
Anxiety: Cycle 2	-2.58 (± 21.72)	-4.11 (± 21.19)		
Anxiety: Cycle 3	-4.14 (± 22.45)	-3.87 (± 23.19)		
Anxiety: Cycle 4	-4.52 (± 23.01)	-7.25 (± 23.16)		
Anxiety: Cycle 5	-4.10 (± 22.94)	-7.39 (± 24.36)		
Anxiety: Cycle 6	-4.54 (± 23.97)	-8.42 (± 25.21)		
Anxiety: Cycle 7	-6.40 (± 24.00)	-10.40 (± 24.37)		
Anxiety: Cycle 8	-9.00 (± 23.17)	-11.92 (± 24.50)		
Anxiety: Cycle 9	-10.09 (± 23.30)	-11.43 (± 23.24)		
Anxiety: Cycle 10	-11.17 (± 25.05)	-12.64 (± 22.09)		
Anxiety: Cycle 11	-10.78 (± 23.47)	-12.09 (± 21.84)		
Anxiety: Cycle 12	-12.62 (± 26.24)	-13.16 (± 23.11)		
Anxiety: Cycle 13	-13.32 (± 25.93)	-13.33 (± 22.47)		
Anxiety: Cycle 14	-14.32 (± 26.49)	-12.43 (± 23.59)		
Anxiety: Cycle 15	-13.42 (± 26.64)	-10.65 (± 25.74)		
Anxiety: Cycle 16	-12.75 (± 26.87)	-12.57 (± 23.89)		
Anxiety: Cycle 17	-13.41 (± 27.30)	-12.79 (± 21.01)		
Anxiety: Cycle 18	-13.53 (± 28.05)	-12.38 (± 22.90)		
Anxiety: Cycle 19	-14.50 (± 27.41)	-12.48 (± 20.08)		
Anxiety: Cycle 20	-15.34 (± 29.21)	-12.37 (± 23.73)		
Anxiety: Cycle 21	-16.03 (± 28.84)	-14.47 (± 25.00)		
Anxiety: Cycle 22	-13.30 (± 30.77)	-15.46 (± 23.83)		
Anxiety: Cycle 23	-17.28 (± 30.64)	-14.47 (± 29.55)		
Anxiety: Cycle 24	-16.11 (± 30.65)	-17.09 (± 23.76)		
Anxiety: Cycle 25	-16.03 (± 29.47)	-17.78 (± 23.68)		
Anxiety: Cycle 26	-19.73 (± 30.28)	-13.26 (± 22.11)		

Anxiety: Cycle 27	-21.71 (± 29.89)	-12.70 (± 20.67)		
Anxiety: Cycle 28	-22.51 (± 29.34)	-12.89 (± 22.38)		
Anxiety: Post-treatment Monitoring Visit 1	-0.73 (± 25.18)	-4.73 (± 27.21)		
Anxiety: Post-treatment Monitoring Visit 2	-4.04 (± 28.24)	-3.98 (± 25.02)		
Body Image: Cycle 2	1.33 (± 28.19)	1.20 (± 26.44)		
Body Image: Cycle 3	1.48 (± 29.06)	3.88 (± 28.03)		
Body Image: Cycle 4	4.20 (± 28.51)	1.15 (± 27.19)		
Body Image: Cycle 5	2.86 (± 30.91)	1.06 (± 25.74)		
Body Image: Cycle 6	0.75 (± 30.11)	2.78 (± 28.48)		
Body Image: Cycle 7	-0.56 (± 28.94)	0.29 (± 25.53)		
Body Image: Cycle 8	-1.74 (± 29.83)	0.00 (± 26.30)		
Body Image: Cycle 9	-3.58 (± 28.74)	-0.69 (± 24.52)		
Body Image: Cycle 10	-5.07 (± 30.15)	-3.25 (± 24.55)		
Body Image: Cycle 11	-4.62 (± 30.24)	-1.53 (± 25.46)		
Body Image: Cycle 12	-5.31 (± 31.92)	-2.66 (± 27.04)		
Body Image: Cycle 13	-4.73 (± 30.23)	-2.73 (± 25.99)		
Body Image: Cycle 14	-5.43 (± 29.70)	-4.62 (± 24.05)		
Body Image: Cycle 15	-3.08 (± 30.63)	-2.43 (± 27.03)		
Body Image: Cycle 16	-1.74 (± 32.99)	-1.19 (± 26.10)		
Body Image: Cycle 17	-2.70 (± 32.76)	-2.28 (± 21.75)		
Body Image: Cycle 18	-2.64 (± 30.44)	-5.71 (± 23.38)		
Body Image: Cycle 19	-2.81 (± 33.57)	-5.21 (± 20.76)		
Body Image: Cycle 20	-3.97 (± 30.79)	-5.38 (± 22.74)		
Body Image: Cycle 21	1.69 (± 30.15)	-8.18 (± 26.07)		
Body Image: Cycle 22	-1.49 (± 32.01)	-10.87 (± 22.28)		
Body Image: Cycle 23	-5.82 (± 24.35)	-8.53 (± 29.18)		
Body Image: Cycle 24	-0.56 (± 31.25)	-11.11 (± 23.36)		
Body Image: Cycle 25	-3.21 (± 28.97)	-11.43 (± 24.18)		
Body Image: Cycle 26	-4.76 (± 29.66)	-6.45 (± 18.09)		
Body Image: Cycle 27	0.78 (± 24.65)	-7.14 (± 21.00)		
Body Image: Cycle 28	-4.27 (± 26.69)	-4.00 (± 24.19)		
Body Image: Post-treatment Monitoring Visit 1	2.48 (± 31.57)	3.42 (± 29.31)		
Body Image: Post-treatment Monitoring Visit 2	2.36 (± 35.40)	6.35 (± 27.38)		

Dry Mouth: Cycle 2	7.72 (± 28.70)	3.00 (± 25.43)		
Dry Mouth: Cycle 3	6.10 (± 28.65)	4.87 (± 27.33)		
Dry Mouth: Cycle 4	4.76 (± 29.40)	2.66 (± 31.06)		
Dry Mouth: Cycle 5	2.47 (± 29.67)	2.57 (± 28.68)		
Dry Mouth: Cycle 6	2.96 (± 30.14)	1.19 (± 27.65)		
Dry Mouth: Cycle 7	-1.96 (± 28.82)	0.44 (± 28.54)		
Dry Mouth: Cycle 8	-2.43 (± 28.68)	-2.66 (± 26.27)		
Dry Mouth: Cycle 9	-3.70 (± 25.70)	-4.32 (± 24.74)		
Dry Mouth: Cycle 10	-6.27 (± 25.04)	-3.46 (± 23.53)		
Dry Mouth: Cycle 11	-7.69 (± 25.46)	-1.96 (± 26.56)		
Dry Mouth: Cycle 12	-8.18 (± 24.22)	-4.35 (± 26.36)		
Dry Mouth: Cycle 13	-9.69 (± 24.08)	-8.48 (± 26.50)		
Dry Mouth: Cycle 14	-8.33 (± 24.60)	-3.63 (± 29.78)		
Dry Mouth: Cycle 15	-7.89 (± 22.20)	-7.29 (± 26.58)		
Dry Mouth: Cycle 16	-6.32 (± 24.44)	-8.33 (± 27.80)		
Dry Mouth: Cycle 17	-7.44 (± 23.12)	-3.20 (± 24.32)		
Dry Mouth: Cycle 18	-5.56 (± 24.86)	-8.10 (± 28.62)		
Dry Mouth: Cycle 19	-5.90 (± 24.18)	-7.69 (± 25.53)		
Dry Mouth: Cycle 20	-6.35 (± 26.62)	-9.68 (± 27.25)		
Dry Mouth: Cycle 21	-7.17 (± 24.27)	-9.43 (± 20.02)		
Dry Mouth: Cycle 22	-3.98 (± 26.29)	-8.70 (± 23.76)		
Dry Mouth: Cycle 23	-7.94 (± 23.73)	-3.88 (± 25.42)		
Dry Mouth: Cycle 24	-6.67 (± 25.15)	-9.40 (± 28.56)		
Dry Mouth: Cycle 25	-8.33 (± 22.75)	-9.52 (± 28.66)		
Dry Mouth: Cycle 26	-2.72 (± 23.41)	-7.53 (± 26.82)		
Dry Mouth: Cycle 27	-6.98 (± 21.28)	-7.14 (± 27.75)		
Dry Mouth: Cycle 28	-8.55 (± 21.24)	-8.00 (± 22.11)		
Dry Mouth: Post-treatment Monitoring Visit 1	0.19 (± 28.70)	2.38 (± 31.58)		
Dry Mouth: Post-treatment Monitoring Visit 2	-1.35 (± 30.09)	1.89 (± 25.95)		
Dysphagia: Cycle 2	-2.27 (± 17.64)	-0.53 (± 19.32)		
Dysphagia: Cycle 3	-3.39 (± 18.57)	-2.15 (± 19.67)		
Dysphagia: Cycle 4	-2.94 (± 18.93)	-1.08 (± 18.79)		
Dysphagia: Cycle 5	-3.22 (± 19.92)	-1.83 (± 18.99)		

Dysphagia: Cycle 6	-4.20 (± 18.99)	-2.25 (± 18.70)		
Dysphagia: Cycle 7	-4.83 (± 20.56)	-1.97 (± 19.94)		
Dysphagia: Cycle 8	-5.96 (± 18.80)	-3.29 (± 18.48)		
Dysphagia: Cycle 9	-6.17 (± 18.21)	-3.86 (± 18.49)		
Dysphagia: Cycle 10	-6.03 (± 17.37)	-4.61 (± 16.87)		
Dysphagia: Cycle 11	-6.25 (± 17.09)	-2.83 (± 17.03)		
Dysphagia: Cycle 12	-7.06 (± 17.65)	-4.19 (± 15.84)		
Dysphagia: Cycle 13	-6.93 (± 18.71)	-3.54 (± 17.61)		
Dysphagia: Cycle 14	-8.01 (± 18.53)	-4.95 (± 18.22)		
Dysphagia: Cycle 15	-6.45 (± 17.38)	-2.14 (± 18.69)		
Dysphagia: Cycle 16	-4.41 (± 18.29)	-3.70 (± 21.08)		
Dysphagia: Cycle 17	-5.36 (± 16.87)	-3.20 (± 14.99)		
Dysphagia: Cycle 18	-4.90 (± 16.44)	-3.33 (± 19.78)		
Dysphagia: Cycle 19	-4.40 (± 17.10)	-3.59 (± 14.31)		
Dysphagia: Cycle 20	-2.51 (± 16.21)	-3.76 (± 15.83)		
Dysphagia: Cycle 21	-3.80 (± 19.24)	-2.10 (± 17.84)		
Dysphagia: Cycle 22	-3.65 (± 20.41)	-4.83 (± 15.65)		
Dysphagia: Cycle 23	-4.23 (± 18.87)	-3.88 (± 17.63)		
Dysphagia: Cycle 24	-5.00 (± 18.35)	-3.70 (± 13.08)		
Dysphagia: Cycle 25	-5.98 (± 19.61)	-2.22 (± 16.79)		
Dysphagia: Cycle 26	-5.67 (± 20.43)	-2.87 (± 16.22)		
Dysphagia: Cycle 27	-5.68 (± 20.91)	-4.37 (± 12.22)		
Dysphagia: Cycle 28	-8.26 (± 19.86)	-3.56 (± 11.44)		
Dysphagia: Post-treatment Monitoring Visit 1	0.44 (± 24.15)	2.83 (± 22.63)		
Dysphagia: Post-treatment Monitoring Visit 2	-2.81 (± 24.40)	3.25 (± 19.81)		
Eating Restrictions: Cycle 2	-1.41 (± 19.36)	-1.54 (± 19.62)		
Eating Restrictions: Cycle 3	-1.04 (± 21.09)	-2.20 (± 20.94)		
Eating Restrictions: Cycle 4	-2.24 (± 20.81)	-1.39 (± 23.36)		
Eating Restrictions: Cycle 5	-1.39 (± 22.10)	-0.09 (± 23.31)		
Eating Restrictions: Cycle 6	-1.35 (± 22.77)	-3.32 (± 23.14)		
Eating Restrictions: Cycle 7	-2.45 (± 22.68)	-2.67 (± 21.66)		

Eating Restrictions: Cycle 8	-4.29 (± 22.70)	-5.56 (± 19.87)		
Eating Restrictions: Cycle 9	-6.99 (± 21.16)	-6.48 (± 19.69)		
Eating Restrictions: Cycle 10	-7.06 (± 21.32)	-5.89 (± 19.30)		
Eating Restrictions: Cycle 11	-8.22 (± 21.25)	-5.05 (± 19.98)		
Eating Restrictions: Cycle 12	-7.74 (± 21.16)	-6.34 (± 19.87)		
Eating Restrictions: Cycle 13	-8.55 (± 20.41)	-8.41 (± 19.57)		
Eating Restrictions: Cycle 14	-8.62 (± 19.16)	-8.58 (± 21.16)		
Eating Restrictions: Cycle 15	-6.85 (± 20.92)	-5.56 (± 21.21)		
Eating Restrictions: Cycle 16	-5.77 (± 22.01)	-6.94 (± 20.36)		
Eating Restrictions: Cycle 17	-5.56 (± 21.95)	-7.42 (± 17.76)		
Eating Restrictions: Cycle 18	-7.27 (± 20.40)	-6.90 (± 21.14)		
Eating Restrictions: Cycle 19	-7.03 (± 21.78)	-5.38 (± 18.07)		
Eating Restrictions: Cycle 20	-4.56 (± 21.03)	-4.44 (± 16.72)		
Eating Restrictions: Cycle 21	-5.80 (± 22.58)	-5.03 (± 19.97)		
Eating Restrictions: Cycle 22	-3.65 (± 21.79)	-6.16 (± 16.80)		
Eating Restrictions: Cycle 23	-3.70 (± 22.74)	-5.23 (± 20.25)		
Eating Restrictions: Cycle 24	-5.00 (± 20.77)	-7.91 (± 15.76)		
Eating Restrictions: Cycle 25	-5.77 (± 21.10)	-5.95 (± 16.61)		
Eating Restrictions: Cycle 26	-6.80 (± 21.22)	-2.42 (± 22.89)		
Eating Restrictions: Cycle 27	-5.62 (± 23.48)	-3.87 (± 10.26)		
Eating Restrictions: Cycle 28	-7.91 (± 21.79)	-5.00 (± 11.02)		
Eating Restrictions: Post-treatment Visit 1	1.52 (± 24.48)	0.94 (± 24.70)		
Eating Restrictions: Post-treatment Visit 2	-2.10 (± 25.32)	0.94 (± 21.46)		
Hair Loss: Cycle 2	0.20 (± 14.85)	1.27 (± 16.59)		
Hair Loss: Cycle 3	4.34 (± 17.51)	4.52 (± 18.71)		
Hair Loss: Cycle 4	5.40 (± 18.46)	6.53 (± 20.99)		
Hair Loss: Cycle 5	6.12 (± 19.38)	7.18 (± 19.49)		
Hair Loss: Cycle 6	6.93 (± 18.87)	10.07 (± 22.94)		
Hair Loss: Cycle 7	5.72 (± 19.91)	9.26 (± 22.92)		
Hair Loss: Cycle 8	5.00 (± 18.96)	7.38 (± 23.05)		
Hair Loss: Cycle 9	2.38 (± 17.43)	6.46 (± 21.06)		
Hair Loss: Cycle 10	0.64 (± 16.88)	4.22 (± 19.51)		
Hair Loss: Cycle 11	-0.10 (± 17.02)	2.54 (± 17.51)		
Hair Loss: Cycle 12	0.21 (± 19.70)	1.96 (± 15.72)		
Hair Loss: Cycle 13	0.36 (± 18.91)	2.29 (± 15.46)		

Hair Loss: Cycle 14	-1.37 (± 17.59)	1.83 (± 15.15)		
Hair Loss: Cycle 15	-0.39 (± 15.65)	1.58 (± 12.65)		
Hair Loss: Cycle 16	-1.47 (± 17.47)	1.42 (± 13.91)		
Hair Loss: Cycle 17	-1.07 (± 17.75)	0.23 (± 12.57)		
Hair Loss: Cycle 18	-1.68 (± 17.58)	-0.71 (± 13.14)		
Hair Loss: Cycle 19	-0.90 (± 18.12)	0.51 (± 14.12)		
Hair Loss: Cycle 20	-0.20 (± 19.21)	-1.61 (± 12.70)		
Hair Loss: Cycle 21	-1.07 (± 19.43)	-1.57 (± 8.81)		
Hair Loss: Cycle 22	-0.50 (± 16.66)	-3.26 (± 11.98)		
Hair Loss: Cycle 23	-0.54 (± 16.79)	-1.19 (± 11.28)		
Hair Loss: Cycle 24	-1.39 (± 17.44)	1.71 (± 16.13)		
Hair Loss: Cycle 25	-1.96 (± 18.75)	-0.95 (± 9.85)		
Hair Loss: Cycle 26	-1.02 (± 19.37)	-0.54 (± 10.08)		
Hair Loss: Cycle 27	-3.10 (± 15.96)	-0.60 (± 10.62)		
Hair Loss: Cycle 28	-4.70 (± 20.57)	-1.33 (± 10.67)		
Hair Loss: Post-Treatment Monitoring Visit 1	4.98 (± 19.73)	4.51 (± 20.39)		
Hair Loss: Post-Treatment Monitoring Visit 2	15.82 (± 25.35)	22.22 (± 30.81)		
Pain: Cycle 2	-4.63 (± 20.30)	-5.86 (± 19.15)		
Pain: Cycle 3	-6.96 (± 20.37)	-5.86 (± 20.68)		
Pain: Cycle 4	-6.45 (± 21.47)	-7.48 (± 21.23)		
Pain: Cycle 5	-7.28 (± 20.95)	-6.89 (± 22.10)		
Pain: Cycle 6	-7.24 (± 20.84)	-7.22 (± 21.62)		
Pain: Cycle 7	-9.52 (± 21.18)	-6.62 (± 21.63)		
Pain: Cycle 8	-10.53 (± 21.62)	-8.16 (± 20.11)		
Pain: Cycle 9	-10.08 (± 19.60)	-8.98 (± 20.29)		
Pain: Cycle 10	-10.63 (± 19.23)	-8.59 (± 20.38)		
Pain: Cycle 11	-11.65 (± 19.35)	-8.01 (± 18.97)		
Pain: Cycle 12	-11.76 (± 19.87)	-7.19 (± 19.11)		
Pain: Cycle 13	-11.92 (± 18.93)	-9.24 (± 19.79)		
Pain: Cycle 14	-11.66 (± 19.51)	-9.82 (± 19.91)		
Pain: Cycle 15	-11.15 (± 18.16)	-8.51 (± 20.94)		

Pain: Cycle 16	-8.72 (± 18.02)	-10.52 (± 21.30)		
Pain: Cycle 17	-8.88 (± 18.17)	-9.93 (± 17.27)		
Pain: Cycle 18	-8.31 (± 18.33)	-11.19 (± 18.16)		
Pain: Cycle 19	-6.63 (± 17.25)	-10.38 (± 14.51)		
Pain: Cycle 20	-5.72 (± 19.98)	-10.35 (± 16.65)		
Pain: Cycle 21	-8.19 (± 18.27)	-7.55 (± 16.77)		
Pain: Cycle 22	-9.08 (± 18.10)	-9.42 (± 16.72)		
Pain: Cycle 23	-9.66 (± 20.75)	-8.53 (± 19.96)		
Pain: Cycle 24	-9.86 (± 21.56)	-8.76 (± 15.53)		
Pain: Cycle 25	-10.58 (± 19.88)	-8.10 (± 18.69)		
Pain: Cycle 26	-9.01 (± 17.99)	-9.41 (± 17.58)		
Pain: Cycle 27	-12.02 (± 17.28)	-9.23 (± 14.58)		
Pain: Cycle 28	-11.54 (± 18.20)	-7.33 (± 13.46)		
Pain: Post-Treatment Monitoring Visit 1	-1.70 (± 23.07)	-2.99 (± 23.86)		
Pain: Post-Treatment Monitoring Visit 2	-7.49 (± 24.09)	-0.03 (± 22.04)		
Reflux Symptoms: Cycle 2	-0.13 (± 16.33)	-1.99 (± 18.03)		
Reflux Symptoms: Cycle 3	-0.52 (± 18.95)	-2.28 (± 19.53)		
Reflux Symptoms: Cycle 4	-0.98 (± 19.18)	-1.90 (± 19.93)		
Reflux Symptoms: Cycle 5	-1.92 (± 18.98)	-1.72 (± 20.10)		
Reflux Symptoms: Cycle 6	-2.90 (± 20.42)	-3.59 (± 19.04)		
Reflux Symptoms: Cycle 7	-4.18 (± 18.36)	-3.20 (± 20.21)		
Reflux Symptoms: Cycle 8	-4.96 (± 19.39)	-5.74 (± 19.53)		
Reflux Symptoms: Cycle 9	-5.02 (± 18.97)	-5.18 (± 19.81)		
Reflux Symptoms: Cycle 10	-6.12 (± 17.81)	-6.48 (± 18.55)		
Reflux Symptoms: Cycle 11	-6.44 (± 18.74)	-6.03 (± 18.07)		
Reflux Symptoms: Cycle 12	-4.82 (± 18.00)	-7.49 (± 16.99)		
Reflux Symptoms: Cycle 13	-6.42 (± 17.09)	-6.77 (± 18.19)		
Reflux Symptoms: Cycle 14	-5.39 (± 18.24)	-7.37 (± 17.45)		
Reflux Symptoms: Cycle 15	-5.00 (± 16.66)	-4.98 (± 18.72)		
Reflux Symptoms: Cycle 16	-3.07 (± 18.39)	-4.89 (± 22.31)		
Reflux Symptoms: Cycle 17	-3.35 (± 18.38)	-4.57 (± 20.44)		

Reflux Symptoms: Cycle 18	-2.94 (± 18.36)	-6.51 (± 20.33)		
Reflux Symptoms: Cycle 19	-2.43 (± 16.38)	-6.15 (± 18.43)		
Reflux Symptoms: Cycle 20	-1.85 (± 18.32)	-5.38 (± 18.63)		
Reflux Symptoms: Cycle 21	-1.83 (± 18.44)	-4.19 (± 17.73)		
Reflux Symptoms: Cycle 22	-3.81 (± 19.30)	-7.00 (± 19.65)		
Reflux Symptoms: Cycle 23	-5.11 (± 17.03)	-6.98 (± 19.70)		
Reflux Symptoms: Cycle 24	-4.07 (± 19.30)	-7.98 (± 18.19)		
Reflux Symptoms: Cycle 25	-5.56 (± 18.86)	-5.71 (± 16.69)		
Reflux Symptoms: Cycle 26	-4.99 (± 20.67)	-4.30 (± 21.98)		
Reflux Symptoms: Cycle 27	-7.75 (± 20.51)	-6.75 (± 16.10)		
Reflux Symptoms: Cycle 28	-7.12 (± 18.64)	-4.44 (± 11.56)		
Reflux Symptoms: Post-Treatment Visit 1	0.88 (± 20.01)	-0.45 (± 22.92)		
Reflux Symptoms: Post-Treatment Visit 2	0.56 (± 18.67)	-1.47 (± 22.28)		
Taste: Cycle 2	12.09 (± 28.78)	6.61 (± 26.94)		
Taste: Cycle 3	16.72 (± 32.11)	9.99 (± 30.16)		
Taste: Cycle 4	18.43 (± 34.70)	11.07 (± 31.93)		
Taste: Cycle 5	17.61 (± 32.93)	11.85 (± 30.25)		
Taste: Cycle 6	17.97 (± 31.20)	11.82 (± 32.21)		
Taste: Cycle 7	16.25 (± 33.51)	9.19 (± 31.09)		
Taste: Cycle 8	11.64 (± 29.81)	3.29 (± 28.13)		
Taste: Cycle 9	9.22 (± 28.25)	1.73 (± 26.30)		
Taste: Cycle 10	7.93 (± 26.41)	1.63 (± 28.79)		
Taste: Cycle 11	4.96 (± 26.72)	2.61 (± 26.91)		
Taste: Cycle 12	5.27 (± 24.82)	0.24 (± 24.66)		
Taste: Cycle 13	4.08 (± 25.53)	-0.91 (± 25.33)		
Taste: Cycle 14	0.49 (± 25.66)	-5.28 (± 24.37)		
Taste: Cycle 15	3.08 (± 24.36)	-1.04 (± 26.25)		
Taste: Cycle 16	5.51 (± 27.90)	-3.57 (± 20.71)		
Taste: Cycle 17	4.80 (± 24.96)	-3.65 (± 23.28)		
Taste: Cycle 18	3.59 (± 23.87)	-4.29 (± 23.34)		
Taste: Cycle 19	3.13 (± 25.17)	-4.62 (± 15.45)		
Taste: Cycle 20	5.56 (± 27.78)	-3.76 (± 18.21)		

Taste: Cycle 21	6.33 (± 27.26)	-5.03 (± 17.78)		
Taste: Cycle 22	9.45 (± 30.04)	-4.35 (± 16.64)		
Taste: Cycle 23	8.99 (± 30.06)	0.00 (± 23.00)		
Taste: Cycle 24	7.78 (± 28.37)	-5.13 (± 19.55)		
Taste: Cycle 25	3.21 (± 28.97)	-4.76 (± 18.33)		
Taste: Cycle 26	4.08 (± 34.45)	-3.23 (± 21.70)		
Taste: Cycle 27	4.65 (± 29.62)	-3.57 (± 20.96)		
Taste: Cycle 28	3.42 (± 21.35)	-6.67 (± 25.46)		
Taste: Post-Treatment Monitoring Visit 1	12.76 (± 34.59)	9.06 (± 33.56)		
Taste: Post-Treatment Monitoring Visit 2	8.42 (± 31.35)	6.67 (± 28.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentrations (Cmax) of Pertuzumab

End point title	Maximum Serum Concentrations (Cmax) of Pertuzumab[4]

End point description:

The pharmacokinetic analysis included all subjects who were treated with study medication and who had at least one measurable concentration of pertuzumab or trastuzumab. Data are reported for evaluable subjects.

End point type	Secondary

End point timeframe:

Pre-dose (0-6 hours [Hr] before infusion) on Day 1 (D1) of Cycles (Cy) 1, 2, 3, 4, 6, 8; 0.5 Hr after end of 30-60 minutes infusion on D1 of Cy 1, 2, 4, 8; at 28 & 60-90 days after D1 of last Cy (up approximately 3.5 years) (1 cycle = 21 days)

Notes:

[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: This endpoint is only applicable to the Pertuzumab arm of the study; no data was collected from subjects in the Placebo arm for this endpoint.

End point values	Pertuzumab + Trastuzumab + Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	374			
Units: micrograms per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
Cycle 1	258 (± 90.3)			
Cycle 4	341 (± 111)			
Cycle 8	371 (± 127)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Trastuzumab

End point title	Cmax of Trastuzumab

End point description:

The pharmacokinetic analysis included all subjects who were treated with study medication and who had at least one measurable concentration of pertuzumab or trastuzumab. Data are reported for evaluable subjects.

End point type	Secondary

End point timeframe:

Pre-dose (0-6 hours [Hr] before infusion) on Day 1 (D1) of Cycles (Cy) 1, 2, 3, 4, 6, 8; 0.5 Hr after end of 30-60 minutes infusion on D1 of Cy 1, 2, 4, 8; at 28 & 60-90 days after D1 of last Cy (up approximately 3.5 years) (1 cycle = 21 days)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	372	375		
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 1	142 (± 86.8)	139 (± 58.6)		
Cycle 4	127 (± 50.9)	129 (± 58.1)		
Cycle 8	130 (± 50.8)	147 (± 90.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Serum Concentration (Cmin) of Pertuzumab

End point title	Minimum Serum Concentration (Cmin) of Pertuzumab[5]

End point description:

The pharmacokinetic analysis included all subjects who were treated with study medication and who had at least one measurable concentration of pertuzumab or trastuzumab. Data are reported for evaluable subjects.

End point type	Secondary

End point timeframe:

Pre-dose (0-6 hours [Hr] before infusion) on Day 1 (D1) of Cycles (Cy) 1, 2, 3, 4, 6, 8; 0.5 Hr after end of 30-60 minutes infusion on D1 of Cy 1, 2, 4, 8; at 28 & 60-90 days after D1 of last Cy (up approximately 3.5 years) (1 cycle = 21 days)

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: This endpoint is only applicable to the Pertuzumab arm of the study; no data was collected from subjects in the Placebo arm for this endpoint.

End point values	Pertuzumab + Trastuzumab + Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	374			
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 4	90.4 (± 42.4)			
Cycle 6	114 (± 51.8)			
Cycle 8	142 (± 67.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of Trastuzumab

End point title	Cmin of Trastuzumab

End point description:

The pharmacokinetic analysis included all subjects who were treated with study medication and who had at least one measurable concentration of pertuzumab or trastuzumab. Data are reported for evaluable subjects.

End point type	Secondary

End point timeframe:

Pre-dose (0-6 hours [Hr] before infusion) on Day 1 (D1) of Cycles (Cy) 1, 2, 3, 4, 6, 8; 0.5 Hr after end of 30-60 minutes infusion on D1 of Cy 1, 2, 4, 8; at 28 & 60-90 days after D1 of last Cy (up approximately 3.5 years) (1 cycle = 21 days)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	372	375		
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 4	22.9 (± 12.7)	24.1 (± 19.0)		
Cycle 6	26.3 (± 14.8)	29.8 (± 21.9)		
Cycle 8	32.7 (± 15.0)	37.4 (± 20.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to the 09 Dec 2016 data cutoff, approximately 3.5 years.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo + Trastuzumab + Chemotherapy

Reporting group description:

Subjects will receive pertuzumab placebo in combination with trastuzumab and chemotherapy (cisplatin and fluoropyrimidine [capecitabine or 5-fluorouracil]) for the first 6 treatment cycles (cycle length = 21 days). Subjects will continue to receive pertuzumab placebo and trastuzumab until disease progression occurrence of unacceptable toxicity or withdrawal from the study for another reason.

Reporting group title	Pertuzumab + Trastuzumab + Chemotherapy

Reporting group description:

Subjects will receive pertuzumab in combination with trastuzumab and chemotherapy (cisplatin and fluoropyrimidine [capecitabine or 5-fluorouracil]) for the first 6 treatment cycles (cycle length = 21 days). Subjects will continue to receive pertuzumab and trastuzumab until disease progression occurrence of unacceptable toxicity or withdrawal from the study for another reason.

Serious adverse events	Placebo + Trastuzumab + Chemotherapy	Pertuzumab + Trastuzumab + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	152 / 388 (39.18%)	175 / 385 (45.45%)	
number of deaths (all causes)	262	240	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectosigmoid cancer stage 0			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 388 (0.00%)	4 / 385 (1.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 388 (0.00%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 388 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemodynamic instability			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 388 (0.26%)	5 / 385 (1.30%)	
occurrences causally related to treatment / all	1 / 1	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	9 / 388 (2.32%)	8 / 385 (2.08%)	
occurrences causally related to treatment / all	1 / 9	0 / 8	
deaths causally related to treatment / all	1 / 9	0 / 8	
Chest pain			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 388 (0.00%)	4 / 385 (1.04%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypothermia			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	3 / 388 (0.77%)	4 / 385 (1.04%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 388 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumatosis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 388 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 388 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epistaxis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 388 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 388 (0.52%)	6 / 385 (1.56%)	
occurrences causally related to treatment / all	2 / 2	2 / 6	
deaths causally related to treatment / all	1 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 388 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	2 / 388 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 388 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Creatinine renal clearance decreased			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic stenosis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 388 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 388 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Head injury			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 388 (0.52%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 388 (0.00%)	4 / 385 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Atrial fibrillation			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial septal defect acquired			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 388 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 388 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 388 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocarditis			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Anticholinergic syndrome			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 388 (0.77%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 388 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 388 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	16 / 388 (4.12%)	8 / 385 (2.08%)	
occurrences causally related to treatment / all	13 / 18	6 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	10 / 388 (2.58%)	6 / 385 (1.56%)	
occurrences causally related to treatment / all	8 / 10	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 388 (0.77%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	3 / 388 (0.77%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 388 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 388 (0.52%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 388 (0.77%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	20 / 388 (5.15%)	17 / 385 (4.42%)	
occurrences causally related to treatment / all	18 / 21	20 / 20	
deaths causally related to treatment / all	1 / 1	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 388 (0.26%)	4 / 385 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	4 / 388 (1.03%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	2 / 388 (0.52%)	6 / 385 (1.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	2 / 388 (0.52%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric stenosis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 388 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 388 (0.77%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 388 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 388 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal mass			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 388 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 388 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	7 / 388 (1.80%)	7 / 385 (1.82%)	
occurrences causally related to treatment / all	7 / 9	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	5 / 388 (1.29%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	1 / 7	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 388 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	2 / 388 (0.52%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 388 (1.03%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	13 / 388 (3.35%)	7 / 385 (1.82%)	
occurrences causally related to treatment / all	12 / 17	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	3 / 388 (0.77%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 388 (1.03%)	7 / 385 (1.82%)	
occurrences causally related to treatment / all	4 / 4	6 / 7	
deaths causally related to treatment / all	0 / 0	1 / 2	
Hydronephrosis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 388 (0.77%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal impairment			
subjects affected / exposed	2 / 388 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 388 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudoaldosteronism			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			

subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 388 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 388 (0.00%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			

subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 388 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 388 (0.77%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 388 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 388 (1.03%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Parotitis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	9 / 388 (2.32%)	11 / 385 (2.86%)	
occurrences causally related to treatment / all	2 / 9	5 / 12	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pneumonia Klebsiella			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 388 (0.52%)	7 / 385 (1.82%)	
occurrences causally related to treatment / all	2 / 2	4 / 7	
deaths causally related to treatment / all	1 / 1	3 / 4	
Septic shock			
subjects affected / exposed	4 / 388 (1.03%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	3 / 4	1 / 3	
deaths causally related to treatment / all	3 / 3	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 388 (0.52%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	0 / 388 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	9 / 388 (2.32%)	17 / 385 (4.42%)	
occurrences causally related to treatment / all	9 / 9	15 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	9 / 388 (2.32%)	9 / 385 (2.34%)	
occurrences causally related to treatment / all	7 / 9	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 388 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 388 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			

subjects affected / exposed	1 / 388 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 388 (0.26%)	7 / 385 (1.82%)	
occurrences causally related to treatment / all	1 / 1	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	2 / 388 (0.52%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 388 (0.52%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 388 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Trastuzumab + Chemotherapy	Pertuzumab + Trastuzumab + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	375 / 388 (96.65%)	373 / 385 (96.88%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	22 / 388 (5.67%)	28 / 385 (7.27%)	
occurrences (all)	31	34	
Creatinine renal clearance decreased			
subjects affected / exposed	51 / 388 (13.14%)	70 / 385 (18.18%)	
occurrences (all)	62	86	
Weight decreased			

subjects affected / exposed	49 / 388 (12.63%)	74 / 385 (19.22%)	
occurrences (all)	51	75	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	23 / 388 (5.93%)	45 / 385 (11.69%)	
occurrences (all)	26	50	
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 388 (5.15%)	20 / 385 (5.19%)	
occurrences (all)	21	20	
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 388 (7.99%)	30 / 385 (7.79%)	
occurrences (all)	39	34	
Neuropathy peripheral			
subjects affected / exposed	29 / 388 (7.47%)	32 / 385 (8.31%)	
occurrences (all)	30	36	
Dysgeusia			
subjects affected / exposed	34 / 388 (8.76%)	37 / 385 (9.61%)	
occurrences (all)	35	46	
Peripheral sensory neuropathy			
subjects affected / exposed	34 / 388 (8.76%)	29 / 385 (7.53%)	
occurrences (all)	35	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	140 / 388 (36.08%)	151 / 385 (39.22%)	
occurrences (all)	178	182	
Leukopenia			
subjects affected / exposed	69 / 388 (17.78%)	77 / 385 (20.00%)	
occurrences (all)	107	136	
Neutropenia			
subjects affected / exposed	202 / 388 (52.06%)	200 / 385 (51.95%)	
occurrences (all)	293	327	
Thrombocytopenia			
subjects affected / exposed	73 / 388 (18.81%)	60 / 385 (15.58%)	
occurrences (all)	97	98	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	61 / 388 (15.72%)	56 / 385 (14.55%)	
occurrences (all)	78	75	
Chills			
subjects affected / exposed	17 / 388 (4.38%)	36 / 385 (9.35%)	
occurrences (all)	19	36	
Fatigue			
subjects affected / exposed	122 / 388 (31.44%)	138 / 385 (35.84%)	
occurrences (all)	163	171	
Mucosal inflammation			
subjects affected / exposed	34 / 388 (8.76%)	43 / 385 (11.17%)	
occurrences (all)	40	61	
Oedema			
subjects affected / exposed	19 / 388 (4.90%)	20 / 385 (5.19%)	
occurrences (all)	32	33	
Oedema peripheral			
subjects affected / exposed	32 / 388 (8.25%)	24 / 385 (6.23%)	
occurrences (all)	35	25	
Pyrexia			
subjects affected / exposed	57 / 388 (14.69%)	55 / 385 (14.29%)	
occurrences (all)	66	75	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	19 / 388 (4.90%)	23 / 385 (5.97%)	
occurrences (all)	24	34	
Abdominal pain			
subjects affected / exposed	50 / 388 (12.89%)	42 / 385 (10.91%)	
occurrences (all)	55	59	
Abdominal pain upper			
subjects affected / exposed	23 / 388 (5.93%)	27 / 385 (7.01%)	
occurrences (all)	25	31	
Constipation			
subjects affected / exposed	83 / 388 (21.39%)	53 / 385 (13.77%)	
occurrences (all)	104	61	
Dyspepsia			

subjects affected / exposed	29 / 388 (7.47%)	22 / 385 (5.71%)	
occurrences (all)	37	24	
Diarrhoea			
subjects affected / exposed	122 / 388 (31.44%)	225 / 385 (58.44%)	
occurrences (all)	165	333	
Dysphagia			
subjects affected / exposed	32 / 388 (8.25%)	25 / 385 (6.49%)	
occurrences (all)	38	31	
Nausea			
subjects affected / exposed	216 / 388 (55.67%)	223 / 385 (57.92%)	
occurrences (all)	308	308	
Stomatitis			
subjects affected / exposed	67 / 388 (17.27%)	80 / 385 (20.78%)	
occurrences (all)	84	100	
Vomiting			
subjects affected / exposed	120 / 388 (30.93%)	142 / 385 (36.88%)	
occurrences (all)	166	194	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 388 (5.15%)	21 / 385 (5.45%)	
occurrences (all)	28	23	
Dyspnoea			
subjects affected / exposed	13 / 388 (3.35%)	20 / 385 (5.19%)	
occurrences (all)	17	23	
Hiccups			
subjects affected / exposed	37 / 388 (9.54%)	33 / 385 (8.57%)	
occurrences (all)	45	37	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	25 / 388 (6.44%)	21 / 385 (5.45%)	
occurrences (all)	26	24	
Dry skin			
subjects affected / exposed	18 / 388 (4.64%)	31 / 385 (8.05%)	
occurrences (all)	21	38	
Rash			

subjects affected / exposed	13 / 388 (3.35%)	26 / 385 (6.75%)	
occurrences (all)	15	28	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	98 / 388 (25.26%)	85 / 385 (22.08%)	
occurrences (all)	109	91	
Pruritus			
subjects affected / exposed	14 / 388 (3.61%)	33 / 385 (8.57%)	
occurrences (all)	22	40	
Skin hyperpigmentation			
subjects affected / exposed	22 / 388 (5.67%)	17 / 385 (4.42%)	
occurrences (all)	22	17	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	44 / 388 (11.34%)	32 / 385 (8.31%)	
occurrences (all)	46	42	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 388 (3.09%)	22 / 385 (5.71%)	
occurrences (all)	15	26	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	158 / 388 (40.72%)	170 / 385 (44.16%)	
occurrences (all)	217	233	
Hypoalbuminaemia			
subjects affected / exposed	19 / 388 (4.90%)	20 / 385 (5.19%)	
occurrences (all)	21	24	
Hypocalcaemia			
subjects affected / exposed	22 / 388 (5.67%)	22 / 385 (5.71%)	
occurrences (all)	25	27	
Hypokalaemia			
subjects affected / exposed	46 / 388 (11.86%)	72 / 385 (18.70%)	
occurrences (all)	56	86	
Hypomagnesaemia			
subjects affected / exposed	21 / 388 (5.41%)	30 / 385 (7.79%)	
occurrences (all)	22	37	
Hyponatraemia			

subjects affected / exposed occurrences (all)	28 / 388 (7.22%) 28	16 / 385 (4.16%) 18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2014	The period for contraception use was extended from 6 to 7 months following the last dose of study treatment. The safety reporting period for pregnancy (occurring during/after trastuzumab treatment) was updated from 6 to 7 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported