Clinical trial results:
A Multicenter Randomized Phase III Study to Compare the Combination Trastuzumab and Capecitabine, With or Without Pertuzumab, in Patients with HER2-Positive Metastatic Breast Cancer That Have Progressed After One Line of Trastuzumab-Based Therapy in the Metastatic Setting (PHEREXA)

Summary

EudraCT number	2008-006801-17
Trial protocol	AT ES DE CZ EE HU GB IT FR BE NL
Global end of trial date	07 August 2017

Results information

Result version number	v2 (current)
This version publication date	01 August 2018
First version publication date	02 September 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MO22324

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01026142
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare progression-free survival (PFS) between the two treatment arms based on assessments by an independent review facility (IRF).

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. All subjects signed an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Hong Kong: 16
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Peru: 15
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Korea, Republic of: 38
Country: Number of subjects enrolled	Spain: 70

Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 35
Worldwide total number of subjects	446
EEA total number of subjects	331

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)	366
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

452 participants were randomized to one of two treatment arms: trastuzumab and capecitabine (Arm A, 224 participants) or pertuzumab with trastuzumab and capecitabine (Arm B, 228 participants). Of participants randomized to Arm A: trastuzumab and capecitabine, 6 participants did not receive study treatment.

Pre-assignment

Screening details:

Study included females with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) with progression during or following 1 line of trastuzumab-based therapy in metastatic setting. 452 participants randomized to 1 of 2 treatment arms (Arm A, n = 224) or (Arm B, n = 228). 6 participants did not receive treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Capecitabine + Trastuzumab

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In Cycle 1, every 3 weeks: the first dose of capecitabine should be administered in the evening of Day 1 and the last dose in the morning of Day 15. 1250 mg/m² twice daily (morning and evening, equivalent to 2500 mg/m2 total daily dose) for 14 days followed by 7-day rest. In Cycle 2 and subsequent cycles, every 3 weeks: 1250 mg/m² twice daily (morning and evening, equivalent to 2500 mg/m2 total daily dose) for 14 days followed by 7-day rest.

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

Dosage and administration details:

In Cycle 1, every 3 weeks, beginning on Day 1: 8 mg/kg intravenous (IV) loading dose over 90 min followed by a 60-min observation period. If the first infusion of trastuzumab is tolerated without infusion-associated AEs (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes. In Cycle 2 and subsequent cycles, every 3 weeks, beginning on Day 1: 6 mg/kg IV over 90 min followed by a 30- to 60-min observation period. If the first infusion of trastuzumab is tolerated without infusion-associated AEs (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.

Arm title	Capecitabine + Trastuzumab + Pertuzumab

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In Cycle 1, every 3 weeks: On Day 2, 1000 mg/m² twice daily (morning and evening, equivalent to 2000 mg/m2 total daily dose) for 14 days followed by 7-day rest. In Cycle 1, the first dose of capecitabine should be administered in the morning of Day 2 and the last dose in the evening of Day 15. In Cycle 2 and subsequent cycles, every 3 weeks: On Day 1, 1000 mg/m² twice daily (morning and evening, equivalent to 2000 mg/m2 total daily dose) for 14 days followed by 7-day rest. If the administration of the three study drugs is well tolerated during the first cycle, starting from Cycle 2, the first dose of capecitabine should be administered in the evening of Day 1 and the last dose in the morning of Day 15.

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

Dosage and administration details:

In Cycle 1, every 3 weeks: On Day 2, 8 mg/kg IV over 90 min followed by a 60-min observation period. If the first infusion of trastuzumab is tolerated without infusion-associated AEs (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes. In Cycle 2 and subsequent cycles, every 3 weeks: On Day 1, after pertuzumab observation 6 mg/kg IV over 90 min followed by a 30-to 60-min observation period. If the first infusion of trastuzumab and pertuzumab is tolerated without infusion-associated AEs (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.

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:

In Cycle 1, every 3 weeks: On Day 1, 840 mg IV loading dose over 60 min followed by a 60-min observation period. In Cycle 2 and subsequent cycles, every 3 weeks: On Day 1, 420 mg IV over 60 min followed by a 30- to 60-min observation period. If the participant misses a dose of pertuzumab for one cycle (i.e., the two sequential administration times are 6 weeks or more apart), a re-loading dose of pertuzumab (840 mg) should be given. If re-loading is required for a given cycle, the three study therapies should be given on the same schedule as Cycle 1 (i.e., pertuzumab on Day 1 and trastuzumab and capecitabine on Day 2). Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

Number of subjects in period 1	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab
Started	218	228
Completed	52	65
Not completed	166	163
Death	136	134
Withdrawn consent or lost to survival follow-up	30	29

Baseline characteristics

Reporting groups	
Reporting group title	Capecitabine + Trastuzumab
Reporting group description: -	
Reporting group title	Capecitabine + Trastuzumab + Pertuzumab
Reporting group description: -	

Reporting group values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab	Total
Number of subjects	218	228	446
Age categorical Units: Subjects			
Adults (18-64 years)	176	190	366
Elderly (From 65-84 years)	42	38	80
Age continuous Units: years			
arithmetic mean	55.1	53.0	
standard deviation	± 10.10	± 11.21	-
Gender categorical Units: Subjects			
Female	218	228	446
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Capecitabine + Trastuzumab
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients were randomized to receive Capecitabine + Trastuzumab in 3-week cycles.	
Subject analysis set title	Capecitabine + Trastuzumab + Pertuzumab
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients were randomized to receive Capecitabine + Trastuzumab + Pertuzumab in 3-week cycles.	

Reporting group values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab	
Number of subjects	224	228	
Age categorical Units: Subjects			
Adults (18-64 years)	181	190	
Elderly (From 65-84 years)	43	38	
Age continuous Units: years			
arithmetic mean	55.1	53.0	
standard deviation	± 10.18	± 11.21	

Gender categorical Units: Subjects			
Female	224	228	
Male	0	0	

End points

End points reporting groups

Reporting group title	Capecitabine + Trastuzumab
Reporting group description: -	
Reporting group title	Capecitabine + Trastuzumab + Pertuzumab
Reporting group description: -	
Subject analysis set title	Capecitabine + Trastuzumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients were randomized to receive Capecitabine + Trastuzumab in 3-week cycles.	
Subject analysis set title	Capecitabine + Trastuzumab + Pertuzumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients were randomized to receive Capecitabine + Trastuzumab + Pertuzumab in 3-week cycles.	

Primary: Progression Free Survival (PFS) - Independent Review Facility (IRF) Assessment

End point title	Progression Free Survival (PFS) - Independent Review Facility (IRF) Assessment
End point description:	
Progression Free Survival (PFS) was defined as the time from randomization to first documented disease progression (PD), as determined by an Independent Review Facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, or death from any cause, whichever occurred first. PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions; or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. IRF review of tumor assessment ceased after the primary PFS analysis. The primary endpoint was analyzed after approximately 337 IRF-assessed PFS events were observed.	
End point type	Primary
End point timeframe:	
Tumor assessments every 9 weeks from randomization until Week 27, then every 12 weeks thereafter, until IRF-determined PD, initiation of alternative anticancer medication, or death (up to 5.5 years).	

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Months				
median (confidence interval 95%)	9 (8 to 10)	11.1 (9 to 13)		

Statistical analyses

Statistical analysis title	IRF-Assessed Progression-Free Survival (PFS)

Statistical analysis description:

The null hypothesis for the primary endpoint is that the survival distributions of IRF-assessed PFS in the two treatment groups are the same. The alternative hypothesis is that the survival distributions of IRF-assessed PFS in the treatment and the control arms are different:

H0: IRF PFS<pertuzumab> = IRF PFS<control> vs. H1: IRF PFS<pertuzumab> ≠ IRF PFS<control>

Comparison groups	Capecitabine + Trastuzumab v Capecitabine + Trastuzumab + Pertuzumab
Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0731 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.02

Notes:

[1] - The primary endpoint, IRF-assessed PFS, is tested at a two-sided 5% significance level.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) was defined as the time from the date of randomization to the date of death from any cause. The results of the final OS analysis are presented here. Participants who were alive or lost to follow-up at the time of the analysis were censored at the last known alive date. Participants with no postbaseline information were censored at the time of randomization plus 1 day. Prior to the final data analysis cut-off, it was ensured that all participants who were in survival follow-up had been contacted as recently as possible within the last 3 months to confirm current survival status.

End point type	Secondary

End point timeframe:

From randomization until death from any cause (up to 7.5 years)

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Months				
median (confidence interval 95%)	28.1 (22 to 35)	37.2 (33 to 42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Based on a 2-year Truncated Analysis

End point title	Overall Survival (OS) Based on a 2-year Truncated Analysis

End point description:

The Overall Survival (OS) 2-year truncated analysis is the Kaplan-Meier estimate of the percentage of participants who were surviving at 2 years. OS is defined as the time from the date of randomization to

the date of death from any cause, with censoring of all events and follow-up beyond the end of the second year.

End point type	Secondary

End point timeframe:

From randomization until death from any cause (up to 2 years)

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Percentage				
number (confidence interval 95%)	55.0 (48.07 to 61.85)	74.9 (69.05 to 80.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator Assessment Progression-Free Survival (PFS)

End point title	Investigator Assessment Progression-Free Survival (PFS)

End point description:

Investigator Assessment Progression-Free Survival (PFS) was defined as the time from randomization to the first documented progressive disease (PD), as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0, or death from any cause, whichever occurred first. PD is defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions; or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

End point type	Secondary

End point timeframe:

Tumor assessments every 9 weeks from randomization until Week 27, then every 12 weeks thereafter, until IRF-determined PD, initiation of alternative anticancer medication, or death (up to 7.5 years).

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Months				
median (confidence interval 95%)	9 (8 to 12)	11.8 (9 to 14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) Based Upon IRF Assessment

End point title	Time to Progression (TTP) Based Upon IRF Assessment

End point description:

Time to Progression (TTP) was defined as time between randomization and the first occurrence of progressive disease.

End point type	Secondary

End point timeframe:

Tumor assessments every 9 weeks from randomization until Week 27, then every 12 weeks thereafter, until IRF-determined PD, initiation of alternative anticancer medication, or death (up to 5.5 years).

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Weeks				
median (confidence interval 95%)	39 (35 to 44)	50.6 (39 to 62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF) Based Upon IRF Assessment

End point title	Time to Treatment Failure (TTF) Based Upon IRF Assessment

End point description:

Time to Treatment Failure (TTF) was defined as time between randomization and date of disease progression based on IRF assessments, death, or withdrawal of treatment due to adverse events, withdrawn informed consent, refusal of treatment/failure to cooperate, or failure to return, whichever occurred first. Based upon Independent Review Facility (IRF) assessment.

End point type	Secondary

End point timeframe:

Tumor assessments every 9 weeks from randomization until Week 27, then every 12 weeks thereafter, until IRF-determined PD, initiation of alternative anticancer medication, or death (up to 5.5 years).

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Weeks				
median (confidence interval 95%)	39 (34 to 44)	50.9 (39 to 62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Objective Response Rate (ORR)

End point title	Overall Objective Response Rate (ORR)

End point description:

Overall Objective Response Rate is based upon investigator and Independent Review Facility (IRF) assessments. Objective Response Rate (ORR) was defined as the percentage of patients with a confirmed complete response (CR) or partial response (PR) among those who had measurable disease at baseline. Patients without a post-baseline tumor assessment were considered to be non-responders.

End point type	Secondary

End point timeframe:

Tumor assessments every 9 weeks from randomization until Week 27, then every 12 weeks thereafter, until IRF-determined PD, initiation of alternative anticancer medication, or death (up to 5.5 years).

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	164	163		
Units: Percentage				
number (not applicable)				
Complete Response (CR) - IRF Assessment	0	1.8		
Partial Response (PR) - IRF Assessment	32.9	38.7		
Complete Response (CR) - Investigator Assessed	1.2	6.7		
Partial Response (PR) - Investigator Assessed	36	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

Clinical Benefit Rate is based upon Independent Review Facility (IRF) assessments; defined as the percentage of patients with a complete response (CR), partial response (PR), or stable disease for at least 8 cycles or 6 months.

End point type	Secondary

End point timeframe:

Tumor assessments every 9 weeks from randomization until Week 27, then every 12 weeks thereafter, until IRF-determined PD, initiation of alternative anticancer medication, or death (up to 5.5 years).

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	145		
Units: Percentage				
number (confidence interval 95%)	54 (47.3 to 60.7)	63.6 (57.0 to 69.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response

End point title	Duration of Objective Response

End point description:

Duration of Objective Response was defined for the subpopulation of responders as time from first Independent Review Facility (IRF)-assessed complete response (CR) or partial response (PR) to subsequent first documented, IRF-confirmed evidence of disease progression. Only patients with an objective response were included in the analysis of duration of objective response.

End point type	Secondary

End point timeframe:

Tumor assessments every 9 weeks from randomization until Week 27, then every 12 weeks thereafter, until IRF-determined PD, initiation of alternative anticancer medication, or death (up to 5.5 years).

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	66		
Units: Weeks				
median (confidence interval 95%)	30 (21 to 42)	51.6 (42 to 57)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded and reported during the study and up to two years after the last dose of the study drug was received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Capecitabine + Trastuzumab

Reporting group description:

Safety data were analyzed and compared between the two arms using standard methods and based on the safety population. The safety analysis population includes all patients who receive any amount of study drug summarized by treatment actually received.

Reporting group title	Capecitabine + Trastuzumab + Pertuzumab

Reporting group description:

Safety data were analyzed and compared between the two arms using standard methods and based on the safety population. The safety analysis population includes all patients who receive any amount of study drug summarized by treatment actually received.

Serious adverse events	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 218 (24.31%)	58 / 228 (25.44%)	
number of deaths (all causes)	136	134	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute promyelocytic leukaemia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	1 / 218 (0.46%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 218 (0.92%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	2 / 218 (0.92%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 218 (1.83%)	3 / 228 (1.32%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	0 / 218 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood sodium decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 218 (0.92%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 218 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fissure			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
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 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Facial bones fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (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 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	4 / 218 (1.83%)	13 / 228 (5.70%)	
occurrences causally related to treatment / all	4 / 4	10 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 218 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (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 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			

subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary cerebellar degeneration			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 218 (2.75%)	8 / 228 (3.51%)	
occurrences causally related to treatment / all	6 / 6	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (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			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureteric stenosis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 218 (0.46%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 218 (0.92%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis infective			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	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	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	209 / 218 (95.87%)	216 / 228 (94.74%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 218 (6.42%)	19 / 228 (8.33%)	
occurrences (all)	18	19	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	51 / 218 (23.39%)	47 / 228 (20.61%)	
occurrences (all)	87	77	
Fatigue			
subjects affected / exposed	39 / 218 (17.89%)	44 / 228 (19.30%)	
occurrences (all)	59	62	
Mucosal inflammation			
subjects affected / exposed	27 / 218 (12.39%)	32 / 228 (14.04%)	
occurrences (all)	36	45	
Pyrexia			

subjects affected / exposed	20 / 218 (9.17%)	29 / 228 (12.72%)	
occurrences (all)	24	41	
Oedema peripheral			
subjects affected / exposed	13 / 218 (5.96%)	18 / 228 (7.89%)	
occurrences (all)	13	19	
Chest pain			
subjects affected / exposed	12 / 218 (5.50%)	9 / 228 (3.95%)	
occurrences (all)	15	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 218 (10.09%)	30 / 228 (13.16%)	
occurrences (all)	27	38	
Dyspnoea			
subjects affected / exposed	24 / 218 (11.01%)	21 / 228 (9.21%)	
occurrences (all)	28	25	
Epistaxis			
subjects affected / exposed	9 / 218 (4.13%)	12 / 228 (5.26%)	
occurrences (all)	9	14	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 218 (5.50%)	23 / 228 (10.09%)	
occurrences (all)	17	27	
Investigations			
Weight decreased			
subjects affected / exposed	13 / 218 (5.96%)	19 / 228 (8.33%)	
occurrences (all)	14	20	
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 218 (5.05%)	17 / 228 (7.46%)	
occurrences (all)	15	26	
Alanine aminotransferase increased			
subjects affected / exposed	8 / 218 (3.67%)	17 / 228 (7.46%)	
occurrences (all)	11	24	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	5 / 218 (2.29%)	13 / 228 (5.70%)	
occurrences (all)	5	15	

Nervous system disorders			
Headache			
subjects affected / exposed	39 / 218 (17.89%)	40 / 228 (17.54%)	
occurrences (all)	68	52	
Dizziness			
subjects affected / exposed	21 / 218 (9.63%)	24 / 228 (10.53%)	
occurrences (all)	28	26	
Neuropathy peripheral			
subjects affected / exposed	14 / 218 (6.42%)	16 / 228 (7.02%)	
occurrences (all)	17	17	
Paraesthesia			
subjects affected / exposed	13 / 218 (5.96%)	9 / 228 (3.95%)	
occurrences (all)	15	9	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	38 / 218 (17.43%)	29 / 228 (12.72%)	
occurrences (all)	88	74	
Anaemia			
subjects affected / exposed	17 / 218 (7.80%)	21 / 228 (9.21%)	
occurrences (all)	23	28	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	13 / 218 (5.96%)	6 / 228 (2.63%)	
occurrences (all)	17	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	128 / 218 (58.72%)	157 / 228 (68.86%)	
occurrences (all)	275	436	
Nausea			
subjects affected / exposed	97 / 218 (44.50%)	88 / 228 (38.60%)	
occurrences (all)	152	129	
Vomiting			
subjects affected / exposed	45 / 218 (20.64%)	37 / 228 (16.23%)	
occurrences (all)	56	58	
Stomatitis			
subjects affected / exposed	32 / 218 (14.68%)	41 / 228 (17.98%)	
occurrences (all)	39	60	

Abdominal pain			
subjects affected / exposed	30 / 218 (13.76%)	28 / 228 (12.28%)	
occurrences (all)	36	50	
Abdominal pain upper			
subjects affected / exposed	24 / 218 (11.01%)	29 / 228 (12.72%)	
occurrences (all)	31	45	
Dyspepsia			
subjects affected / exposed	22 / 218 (10.09%)	24 / 228 (10.53%)	
occurrences (all)	23	33	
Constipation			
subjects affected / exposed	21 / 218 (9.63%)	18 / 228 (7.89%)	
occurrences (all)	27	22	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	159 / 218 (72.94%)	129 / 228 (56.58%)	
occurrences (all)	242	179	
Rash			
subjects affected / exposed	11 / 218 (5.05%)	35 / 228 (15.35%)	
occurrences (all)	12	45	
Pruritus			
subjects affected / exposed	7 / 218 (3.21%)	21 / 228 (9.21%)	
occurrences (all)	7	29	
Dry skin			
subjects affected / exposed	9 / 218 (4.13%)	16 / 228 (7.02%)	
occurrences (all)	10	17	
Nail disorder			
subjects affected / exposed	8 / 218 (3.67%)	14 / 228 (6.14%)	
occurrences (all)	8	15	
Alopecia			
subjects affected / exposed	11 / 218 (5.05%)	6 / 228 (2.63%)	
occurrences (all)	12	6	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	15 / 218 (6.88%)	27 / 228 (11.84%)	
occurrences (all)	24	32	
Arthralgia			

subjects affected / exposed	17 / 218 (7.80%)	21 / 228 (9.21%)	
occurrences (all)	19	27	
Back pain			
subjects affected / exposed	18 / 218 (8.26%)	20 / 228 (8.77%)	
occurrences (all)	23	23	
Muscle spasms			
subjects affected / exposed	12 / 218 (5.50%)	17 / 228 (7.46%)	
occurrences (all)	20	21	
Bone pain			
subjects affected / exposed	12 / 218 (5.50%)	8 / 228 (3.51%)	
occurrences (all)	16	9	
Myalgia			
subjects affected / exposed	6 / 218 (2.75%)	12 / 228 (5.26%)	
occurrences (all)	8	19	
Musculoskeletal chest pain			
subjects affected / exposed	5 / 218 (2.29%)	12 / 228 (5.26%)	
occurrences (all)	7	13	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	12 / 218 (5.50%)	25 / 228 (10.96%)	
occurrences (all)	15	37	
Urinary tract infection			
subjects affected / exposed	17 / 218 (7.80%)	21 / 228 (9.21%)	
occurrences (all)	20	28	
Upper respiratory tract infection			
subjects affected / exposed	9 / 218 (4.13%)	19 / 228 (8.33%)	
occurrences (all)	12	46	
Paronychia			
subjects affected / exposed	11 / 218 (5.05%)	15 / 228 (6.58%)	
occurrences (all)	15	16	
Influenza			
subjects affected / exposed	4 / 218 (1.83%)	12 / 228 (5.26%)	
occurrences (all)	5	12	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	28 / 218 (12.84%)	36 / 228 (15.79%)	
occurrences (all)	43	43	
Hypokalaemia			
subjects affected / exposed	13 / 218 (5.96%)	28 / 228 (12.28%)	
occurrences (all)	19	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2010	Protocol version B included the following amendments: -To clarify and simplify the guidance regarding capecitabine dose modifications for toxicity; -To clarify that left ventricular ejection fraction (LVEF) assessments performed locally will also be read centrally by an Independent Review Facility (IRF). All patient management decisions will be made by the Investigator based on the local LVEF assessments. The Independent Data Monitoring Committee (IDMC) will review both local and central LVEF results as part of their interim safety data review.; -To clarify that MRI or PET scans are allowed as an alternative to isotope bone scans at Investigator sites where there is a lack of radioisotope. Skeletal X-rays can now be used instead of bone scans for tumour assessments if there is no suitable alternative.; -Information on concomitant medication within 90 days prior to randomization is collected.; -Clarification regarding patient contact following premature withdrawal.; -To clarify that death due solely to progression of the underlying malignancy is not reported as an SAE.; -To clarify recording of deaths and provides information on SUSAR reporting.; -Clarification regarding the time interval allowed following the previous dose of pertuzumab/trastuzumab before the patient is required to be withdrawn from all study treatment.
01 June 2010	Protocol version C included the following amendments: -The IDMC, at its kick-off meeting, recommended additional cardiac safety monitoring as a precautionary measure to provide added reassurance to what was already in the protocol. Their recommendation is not as a result of any emergent safety signal observed in the study. The protocol has been amended to incorporate the IDMC recommendations regarding additional cardiac monitoring. As recommended by the IDMC, all additional cardiac safety assessments are to be performed on new patients randomized into the study. For those patients already in the study, any remaining additional cardiac assessments are to be performed. The additional cardiac assessments on all patients in the study are to continue until the IDMC recommends that they are no longer required.; -Exclusion criteria amended to clarify that patients with known infection with HIV, HBV or HCV, either active infection or carriers, are not eligible for the study.
01 October 2013	Protocol version D included the following amendments: -Statistical analysis plan (SAP): Revision to the final OS analysis timepoint from death or withdrawals in 90% of enrolled patients to death in 67% of enrolled patients (approximately 300 deaths), Incorporation of an interim OS analysis at the time of the primary PFS endpoint analysis of 337 IRF−assessed PFS events, Addition of a 2-year truncated OS analysis as a secondary endpoint; -Now referred to as a Phase III rather than a Phase II study; -If any analysis of OS meets the predefined criteria for statistical significance and is considered clinically meaningful, pertuzumab (in addition to current study drugs) will be offered to those patients who are still on treatment in the comparator arm (Arm A).; -After the cutoff for the primary PFS analysis, tumor assessments are to continue per protocol until investigator−assessed progressive disease. However, no additional IRF reviews will be performed. -After the cutoff for the final OS analysis, tumor assessments are to continue according to routine clinical practice until investigator-assessed progressive disease.; The IDMC met on 17 April 2013 to review the safety data in patients in the MO22324 study. No safety concerns were identified. The Sponsor and the IDMC have agreed that the additional assessments that had been previously implemented in Protocol Amendment C as a precautionary measure at the request of the IDMC are now no longer required. Patients will continue to have cardiac monitoring, and all other cardiac assessments will be performed.; -All patients will enter a 2 year safety follow-up.; -Potential Hy’s law cases are to be reported to the Sponsor within 24 hours as non-serious AE of special interest.

02 December 2014	Protocol version E included the following amendments: -To clarify that all patients should be followed for survival until the planned final OS analysis after 300 deaths.; -A change to the duration of required contraceptive use and the prohibition of breastfeeding from 6 to 7 months after receipt of the final dose of all study drugs for consistency with the updated pharmacokinetic (PK) findings for trastuzumab. This change was not based on any new safety findings, and the benefit−risk assessment for patients treated with trastuzumab remains positive.; -The mandatory baseline serum samples that have been collected in Study MO22324 will not be immediately used to measure HER2-ECD (human epidermal growth factor receptor-2, extracellular domain) and HER ligands. However, the mandatory blood samples will be retained in case improved technology becomes available in the future for HER ligands and/or if a strong scientific rationale evolves to measure HER2-ECD.; -Those patients who are still on capecitabine study drug treatment will be informed about additional possible side effects, in line with the recent update to the Xeloda® IB, version 16.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported