Clinical trial results:
A Randomized, 3 Arm, Multicenter, Phase III Study to Evaluate the Efficacy and the Safety of T-DM1 Combined With Pertuzumab or T-DM1 Combined With Pertuzumab-Placebo (Blinded for Pertuzumab), Versus the Combination of Trastuzumab Plus Taxane, as First Line Treatment in HER2 Positive Progressive or Recurrent Locally Advanced or Metastatic Breast Cancer (MBC)

Summary

EudraCT number	2009-017905-13
Trial protocol	AT ES DE FR SE DK HU CZ GB IT BE PT GR
Global end of trial date	

Results information

Result version number	v1
This version publication date	07 January 2017
First version publication date	07 January 2017

Trial information

Trial identification

Sponsor protocol code	BO22589

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01120184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, CH, Basel, Switzerland, 4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 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	Interim
Date of interim/final analysis	16 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 September 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized, three-arm, multicenter, Phase III study was designed to evaluate the efficacy and safety of trastuzumab emtansine with and without pertuzumab, versus the combination of trastuzumab with taxane therapy, among participants with human epidermal growth factor receptor 2 (HER2)-positive locally advanced breast cancer (LABC) or metastatic breast cancer (MBC) who had not received prior chemotherapy for their metastatic disease.

Protection of trial subjects:

All investigators were trained according to applicable Sponsor Standard Operating Procedures (SOPs). Roche and the investigators strictly adhered to the stated provisions in these guidelines. This was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and law and to follow International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	67 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Korea, Republic of: 79
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Bahamas: 6
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Panama: 5
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United States: 131
Country: Number of subjects enrolled	Brazil: 88
Country: Number of subjects enrolled	Japan: 82
Country: Number of subjects enrolled	United Kingdom: 74
Country: Number of subjects enrolled	France: 72

Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Spain: 43
Country: Number of subjects enrolled	Thailand: 39
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Bosnia and Herzegovina: 25
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Philippines: 23
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 21
Country: Number of subjects enrolled	Peru: 20
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Guatemala: 12
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Malaysia: 10
Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Argentina: 6
Worldwide total number of subjects	1095
EEA total number of subjects	405

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)	912
From 65 to 84 years	179
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 1629 participants were screened, of whom 1095 were randomized. There were 534 participants who failed screening, most often due to non-centrally confirmed HER2 status or abnormal laboratory results.

Pre-assignment

Screening details:

A total of 1629 participants were screened, of whom 1095 were randomized. There were 534 participants who failed screening, most often due to non-centrally confirmed HER2 status or abnormal laboratory results.

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	Subject, Investigator

Blinding implementation details:

The study was considered open-label with respect to trastuzumab and trastuzumab emtansine treatment; however, participants and investigators were blinded with respect to pertuzumab or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab + Taxane

Arm description:

Participants received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab, docetaxel or paclitaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

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

Dosage and administration details:

Trastuzumab was administered via IV infusion and dosed depending upon the taxane selected. Participants received either 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg on Day 1 of each subsequent 3-week cycle, or 4 mg/kg on Day 1 of Cycle 1 followed by 2 mg/kg weekly beginning on Day 8 of Cycle 1.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel was administered via IV infusion as 75 or 100 mg/m^2 on Day 1 of each 3-week cycle.

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

Dosage and administration details:

Paclitaxel was administered via IV infusion as 80 mg/m^2 weekly.

Arm title	Trastuzumab Emtansine + Placebo

Arm description:

Participants received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received the placebo equivalent to pertuzumab via IV infusion on Day 1 of each 3-week cycle.

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

Dosage and administration details:

Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion on Day 1 of each 3-week cycle.

Arm title	Trastuzumab Emtansine + Pertuzumab

Arm description:

Participants received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

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

Dosage and administration details:

Pertuzumab was administered via IV infusion as 840 mg on Day 1 of Cycle 1, followed by 420 mg on Day 1 of each subsequent 3-week cycle.

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

Dosage and administration details:

Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion on Day 1 of each 3-week cycle.

Number of subjects in period 1	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab
Started	365	367	363
Treated	355	365	360
Completed	196	213	209
Not completed	169	154	154
Physician decision	9	2	2
Consent withdrawn by subject	28	28	22
Death	123	116	115
Not Specified	4	2	8
Lost to follow-up	5	6	7

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab + Taxane

Reporting group description:

Participants received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab, docetaxel or paclitaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

Reporting group title	Trastuzumab Emtansine + Placebo

Reporting group description:

Participants received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Reporting group title	Trastuzumab Emtansine + Pertuzumab

Reporting group description:

Participants received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Reporting group values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab
Number of subjects	365	367	363
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	54.2	52.6	52.2
standard deviation	± 11.3	± 11.4	± 12
Gender, Male/Female Units: participants			
Female	362	365	361
Male	3	2	2

Reporting group values	Total		
Number of subjects	1095		
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender, Male/Female Units: participants			
Female	1088		
Male	7		

End points

End points reporting groups

Reporting group title	Trastuzumab + Taxane

Reporting group description:

Participants received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab, docetaxel or paclitaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

Reporting group title	Trastuzumab Emtansine + Placebo

Reporting group description:

Participants received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Reporting group title	Trastuzumab Emtansine + Pertuzumab

Reporting group description:

Participants received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Subject analysis set title	Trastuzumab + Taxane - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population for this group included all treated participants; however, 2 participants randomized to this group received 3 cycles of trastuzumab emtansine and were excluded for safety analysis. Hence, safety population for this group=353.

Subject analysis set title	Trastuzumab Emtansine + Placebo - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population for this group included all treated participants; however, 2 participants randomized to trastuzumab+taxane received 3 cycles of trastuzumab emtansine and were included in this group for safety analysis. Six participants randomized to this group received pertuzumab and were excluded from this group. Hence, safety population for this group=361.

Subject analysis set title	Trastuzumab Emtansine + Pertuzumab - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population for this group included all treated participants; however, 6 participants randomized to trastuzumab emtansine+placebo received pertuzumab and were included in this arm for safety analysis. Hence, safety population for this group=366.

Primary: Percentage of Participants with Death or Disease Progression According to Independent Review Facility (IRF) Assessment

End point title	Percentage of Participants with Death or Disease Progression According to Independent Review Facility (IRF) Assessment[1]

End point description:

Tumor assessments were performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a greater than or equal to (≥) 20 percent (%) and 5-millimeter (mm) increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of participants with death or disease progression was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population (all participants randomized in the study).

End point type	Primary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The data for this endpoint is descriptive and hence, no statistical analysis is provided.

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of participants				
number (not applicable)	63.3	64.3	59.8	

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival (PFS) According to IRF Assessment

End point title	Progression-Free Survival (PFS) According to IRF Assessment

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. PFS was defined as the time from randomization to first documented disease progression as assessed by IRF or death from any cause. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis, and corresponding confidence intervals (CIs) were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population.

End point type	Primary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	13.7 (12.4 to 14.9)	14.1 (10.9 to 16.8)	15.2 (12.5 to 18.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.3125 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.73
upper limit	1.13

Notes:

[2] - The study was powered for superiority with target hazard ratio (HR) equal to 0.75, as well as for non-inferiority with HR equal to 1.1765 for comparison between each of the trastuzumab emtansine-containing arms and the trastuzumab + taxane arm. Non-inferiority was established if the upper bound of the 97.5% CI was less than (<) 1.1765. Superiority was achieved if the upper bound of the 97.5% CI was <1.00.

[3] - Test and p-value apply for superiority test. Two-sided significance level of 2.5% was used to adjust for independent comparison between each of the trastuzumab emtansine-containing arms and the trastuzumab + taxane arm.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.1407 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.69
upper limit	1.08

Notes:

[4] - The study was powered for superiority with target HR equal to 0.75, as well as for non-inferiority with HR equal to 1.1765 for comparison between each of the trastuzumab emtansine-containing arms and the trastuzumab + taxane arm. Non-inferiority was established if the upper bound of the 97.5% CI was <1.1765. Superiority was achieved if the upper bound of the 97.5% CI was <1.00.

[5] - Test and p-value apply for superiority test. Two-sided significance level of 2.5% was used to adjust for independent comparison between each of the trastuzumab emtansine-containing arms and the

trastuzumab + taxane arm.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent). Formal comparison planned depending on superiority for trastuzumab emtansine + pertuzumab versus trastuzumab + taxane.

Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	= 0.3075 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.73
upper limit	1.13

Notes:

[6] - The study was powered for superiority with target HR equal to 0.75, as well as for non-inferiority with HR equal to 1.1765 for comparison between each of the trastuzumab emtansine-containing arms and the trastuzumab + taxane arm. Non-inferiority was established if the upper bound of the 97.5% CI was <1.1765. Superiority was achieved if the upper bound of the 97.5% CI was < 1.00. Formal comparison planned depending on superiority for trastuzumab emtansine + pertuzumab versus trastuzumab + taxane.

[7] - Test and p-value apply for superiority test. Primary endpoint did not meet superiority of PFS for trastuzumab emtansine + pertuzumab versus trastuzumab + taxane (two-sided significance level 2.5%); thus, tests and p-value are considered descriptive.

Secondary: Percentage of Participants Who Died Prior to Clinical Cutoff

End point title	Percentage of Participants Who Died Prior to Clinical Cutoff

End point description:

The percentage of participants who died prior to clinical cutoff was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of participants				
number (not applicable)	33.7	31.6	31.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at Clinical Cutoff

End point title	Overall Survival (OS) at Clinical Cutoff

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Here, "9999" represents that the value is not applicable because Median duration of OS was not reached due to insufficient followup. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	9999 (41.1 to 9999)	9999 (44.7 to 9999)	9999 (9999 to 9999)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.64
upper limit	1.16

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.61
upper limit	1.11

Secondary: Percentage of Participants with Death or Disease Progression According to Investigator Assessment

End point title	Percentage of Participants with Death or Disease Progression According to Investigator Assessment

End point description:

Tumor assessments were performed by the investigator according to RECIST version 1.1. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of participants with death or disease progression was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of participants				
number (not applicable)	72.1	70.3	67.5	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS According to Investigator Assessment

End point title	PFS According to Investigator Assessment

End point description:

Tumor assessments were performed by the investigator according to RECIST version 1.1. PFS was defined as the time from randomization to progression of disease as assessed by Investigator or death from any cause. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	12.5 (10.5 to 13.6)	14.1 (12.2 to 16.7)	14.8 (12.4 to 17.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.69
upper limit	1.04

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.63
upper limit	0.95

Secondary: Percentage of Participants Experiencing Treatment Failure

End point title	Percentage of Participants Experiencing Treatment Failure

End point description:

Treatment failure was defined as the discontinuation of all study medications in the treatment arm for any reason including disease progression, treatment toxicity, death, physician decision, or participant withdrawal. The percentage of participants with treatment failure was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of participants				
number (not applicable)	85.8	82.6	80.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)

End point description:

Treatment failure was defined as the discontinuation of all study medications in the treatment arm for any reason including disease progression, treatment toxicity, death, physician decision, or participant withdrawal. TTF is the time from randomization to discontinuation of all
agents in the respective treatment arm for any reason, including disease progression, treatment toxicity, death from any cause, or patient/physician decision to discontinue study treatment. Median TTF was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	10.2 (9.2 to 11.8)	12.1 (9.9 to 13.9)	11.8 (9.9 to 14.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.65
upper limit	0.95

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.66
upper limit	0.97

Secondary: One-Year Survival Rate

End point title	One-Year Survival Rate

End point description:

The percentage of participants alive at 1 year after randomization was estimated as the one-year survival rate using Kaplan-Meier analysis, and corresponding CIs were computed using Greenwood's estimate of the standard error. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomization until 1 year

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage probability of being alive				
number (confidence interval 95%)	91.4 (88.44 to 94.41)	92.4 (89.62 to 95.15)	91.9 (89 to 94.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Grade ≥3 Adverse Events

End point title	Percentage of Participants with Grade ≥3 Adverse Events

End point description:

Adverse events were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden. Grade 4: An immediate threat to life. Urgent medical intervention is required in order to maintain survival. Grade 5: Death. Safety Population: All treated participants. Additionally, 2 participants randomized to trastuzumab+taxane received 3 cycles of trastuzumab emtansine and were included in trastuzumab emtansine+placebo arm. 6 participants randomized to trastuzumab emtansine+placebo received pertuzumab and were included in trastuzumab emtansine+pertuzumab arm.

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (continuously until 28 days after last dose

End point values	Trastuzumab + Taxane - Safety Population	Trastuzumab Emtansine + Placebo - Safety Population	Trastuzumab Emtansine + Pertuzumab - Safety Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of participants				
number (not applicable)	54.1	45.4	46.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died at 2 Years

End point title	Percentage of Participants Who Died at 2 Years

End point description:

Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomization until 2 years

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of participants				
number (not applicable)	20.3	20.2	19.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Truncated at 2 Years

End point title	Overall Survival Truncated at 2 Years

End point description:

Overall Survival truncated at 2 years was defined as the time from the date of randomization to the date of death from any cause. Participants who were alive at 2 years had been censored at 2 years. Median duration of overall survival truncated at 2 years was estimated using Kaplan-Meier analyses, and corresponding CIs were computed using the Brookmeyer-Crowley method. Here, "9999" represents that data was not applicable because median was not reached at 2 years as most of the participants were alive at that time point. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomization until 2 years

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.62
upper limit	1.31

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).	
Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.6
upper limit	1.29

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).	
Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.68
upper limit	1.46

Secondary: Percentage of Participants with Grade 5 Adverse Events

End point title	Percentage of Participants with Grade 5 Adverse Events

End point description:

Adverse events were graded according to NCI CTCAE version 4.0. Grade 5 adverse events are those events which led to death.Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (continuously until 28 days after last dose

End point values	Trastuzumab + Taxane - Safety Population	Trastuzumab Emtansine + Placebo - Safety Population	Trastuzumab Emtansine + Pertuzumab - Safety Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of participants				
number (not applicable)	1.7	1.1	1.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Grade 3-4 Laboratory Parameters

End point title	Percentage of Participants with Grade 3-4 Laboratory Parameters

End point description:

Laboratory results were graded according to NCI CTCAE version 4.0. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden. Grade 4: An immediate threat to life. Urgent medical intervention is required in order to maintain survival. Analysis was performed on safety population. Number of participants analyzed=participants with available data for the outcome.

End point type	Secondary

End point timeframe:

Day 1, 8, and 15 of Cycle 1–3 and on Day 1 of each subsequent cycle up to 50 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	352	361	363	
Units: percentage of participants				
number (not applicable)				
Hemoglobin-Low: Grade 3	4.3	5.8	6.9	
Neutrophils-Low: Grade 3	20.2	5.5	5	
Neutrophils-Low: Grade 4	43.8	1.9	0.8	
Platelets-Low: Grade 3	0.9	12.7	12.9	
Platelets-Low: Grade 4	0.3	2.8	2.5	
Alkaline Phosphate-High: Grade 3	1.1	3.9	3	
Alanine Transaminase-High: Grade 3	3.4	9.1	8	
Alanine Transaminase-High: Grade 4	0	0.3	0.6	
Aspartate Aminotransferase-High: Grade 3	1.1	11.9	6.9	
Aspartate Aminotransferase-High: Grade 4	0	0.3	0.3	
Creatinine-High: Grade 3	0.9	0.3	1.1	
Creatinine-High: Grade 4	0	0	0.3	
Potassium-Low: Grade 3	4.3	4.7	5.2	
Potassium-Low: Grade 4	0.6	1.7	0.6	
Total Bilirubin-High: Grade 3	0.3	0.3	0.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Decline of ≥2 points from Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Percentage of Participants with Decline of ≥2 points from Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point description:

The ECOG performance status is a scale used to quantify cancer participants' general well-being and activities of daily life. The scale ranges from 0 to 5, with 0 denoting perfect health and 5 indicating death. The 6 categories are 0=Asymptomatic (Fully active, able to carry on all predisease activities without restriction), 1=Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), 2=Symptomatic, < 50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours), 3=Symptomatic, > 50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours), 4=Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair), 5=Death. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of every Cycle up to Clinical Data Cut (up to 48 months)

End point values	Trastuzumab + Taxane - Safety Population	Trastuzumab Emtansine + Placebo - Safety Population	Trastuzumab Emtansine + Pertuzumab - Safety Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of participants				
number (not applicable)	7.6	6.1	7.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalization Days

End point title	Hospitalization Days

End point description:

Hospitalization was defined as a non-administration-related hospitalization due to serious adverse event, while on study treatment. Reported values represent number of days admitted per participants. Analysis was performed on safety population .Number of participants analyzed=participants with hospitalization and data available for calculation of the parameter.

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane - Safety Population	Trastuzumab Emtansine + Placebo - Safety Population	Trastuzumab Emtansine + Pertuzumab - Safety Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: days				
median (full range (min-max))	6 (1 to 50)	5 (1 to 117)	8 (1 to 381)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hospitalization

End point title	Percentage of participants with Hospitalization

End point description:

Hospitalization was defined as a non-administration-related hospitalization due to serious adverse event, while on study treatment. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane - Safety Population	Trastuzumab Emtansine + Placebo - Safety Population	Trastuzumab Emtansine + Pertuzumab - Safety Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of participants				
number (confidence interval 95%)	21.8 (17.62 to 26.36)	20.2 (16.2 to 24.71)	22.1 (18.03 to 26.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response According to IRF Assessment

End point title	Percentage of Participants with Objective Response According to IRF Assessment

End point description:

Objective response was defined as having complete response (CR) or partial response (PR), assessed according to RECIST version 1.1, using radiographic images submitted to IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR: disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR: a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of participants with a best overall response of CR or PR (ie, the objective response rate [ORR]) was calculated as [number of participants meeting the respective criteria divided by the number analyzed] multiplied by 100. Corresponding CIs were computed using the Blyth-Still-Casella exact method. ITT population. Only participants with measurable disease by IRF at Baseline were included.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	287	303	299	
Units: percentage of participants				
number (confidence interval 95%)	67.9 (62.26 to 73.31)	59.7 (54.07 to 65.3)	64.2 (58.62 to 69.65)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Response Rate
Point estimate	-8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.9
upper limit	-0.5

Statistical analysis title	Statistical Analysis 2
Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Response Rate
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.4
upper limit	3.9

Statistical analysis title	Statistical Analysis 3
Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Response Rate
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	12.2

Secondary: Percentage of Participants with Objective Response According to Investigator Assessment

End point title	Percentage of Participants with Objective Response According

	to Investigator Assessment

End point description:

Objective response was defined as having CR or PR, assessed according to RECIST version 1.1, by investigator. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of participants with a best overall response of CR or PR (ie, the ORR) was calculated as [number of participants meeting the respective criteria divided by the number analyzed] multiplied by 100. Corresponding CIs were computed using the Blyth-Still-Casella exact method. Only participants with measurable disease by Investigator at Baseline were included in the analysis. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	293	314	311	
Units: percentage of participants				
number (confidence interval 95%)	69.3 (63.74 to 74.52)	64.6 (59.12 to 69.87)	67.5 (62.17 to 72.68)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	607
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Response Rate
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	2.8

Statistical analysis title	Statistical Analysis 2
Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane

Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Response Rate
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	5.7

Statistical analysis title	Statistical Analysis 3
Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Response Rate
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	10.3

Secondary: Duration of Response According to IRF Assessment

End point title	Duration of Response According to IRF Assessment

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Duration of response was defined as the time from confirmed PR or CR to first documented disease progression or death from any cause. CR was defined as the disappearance of all target lesions and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. Median duration of response was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population. Only participants achieving CR or PR were included in the analysis.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	195	181	192	
Units: months				
median (confidence interval 95%)	12.5 (10.5 to 16.6)	20.7 (14.8 to 25)	21.2 (15.8 to 29.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).	
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.43
upper limit	0.84

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).	
Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.45
upper limit	0.85

Secondary: Percentage of Participants with a Best Overall Response of CR, PR, or Stable Disease (SD) According to IRF Assessment

End point title	Percentage of Participants with a Best Overall Response of CR, PR, or Stable Disease (SD) According to IRF Assessment

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. SD was defined as neither sufficient shrinkage to quality for PR nor sufficient (20%) increase to qualify for disease progression. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of participants with a best overall response of CR, PR, or SD was calculated as [number of participants meeting the respective criteria divided by the number analyzed] multiplied by 100.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[8]	0[9]	0[10]	
Units: percentage of participants				
number (not applicable)				

Notes:

[8] - This outcome was removed because it was redundant to another prespecified secondary endpoint.

[9] - This outcome was removed because it was redundant to another prespecified secondary endpoint.

[10] - This outcome was removed because it was redundant to another prespecified secondary endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing a Clinically Significant Increase in Taxane-Related Treatment Symptoms as Measured by Taxane Subscale of the Functional Assessment of Cancer Therapy (FACT) Taxane (FACT-TaxS) Score

End point title	Percentage of Participants Experiencing a Clinically Significant Increase in Taxane-Related Treatment Symptoms as Measured by Taxane Subscale of the Functional Assessment of Cancer Therapy (FACT) Taxane (FACT-TaxS) Score

End point description:

The FACT-Taxane is a self-reported instrument which measures health-related quality of life (HRQOL) of participants receiving taxane-containing chemotherapy. FACT-TaxS consists of 16 items (11 neurotoxicity-related questions and 5 additional questions assessing arthralgia, myalgia, and skin discoloration). Items are rated from 0 (not at all) to 4 (very much) and total score is inversely derived. Scores may range from 0 to 64, with higher scores indicating fewer/no symptoms. A minimally clinically important difference in treatment-related symptoms was defined as ≥5% decrease (ie, 3.2 points) in FACT-TaxS score from Baseline. Percentage of participants with treatment-related symptoms was calculated using following formula: [participants meeting above threshold divided by the number analyzed] multiplied by 100. Corresponding CIs were computed using the Blyth-Still-Casella exact method. Protocol Amendment C Subpopulation: All randomized participants who entered after Protocol

Amendment C.

End point type	Secondary

End point timeframe:

Up to 39 months from randomization until clinical cutoff of 16-Sept-2014 (at Baseline, on Day 1 of Cycles 2 to 8 and every even-numbered cycle thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	171	154	
Units: percentage of participants				
number (confidence interval 95%)	93.1 (88.48 to 96.06)	60.8 (53.39 to 67.93)	68.8 (61.32 to 75.92)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs Tratuzumab + Taxane
Point estimate	-32.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40
upper limit	-24

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs Tratuzumab + Taxane
Point estimate	-24.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32
upper limit	-16

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % vs TDM-1+Placebo
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	18.4

Secondary: Percentage of Participants Reporting Nausea According to Item GP2 of The FACT Colorectal Cancel (FACT-C) Module

End point title	Percentage of Participants Reporting Nausea According to Item GP2 of The FACT Colorectal Cancel (FACT-C) Module

End point description:

The FACT-C is a self-reported instrument which measures HRQOL pertaining to colorectal cancer. Response options on each question may range from 0 (not at all) to 4 (very much). The percentage of participants with nausea was calculated using following formula: [number of participants with any level of either symptom divided by the number analyzed] multiplied by 100. Protocol Amendment C Subpopulation. Only participants with a FACT-C score at the designated visit (n) were included in the analysis.

End point type	Secondary

End point timeframe:

At Baseline, Day 8 of Cycle 1, and Days 1 and 8 of Cycle 2

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	171	154	
Units: percentage of participants				
number (not applicable)				
Nausea, Baseline (n=166,166,150)	22.3	14.5	21.3	
Nausea, Cycle 1 Day 8 (n=121,114,95)	38	36	52.6	
Nausea, Cycle 2 Day 1 (n=147,151,138)	27.2	20.5	36.2	
Nausea, Cycle 2 Day 8 (n=122,121,105)	35.2	28.1	45.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Reporting Diarrhea According to Single Item C5 of The FACT-C Module

End point title	Percentage of Participants Reporting Diarrhea According to Single Item C5 of The FACT-C Module

End point description:

The FACT-C is a self-reported instrument which measures HRQOL pertaining to colorectal cancer. Response options on each question may range from 0 (not at all) to 4 (very much). The percentage of participants with diarrhea was calculated using following formula: [number of participants with any level of either symptom divided by the number analyzed] multiplied by 100. Protocol Amendment C Subpopulation. Only participants with a FACT-C score at the designated visit (n) were included in the analysis.

End point type	Secondary

End point timeframe:

At Baseline, Day 8 of Cycle 1, and Days 1 and 8 of Cycle 2

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	171	154	
Units: percentage of participants				
number (not applicable)				
Diarrhea, Baseline (n=173,170,153)	15	7.6	11.8	
Diarrhea, Cycle 1 Day 8 (n=124,117,98)	34.7	17.9	34.7	
Diarrhea, Cycle 2 Day 1 (n=161,160,144)	24.2	11.3	39.6	
Diarrhea, Cycle 2 Day 8 (n=125,123,107)	34.4	8.1	41.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Clinically Significant Deterioration in Health Related Quality of Life (HRQoL) as measured by FACT Breast (FACT-B) Trial Outcome Index-Physical Function Breast (TOI-PFB) Score

End point title	Percentage of Participants with a Clinically Significant Deterioration in Health Related Quality of Life (HRQoL) as measured by FACT Breast (FACT-B) Trial Outcome Index-Physical Function Breast (TOI-PFB) Score

End point description:

The FACT-B is self-reported instrument which measures HRQOL of participants with breast cancer. It consists of 5 subscales including physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and a breast cancer subscale (BCS). The TOI-PFB score is taken by adding the scores from the PWB (7 items), FWB (7 items), and BCS (9 items) subscales. Items are rated from 0 (not at all) to 4 (very much) and total score is derived. Scores may range from 0 to 92, with higher scores indicating better HRQOL. A 5 point change has been identified as the clinically minimal important difference (CMID) on the FACT-TOI-PFB scale. The percentage of participants with deterioration was calculated as [number of participants meeting above threshold divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population. Number of participants analyzed=participants with baseline and at least 1 post baseline FACT-B TOI-PFB score.

End point type	Secondary

End point timeframe:

Up to 39 months from randomization until progression or clinical cutoff of 16-Sept-2014 (Pre amendment C: every 9 weeks for 1st 81 weeks, every 12 weeks thereafter; post amendment C: 1st day of every cycle for first 8 cycles, every other cycle thereafter)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	327	352	338	
Units: percentage of participants				
number (not applicable)	61.8	50.9	50.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration in HRQoL as Assessed by FACT-B TOI-PFB Score

End point title	Time to Deterioration in HRQoL as Assessed by FACT-B TOI-PFB Score

End point description:

The FACT-B is a self-reported instrument which measures HRQOL of participants with breast cancer. It consists of 5 subscales including PWB, SWB, EWB, FWB, and BCS. The TOI-PFB score is taken by adding the scores from the PWB (7 items), FWB (7 items), and BCS (9 items) subscales. Items are rated from 0 (not at all) to 4 (very much) and a total score is derived. Scores may range from 0 to 92, with higher scores indicating better HRQOL. A 5 point change has been identified as the clinically minimal important difference (CMID) on the FACT-TOI-PFB scale. Time to deterioration was defined as the time from Baseline until the first decrease in FACT-B TOI-PFB score. Median time to deterioration was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT Population. Number of participants analyzed=participants with baseline and at least one post baseline FACT-B
TOI-PFB score.

End point type	Secondary

End point timeframe:

Up to 39 months from randomization until progression or clinical cutoff of 16-Sept-2014 (Pre amendment C: every 9 weeks for 1st 81 weeks, every 12 weeks thereafter; post amendment C: 1st day of every cycle for first 8 cycles, every other cycle thereafter)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	327	352	338	
Units: months				
median (confidence interval 95%)	3.6 (3 to 4.4)	7.7 (6.2 to 11.9)	9 (5.1 to 14.5)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.86

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane

Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.84

Secondary: Change from Baseline in Rotterdam Symptom Checklist (RSCL) Activity Level Scale Score

End point title	Change from Baseline in Rotterdam Symptom Checklist (RSCL) Activity Level Scale Score

End point description:

The RSCL is a self-reported instrument which consists of 4 domains including physical symptom distress, psychological distress, activity level, and overall global life quality. Only the activity level scale was collected and assessed. Scores may range from 0 to 100, with higher scores indicating increased burden of disease. Mean RSCL activity scale score changes were calculated as [mean score at the assessment visit minus mean score at Baseline]. The higher the score, the higher the level of impairment or burden. Analysis was performed on ITT Population. Here, 'n' signifies the number of participants with available data at baseline and Cycle 7 (Week 18).

End point type	Secondary

End point timeframe:

Baseline, Cycle 7 (Week 18)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Baseline (n=344,355,344)	85 (82.9 to 87.2)	85.5 (83.3 to 87.8)	85.7 (83.5 to 87.8)	
Change From Baseline at Cycle 7 (n=261,252,261)	-1.6 (-4.2 to 1)	2.3 (0.4 to 4.2)	-0.2 (-2.1 to 1.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

End point title	Change From Baseline in Work Productivity According to Work Productivity and Activity Impairment (WPAI) Questionnaire

	Score

End point description:

The WPAI is patient-reported measure which assesses the effect of general health and symptom severity on work productivity and regular activities. The General Health questionnaire asks participants to estimate number of hours missed from work due to reasons related and unrelated to their health problems, as well as total number of hours actually worked in preceding 7-day period. Percentage of participants reporting that they were employed (working for pay) was assessed at baseline along with Absenteeism (work time missed), Presenteeism (impairment at work/reduced on-job effectiveness), Work productivity loss (overall work impairment/absenteeism plus presenteeism), and Activity Impairment. Reported changes represent change from baseline at Cycle 7. The score range for scales of the WPAI is 0 (no effect) to 100% (max effect). Number of participants analysed=participants from ITT population who were employed at baseline. Here, 'n' signifies the number of participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Cycle 7 (Week 18)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	64	67	
Units: percent of work				
arithmetic mean (confidence interval 95%)				
% Work Time Missed at Baseline (n=66,63,67)	15.3 (9.2 to 21.4)	9.5 (4.2 to 14.8)	13.6 (7.7 to 19.6)	
Change in % Work Time Missed (n=35,33,36)	0.4 (-7.3 to 8.2)	0 (-4.5 to 4.5)	-4.3 (-13 to 4.6)	
% Impairment While Working at Baseline(n=67,64,67)	20 (14.1 to 25.9)	15.3 (9.5 to 21.1)	19.9 (13.6 to 26.1)	
Change in % Impairment While Working (n=34,32,35)	8.8 (2 to 15.6)	-0.3 (-11 to 10.5)	-2.7 (-11 to 5.2)	
% Overall Work Impairment at Baseline (n=65,62,66)	28.5 (20.7 to 36.2)	21.2 (13.8 to 28.7)	28.1 (20.3 to 35.9)	
Change in % Overall Work Impairment (n=34,31,35)	9.1 (-0.4 to 18.6)	-1.1 (-13 to 11)	-4.6 (-14 to 5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Activity Impairment According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

End point title	Change From Baseline in Activity Impairment According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

End point description:

The WPAI is patient-reported measure which assesses effect of general health and symptom severity on work productivity and regular activities. The General Health questionnaire asks participants to estimate number of hours missed from work due to reasons related and unrelated to their health problems, as well as total number of hours actually worked in preceding 7-day period. Percentage of participants reporting that they were employed (working for pay) was assessed at baseline along with Absenteeism (work time missed), Presenteeism (impairment at work/reduced on-the-job effectiveness), Work

productivity loss (overall work mpairment/absenteeism plus presenteeism), and Activity Impairment. Reported changes represent change from baseline at Cycle 7. The score range for the scales of WPAI is 0 (no effect) to 100% (max effect). Number of participants analysed=participants from ITT population who were employed at baseline. Here, 'n' signifies the number of participants with available data.

End point type	Secondary

End point timeframe:

Baseline, Cycle 7 (Week 18)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	312	334	321	
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
% Activity Impairment at Baseline (n=312,334,321)	32.9 (29.6 to 36.3)	33.6 (30.2 to 37)	32.7 (29.5 to 36)	
Change in % Activity Impairment (n=227,222,234)	4.5 (0.2 to 8.7)	-5.3 (-9.5 to -1.1)	-3.7 (-7.2 to -0.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Best Overall Response of CR or PR According to IRF Assessment Among Those with High Human Epidermal Growth Factor Receptor 2 (HER2) Messenger Ribonucleic Acid (mRNA) Levels

End point title	Percentage of Participants with a Best Overall Response of CR or PR According to IRF Assessment Among Those with High Human Epidermal Growth Factor Receptor 2 (HER2) Messenger Ribonucleic Acid (mRNA) Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of participants with a best overall response of CR or PR (ie, the ORR) was calculated as [number of participants meeting the respective criteria divided by the number analyzed] multiplied by 100. ITT Population (High HER2 mRNA Subpopulation): All randomized participants with above the median HER2 mRNA expression (value greater than [>] 59.71). Only participants with measurable disease at Baseline were included in the analysis.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	136	147	
Units: percentage of participants				
number (not applicable)	75	66.9	63.9	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.15

Secondary: Percentage of Participants with a Best Overall Response of CR or PR According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point title	Percentage of Participants with a Best Overall Response of CR or PR According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of participants with a best overall response of CR or PR (ie, the ORR) was calculated as [number of participants meeting the respective criteria divided by the number analyzed] multiplied by 100. ITT Population (Low HER2 mRNA Subpopulation): All randomized participants with below-the-median HER2 mRNA expression (value less than or equal to [≤] 59.71). Only participants with measurable disease at Baseline were included in the analysis.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	147	127	
Units: percentage of participants				
number (not applicable)	61.9	51.7	66.1	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.07

Secondary: Percentage of Participants with Death or Disease Progression According to IRF Assessment Among Those with High HER2 mRNA Levels

End point title	Percentage of Participants with Death or Disease Progression According to IRF Assessment Among Those with High HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of participants with death or disease progression was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population (High HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	173	
Units: percentage of participants				
number (not applicable)	59.4	57.6	56.1	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS According to IRF Assessment Among Those with High HER2 mRNA Levels

End point title	PFS According to IRF Assessment Among Those with High HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis. Analysis was performed on ITT Population (High HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	173	
Units: months				
median (full range (min-max))	15.9 (0.1 to 46.4)	18.6 (0.1 to 46)	18.7 (0.1 to 48.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane

Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.65
upper limit	1.25

Secondary: Percentage of Participants with Death or Disease Progression According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point title	Percentage of Participants with Death or Disease Progression According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of participants with death or disease progression was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population (Low HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	174	157	
Units: percentage of participants				
number (not applicable)	66.5	70.1	62.4	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point title	PFS According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study

drug discontinuation. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis. Analysis was performed on ITT Population (Low HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	174	157	
Units: months				
median (full range (min-max))	12.4 (0.1 to 47.3)	10.2 (0.1 to 43.6)	14.5 (0.1 to 40.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.74
upper limit	1.34

Secondary: Percentage of Participants Who Died Prior to Clinical Cutoff Among Those with High HER2 mRNA Levels

End point title	Percentage of Participants Who Died Prior to Clinical Cutoff Among Those with High HER2 mRNA Levels

End point description:

The percentage of participants who died prior to clinical cutoff was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population (High HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	173	
Units: percentage of participants				
number (not applicable)	28.1	27.9	29.5	

Statistical analyses

No statistical analyses for this end point

Secondary: OS at Clinical Cutoff Among Those with High HER2 mRNA Levels

End point title	OS at Clinical Cutoff Among Those with High HER2 mRNA Levels

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis. Here, 9.99 represents data not applicable because median duration of OS was not reached due to insufficient follow up. Confidence interval values are censored values. Analysis was performed on ITT Population (High HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	173	
Units: months				
median (full range (min-max))	9.99 (0.1 to 48.4)	9.99 (0.6 to 48.1)	9.99 (0.1 to 48.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane

Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.59
upper limit	1.51

Secondary: Percentage of Participants Who Died Prior to Clinical Cutoff Among Those with Low HER2 mRNA Levels

End point title	Percentage of Participants Who Died Prior to Clinical Cutoff Among Those with Low HER2 mRNA Levels

End point description:

The percentage of participants who died prior to clinical cutoff was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population (Low HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	174	157	
Units: percentage of participants				
number (not applicable)	37.6	33.9	30.6	

Statistical analyses

No statistical analyses for this end point

Secondary: OS at Clinical Cutoff Among Those with Low HER2 mRNA Levels

End point title	OS at Clinical Cutoff Among Those with Low HER2 mRNA Levels

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis. Here, "9.99" represents that data is not applicable because median duration of OS was not reached due to insufficient followup. Reported upper bound of confidence interval for "Trastuzumab Emtansine + Placebo" and confidence interval values for "Trastuzumab + Taxane" and "Trastuzumab Emtansine + Pertuzumab" are censored values. Analysis was performed on ITT Population (Low HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	174	157	
Units: months				
median (full range (min-max))	41.9 (0.1 to 48)	9.99 (0.3 to 49.8)	9.99 (0.1 to 47.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.57
upper limit	1.27

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (continuously until 28 days after last dose)

Adverse event reporting additional description:

Safety Population: All randomized participants who received at least one dose of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Trastuzumab + Taxane

Reporting group description:

Participants received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

Reporting group title	Trastuzumab Emtansine + Pertuzumab

Reporting group description:

Participants received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Reporting group title	Trastuzumab Emtansine + Placebo

Reporting group description:

Participants received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Serious adverse events	Trastuzumab + Taxane	Trastuzumab Emtansine + Pertuzumab	Trastuzumab Emtansine + Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 353 (22.66%)	85 / 366 (23.22%)	77 / 361 (21.33%)
number of deaths (all causes)	123	116	114
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast neoplasm			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon neoplasm			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 353 (0.57%)	4 / 366 (1.09%)	5 / 361 (1.39%)
occurrences causally related to treatment / all	0 / 2	2 / 5	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	3 / 353 (0.85%)	1 / 366 (0.27%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Device breakage			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pain			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site haematoma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 353 (0.00%)	5 / 366 (1.37%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 0	6 / 6	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	2 / 353 (0.57%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytokine release syndrome			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hypertrophy			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	3 / 353 (0.85%)	3 / 366 (0.82%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	2 / 3	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	4 / 353 (1.13%)	0 / 366 (0.00%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 353 (0.57%)	1 / 366 (0.27%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 2	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 353 (0.00%)	3 / 366 (0.82%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 353 (0.28%)	1 / 366 (0.27%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolitis allergic			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal turbinate hypertrophy			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			

subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 353 (0.28%)	11 / 366 (3.01%)	6 / 361 (1.66%)
occurrences causally related to treatment / all	1 / 1	11 / 11	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	1 / 353 (0.28%)	3 / 366 (0.82%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	1 / 353 (0.28%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haematoma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation retinopathy			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound secretion			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial injury			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			

subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial injury ABC	Additional description: ABCD		
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Convulsion			

subjects affected / exposed	1 / 353 (0.28%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular dementia			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 353 (0.28%)	4 / 366 (1.09%)	4 / 361 (1.11%)
occurrences causally related to treatment / all	0 / 1	2 / 5	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	14 / 353 (3.97%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	15 / 15	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	6 / 353 (1.70%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercoagulation			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness transient			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ocular hypertension			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 353 (1.13%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 353 (0.28%)	3 / 366 (0.82%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain			
subjects affected / exposed	2 / 353 (0.57%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	2 / 353 (0.57%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic artery aneurysm			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatomyositis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peau D’orange			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 353 (0.28%)	1 / 366 (0.27%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 353 (0.85%)	3 / 366 (0.82%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	2 / 3	1 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Cellulitis			
subjects affected / exposed	3 / 353 (0.85%)	1 / 366 (0.27%)	3 / 361 (0.83%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 353 (0.28%)	3 / 366 (0.82%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Device related infection			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	1 / 353 (0.28%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 353 (0.28%)	1 / 366 (0.27%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	3 / 353 (0.85%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 353 (0.57%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 353 (0.00%)	2 / 366 (0.55%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	2 / 353 (0.57%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 353 (0.57%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chorioretinitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	1 / 361 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			

subjects affected / exposed	0 / 353 (0.00%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 353 (0.28%)	1 / 366 (0.27%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 353 (0.00%)	0 / 366 (0.00%)	2 / 361 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	1 / 353 (0.28%)	0 / 366 (0.00%)	0 / 361 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Trastuzumab + Taxane	Trastuzumab Emtansine + Pertuzumab	Trastuzumab Emtansine + Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	342 / 353 (96.88%)	350 / 366 (95.63%)	351 / 361 (97.23%)
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 353 (5.67%)	43 / 366 (11.75%)	36 / 361 (9.97%)
occurrences (all)	28	66	75
Hot flush			
subjects affected / exposed	26 / 353 (7.37%)	12 / 366 (3.28%)	15 / 361 (4.16%)
occurrences (all)	31	18	21
Lymphoedema			
subjects affected / exposed	25 / 353 (7.08%)	7 / 366 (1.91%)	7 / 361 (1.94%)
occurrences (all)	33	8	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	127 / 353 (35.98%)	125 / 366 (34.15%)	117 / 361 (32.41%)
occurrences (all)	241	258	222
Pyrexia			
subjects affected / exposed	57 / 353 (16.15%)	117 / 366 (31.97%)	96 / 361 (26.59%)
occurrences (all)	85	176	155
Asthenia			
subjects affected / exposed	57 / 353 (16.15%)	63 / 366 (17.21%)	61 / 361 (16.90%)
occurrences (all)	163	202	190
Chills			
subjects affected / exposed	14 / 353 (3.97%)	98 / 366 (26.78%)	56 / 361 (15.51%)
occurrences (all)	15	127	70
Oedema peripheral			

subjects affected / exposed	98 / 353 (27.76%)	31 / 366 (8.47%)	34 / 361 (9.42%)
occurrences (all)	176	38	48
Mucosal inflammation			
subjects affected / exposed	45 / 353 (12.75%)	35 / 366 (9.56%)	33 / 361 (9.14%)
occurrences (all)	62	54	55
Influenza like illness			
subjects affected / exposed	16 / 353 (4.53%)	31 / 366 (8.47%)	29 / 361 (8.03%)
occurrences (all)	30	71	43
Non-cardiac chest pain			
subjects affected / exposed	23 / 353 (6.52%)	26 / 366 (7.10%)	25 / 361 (6.93%)
occurrences (all)	27	34	36
Pain			
subjects affected / exposed	28 / 353 (7.93%)	19 / 366 (5.19%)	25 / 361 (6.93%)
occurrences (all)	37	24	28
Oedema			
subjects affected / exposed	31 / 353 (8.78%)	3 / 366 (0.82%)	9 / 361 (2.49%)
occurrences (all)	51	3	9
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	18 / 353 (5.10%)	15 / 366 (4.10%)	13 / 361 (3.60%)
occurrences (all)	26	18	13
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	52 / 353 (14.73%)	125 / 366 (34.15%)	112 / 361 (31.02%)
occurrences (all)	82	282	233
Cough			
subjects affected / exposed	72 / 353 (20.40%)	74 / 366 (20.22%)	70 / 361 (19.39%)
occurrences (all)	122	103	100
Dyspnoea			
subjects affected / exposed	54 / 353 (15.30%)	49 / 366 (13.39%)	41 / 361 (11.36%)
occurrences (all)	85	69	71
Oropharyngeal pain			
subjects affected / exposed	28 / 353 (7.93%)	28 / 366 (7.65%)	29 / 361 (8.03%)
occurrences (all)	35	39	31
Rhinorrhoea			

subjects affected / exposed	25 / 353 (7.08%)	31 / 366 (8.47%)	23 / 361 (6.37%)
occurrences (all)	37	35	28
Psychiatric disorders			
Insomnia			
subjects affected / exposed	51 / 353 (14.45%)	50 / 366 (13.66%)	48 / 361 (13.30%)
occurrences (all)	61	70	68
Anxiety			
subjects affected / exposed	22 / 353 (6.23%)	33 / 366 (9.02%)	25 / 361 (6.93%)
occurrences (all)	39	34	30
Depression			
subjects affected / exposed	17 / 353 (4.82%)	20 / 366 (5.46%)	32 / 361 (8.86%)
occurrences (all)	18	23	40
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 353 (2.27%)	26 / 366 (7.10%)	55 / 361 (15.24%)
occurrences (all)	10	47	80
Alanine aminotransferase increased			
subjects affected / exposed	10 / 353 (2.83%)	33 / 366 (9.02%)	40 / 361 (11.08%)
occurrences (all)	12	55	66
Weight decreased			
subjects affected / exposed	7 / 353 (1.98%)	29 / 366 (7.92%)	22 / 361 (6.09%)
occurrences (all)	10	39	40
Ejection fraction decreased			
subjects affected / exposed	31 / 353 (8.78%)	14 / 366 (3.83%)	8 / 361 (2.22%)
occurrences (all)	36	15	9
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 353 (0.28%)	17 / 366 (4.64%)	27 / 361 (7.48%)
occurrences (all)	1	23	34
Nervous system disorders			
Headache			
subjects affected / exposed	78 / 353 (22.10%)	118 / 366 (32.24%)	116 / 361 (32.13%)
occurrences (all)	150	241	252
Neuropathy peripheral			
subjects affected / exposed	99 / 353 (28.05%)	65 / 366 (17.76%)	48 / 361 (13.30%)
occurrences (all)	169	120	77
Peripheral sensory neuropathy			

subjects affected / exposed	70 / 353 (19.83%)	44 / 366 (12.02%)	47 / 361 (13.02%)
occurrences (all)	123	70	66
Dysgeusia			
subjects affected / exposed	54 / 353 (15.30%)	50 / 366 (13.66%)	29 / 361 (8.03%)
occurrences (all)	67	81	41
Paraesthesia			
subjects affected / exposed	39 / 353 (11.05%)	40 / 366 (10.93%)	30 / 361 (8.31%)
occurrences (all)	53	68	50
Dizziness			
subjects affected / exposed	33 / 353 (9.35%)	36 / 366 (9.84%)	36 / 361 (9.97%)
occurrences (all)	46	74	53
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	75 / 353 (21.25%)	32 / 366 (8.74%)	41 / 361 (11.36%)
occurrences (all)	167	122	169
Anaemia			
subjects affected / exposed	38 / 353 (10.76%)	55 / 366 (15.03%)	42 / 361 (11.63%)
occurrences (all)	60	111	63
Thrombocytopenia			
subjects affected / exposed	0 / 353 (0.00%)	53 / 366 (14.48%)	49 / 361 (13.57%)
occurrences (all)	0	162	139
Eye disorders			
Lacrimation increased			
subjects affected / exposed	48 / 353 (13.60%)	19 / 366 (5.19%)	13 / 361 (3.60%)
occurrences (all)	58	22	18
Dry eye			
subjects affected / exposed	13 / 353 (3.68%)	25 / 366 (6.83%)	24 / 361 (6.65%)
occurrences (all)	14	29	25
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	172 / 353 (48.73%)	176 / 366 (48.09%)	91 / 361 (25.21%)
occurrences (all)	456	527	148
Nausea			
subjects affected / exposed	131 / 353 (37.11%)	191 / 366 (52.19%)	170 / 361 (47.09%)
occurrences (all)	300	579	484
Vomiting			

subjects affected / exposed	67 / 353 (18.98%)	110 / 366 (30.05%)	78 / 361 (21.61%)
occurrences (all)	140	212	126
Constipation			
subjects affected / exposed	72 / 353 (20.40%)	71 / 366 (19.40%)	80 / 361 (22.16%)
occurrences (all)	119	128	139
Stomatitis			
subjects affected / exposed	57 / 353 (16.15%)	40 / 366 (10.93%)	36 / 361 (9.97%)
occurrences (all)	76	60	50
Dyspepsia			
subjects affected / exposed	38 / 353 (10.76%)	46 / 366 (12.57%)	35 / 361 (9.70%)
occurrences (all)	48	88	54
Abdominal pain upper			
subjects affected / exposed	30 / 353 (8.50%)	45 / 366 (12.30%)	38 / 361 (10.53%)
occurrences (all)	49	60	60
Dry mouth			
subjects affected / exposed	13 / 353 (3.68%)	48 / 366 (13.11%)	52 / 361 (14.40%)
occurrences (all)	20	55	72
Abdominal pain			
subjects affected / exposed	30 / 353 (8.50%)	40 / 366 (10.93%)	33 / 361 (9.14%)
occurrences (all)	41	64	48
Gingival bleeding			
subjects affected / exposed	4 / 353 (1.13%)	25 / 366 (6.83%)	31 / 361 (8.59%)
occurrences (all)	5	38	49
Haemorrhoids			
subjects affected / exposed	9 / 353 (2.55%)	21 / 366 (5.74%)	11 / 361 (3.05%)
occurrences (all)	9	37	14
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	211 / 353 (59.77%)	33 / 366 (9.02%)	24 / 361 (6.65%)
occurrences (all)	249	35	25
Rash			
subjects affected / exposed	86 / 353 (24.36%)	86 / 366 (23.50%)	62 / 361 (17.17%)
occurrences (all)	146	134	105
Pruritus			
subjects affected / exposed	32 / 353 (9.07%)	51 / 366 (13.93%)	26 / 361 (7.20%)
occurrences (all)	40	77	42

Nail disorder			
subjects affected / exposed	54 / 353 (15.30%)	22 / 366 (6.01%)	18 / 361 (4.99%)
occurrences (all)	67	25	20
Dry skin			
subjects affected / exposed	23 / 353 (6.52%)	28 / 366 (7.65%)	21 / 361 (5.82%)
occurrences (all)	28	30	22
Erythema			
subjects affected / exposed	24 / 353 (6.80%)	19 / 366 (5.19%)	14 / 361 (3.88%)
occurrences (all)	37	26	14
Dermatitis acneiform			
subjects affected / exposed	5 / 353 (1.42%)	27 / 366 (7.38%)	15 / 361 (4.16%)
occurrences (all)	5	41	15
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	26 / 353 (7.37%)	10 / 366 (2.73%)	6 / 361 (1.66%)
occurrences (all)	29	13	7
Nail discolouration			
subjects affected / exposed	24 / 353 (6.80%)	2 / 366 (0.55%)	5 / 361 (1.39%)
occurrences (all)	24	2	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	87 / 353 (24.65%)	68 / 366 (18.58%)	79 / 361 (21.88%)
occurrences (all)	136	93	121
Myalgia			
subjects affected / exposed	82 / 353 (23.23%)	62 / 366 (16.94%)	64 / 361 (17.73%)
occurrences (all)	158	113	147
Back pain			
subjects affected / exposed	44 / 353 (12.46%)	58 / 366 (15.85%)	54 / 361 (14.96%)
occurrences (all)	62	79	69
Pain in extremity			
subjects affected / exposed	44 / 353 (12.46%)	51 / 366 (13.93%)	50 / 361 (13.85%)
occurrences (all)	56	73	73
Muscle spasms			
subjects affected / exposed	13 / 353 (3.68%)	61 / 366 (16.67%)	25 / 361 (6.93%)
occurrences (all)	18	91	33
Musculoskeletal pain			

subjects affected / exposed	20 / 353 (5.67%)	35 / 366 (9.56%)	29 / 361 (8.03%)
occurrences (all)	26	44	37
Bone pain			
subjects affected / exposed	32 / 353 (9.07%)	28 / 366 (7.65%)	17 / 361 (4.71%)
occurrences (all)	49	66	21
Musculoskeletal chest pain			
subjects affected / exposed	16 / 353 (4.53%)	19 / 366 (5.19%)	13 / 361 (3.60%)
occurrences (all)	21	19	16
Neck pain			
subjects affected / exposed	12 / 353 (3.40%)	23 / 366 (6.28%)	11 / 361 (3.05%)
occurrences (all)	12	29	12
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	53 / 353 (15.01%)	66 / 366 (18.03%)	45 / 361 (12.47%)
occurrences (all)	92	129	70
Nasopharyngitis			
subjects affected / exposed	47 / 353 (13.31%)	59 / 366 (16.12%)	50 / 361 (13.85%)
occurrences (all)	81	113	70
Urinary tract infection			
subjects affected / exposed	26 / 353 (7.37%)	41 / 366 (11.20%)	28 / 361 (7.76%)
occurrences (all)	35	62	46
Rhinitis			
subjects affected / exposed	17 / 353 (4.82%)	21 / 366 (5.74%)	22 / 361 (6.09%)
occurrences (all)	21	25	24
Influenza			
subjects affected / exposed	12 / 353 (3.40%)	24 / 366 (6.56%)	22 / 361 (6.09%)
occurrences (all)	16	35	24
Paronychia			
subjects affected / exposed	22 / 353 (6.23%)	29 / 366 (7.92%)	7 / 361 (1.94%)
occurrences (all)	30	53	10
Pharyngitis			
subjects affected / exposed	16 / 353 (4.53%)	19 / 366 (5.19%)	20 / 361 (5.54%)
occurrences (all)	17	20	24
Conjunctivitis			
subjects affected / exposed	21 / 353 (5.95%)	15 / 366 (4.10%)	13 / 361 (3.60%)
occurrences (all)	25	18	15

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	75 / 353 (21.25%)	80 / 366 (21.86%)	82 / 361 (22.71%)
occurrences (all)	128	149	143
Hypokalaemia			
subjects affected / exposed	15 / 353 (4.25%)	28 / 366 (7.65%)	17 / 361 (4.71%)
occurrences (all)	18	38	21

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2011	Updates to the protocol included truncation of OS at 2 years as a secondary endpoint, addition of several quality of life assessments including FACT instruments, changes in the assessment schedule, clarification of the study population and eligibility criteria, and addition of treatment guidelines for cases of study drug discontinuation.
11 October 2011	The protocol was amended to remove an interim futility analysis and to specify the new nonproprietary name 'trastuzumab emtansine' (formerly T-DM1).
29 May 2013	The protocol was revised in order to allow for formal comparison of both trastuzumab emtansine arms, specify statistical assumptions, evaluate OS within high and low HER2 mRNA subsets, remove the clinical benefit rate (CR/PR/SD) as a redundant secondary endpoint, clarify committee procedures, further update the schedule of assessments, and add the option for participants to cross over to the best treatment arm if OS was more favorable in one of the trastuzumab emtansine arms.
01 November 2013	The protocol was modified to add safety guidance on hepatotoxicity, including updated language for hemorrhage and Hy's Law.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported