Clinical trial results:
A Randomized, Multicenter, Open-Label, Two-Arm, Phase III Neoadjuvant Study Evaluating Trastuzumab Emtansine Plus Pertuzumab Compared with Chemotherapy Plus Trastuzumab and Pertuzumab for Patients with HER2-Positive Breast Cancer

Summary

EudraCT number	2012-004879-38
Trial protocol	BE ES DE FR IE
Global end of trial date	29 May 2018

Results information

Result version number	v2 (current)
This version publication date	14 June 2019
First version publication date	19 December 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO28408

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A Study Evaluating Trastuzumab Emtansine Plus Pertuzumab Compared With Chemotherapy Plus Trastuzumab and Pertuzumab for Participants With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	United States: 83
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Russian Federation: 61
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Taiwan: 42
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Spain: 88
Worldwide total number of subjects	444
EEA total number of subjects	169

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)	398
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 574 participants were screened at 65 sites in 10 countries, of which 444 participants were randomized in two arms: Trastuzumab (TCH) + Pertuzumab (P) (Arm A) and Trastuzumab Emtansine (TDM1) + P (Arm B)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TCH + P

Arm description:

Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m^2) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter* minute (mg/mL*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).

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

Dosage and administration details:

Carboplatin IV infusion at a dose to achieve an AUC of 6 mg*min/mL q3w

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta®, RO4368451
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab 840 mg (loading dose); and 420 mg (maintenance dose) IV infusion q3w

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin®
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab 8 mg/kg (loading dose); and 6 mg/kg (maintenance dose) IV infusion q3w

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

Dosage and administration details:

Docetaxel 75 mg/m^2 IV infusion q3w

Arm title	T-DM1 + P

Arm description:

Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).

Arm type	Experimental
Investigational medicinal product name	Trastuzumab Emtansine
Investigational medicinal product code	
Other name	Kadcyla®, RO5304020
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab Emtansine 3.6 mg/kg IV infusion q3w

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta®, RO4368451
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab 840 mg (loading dose); and 420 mg (maintenance dose) IV infusion q3w

Number of subjects in period 1	TCH + P	T-DM1 + P
Started	221	223
Completed	196	189
Not completed	25	34
Adverse event, serious fatal	5	6
Consent withdrawn by subject	14	18
Unspecified	2	2
Lost to follow-up	4	8

Baseline characteristics

Reporting groups	
Reporting group title	TCH + P
Reporting group description:	
Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m^2) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter* minute (mg/mL*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).	
Reporting group title	T-DM1 + P
Reporting group description:	
Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).	

Reporting group values	TCH + P	T-DM1 + P	Total
Number of subjects	221	223	444
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	200	198	398
From 65-84 years	21	25	46
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	49.3	50.5	
standard deviation	± 11.2	± 10.6	-
Sex: Female, Male Units: Subjects			
Female	221	222	443
Male	0	1	1

End points

End points reporting groups

Reporting group title	TCH + P
Reporting group description:	
Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m^2) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter* minute (mg/mL*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).	
Reporting group title	T-DM1 + P
Reporting group description:	
Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).	

Primary: Percentage of Subjects With Total Pathological Complete Response (tpCR) Assessed Based on Tumor Samples

End point title	Percentage of Subjects With Total Pathological Complete Response (tpCR) Assessed Based on Tumor Samples
End point description:	
tpCR was assessed by local pathology review on samples taken at surgery following completion of neoadjuvant therapy. tpCR was defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes (that is [i.e.], ypT0/is, ypN0 in the American Joint Committee on Cancer [AJCC] staging system, 7th edition). Percentage of subjects with tpCR was reported.	
End point type	Primary
End point timeframe:	
Pre-surgery (within 6 weeks after neoadjuvant therapy; up to approximately 6 months)	

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	223		
Units: Percentage of Subjects				
number (confidence interval 95%)	56.1 (49.29 to 62.76)	44.4 (37.76 to 51.18)		

Statistical analyses

Statistical analysis title	tpCR Analysis
Statistical analysis description:	
95% CI for the difference in tPCR rates between treatment arms was calculated using normal approximation.	
Comparison groups	TCH + P v T-DM1 + P

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0126 [1]
Method	Cochran-Mantel-Haenszel Chi-Square
Parameter estimate	Difference in tpCR rate
Point estimate	-11.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.95
upper limit	-2.48

Notes:

[1] - Threshold for significance at 5%

Secondary: Percentage of Subjects Who Received Breast-Conserving Surgery (BCS)

End point title	Percentage of Subjects Who Received Breast-Conserving Surgery (BCS)

End point description:

BCS rate was defined as the percentage of subjects who achieve BCS out of the ITT population of subjects without inflammatory breast cancer.

End point type	Secondary

End point timeframe:

Surgery performed after completion of neoadjuvant therapy (approximately 6 months after neoadjuvant period)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	218		
Units: Percentage of Subjects				
number (confidence interval 95%)	52.6 (45.65 to 59.45)	41.7 (35.12 to 48.33)		

Statistical analyses

Statistical analysis title	BCS Analysis

Statistical analysis description:

95% CI for the difference in BCS rate between treatment arms was calculated using normal approximation.

Comparison groups	T-DM1 + P v TCH + P
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0228
Method	Cochran-Mantel-Haenszel Chi-square Test
Parameter estimate	Difference in BCS rate
Point estimate	-10.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.21
upper limit	-1.47

Secondary: Percentage of Subjects With Selected Adverse Events (AEs)

End point title	Percentage of Subjects With Selected Adverse Events (AEs)

End point description:

Selected AEs included hepatotoxicity, pulmonary toxicity, cardiac dysfunction, neutropenia, thrombocytopenia, peripheral neuropathy, hemorrhage, infusion related reaction (IRR)/hypersensitivity, IRR/Hypersensitivity symptoms, rash, diarrhea and mucositis. An AE was defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution.

End point type	Secondary

End point timeframe:

Baseline to end of study (approximately 47 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	223		
Units: Percentage of Subjects				
number (not applicable)				
Hepatotoxicity	14.2	39.0		
Pulmonary Toxicity	0.9	4.9		
Cardiac Dysfunction	4.6	1.3		
Neutropenia	39.7	8.1		
Thrombocytopenia	22.8	17.9		
Peripheral Neuropathy	47.5	28.7		
Hemorrhage	19.2	33.2		
IRR/Hypersensitivity	13.7	22.9		
IRR/Hypersensitivity symptoms	7.8	19.3		
Rash	44.7	36.8		
Diarrhea	76.7	38.6		
Mucositis	43.8	24.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects by Response for Neuropathy Single Item

End point title	Percentage of Subjects by Response for Neuropathy Single Item

End point description:

Subjects answered the question “Did you have tingling hands/feet?”, from the Modified Quality of Life

Questionnaire Breast Cancer 23 (mQLQ-BR23), on a 5-point scale (1 ‘Not at all’, 2 ‘A little’, 3 'Somewhat', 4 ‘Quite a bit’, 5 ‘Very much’). Percentage of subjects by each response was reported.

End point type	Secondary

End point timeframe:

Baseline,Cycle(C) 3,C5 of neoadjuvant period (each C=21 days); pre-surgery visit (within 6weeks after neoadjuvant therapy; up to approx 6months), C4 & 8 of Adjuvant Period (each C=21 days), End of Treatment, Follow up 2 & 4 (approx 47 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	205		
Units: Percentage of Subjects				
number (not applicable)				
Not at all: Baseline	78.7	81.2		
A little bit: Baseline	9.5	9.4		
Somewhat: Baseline	0	0		
Quite a bit: Baseline	0.9	0.9		
Very much: Baseline	0.5	0		
Not at all: Neoadjuvant Cycle 3	54.3	59.6		
A little bit: Neoadjuvant Cycle 3	20.8	19.3		
Somewhat: Neoadjuvant Cycle 3	0	0		
Quite a bit: Neoadjuvant Cycle 3	3.2	2.7		
Very much: Neoadjuvant Cycle 3	1.8	0.4		
Not at all: Neoadjuvant Cycle 5	37.1	54.3		
A little bit: Neoadjuvant Cycle 5	29.9	21.1		
Somewhat: Neoadjuvant Cycle 5	0	0		
Quite a bit: Neoadjuvant Cycle 5	8.6	2.7		
Very much: Neoadjuvant Cycle 5	6.8	1.8		
Not at all: Pre-Surgery	22.6	52.0		
A little bit: Pre-Surgery	29.0	17.9		
Somewhat: Pre-Surgery	0	0		
Quite a bit: Pre-Surgery	15.4	5.4		
Very much: Pre-Surgery	10.0	1.3		
Not at all: Adjuvant Cycle 4	31.2	42.6		
A little bit: Adjuvant Cycle 4	31.7	15.2		
Somewhat: Adjuvant Cycle 4	0	0		
Quite a bit: Adjuvant Cycle 4	9.5	9		
Very much: Adjuvant Cycle 4	6.3	2.7		
Not at all: Adjuvant Cycle 8	33.0	31.8		
A little bit: Adjuvant Cycle 8	28.1	19.3		
Somewhat: Adjuvant Cycle 8	0	0		
Quite a bit: Adjuvant Cycle 8	10.9	9.0		
Very much: Adjuvant Cycle 8	4.1	4.0		
Not at all: End of Therapy	31.2	31.4		
A little bit: End of Therapy	30.8	23.8		
Somewhat: End of Therapy	0	0		
Quite a bit: End of Therapy	10.9	12.1		
Very much: End of Therapy	5.0	6.7		
Not at all: Follow-up 2	38.0	32.7		

A little bit: Follow-up 2	19.9	19.3		
Somewhat: Follow-up 2	0	0		
Quite a bit: Follow-up 2	5.9	7.6		
Very much: Follow-up 2	4.1	1.3		
Not at all: Follow-up 4	39.8	32.7		
A little bit: Follow-up 4	15.4	17.9		
Somewhat: Follow-up 4	0	0		
Quite a bit: Follow-up 4	4.1	3.1		
Very much: Follow-up 4	2.3	1.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects by Response for Skin Problem Single Items

End point title	Percentage of Subjects by Response for Skin Problem Single Items

End point description:

Subjects answered the Question 1 "Did itching skin bother you?" and Question 2 "Have you had skin problems?", from the mQLQ-BR23, on a 5-point scale (1 'Not at all', 2 'A little', 3 'Somewhat', 4 'Quite a bit', 5 'Very much'). Percentage of subjects by each response was reported.

End point type	Secondary

End point timeframe:

Baseline,Cycle(C) 3,C5 of neoadjuvant period (each C=21 days); pre-surgery visit (within 6weeks after neoadjuvant therapy; up to approx 6months), C4 & 8 of Adjuvant Period (each C=21 days), End of Treatment, Follow up 2 & 4 (approx 47 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	205		
Units: Percentage of Subjects				
number (not applicable)				
Q1: Not at all: Baseline	71.9	72.6		
Q1: A little bit: Baseline	14.9	16.1		
Q1: Somewhat: Baseline	0	0		
Q1: Quite a bit: Baseline	2.3	2.2		
Q1: Very much: Baseline	0	0.4		
Q1: Not at all: Neoadjuvant Cycle 3	35.3	48.9		
Q1: A little bit: Neoadjuvant Cycle 3	31.2	27.4		
Q1: Somewhat: Neoadjuvant Cycle 3	0	0		
Q1: Quite a bit: Neoadjuvant Cycle 3	10.9	4.0		
Q1: Very much: Neoadjuvant Cycle 3	2.3	1.8		
Q1: Not at all: Neoadjuvant Cycle 5	48.9	46.2		
Q1: A little bit: Neoadjuvant Cycle 5	23.1	26.0		
Q1: Somewhat: Neoadjuvant Cycle 5	0	0		
Q1: Quite a bit: Neoadjuvant Cycle 5	7.7	6.3		
Q1: Very much: Neoadjuvant Cycle 5	2.3	1.3		

Q1: Not at all: Pre-Surgery	40.3	48.0		
Q1: A little bit: Pre-Surgery	26.7	21.5		
Q1: Somewhat: Pre-Surgery	0	0		
Q1: Quite a bit: Pre-Surgery	7.2	5.8		
Q1: Very much: Pre-Surgery	2.7	1.3		
Q1: Not at all: Adjuvant Cycle 4	38.5	39.0		
Q1: A little bit: Adjuvant Cycle 4	23.5	21.5		
Q1: Somewhat: Adjuvant Cycle 4	0	0		
Q1: Quite a bit: Adjuvant Cycle 4	9.5	6.7		
Q1: Very much: Adjuvant Cycle 4	6.8	2.2		
Q1: Not at all: Adjuvant Cycle 8	34.8	39.0		
Q1: A little bit: Adjuvant Cycle 8	27.6	15.7		
Q1: Somewhat: Adjuvant Cycle 8	0	0		
Q1: Quite a bit: Adjuvant Cycle 8	9.0	6.3		
Q1: Very much: Adjuvant Cycle 8	4.1	3.1		
Q1: Not at all: End of Therapy	39.4	42.6		
Q1: A little bit: End of Therapy	26.7	22.9		
Q1: Somewhat: End of Therapy	0	0		
Q1: Quite a bit: End of Therapy	6.8	6.7		
Q1: Very much: End of Therapy	4.5	1.8		
Q1: Not at all: Follow-up 2	43.9	39.9		
Q1: A little bit: Follow-up 2	19.0	14.8		
Q1: Somewhat: Follow-up 2	0	0		
Q1: Quite a bit: Follow-up 2	3.6	4.0		
Q1: Very much: Follow-up 2	0.9	2.2		
Q1: Not at all: Follow-up 4	46.2	37.7		
Q1: A little bit: Follow-up 4	10.4	12.1		
Q1: Somewhat: Follow-up 4	0	0		
Q1: Quite a bit: Follow-up 4	3.2	4.5		
Q1: Very much: Follow-up 4	1.4	1.3		
Q2: Not at all: Baseline	64.7	67.3		
Q2: A little bit: Baseline	21.3	17.9		
Q2: Somewhat: Baseline	0	0		
Q2: Quite a bit: Baseline	3.2	5.8		
Q2: Very much: Baseline	0.5	0.4		
Q2: Not at all: Neoadjuvant Cycle 3	14.0	24.2		
Q2: A little bit: Neoadjuvant Cycle 3	40.7	38.6		
Q2: Somewhat: Neoadjuvant Cycle 3	0	0		
Q2: Quite a bit: Neoadjuvant Cycle 3	18.6	14.8		
Q2: Very much: Neoadjuvant Cycle 3	6.8	4.5		
Q2: Not at all: Neoadjuvant Cycle 5	21.3	25.6		
Q2: A little bit: Neoadjuvant Cycle 5	35.7	37.7		
Q2: Somewhat: Neoadjuvant Cycle 5	0	0		
Q2: Quite a bit: Neoadjuvant Cycle 5	20.4	12.6		
Q2: Very much: Neoadjuvant Cycle 5	5.0	4.0		
Q2: Not at all: Pre-Surgery	21.3	27.4		
Q2: A little bit: Pre-Surgery	33.9	37.2		
Q2: Somewhat: Pre-Surgery	0	0		
Q2: Quite a bit: Pre-Surgery	15.4	8.1		
Q2: Very much: Pre-Surgery	6.3	4.0		
Q2: Not at all: Adjuvant Cycle 4	23.5	24.2		
Q2: A little bit: Adjuvant Cycle 4	33.0	30.9		

Q2: Somewhat: Adjuvant Cycle 4	0	0		
Q2: Quite a bit: Adjuvant Cycle 4	13.1	9.4		
Q2: Very much: Adjuvant Cycle 4	9.0	4.9		
Q2: Not at all: Adjuvant Cycle 8	23.1	25.6		
Q2: A little bit: Adjuvant Cycle 8	35.7	24.2		
Q2: Somewhat: Adjuvant Cycle 8	0	0		
Q2: Quite a bit: Adjuvant Cycle 8	12.2	9.9		
Q2: Very much: Adjuvant Cycle 8	5.0	4.5		
Q2: Not at all: End of Therapy	27.1	27.4		
Q2: A little bit: End of Therapy	33.9	30.9		
Q2: Somewhat: End of Therapy	0	0		
Q2: Quite a bit: End of Therapy	10.0	13.5		
Q2: Very much: End of Therapy	6.8	3.1		
Q2: Not at all: Follow-up 2	36.2	27.8		
Q2: A little bit: Follow-up 2	25.8	25.6		
Q2: Somewhat: Follow-up 2	0	0		
Q2: Quite a bit: Follow-up 2	4.1	6.3		
Q2: Very much: Follow-up 2	1.8	1.3		
Q2: Not at all: Follow-up 4	39.8	30.0		
Q2: A little bit: Follow-up 4	14.5	18.8		
Q2: Somewhat: Follow-up 4	0	0		
Q2: Quite a bit: Follow-up 4	4.5	4.5		
Q2: Very much: Follow-up 4	2.7	2.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects by Response for Hair Loss Single Item

End point title	Percentage of Subjects by Response for Hair Loss Single Item

End point description:

Subjects answered the Question “Have you lost any hair?”, from the mQLQ-BR23, on a 5-point scale (1 ‘Not at all’, 2 ‘A little’, 3 'Somewhat', 4 ‘Quite a bit’, 5 ‘Very much’). Percentage of subjects by each response was reported.

End point type	Secondary

End point timeframe:

Baseline,Cycle(C) 3, C5 of neoadjuvant period (each C=21 days); pre-surgery visit (within 6weeks after neoadjuvant therapy; up to approx 6months), C4 & 8 of Adjuvant Period (each C=21 days), End of Treatment, Follow up 2 & 4(approx 47 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	205		
Units: Percentage of Subjects				
number (not applicable)				
Not at all: Baseline	81.4	87.4		
A little bit: Baseline	7.7	4.0		

Somewhat: Baseline	0	0		
Quite a bit: Baseline	0.5	0		
Very much: Baseline	0	0		
Not at all: Neoadjuvant Cycle 3	8.6	65.0		
A little bit: Neoadjuvant Cycle 3	11.3	16.6		
Somewhat: Neoadjuvant Cycle 3	0	0		
Quite a bit: Neoadjuvant Cycle 3	20.8	0.4		
Very much: Neoadjuvant Cycle 3	39.4	0		
Not at all: Neoadjuvant Cycle 5	20.4	58.7		
A little bit: Neoadjuvant Cycle 5	19.9	19.3		
Somewhat: Neoadjuvant Cycle 5	0	0		
Quite a bit: Neoadjuvant Cycle 5	15.8	1.3		
Very much: Neoadjuvant Cycle 5	26.2	0.4		
Not at all: Pre-Surgery	30.8	49.8		
A little bit: Pre-Surgery	13.6	24.7		
Somewhat: Pre-Surgery	0	0		
Quite a bit: Pre-Surgery	11.3	2.2		
Very much: Pre-Surgery	21.3	0		
Not at all: Adjuvant Cycle 4	67.9	50.2		
A little bit: Adjuvant Cycle 4	5.0	15.7		
Somewhat: Adjuvant Cycle 4	0	0		
Quite a bit: Adjuvant Cycle 4	3.2	2.2		
Very much: Adjuvant Cycle 4	2.7	1.3		
Not at all: Adjuvant Cycle 8	70.1	48.9		
A little bit: Adjuvant Cycle 8	4.1	14.3		
Somewhat: Adjuvant Cycle 8	0	0		
Quite a bit: Adjuvant Cycle 8	0.9	0.9		
Very much: Adjuvant Cycle 8	0.9	0		
Not at all: End of Therapy	69.7	57.8		
A little bit: End of Therapy	5.4	14.8		
Somewhat: End of Therapy	0	0		
Quite a bit: End of Therapy	0.9	0		
Very much: End of Therapy	1.8	1.3		
Not at all: Follow-up 2	55.7	48.4		
A little bit: Follow-up 2	9.0	11.7		
Somewhat: Follow-up 2	0	0		
Quite a bit: Follow-up 2	1.4	0.4		
Very much: Follow-up 2	1.8	0.4		
Not at all: Follow-up 4	52.9	41.3		
A little bit: Follow-up 4	7.2	11.2		
Somewhat: Follow-up 4	0	0		
Quite a bit: Follow-up 4	0	2.7		
Very much: Follow-up 4	1.4	0.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Clinically Meaningful Deterioration in

Global Health Status (GHS)/Quality of Life (QoL) Score

End point title	Percentage of Subjects With a Clinically Meaningful Deterioration in Global Health Status (GHS)/Quality of Life (QoL) Score

End point description:

Subjects rated their quality of life (global health status) on European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ- C30), with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better quality of life. Clinically meaningful deterioration in GHS/QoL was defined as a decrease in score of 10 points in GHS/QoL.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	205		
Units: Percentage of Subjects				
number (not applicable)	69.9	45.4		

Statistical analyses

Statistical analysis title	GHS/QoL Score Analysis

Statistical analysis description:

95% CI for the difference in clinically meaningful deterioration in GHS/QoL score between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Deterioration
Point estimate	-24.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.98
upper limit	-15.19

Secondary: Time to Clinically Meaningful Deterioration in GHS/QoL Score

End point title	Time to Clinically Meaningful Deterioration in GHS/QoL Score

End point description:

Participants rated their quality of life (global health status) on EORTC QLQ C-30, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better quality of life. Time to deterioration was defined as the time from baseline to first 10-point (or greater) decrease as measured by GHS/QoL. All valid GHS/QoL questionnaires of the neoadjuvant phase including surgery were used. Participants without deterioration were censored at the time of completing the last GHS/QoL plus 1 day. Median time to deterioration was estimated with Kaplan-Meier method. The 95% confidence interval (CI) for the median was computed using the method of Brookmeyer and Crowley.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	200		
Units: months				
median (confidence interval 95%)	3.02 (2.83 to 3.38)	4.63 (4.11 to 7.98)		

Statistical analyses

Statistical analysis title	GHS/QoL Score Analysis

Statistical analysis description:

Stratified cox proportional hazards regression model was used to estimate Hazard Ratio and CI. Stratification by hormonal receptor status and clinical stage at presentation (stratification factors).

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.78

Secondary: Percentage of Subjects With a Clinically Meaningful Deterioration in Function Subscales

End point title	Percentage of Subjects With a Clinically Meaningful Deterioration in Function Subscales

End point description:

Subjects rated their function on EORTC QLQ C-30, with total score and single-item (physical, cognitive and role functioning) scores ranging from 0 (worst) to 100 (best); where higher score indicates better functioning. Clinically meaningful deterioration was defined as a decrease in score of 10 points in physical function; decrease of 7 points in cognitive function and decrease of 14 points in role function.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	205		
Units: Percentage of Subjects				
number (not applicable)				
Cognitive Functioning	59.1	42.4		
Physical Functioning	72.5	40.0		
Role Functioning	76.7	47.8		

Statistical analyses

Statistical analysis title	Cognitive Functioning Analysis

Statistical analysis description:

This is the statistical analysis for cognitive functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Deterioration
Point estimate	-16.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.32
upper limit	-6.94

Statistical analysis title	Role Functioning Analysis

Statistical analysis description:

This is the statistical analysis for role functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Deterioration
Point estimate	-28.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.95
upper limit	-19.8

Statistical analysis title	Physical Functioning Analysis

Statistical analysis description:

This is the statistical analysis for physical functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Deterioration
Point estimate	-32.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.74
upper limit	-23.34

Secondary: Time to Clinically Meaningful Deterioration in Function Subscale

End point title	Time to Clinically Meaningful Deterioration in Function Subscale

End point description:

Participants rated their function on EORTC QLQ C-30, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better functioning. Time to deterioration was defined as the time from baseline to first 10-point (or greater) decrease as measured by physical function; to first 14-point (or greater) decrease as measured by role function, to first 7-point (or greater) decrease as measured by cognitive function. Median time to deterioration was estimated with Kaplan-Meier method. The 95% CI for the median was computed using the method of Brookmeyer and Crowley. 9999 = not estimable value

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	200		
Units: months				
median (confidence interval 95%)				
Physical Function	2.79 (2.79 to 2.96)	4.86 (4.40 to 7.98)		
Role Function	2.79 (2.17 to 2.89)	4.44 (4.04 to 4.53)		
Cognitive Function	3.42 (3.02 to 4.24)	4.44 (4.21 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Clinically Meaningful Increase in

Symptom Subscales

End point title	Percentage of Subjects With a Clinically Meaningful Increase in Symptom Subscales

End point description:

Subjects rated their symptoms on EORTC QLQ C-30 and mQLQ-BR23, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates greater degree of symptoms. Clinically meaningful increase in symptoms was defined as an increase in score (deterioration) of 11 points in nausea and vomiting, pain, dyspnea; increase of 9 points in insomnia; increase of 14 points in appetite loss; increase of 15 points in diarrhea, constipation; increase of 10 points in fatigue, systemic therapy side effects, hair loss.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	205		
Units: Percentage of Subjects				
number (not applicable)				
Appetite Loss	61.1	47.8		
Any Hair Loss	91.2	40.5		
Systemic Therapy Side-Effects	89.7	75.1		
Constipation	33.2	32.7		
Diarrhea	79.3	50.7		
Dyspnea	56.0	31.2		
Fatigue	87.6	68.8		
Nausea/Vomiting	66.3	43.9		
Pain	56.0	36.6		
Insomnia	42.5	30.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Trastuzumab

End point title	Maximum Observed Serum Concentration (Cmax) of Trastuzumab[2]

End point description:

Only participants who received trastuzumab were to be analyzed for this outcome.

End point type	Secondary

End point timeframe:

15-30 minutes (min) post-study treatment infusion (infusion duration = 90 min) on Day 1 of Cycle 1 and 6 (each cycle = 21 days) in neoadjuvant and adjuvant period

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistics reported for this endpoint.

End point values	TCH + P			
Subject group type	Reporting group			
Number of subjects analysed	214			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 (neoadjuvant period)	167 (± 47.1)			
Cycle 6 (neoadjuvant period)	148 (± 44.7)			
Cycle 1 (adjuvant period)	159 (± 36.2)			
Cycle 6 (adjuvant period)	181 (± 30.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Trastuzumab Emtansine and Total Trastuzumab

End point title	Cmax of Trastuzumab Emtansine and Total Trastuzumab[3]

End point description:

Only participants who received trastuzumab emtansine were to be analyzed for this outcome.

End point type	Secondary

End point timeframe:

15-30 min post-study treatment infusion (infusion duration = 90 min) on Day 1 of Cycle 1 and 6 (each cycle = 21 days) in neoadjuvant and adjuvant period.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistics reported for this endpoint.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Trastuzumab emtansine: C1 (neoadjuvant)	80.4 (± 26.5)			
Trastuzumab emtansine: C6 (neoadjuvant)	71.7 (± 30.2)			
Total Trastuzumab: C1 (neoadjuvant)	79.1 (± 25.7)			
Total Trastuzumab: C6 (neoadjuvant)	79.1 (± 31.1)			
Trastuzumab emtansine: C1 (adjuvant)	70.4 (± 22.7)			
Trastuzumab emtansine: C6 (adjuvant)	73.1 (± 21.8)			
Total Trastuzumab: C1 (adjuvant)	73.0 (± 23.2)			
Total Trastuzumab: C6 (adjuvant)	82.6 (± 23.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Trastuzumab

End point title	Minimum Observed Serum Concentration (Cmin) of Trastuzumab[4]

End point description:

Only participants who received trastuzumab were to be analyzed for this outcome.

End point type	Secondary

End point timeframe:

Pre-study treatment infusion (0 hours [hr]) (infusion duration = 90 min) on Day 1 of Cycle 6 (cycle length = 21 days) in neoadjuvant and adjuvant period

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistics reported for this endpoint.

End point values	TCH + P			
Subject group type	Reporting group			
Number of subjects analysed	214			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Trastuzumab (neoadjuvant period)	45.8 (± 17.8)			
Trastuzumab (adjuvant period)	21.8 (± 0.153)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of Trastuzumab Emtansine and Total Trastuzumab

End point title	Cmin of Trastuzumab Emtansine and Total Trastuzumab[5]

End point description:

Only participants who received trastuzumab emtansine were to be analyzed for this outcome.

End point type	Secondary

End point timeframe:

Pre-study treatment infusion (0 hr) (infusion duration = 90 min) on Day 1 of Cycle 6 (cycle length = 21 days) in neoadjuvant and adjuvant period

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistics reported for this endpoint.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Trastuzumab emtansine (neoadjuvant)	3.04 (± 7.43)			
Total Trastuzumab (neoadjuvant)	12.3 (± 8.68)			
Trastuzumab emtansine (adjuvant)	4.09 (± 11.7)			
Total Trastuzumab (adjuvant)	8.70 (± 6.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine (DM1) Concentrations

End point title	Plasma N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine (DM1) Concentrations[6]

End point description:

DM1 is the metabolite of trastuzumab emtansine. Only participants who received trastuzumab emtansine were to be analyzed for this outcome.

End point type	Secondary

End point timeframe:

15-30 min post-study treatment infusion (Cmax) on Day 1 of Cycle 1 and 6 in neoadjuvant and adjuvant period

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistics reported for this endpoint.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
C1: 15-30 min post-dose (neoadjuvant)	4.64 (± 2.33)			
C6: 15-30 min post-dose (neoadjuvant)	4.73 (± 2.61)			
C1: 15-30 min post-dose (adjuvant)	4.49 (± 2.33)			
C6: 15-30 min post-dose (adjuvant)	5.15 (± 8.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Levels of Plasma DM1-Containing Catabolites Concentrations (in ng/mL) (Nonreducible Thioether Linker [MCC]-DM1 and Lysine [Lys]-MCC-DM1)

End point title	Serum Levels of Plasma DM1-Containing Catabolites Concentrations (in ng/mL) (Nonreducible Thioether Linker [MCC]-DM1 and Lysine [Lys]-MCC-DM1)[7]

End point description:

9999 = not applicable

End point type	Secondary

End point timeframe:

15-30 min post-study treatment infusion (Cmax) on Day 1 of Cycle 1 and 6 in neoadjuvant and adjuvant period

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistics reported for this endpoint.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: ng/mL				
arithmetic mean (standard deviation)				
C1: MCC-DM1 (Neoadjuvant Period)	8.18 (± 7.23)			
C1: Lys-MCC-DM1 (Neoadjuvant period)	9999 (± 9999)			
C6: MCC-DM1 (Neoadjuvant Period)	8.22 (± 8.03)			
C6: Lys-MCC-DM1 (Neoadjuvant period)	9999 (± 9999)			
C1: MCC-DM1 (Adjuvant Period)	7.98 (± 6.46)			
C1: Lys-MCC-DM1 (Adjuvant period)	9999 (± 9999)			
C6: MCC-DM1 (Adjuvant Period)	7.90 (± 5.37)			
C6: Lys-MCC-DM1 (Adjuvant period)	9999 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anti-Therapeutic Antibodies (ATA) to TDM-1

End point title	Percentage of Subjects With Anti-Therapeutic Antibodies (ATA) to TDM-1[8]

End point description:

Subjects were considered post-baseline ATA positive if they had ATAs post-baseline that were either treatment-induced or treatment-enhanced. Subjects had treatment-induced ATAs if they had a negative or missing ATA result at baseline, and at least one positive ATA result post-baseline. Subjects had treatment-enhanced ATAs if they had a positive ATA result at baseline, and at least one positive ATA result post-baseline that was greater than or equal to (>/=) 0.60 titer units higher than the result at baseline.

End point type	Secondary

End point timeframe:

Baseline (b) (Pre-TDM1 [0 hr] infusion [infusion duration = 90 min] on Day 1 of Cycle 1); post-baseline (pb) (Pre-TDM1 infusion [0 hr] on Day 1 of Cycle 6) (each cycle = 21 days) in neoadjuvant and adjuvant period

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistics reported for this endpoint.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	219			
Units: Percentage of Subjects				
number (not applicable)				
Neoadjuvant Phase (Baseline)	5.5			
Neoadjuvant Phase (Post-Baseline)	7.5			
Adjuvant Phase (Baseline)	11.7			

Adjuvant Phase (Post-baseline)	13.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With ATA to Trastuzumab

End point title	Percentage of Subjects With ATA to Trastuzumab[9]

End point description:

End point type	Secondary

End point timeframe:

Baseline (Pre-trastuzumab [0 hr] infusion [infusion duration = 90 min] on Day 1 of Cycle 1); post-baseline (Pre-trastuzumab infusion [0 hr] on Day 1 of Cycle 6) (each cycle = 21 days) in neoadjuvant and adjuvant period

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistics reported for this endpoint.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	210			
Units: Percentage of Subjects				
number (not applicable)				
Neoadjuvant Phase (baseline)	11			
Neoadjuvant Phase (post-baseline)	2.6			
Adjuvant Phase (baseline)	5.4			
Adjuvant Phase (post-baseline)	5.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival in the overall study population was defined as the time from the date of randomization to the date of death from any cause. 3 years OS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after treatment.

End point type	Secondary

End point timeframe:

From randomization until death or end of study period (up to approximately 47 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	223		
Units: Probability				
number (confidence interval 95%)	97.6 (95.5 to 99.7)	97.0 (94.6 to 99.4)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7557
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	3.96

Secondary: Event-free survival (EFS)

End point title	Event-free survival (EFS)

End point description:

EFS is defined as the time from randomization to disease progression or disease recurrence (local, regional, distant, or contralateral, invasive or non-invasive), or death from any cause. 3 years EFS rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after treatment.

End point type	Secondary

End point timeframe:

From randomization up to disease progression or recurrence or death (up to approximately 47 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	223		
Units: Probability				
number (confidence interval 95%)	94.21 (91.02 to 97.39)	85.28 (80.47 to 90.08)		

Statistical analyses

Statistical analysis title	Event-Free Survival Analysis
Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0027
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	4.98

Secondary: Invasive disease-free survival (IDFS)

End point title	Invasive disease-free survival (IDFS)

End point description:

IDFS is defined only for participants who undergo surgery. IDFS is defined as the time from surgery to the first documented occurrence of an IDFS event, defined as: Ipsilateral invasive breast tumor recurrence; Ipsilateral local−regional invasive breast cancer recurrence; Distant recurrence; Contralateral invasive breast cancer; and death from any cause. 3 years of IDFS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after treatment.

End point type	Secondary

End point timeframe:

From surgery to the first documented occurrence of IDFC event (up to approximately 45 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	204		
Units: Probability				
number (confidence interval 95%)	91.99 (86.73 to 97.26)	93.04 (89.39 to 96.69)		

Statistical analyses

Statistical analysis title	IDFS Event-Free Analysis
Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	2.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period	
Adverse event reporting additional description:	
Safety population was analyzed.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	TCH + P
Reporting group description:	
Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m^2) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter* minute (mg/mL*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).	
Reporting group title	T-DM1 + P
Reporting group description:	
Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).	

Serious adverse events	TCH + P	T-DM1 + P	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 219 (32.42%)	30 / 223 (13.45%)	
number of deaths (all causes)	5	6	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carinoma			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			

subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 219 (0.91%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device related thrombosis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast haematoma			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	0 / 219 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	3 / 219 (1.37%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Subcutaneous haematoma			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural intestinal perforation			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 219 (0.91%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	2 / 219 (0.91%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 219 (0.46%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			

subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 219 (0.00%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	26 / 219 (11.87%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	33 / 33	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	7 / 219 (3.20%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 219 (0.46%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 219 (1.37%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	9 / 219 (4.11%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	9 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 219 (1.83%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Nodular regenerative hyperplasia			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			

subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 219 (0.91%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 219 (0.91%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 219 (0.91%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 219 (0.46%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 219 (0.00%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	0 / 219 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypermagnesaemia			
subjects affected / exposed	1 / 219 (0.46%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	2 / 219 (0.91%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TCH + P	T-DM1 + P	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	215 / 219 (98.17%)	198 / 223 (88.79%)	
Vascular disorders			
Hot flush			
alternative assessment type: Non-systematic			
subjects affected / exposed	45 / 219 (20.55%)	22 / 223 (9.87%)	
occurrences (all)	47	25	
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 219 (6.85%)	14 / 223 (6.28%)	
occurrences (all)	18	14	
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	61 / 219 (27.85%)	42 / 223 (18.83%)	
occurrences (all)	115	73	
Chills			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 219 (4.11%)	27 / 223 (12.11%)	
occurrences (all)	9	32	
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	95 / 219 (43.38%)	83 / 223 (37.22%)	
occurrences (all)	143	116	
Influenza like illness			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 219 (4.57%)	16 / 223 (7.17%)	
occurrences (all)	12	21	
Mucosal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	30 / 219 (13.70%)	22 / 223 (9.87%)	
occurrences (all)	37	29	
Oedema peripheral			
alternative assessment type: Non-systematic			

subjects affected / exposed	31 / 219 (14.16%)	10 / 223 (4.48%)	
occurrences (all)	38	11	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	34 / 219 (15.53%)	38 / 223 (17.04%)	
occurrences (all)	43	53	
Immune system disorders			
Hypersensitivity			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 219 (5.02%)	6 / 223 (2.69%)	
occurrences (all)	17	8	
Reproductive system and breast disorders			
Breast pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 219 (5.48%)	17 / 223 (7.62%)	
occurrences (all)	13	18	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	21 / 219 (9.59%)	30 / 223 (13.45%)	
occurrences (all)	26	38	
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 219 (8.22%)	18 / 223 (8.07%)	
occurrences (all)	21	22	
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	24 / 219 (10.96%)	49 / 223 (21.97%)	
occurrences (all)	31	82	
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 219 (5.02%)	10 / 223 (4.48%)	
occurrences (all)	17	11	
Rhinorrhoea			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	12 / 219 (5.48%)	11 / 223 (4.93%)	
occurrences (all)	16	14	
Psychiatric disorders			
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 219 (7.31%)	10 / 223 (4.48%)	
occurrences (all)	17	10	
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	31 / 219 (14.16%)	36 / 223 (16.14%)	
occurrences (all)	37	40	
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 219 (6.39%)	13 / 223 (5.83%)	
occurrences (all)	15	15	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	24 / 219 (10.96%)	64 / 223 (28.70%)	
occurrences (all)	37	83	
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	21 / 219 (9.59%)	55 / 223 (24.66%)	
occurrences (all)	37	74	
Neutrophil count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 219 (10.05%)	5 / 223 (2.24%)	
occurrences (all)	44	6	
Platelet count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	26 / 219 (11.87%)	23 / 223 (10.31%)	
occurrences (all)	37	38	
Weight decreased			
alternative assessment type: Non-systematic			

subjects affected / exposed	24 / 219 (10.96%)	18 / 223 (8.07%)	
occurrences (all)	24	19	
White blood cell count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 219 (7.76%)	8 / 223 (3.59%)	
occurrences (all)	22	11	
Blood bilirubin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 219 (0.46%)	20 / 223 (8.97%)	
occurrences (all)	3	28	
Injury, poisoning and procedural complications			
Radiation skin injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	46 / 219 (21.00%)	21 / 223 (9.42%)	
occurrences (all)	48	22	
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 219 (12.33%)	22 / 223 (9.87%)	
occurrences (all)	30	28	
Dysgeusia			
alternative assessment type: Non-systematic			
subjects affected / exposed	44 / 219 (20.09%)	31 / 223 (13.90%)	
occurrences (all)	58	39	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	37 / 219 (16.89%)	68 / 223 (30.49%)	
occurrences (all)	53	95	
Hypoaesthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	19 / 219 (8.68%)	7 / 223 (3.14%)	
occurrences (all)	21	9	
Neuropathy peripheral			
alternative assessment type: Non-systematic			

subjects affected / exposed	29 / 219 (13.24%)	21 / 223 (9.42%)	
occurrences (all)	36	37	
Paraesthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	23 / 219 (10.50%)	11 / 223 (4.93%)	
occurrences (all)	28	14	
Peripheral sensory neuropathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	26 / 219 (11.87%)	26 / 223 (11.66%)	
occurrences (all)	26	27	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	81 / 219 (36.99%)	43 / 223 (19.28%)	
occurrences (all)	103	47	
Neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	59 / 219 (26.94%)	13 / 223 (5.83%)	
occurrences (all)	92	20	
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	24 / 219 (10.96%)	18 / 223 (8.07%)	
occurrences (all)	36	23	
Eye disorders			
Dry eye			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 219 (6.39%)	16 / 223 (7.17%)	
occurrences (all)	16	16	
Lacrimation increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 219 (8.22%)	6 / 223 (2.69%)	
occurrences (all)	21	9	
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	30 / 219 (13.70%)	21 / 223 (9.42%)	
occurrences (all)	45	29	
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 219 (10.05%)	7 / 223 (3.14%)	
occurrences (all)	29	8	
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	43 / 219 (19.63%)	34 / 223 (15.25%)	
occurrences (all)	48	52	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	163 / 219 (74.43%)	86 / 223 (38.57%)	
occurrences (all)	372	179	
Dry mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 219 (1.83%)	27 / 223 (12.11%)	
occurrences (all)	4	33	
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 219 (6.85%)	25 / 223 (11.21%)	
occurrences (all)	18	30	
Gastrooesophageal reflux disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 219 (7.31%)	7 / 223 (3.14%)	
occurrences (all)	18	8	
Haemorrhoids			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 219 (6.39%)	5 / 223 (2.24%)	
occurrences (all)	19	5	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	139 / 219 (63.47%)	103 / 223 (46.19%)	
occurrences (all)	249	248	

Stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	49 / 219 (22.37%)	23 / 223 (10.31%)	
occurrences (all)	70	30	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	68 / 219 (31.05%)	35 / 223 (15.70%)	
occurrences (all)	83	47	
Gingival bleeding			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 219 (0.46%)	15 / 223 (6.73%)	
occurrences (all)	1	17	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	146 / 219 (66.67%)	37 / 223 (16.59%)	
occurrences (all)	149	38	
Dermatitis acneiform			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 219 (7.31%)	12 / 223 (5.38%)	
occurrences (all)	16	14	
Dry skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 219 (12.33%)	30 / 223 (13.45%)	
occurrences (all)	32	32	
Nail discolouration			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 219 (9.13%)	0 / 223 (0.00%)	
occurrences (all)	21	0	
Nail disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 219 (5.02%)	2 / 223 (0.90%)	
occurrences (all)	13	2	
Pruritus			
alternative assessment type: Non-systematic			

subjects affected / exposed	26 / 219 (11.87%)	20 / 223 (8.97%)	
occurrences (all)	34	22	
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	57 / 219 (26.03%)	43 / 223 (19.28%)	
occurrences (all)	77	60	
Erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 219 (3.65%)	16 / 223 (7.17%)	
occurrences (all)	10	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	41 / 219 (18.72%)	31 / 223 (13.90%)	
occurrences (all)	55	37	
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 219 (9.13%)	14 / 223 (6.28%)	
occurrences (all)	22	20	
Bone pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 219 (7.76%)	8 / 223 (3.59%)	
occurrences (all)	25	8	
Muscle spasms			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 219 (6.39%)	20 / 223 (8.97%)	
occurrences (all)	16	21	
Musculoskeletal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 219 (9.13%)	10 / 223 (4.48%)	
occurrences (all)	22	10	
Myalgia			
alternative assessment type: Non-systematic			

subjects affected / exposed	37 / 219 (16.89%)	28 / 223 (12.56%)	
occurrences (all)	41	42	
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 219 (5.94%)	15 / 223 (6.73%)	
occurrences (all)	16	15	
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	23 / 219 (10.50%)	29 / 223 (13.00%)	
occurrences (all)	29	34	
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 219 (6.85%)	21 / 223 (9.42%)	
occurrences (all)	18	24	
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 219 (7.76%)	12 / 223 (5.38%)	
occurrences (all)	20	16	
Metabolism and nutrition disorders			
Decreased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	40 / 219 (18.26%)	33 / 223 (14.80%)	
occurrences (all)	46	41	
Hypokalaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 219 (9.13%)	13 / 223 (5.83%)	
occurrences (all)	23	17	
Hypomagnesaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 219 (5.94%)	0 / 223 (0.00%)	
occurrences (all)	13	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2014	Wording regarding the timing between neoadjuvant treatment and surgery was aligned in the protocol synopsis. The Investigational Medicinal Product was updated to provide guidance to refer to national prescribing information for contraindications, adverse reactions, warnings, and precautions for docetaxel and carboplatin. The inclusion and exclusion criteria was updated. The study schema was updated. Language in the Permitted Therapy section was updated. Language was updated in the section with patients receiving optional adjuvant chemotherapy. Language regarding post-study adverse events reporting was updated. Language regarding pulmonary toxicity was clarified. Information regarding potential neurotoxicity was updated and a section on extravasation was added. Clarifications were updated regarding dose modifications/delays in response to trastuzumab emtansine-specific adverse events. Appendix 11 was added to provide guidance on carboplatin dosing for patients for whom the isotope dilution mass spectrometry method of serum creatine measurement is used.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported