Clinical trial results:
A Phase III Randomized, Multicenter, Two Arm, Open-Label Trial to Evaluate the Efficacy of Trastuzumab Emtansine Compared with Treatment of Physician's Choice in Patients with HER2-positive Metastatic Breast Cancer who have Received at Least Two Prior Regimens of HER2 Directed Therapy.

Summary

EudraCT number	2011-000509-29
Trial protocol	GB SE DE SK BE CZ HU NO IT ES
Global end of trial date	31 August 2015

Results information

Result version number	v1 (current)
This version publication date	02 September 2016
First version publication date	02 September 2016

Trial information

Trial identification

Sponsor protocol code	BO25734/TDM4997g

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized, multicenter, 2-arm, open-label study (TH3RESA) evaluated the efficacy and safety of trastuzumab emtansine (T-DM1) in comparison with treatment of the physician’s choice in subjects with metastatic or unresectable locally advanced/recurrent human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Eligible subjects were randomized to receive either trastuzumab emtansine 3.6 mg/kg intravenously every 21 days or treatment of the physician’s choice. Subjects continued to receive study treatment until disease progression or occurrence of unacceptable toxicity. This study is also known under Roche study protocol number BO25734.

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	14 September 2011
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	Norway: 2
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	France: 80
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 56
Country: Number of subjects enrolled	United States: 147
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	India: 5

Country: Number of subjects enrolled	Israel: 26
Country: Number of subjects enrolled	Korea, Republic of: 52
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Thailand: 15
Worldwide total number of subjects	602
EEA total number of subjects	297

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)	509
From 65 to 84 years	91
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 602 patients were randomized to the study (404 to receive Trastuzumab Emtansine and 198 to receive Treatment of Physician’s Choice).

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	Trastuzumab Emtansine

Arm description:

Trastuzumab emtansine 3.6 mg/kg intravenously every 3 weeks until disease progression (as assessed by the investigator) or unmanageable toxicity.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab emtansine
Investigational medicinal product code	
Other name	Kadcyla, T-DM1
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose was calculated based on the subject’s Baseline weight on Day 1 of each 3-week treatment cycle. The same dose was administered in subsequent cycles if the subject’s weight stayed within 10% of the Baseline weight. If there was a weight change > 10%, the dose was adjusted accordingly and the recorded weight became the new Baseline weight. Trastuzumab emtansine was provided as a single-use lyophilized formulation.

Arm title	Treatment of Physician’s Choice

Arm description:

Treatment of physician's choice until disease progression (as assessed by the investigator) or unmanageable toxicity. The treatments included single-agent chemotherapy, single-agent or dual-agent hormonal therapy for hormone receptor positive-disease, and human epidermal growth factor receptor 2 (HER2)-directed therapy.

Arm type	Active comparator
Investigational medicinal product name	Treatment of physician’s choice
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

The treatment of physician’s choice (TPC) was a protocol-specified approved or standard of care therapy or combination of therapies, based on frequently used regimens for late-line HER2-positive metastatic breast cancer treatment after receipt of both trastuzumab- and lapatinib-containing regimens. The therapies included single-agent chemotherapy, single-agent (eg, tamoxifen or aromatase inhibitor) or dual-agent (e.g., aromatase inhibitor with luteinizing hormone releasing hormone [LHRH] agonist) hormonal therapy for hormone receptor positive-disease, and HER2-directed therapy. Subjects who had documented progressive disease (PD) were eligible to switch treatment to receive trastuzumab emtansine 3.6 mg/kg. Subjects who switched treatment remained on trastuzumab emtansine treatment until another PD event or unmanageable toxicity. The formulation, storage, and preparation of all TPC were as per the appropriate package insert or national prescribing information.

Number of subjects in period 1	Trastuzumab Emtansine	Treatment of Physician's Choice
Started	404	198
Switched to Trastuzumab Emtansine	0	94
Completed	0	0
Not completed	404	198
Study completed by Sponsor	103	34
Physician decision	4	4
Death	247	122
Non-compliance	3	1
Lost to follow-up	14	4
Reason not specified	-	1
Withdrawal by subject	33	32

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab Emtansine
Reporting group description:	
Trastuzumab emtansine 3.6 mg/kg intravenously every 3 weeks until disease progression (as assessed by the investigator) or unmanageable toxicity.	
Reporting group title	Treatment of Physician’s Choice
Reporting group description:	
Treatment of physician's choice until disease progression (as assessed by the investigator) or unmanageable toxicity. The treatments included single-agent chemotherapy, single-agent or dual-agent hormonal therapy for hormone receptor positive-disease, and human epidermal growth factor receptor 2 (HER2)-directed therapy.	

Reporting group values	Trastuzumab Emtansine	Treatment of Physician’s Choice	Total
Number of subjects	404	198	602
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 53.3 ± 10.4	 54.3 ± 10.8	 -
Gender categorical Units: Subjects			
Female	401	197	598
Male	3	1	4

End points

End points reporting groups

Reporting group title	Trastuzumab Emtansine

Reporting group description:

Trastuzumab emtansine 3.6 mg/kg intravenously every 3 weeks until disease progression (as assessed by the investigator) or unmanageable toxicity.

Reporting group title	Treatment of Physician’s Choice

Reporting group description:

Treatment of physician's choice until disease progression (as assessed by the investigator) or unmanageable toxicity. The treatments included single-agent chemotherapy, single-agent or dual-agent hormonal therapy for hormone receptor positive-disease, and human epidermal growth factor receptor 2 (HER2)-directed therapy.

Primary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival was defined as the time from randomization to the first documented disease progression by investigator assessment using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 or death from any cause, whichever occurred first. Progression-free survival was a co-primary endpoint.

Randomized population: All subjects who were randomized to the study. Subjects were included in the treatment group to which they were randomized.

End point type	Primary

End point timeframe:

Baseline to the clinical cut-off date of 11 Feb 2013 (up to 2 years)

End point values	Trastuzumab Emtansine	Treatment of Physician’s Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	198		
Units: Months				
median (confidence interval 95%)	6.2 (5.59 to 6.87)	3.3 (2.89 to 4.14)		

Statistical analyses

Statistical analysis title	Stratified analysis

Statistical analysis description:

The analysis was stratified for 1) World region (United States, Western Europe, or Other); 2) Number of prior regimens, excluding single-agent hormones, for treatment of metastatic or unresectable locally advanced/recurrent disease (≤ 3 or > 3); and 3) Presence of visceral disease (any visceral disease vs no visceral disease).

The hazard ratio was estimated by Cox regression.

Comparison groups	Trastuzumab Emtansine v Treatment of Physician’s Choice

Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.528
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.422
upper limit	0.661

Notes:

[1] - The two-sided stratified log-rank test was used to compare progression-free survival between the two treatment arms at the overall two-sided significance level of 0.5%.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from randomization to death from any cause. Overall survival was a co-primary endpoint.

Randomized population: All subjects who were randomized to the study. Subjects were included in the treatment group to which they were randomized.

999 = The median and/or the upper limit of the confidence interval could not be estimated due to too few events.

End point type	Primary

End point timeframe:

Baseline to the clinical cut-off date of 11 Feb 2013 (up to 2 years)

End point values	Trastuzumab Emtansine	Treatment of Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	198		
Units: Months				
median (confidence interval 95%)	999 (13.14 to 999)	14.9 (11.27 to 999)		

Statistical analyses

Statistical analysis title	Stratified analysis

Statistical analysis description:

The analysis was stratified for 1) World region (United States, Western Europe, or Other); 2) Number of prior regimens, excluding single-agent hormones, for treatment of metastatic or unresectable locally advanced/recurrent disease (≤ 3 or > 3); and 3) Presence of visceral disease (any visceral disease vs no visceral disease).

The hazard ratio was estimated by Cox regression.

Comparison groups	Trastuzumab Emtansine v Treatment of Physician's Choice
Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0034 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.552
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.369
upper limit	0.826

Notes:

[2] - The 2-sided stratified log-rank test was used at the overall two-sided significance level of 4.5%. The pre-specified O'Brien-Fleming stopping boundary for this first OS interim analysis was HR<0.363 (p-value < 0.0000013).

Secondary: Percentage of Subjects With an Objective Response

End point title	Percentage of Subjects With an Objective Response

End point description:

An objective response was defined as a complete or partial response determined on 2 consecutive occasions ≥ 4 weeks apart using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Complete response was defined as the disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must be < 10 mm on the short axis. Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum. Participants who had no post-baseline tumor assessment were counted as non-responders.

Randomized population: All subjects who were randomized to the study. Only subjects with measurable disease at Baseline were included in the analysis. Subjects were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Baseline to the clinical cut-off date of 11 Feb 2013 (up to 2 years)

End point values	Trastuzumab Emtansine	Treatment of Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	163		
Units: Percentage of Subjects				
number (confidence interval 95%)	31.3 (26.5 to 36.5)	8.6 (5.1 to 13.8)		

Statistical analyses

Statistical analysis title	Stratified analysis

Statistical analysis description:

The analysis was stratified for 1) World region (United States, Western Europe, or Other); 2) Number of prior regimens, excluding single-agent hormones, for treatment of metastatic or unresectable locally advanced/recurrent disease (≤ 3 or > 3); and 3) Presence of visceral disease (any visceral disease vs

no visceral disease).

Comparison groups	Treatment of Physician’s Choice v Trastuzumab Emtansine
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mantel-Haenszel
Parameter estimate	Difference in Response Percentage
Point estimate	22.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.2
upper limit	29.2

Secondary: Duration of the Objective Response

End point title	Duration of the Objective Response

End point description:

Duration of the objective response was defined as the time from the first tumor assessment that was judged to indicate that the subject had an objective response to the time of first documented disease progression using RECIST v1.1 per investigator assessment or death from any cause, whichever occurred first.

Randomized population: All subjects who were randomized to the study. Only subjects with an objective response were included in the analysis. Subjects were included in the treatment group to which they were randomized.

999 = The median and the upper confidence interval value could not be estimated due to too few events.

End point type	Secondary

End point timeframe:

Baseline to the clinical cut-off date of 11 Feb 2013 (up to 2 years)

End point values	Trastuzumab Emtansine	Treatment of Physician’s Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	14		
Units: Months				
median (confidence interval 95%)	9.7 (6.6 to 10.51)	999 (2.4 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6-month and 1-year Survival

End point title	6-month and 1-year Survival

End point description:

6-month and 1-year survival were defined as the percentage of subjects who were alive at 6 months and 1 year, respectively, as estimated using Kaplan-Meier method.

Randomized population: All subjects who were randomized to the study. Subjects were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Baseline to the clinical cut-off date of 11 Feb 2013 (up to 2 years)

End point values	Trastuzumab Emtansine	Treatment of Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	198		
Units: Percentage of Subjects				
number (confidence interval 95%)				
6-Month Survival	90.9 (87.79 to 94.01)	78.3 (71.49 to 85.19)		
1-Year Survival	68.6 (59.91 to 77.28)	56.9 (42.22 to 71.63)		

Statistical analyses

Statistical analysis title	Difference in Survival Percentage (6 month)
Comparison groups	Trastuzumab Emtansine v Treatment of Physician's Choice
Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011 [3]
Method	z-test
Parameter estimate	Difference in Survival Percentage
Point estimate	12.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.03
upper limit	20.09

Notes:

[3] - The p-value for the difference in survival rate was derived from the z-test using the standard errors computed using Greenwood`s method.

Statistical analysis title	Difference in Survival Percentage (1 year)
Comparison groups	Trastuzumab Emtansine v Treatment of Physician's Choice

Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1805 [4]
Method	z-test
Parameter estimate	Difference in Survival Percentage
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.41
upper limit	28.75

Notes:

[4] - The p-value for the difference in survival rates was derived from the z-test using the standard errors computed using Greenwood`s method.

Secondary: Time to Pain Symptom Progression

End point title	Time to Pain Symptom Progression

End point description:

Time to pain symptom progression was defined as the time from randomization to the first documentation of an increase in narcotic use and/or a 10 point increase from Baseline in the pain score as measured by the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire for patients with bone metastases (EORTC QLQ-BM22). The EORTC QLQ-BM22 assesses the symptoms of bone metastases using 22 items: 5 items for sites of pain, 3 pain characteristics, 8 functional interference aspects, and 6 psychosocial aspects. The pain score was derived from the 3 pain characteristic items. Each item was rated on a 4-point scale, where 1=Not at all to 4=Very much. The pain score was the sum of the 3 pain characteristic scores and was normalized to a scale of 0 to 100. A higher score indicates greater pain.

Subjects with Baseline pain score and ≥1 post-baseline pain score were included. Subjects were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Baseline to the clinical cut-off date of 11 Feb 2013 (up to 2 years)

End point values	Trastuzumab Emtansine	Treatment of Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	117		
Units: Months				
median (confidence interval 95%)	2.9 (2.2 to 3.7)	3.6 (2.7 to 4.5)		

Statistical analyses

Statistical analysis title	Stratified analysis

Statistical analysis description:

The analysis was stratified for 1) World region (United States, Western Europe, or Other); 2) Number of prior regimens, excluding single-agent hormones, for treatment of metastatic or unresectable locally advanced/recurrent disease (≤ 3 or > 3); and 3) Presence of visceral disease (any visceral disease vs no visceral disease).

Comparison groups	Treatment of Physician's Choice v Trastuzumab Emtansine
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4952
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.819
upper limit	1.517

Secondary: Change From Baseline in the EORTC QLQ-BM22 Pain Score on Day 1 of Each Cycle

End point title	Change From Baseline in the EORTC QLQ-BM22 Pain Score on Day 1 of Each Cycle

End point description:

The EORTC QLQ-BM22 assesses the symptoms of bone metastases using 22 items: 5 items for sites of pain, 3 pain characteristics, 8 functional interference aspects, and 6 psychosocial aspects. The pain score was derived from the 3 pain characteristic items. Each item was rated on a 4-point scale, where 1=Not at all to 4=Very much. The pain score was the sum of the 3 pain characteristic scores and was normalized to a scale of 0 to 100. A higher score indicates greater pain. A negative change score indicates improvement.

Randomized population: All subjects who were randomized to the study. Only subjects with a Baseline pain score and at least 1 post-baseline pain score were included in the analysis. Subjects were included in the treatment group to which they were randomized.

Here, 999 signifies that there were no participants with available data.

End point type	Secondary

End point timeframe:

Baseline to the clinical cut-off date of 11 Feb 2013 (up to 2 years)

End point values	Trastuzumab Emtansine	Treatment of Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	117		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Cycle 2 (n=282,98)	-3.4 (± 21.1)	-9.4 (± 22.1)		
Cycle 3 (n=257,86)	-4.6 (± 21.1)	-6.1 (± 21.4)		
Cycle 4 (n=236,74)	-4.8 (± 19.6)	-3.8 (± 24.1)		
Cycle 5 (n=224,54)	-6.6 (± 22.8)	-2.7 (± 18.9)		
Cycle 6 (n=195,42)	-4.8 (± 23.5)	2.4 (± 17.1)		
Cycle 7 (n=163,30)	-4.2 (± 23.8)	-1.5 (± 15.6)		
Cycle 8 (n=130,20)	-7 (± 21)	2.2 (± 18.6)		
Cycle 9 (n=97,15)	-5.8 (± 22.2)	6.7 (± 20.1)		

Cycle 10 (n=80,7)	-8.9 (± 21.2)	1.6 (± 11.9)		
Cycle 11 (n=56,8)	-10.5 (± 23.1)	0 (± 8.4)		
Cycle 12 (n=48,7)	-11.3 (± 25.8)	1.6 (± 7.7)		
Cycle 13 (n=40,5)	-10 (± 23.3)	2.2 (± 12.2)		
Cycle 14 (n=33,5)	-10.1 (± 21.8)	0 (± 7.9)		
Cycle 15 (n=27,3)	-13.2 (± 22)	0 (± 0)		
Cycle 16 (n=19,3)	-12.3 (± 19.6)	-3.7 (± 6.4)		
Cycle 17 (n=15,2)	-7.4 (± 22.9)	-5.6 (± 7.9)		
Cycle 18 (n=11,0)	-9.1 (± 12)	999 (± 999)		
Cycle 19 (n=8,0)	1.4 (± 9.3)	999 (± 999)		
Cycle 20 (n=4,0)	-5.6 (± 23.1)	999 (± 999)		
Cycle 21 (n=3,0)	-3.7 (± 6.4)	999 (± 999)		
Termination Visit (n=84,37)	-1.6 (± 21.8)	-9 (± 23.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Final Analysis)

End point title	Overall Survival (Final Analysis)

End point description:

Overall survival was defined as the time from randomization to death from any cause.

Randomized population: All subjects who were randomized to the study. Subjects were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Baseline to the clinical cut-off date of 13 Feb 2015 (up to 4 years)

End point values	Trastuzumab Emtansine	Treatment of Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	198		
Units: Months				
median (confidence interval 95%)	22.7 (19.35 to 27.47)	15.8 (13.5 to 18.66)		

Statistical analyses

Statistical analysis title	Stratified analysis

Statistical analysis description:

The analysis was stratified for 1) World region (United States, Western Europe, or Other); 2) Number of prior regimens, excluding single-agent hormones, for treatment of metastatic or unresectable locally advanced/recurrent disease (≤ 3 or > 3); and 3) Presence of visceral disease (any visceral disease vs no visceral disease).

The hazard ratio was estimated by Cox regression.

Comparison groups	Trastuzumab Emtansine v Treatment of Physician's Choice
Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.677
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.539
upper limit	0.85

Notes:

[5] - The two-sided stratified log-rank test was used at the overall two-sided significance level of 4.5%. The pre-specified O'Brien-Fleming stopping boundary for this second and final interim analysis was HR<0.748 (p value < 0.012).

Secondary: 6-month and 1-year Survival (Final Analysis)

End point title	6-month and 1-year Survival (Final Analysis)

End point description:

6-month and 1-year survival were defined as the percentage of subjects who were alive at 6 months and 1 year, respectively, as estimated using Kaplan-Meier method.

Randomized population: All subjects who were randomized to the study. Subjects were included in the treatment group to which they were randomized.

End point type	Secondary

End point timeframe:

Baseline to the clinical cut-off date of 13 Feb 2015 (up to 4 years)

End point values	Trastuzumab Emtansine	Treatment of Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	404	198		
Units: Percentage of subjects				
number (confidence interval 95%)				
6-Month Survival	91.3 (88.52 to 94.11)	78.9 (72.78 to 85.04)		
1-Year Survival	76.5 (72.23 to 80.79)	65.6 (58.36 to 72.76)		

Statistical analyses

Statistical analysis title	Difference in Survival Percentage (6 month)
Comparison groups	Treatment of Physician's Choice v Trastuzumab Emtansine

Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003 [6]
Method	z-test
Parameter estimate	Difference in Survival Percentage
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.67
upper limit	19.14

Notes:

[6] - The p-value for the difference in survival rate was derived from the z-test using the standard errors computed using Greenwood`s method.

Statistical analysis title	Difference in Survival Percentage (1 year)
Comparison groups	Trastuzumab Emtansine v Treatment of Physician’s Choice
Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0104 [7]
Method	z-test
Parameter estimate	Difference in Survival Percentage
Point estimate	11
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.58
upper limit	19.33

Notes:

[7] - The p-value for the difference in survival rate was derived from the z-test using the standard errors computed using Greenwood`s method.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from treatment initiation until 30 days following the last administration of study treatment or study discontinuation on 31 August 2015 (up to approximately 4 years).

Adverse event reporting additional description:

Safety population: All subjects who received any amount of planned study treatment, according to treatment actually received. Data for subjects in the Treatment of Physician's Choice (TPC) arm who switched treatment to receive trastuzumab emtansine following disease progression on TPC are presented separately.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Trastuzumab Emtansine

Reporting group description:

Trastuzumab emtansine 3.6 mg/kg intravenously every 3 weeks until disease progression (as assessed by the investigator) or unmanageable toxicity.

Reporting group title	Treatment of Physician’s Choice (TPC)

Reporting group description:

Treatment of physician's choice (TPC) until disease progression (as assessed by the investigator) or unmanageable toxicity. The treatments included single-agent chemotherapy, single-agent or dual-agent hormonal therapy for hormone receptor positive-disease, and HER2-directed therapy.

Reporting group title	Trastuzumab Emtansine - Post TPC Treatment Switch

Reporting group description:

Subjects, who switched treatment in the Treatment of Physician’s Choice arm to trastuzumab emtansine, were administered trastuzumab emtansine 3.6 mg/kg intravenously every 3 weeks until disease progression (as assessed by the investigator) or unmanageable toxicity.

Serious adverse events	Trastuzumab Emtansine	Treatment of Physician’s Choice (TPC)	Trastuzumab Emtansine - Post TPC Treatment Switch
Total subjects affected by serious adverse events			
subjects affected / exposed	102 / 403 (25.31%)	41 / 184 (22.28%)	19 / 94 (20.21%)
number of deaths (all causes)	247	67	55
number of deaths resulting from adverse events	3	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal adenocarcinoma			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			

subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Tumour pain			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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 necrosis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Embolism			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Embolism venous			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Hypertensive crisis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Hypotension			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Lymphoedema			

subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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			
Adverse drug reaction			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Asthenia			
subjects affected / exposed	3 / 403 (0.74%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Fatigue			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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
General physical health deterioration			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Malaise			

subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Oedema peripheral			
subjects affected / exposed	2 / 403 (0.50%)	2 / 184 (1.09%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Pyrexia			
subjects affected / exposed	7 / 403 (1.74%)	2 / 184 (1.09%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	3 / 7	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vessel puncture site haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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			
Drug hypersensitivity			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Hypersensitivity			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Vaginal haemorrhage			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 403 (1.49%)	5 / 184 (2.72%)	2 / 94 (2.13%)
occurrences causally related to treatment / all	2 / 7	0 / 7	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Haemoptysis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Obliterative bronchiolitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Pleural effusion			
subjects affected / exposed	3 / 403 (0.74%)	2 / 184 (1.09%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia aspiration			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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	2 / 403 (0.50%)	1 / 184 (0.54%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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
Pulmonary embolism			
subjects affected / exposed	1 / 403 (0.25%)	2 / 184 (1.09%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Pulmonary fibrosis			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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

White blood cell count decreased			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Femoral neck fracture			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Femur fracture			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Infusion related reaction			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Subdural haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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

Thoracic vertebral fracture			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Wound decomposition			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Wound haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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
Toxicity to various agents			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
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			
Cardiac failure			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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

Brain oedema			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Cognitive disorder			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Depressed level of consciousness			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Dizziness			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Hepatic encephalopathy			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Loss of consciousness			

subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Paraesthesia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Paraparesis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Seizure			
subjects affected / exposed	5 / 403 (1.24%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 10	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Visual field defect			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Epilepsy			

subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
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 / 403 (0.25%)	2 / 184 (1.09%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 403 (0.25%)	7 / 184 (3.80%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	6 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocytopenia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Neutropenia			
subjects affected / exposed	1 / 403 (0.25%)	2 / 184 (1.09%)	0 / 94 (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
Thrombocytopenia			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Eye disorders			

Vision blurred			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	4 / 403 (0.99%)	3 / 184 (1.63%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Colitis			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Diarrhoea			
subjects affected / exposed	2 / 403 (0.50%)	1 / 184 (0.54%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Ileus			

subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Nausea			
subjects affected / exposed	0 / 403 (0.00%)	2 / 184 (1.09%)	0 / 94 (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
Obstruction gastric			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Proctitis haemorrhagic			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Vomiting			
subjects affected / exposed	2 / 403 (0.50%)	2 / 184 (1.09%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			

subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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
Cholangitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Nodular regenerative hyperplasia			
subjects affected / exposed	3 / 403 (0.74%)	0 / 184 (0.00%)	0 / 94 (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
Hepatotoxicity			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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

Back pain			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Bone pain			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Muscle haemorrhage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Musculoskeletal chest pain			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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
Myalgia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Spinal pain			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Bronchopneumonia			

subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 403 (0.50%)	4 / 184 (2.17%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	2 / 4	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium bacteraemia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Device related infection			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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
Device related sepsis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Gastroenteritis			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Infected fistula			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Infection			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Infectious colitis			

subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Lung infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Pharyngotonsillitis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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
Pneumonia			
subjects affected / exposed	5 / 403 (1.24%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 6	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Sepsis			

subjects affected / exposed	3 / 403 (0.74%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 403 (0.25%)	1 / 184 (0.54%)	0 / 94 (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
Tracheitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Upper respiratory tract infection			
subjects affected / exposed	2 / 403 (0.50%)	0 / 184 (0.00%)	0 / 94 (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
Urinary tract infection			
subjects affected / exposed	4 / 403 (0.99%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Wound infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Abdominal infection			

subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Hyperglycaemia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Hyponatraemia			

subjects affected / exposed	4 / 403 (0.99%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 184 (0.00%)	0 / 94 (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
Malnutrition			
subjects affected / exposed	0 / 403 (0.00%)	1 / 184 (0.54%)	0 / 94 (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

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

Non-serious adverse events	Trastuzumab Emtansine	Treatment of Physician's Choice (TPC)	Trastuzumab Emtansine - Post TPC Treatment Switch
Total subjects affected by non-serious adverse events			
subjects affected / exposed	371 / 403 (92.06%)	148 / 184 (80.43%)	74 / 94 (78.72%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	38 / 403 (9.43%)	10 / 184 (5.43%)	7 / 94 (7.45%)
occurrences (all)	50	11	9
Aspartate aminotransferase increased			
subjects affected / exposed	51 / 403 (12.66%)	13 / 184 (7.07%)	13 / 94 (13.83%)
occurrences (all)	64	13	15
Blood alkaline phosphatase increased			
subjects affected / exposed	21 / 403 (5.21%)	5 / 184 (2.72%)	7 / 94 (7.45%)
occurrences (all)	24	5	7
Blood bilirubin increased			
subjects affected / exposed	38 / 403 (9.43%)	2 / 184 (1.09%)	5 / 94 (5.32%)
occurrences (all)	50	2	8
Ejection fraction decreased			
subjects affected / exposed	11 / 403 (2.73%)	12 / 184 (6.52%)	0 / 94 (0.00%)
occurrences (all)	13	13	0

Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 403 (7.69%)	6 / 184 (3.26%)	6 / 94 (6.38%)
occurrences (all)	39	7	7
Headache			
subjects affected / exposed	100 / 403 (24.81%)	22 / 184 (11.96%)	16 / 94 (17.02%)
occurrences (all)	182	34	22
Neuropathy peripheral			
subjects affected / exposed	20 / 403 (4.96%)	10 / 184 (5.43%)	7 / 94 (7.45%)
occurrences (all)	22	12	7
Paraesthesia			
subjects affected / exposed	28 / 403 (6.95%)	11 / 184 (5.98%)	9 / 94 (9.57%)
occurrences (all)	31	12	10
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	45 / 403 (11.17%)	19 / 184 (10.33%)	7 / 94 (7.45%)
occurrences (all)	60	22	10
Leukopenia			
subjects affected / exposed	9 / 403 (2.23%)	11 / 184 (5.98%)	0 / 94 (0.00%)
occurrences (all)	20	11	0
Neutropenia			
subjects affected / exposed	30 / 403 (7.44%)	39 / 184 (21.20%)	5 / 94 (5.32%)
occurrences (all)	81	84	8
Thrombocytopenia			
subjects affected / exposed	81 / 403 (20.10%)	6 / 184 (3.26%)	17 / 94 (18.09%)
occurrences (all)	167	17	25
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	76 / 403 (18.86%)	33 / 184 (17.93%)	15 / 94 (15.96%)
occurrences (all)	136	44	23
Chills			
subjects affected / exposed	21 / 403 (5.21%)	4 / 184 (2.17%)	0 / 94 (0.00%)
occurrences (all)	26	4	0
Fatigue			
subjects affected / exposed	123 / 403 (30.52%)	48 / 184 (26.09%)	10 / 94 (10.64%)
occurrences (all)	194	55	18

Influenza like illness			
subjects affected / exposed	21 / 403 (5.21%)	2 / 184 (1.09%)	0 / 94 (0.00%)
occurrences (all)	27	2	0
Mucosal inflammation			
subjects affected / exposed	17 / 403 (4.22%)	10 / 184 (5.43%)	7 / 94 (7.45%)
occurrences (all)	19	16	9
Oedema peripheral			
subjects affected / exposed	26 / 403 (6.45%)	11 / 184 (5.98%)	0 / 94 (0.00%)
occurrences (all)	30	11	0
Pyrexia			
subjects affected / exposed	77 / 403 (19.11%)	22 / 184 (11.96%)	14 / 94 (14.89%)
occurrences (all)	118	49	20
Pain			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	5 / 94 (5.32%)
occurrences (all)	0	0	6
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	5 / 94 (5.32%)
occurrences (all)	0	0	6
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 403 (6.70%)	20 / 184 (10.87%)	9 / 94 (9.57%)
occurrences (all)	40	21	12
Constipation			
subjects affected / exposed	90 / 403 (22.33%)	32 / 184 (17.39%)	7 / 94 (7.45%)
occurrences (all)	129	35	11
Abdominal pain upper			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	7 / 94 (7.45%)
occurrences (all)	0	0	8
Diarrhoea			
subjects affected / exposed	52 / 403 (12.90%)	40 / 184 (21.74%)	10 / 94 (10.64%)
occurrences (all)	67	84	12
Dry mouth			
subjects affected / exposed	51 / 403 (12.66%)	2 / 184 (1.09%)	9 / 94 (9.57%)
occurrences (all)	55	2	13
Dyspepsia			

subjects affected / exposed	21 / 403 (5.21%)	12 / 184 (6.52%)	0 / 94 (0.00%)
occurrences (all)	29	13	0
Gingival bleeding			
subjects affected / exposed	21 / 403 (5.21%)	0 / 184 (0.00%)	0 / 94 (0.00%)
occurrences (all)	30	0	0
Nausea			
subjects affected / exposed	144 / 403 (35.73%)	40 / 184 (21.74%)	16 / 94 (17.02%)
occurrences (all)	268	54	17
Stomatitis			
subjects affected / exposed	13 / 403 (3.23%)	11 / 184 (5.98%)	0 / 94 (0.00%)
occurrences (all)	14	11	0
Vomiting			
subjects affected / exposed	77 / 403 (19.11%)	16 / 184 (8.70%)	10 / 94 (10.64%)
occurrences (all)	104	31	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	76 / 403 (18.86%)	24 / 184 (13.04%)	12 / 94 (12.77%)
occurrences (all)	97	27	14
Dyspnoea			
subjects affected / exposed	42 / 403 (10.42%)	21 / 184 (11.41%)	6 / 94 (6.38%)
occurrences (all)	53	25	8
Epistaxis			
subjects affected / exposed	67 / 403 (16.63%)	7 / 184 (3.80%)	12 / 94 (12.77%)
occurrences (all)	135	9	20
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	9 / 403 (2.23%)	20 / 184 (10.87%)	0 / 94 (0.00%)
occurrences (all)	9	20	0
Pruritus			
subjects affected / exposed	23 / 403 (5.71%)	17 / 184 (9.24%)	0 / 94 (0.00%)
occurrences (all)	29	18	0
Rash			
subjects affected / exposed	27 / 403 (6.70%)	19 / 184 (10.33%)	0 / 94 (0.00%)
occurrences (all)	30	20	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	35 / 403 (8.68%)	6 / 184 (3.26%)	8 / 94 (8.51%)
occurrences (all)	35	6	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	60 / 403 (14.89%)	8 / 184 (4.35%)	7 / 94 (7.45%)
occurrences (all)	75	9	8
Back pain			
subjects affected / exposed	35 / 403 (8.68%)	13 / 184 (7.07%)	6 / 94 (6.38%)
occurrences (all)	40	15	6
Bone pain			
subjects affected / exposed	22 / 403 (5.46%)	7 / 184 (3.80%)	0 / 94 (0.00%)
occurrences (all)	32	7	0
Muscle spasms			
subjects affected / exposed	26 / 403 (6.45%)	9 / 184 (4.89%)	0 / 94 (0.00%)
occurrences (all)	39	9	0
Musculoskeletal pain			
subjects affected / exposed	18 / 403 (4.47%)	10 / 184 (5.43%)	7 / 94 (7.45%)
occurrences (all)	22	11	9
Myalgia			
subjects affected / exposed	47 / 403 (11.66%)	14 / 184 (7.61%)	6 / 94 (6.38%)
occurrences (all)	83	17	6
Pain in extremity			
subjects affected / exposed	44 / 403 (10.92%)	9 / 184 (4.89%)	0 / 94 (0.00%)
occurrences (all)	54	10	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	35 / 403 (8.68%)	12 / 184 (6.52%)	6 / 94 (6.38%)
occurrences (all)	45	12	7
Upper respiratory tract infection			
subjects affected / exposed	35 / 403 (8.68%)	8 / 184 (4.35%)	8 / 94 (8.51%)
occurrences (all)	51	11	9
Urinary tract infection			
subjects affected / exposed	26 / 403 (6.45%)	7 / 184 (3.80%)	9 / 94 (9.57%)
occurrences (all)	37	15	12
Sinusitis			

subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	5 / 94 (5.32%)
occurrences (all)	0	0	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	66 / 403 (16.38%)	25 / 184 (13.59%)	15 / 94 (15.96%)
occurrences (all)	85	30	19
Hypokalaemia			
subjects affected / exposed	30 / 403 (7.44%)	4 / 184 (2.17%)	6 / 94 (6.38%)
occurrences (all)	39	4	6
Hyperglycaemia			
subjects affected / exposed	0 / 403 (0.00%)	0 / 184 (0.00%)	5 / 94 (5.32%)
occurrences (all)	0	0	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2011	The inclusion criteria were modified as follows: 1) screening requirements were added for subjects with a history of bilateral breast cancer, 2) the maximum total bilirubin was changed to a direct bilirubin upper limit of normal for subjects with documented Gilbert's syndrome, 3) to ensure that subjects, who had a history of or newly diagnosed brain metastases, were not enrolled after only receiving prior systemic therapy without localised treatment. To conduct screening tumor assessments (computed tomography [CT]/magnetic resonance imaging and bone scans) within 28 days prior to randomization to align with the Response Evaluation Criteria in Solid Tumors guidelines Version 1.1. This amendment also modified the required tumor assessment interval to every 12 weeks (±7 days) for subjects in either treatment arm who had remained on a stable dose of study treatment with a maintained clinical response of stable disease (SD) or better at least 54 weeks after randomization. To clarify that patients who develop isolated progression in the brain but have systemic control of disease would be allowed to continue study treatment after localized treatment of brain metastasis. To clarify acceptable options and provide examples for the treatment of physician's choice (TPC). The dose modification criteria for trastuzumab emtansine were adjusted for thrombocytopenia and hepatotoxicity.
16 May 2012	The eligibility criteria were modified as follows: 1) removed the requirements for prior anthracycline and capecitabine, 2) removed the requirements around prior hormonal therapy, 3) shortened the time from treatment of brain metastases from 2 months to 1 month, 4) removed the specification that no more than 25% of a patient's bone marrow has received radiotherapy. Clarified that, in the control group with subjects receiving TPC, a combination of two agents maximum is allowed, except doublet chemotherapies. Clarified the doses of trastuzumab emtansine administered at cycles following the first cycle depend on the subject's weight variability. Clarified guidance around discontinuation or dose modification of trastuzumab emtansine. Clarified that subjects may withdraw from study treatment but still consent to follow-up for overall survival.
17 September 2012	The co-primary efficacy endpoints were changed from objective response rate (ORR) and overall survival (OS) to progression-free-survival (PFS) per investigator assessment and OS. ORR became a secondary efficacy endpoint. The sample size was reduced from 795 to 600 subjects. Independent review of tumor assessments was removed. One additional OS interim analysis was added. The secondary endpoint of clinical benefit rate was removed. Additional efficacy and safety analyses were added for subjects in the TPC arm who receive trastuzumab emtansine treatment after disease progression. The independent Data Monitoring Committee (iDMC) safety data review was to continue until the primary PFS analysis. To ensure the safety of subjects who wish to switch from TPC treatment to trastuzumab emtansine, specific eligibility criteria must be met prior to administration of their first dose of trastuzumab emtansine. The safety plan for subjects receiving trastuzumab emtansine arm was modified to reflect clinical experience with trastuzumab emtansine in multiple breast cancer studies.

03 July 2013	To facilitate a PFS audit, an Independent Review Facility (IRF) were to perform a blinded review of tumor scans from a subset of 160 subjects selected at random prior to unblinding of data for the primary PFS analysis. Following completion of the primary analysis of PFS, the following were to occur: 1)The frequency, method, and evaluation criteria for tumor assessments was to be determined by the investigator per local clinical practice, 2) The quality-of-life (patient-reported outcome [PRO]) assessments were to be discontinued. Updates were made to the safety plan for trastuzumab emtansine for clarity. Additional details on potential toxicities associated with trastuzumab emtansine, as well as suggestions for managing those toxicities, were provided. Exclusion criteria were added for subjects in the TPC arm who switched to receive trastuzumab emtansine treatment: 1) History of intolerance or hypersensitivity to trastuzumab or murine proteins, 2) History of pulmonary toxicity (e.g., interstitial lung disease, pneumonitis) due to trastuzumab, 3) Current bleeding of Grade ≥ 2. The dosing and administration section on trastuzumab emtansine was updated to include instructions on monitoring the infusion site. It has been clarified that hospitalization due solely to progression of the underlying cancer should not be reported as a serious adverse event. Suspected transmission of an infectious agent by the study drug has been added as an adverse event that requires expedited reporting to the Sponsor. A new safety section has been added regarding pregnancy and breastfeeding.
28 April 2014	Severe or fatal hemorrhage was added as an identified risk. The inclusion criterion with respect to pregnancy avoidance was amended. The time period to maintain pregnancy avoidance and notification to the Sponsor was increased from 6 months to at least 7 months after last dose of study drug. The period of time required for use of contraceptive measures and abstention from breastfeeding was extended from 6 months to 7 months after the last dose of study treatment. The adverse event reporting period was clarified. New adverse events were to be collected until 30 days after the last dose of study treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported