



Clinical trial results:

A Randomized, Multicenter, Phase III Open-label Study of the Efficacy and Safety of Trastuzumab MCC-DM1 vs. Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-Based Therapy

Summary

EudraCT number	2008-005713-22
Trial protocol	ES DE SE PT DK FR SI GB BG FI IT
Global end of trial date	23 September 2015

Results information

Result version number	v1 (current)
This version publication date	29 September 2016
First version publication date	29 September 2016

Trial information

Trial identification

Sponsor protocol code	BO21977
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00829166
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol ID: TDM4370g

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 December 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To compare the efficacy of trastuzumab emtansine versus capecitabine plus lapatinib in participants with human epidermal growth factor receptor 2 (HER2)-positive, unresectable, locally advanced breast cancer or metastatic breast cancer (MBC) as measured by progression-free survival (PFS) based on an independent review of tumor assessments, overall survival (OS), and to assess landmark (1-year and 2-year) survival rates within each treatment group, as appropriate
- To assess the safety of trastuzumab emtansine relative to the safety of capecitabine plus lapatinib

Protection of trial subjects:

This study was conducted in accordance with Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (October 1996), and applicable local, state, and federal laws, as well as other applicable country laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2009
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	United States: 270
Country: Number of subjects enrolled	Korea, Republic of: 103
Country: Number of subjects enrolled	Canada: 73
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	United Kingdom: 56
Country: Number of subjects enrolled	Brazil: 55
Country: Number of subjects enrolled	Italy: 52
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Bulgaria: 38
Country: Number of subjects enrolled	Taiwan: 28
Country: Number of subjects enrolled	Singapore: 22
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Mexico: 11

Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Bosnia and Herzegovina: 8
Country: Number of subjects enrolled	Slovenia: 7
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	New Zealand: 1
Worldwide total number of subjects	991
EEA total number of subjects	388

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)	853
From 65 to 84 years	138
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants of "Lapatinib + Capecitabine" arm were allowed to cross over to receive trastuzumab emtansine based on statistically significant Overall Survival (OS) benefit in favor of trastuzumab emtansine demonstrated in second interim analysis (cut-off date 31 July 2012). The safety analysis of the arm was then reported.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Trastuzumab Emtansine
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Arm description:

Participants received trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) intravenous (IV) infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle until disease progression (PD) (as assessed by the investigator), unmanageable toxicity, or study termination.

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

Dosage and administration details:

Trastuzumab emtansine 3.6 mg/kg IV infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle.

Arm title	Lapatinib + Capecitabine
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Arm description:

Participants received lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle + capecitabine 1000 milligrams per square meter (mg/m²) orally twice daily on Days 1-14 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination. Participants of this group were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.

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

Dosage and administration details:

Lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle.

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

Number of subjects in period 1	Trastuzumab Emtansine	Lapatinib + Capecitabine
Started	495	496
Treated	490	488
Completed	0	0
Not completed	495	496
Physician decision	4	3
Death	305	333
Subject's Decision	41	55
Sponsor's Decision	137	98
Not Specified	3	3
Lost to follow-up	5	4

Baseline characteristics

Reporting groups

Reporting group title	Trastuzumab Emtansine
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Reporting group description:

Participants received trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) intravenous (IV) infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle until disease progression (PD) (as assessed by the investigator), unmanageable toxicity, or study termination.

Reporting group title	Lapatinib + Capecitabine
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Reporting group description:

Participants received lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle + capecitabine 1000 milligrams per square meter (mg/m²) orally twice daily on Days 1-14 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination. Participants of this group were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.

Reporting group values	Trastuzumab Emtansine	Lapatinib + Capecitabine	Total
Number of subjects	495	496	991
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	52.2 ± 11	53.2 ± 10.8	-
Gender categorical Units: Subjects			
Female	494	492	986
Male	1	4	5

End points

End points reporting groups

Reporting group title	Trastuzumab Emtansine
Reporting group description: Participants received trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) intravenous (IV) infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle until disease progression (PD) (as assessed by the investigator), unmanageable toxicity, or study termination.	
Reporting group title	Lapatinib + Capecitabine
Reporting group description: Participants received lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle + capecitabine 1000 milligrams per square meter (mg/m ²) orally twice daily on Days 1-14 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination. Participants of this group were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.	

Primary: Percentage of Participants With PD or Death as Assessed by an Independent Review Committee (IRC)

End point title	Percentage of Participants With PD or Death as Assessed by an Independent Review Committee (IRC) ^[1]
End point description: PD was assessed by an IRC using modified Response Evaluation Criteria in Solid Tumors (RECIST). All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as target lesions (TLs) and recorded at baseline. TLs should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements either by imaging or clinically. A sum of the longest diameter for all TLs was calculated as baseline sum longest diameter (SLD). All other lesions (or sites of disease) should be identified as non-TLs and recorded at baseline. PD for TLs was defined as greater than or equal to (>/=) 20 percent (%) increase in SLD, taking as reference smallest SLD recorded since treatment started or appearance of 1 or more new lesions. PD for non-TLs was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Percentage of Participants with PD by IRC or death from any cause was reported.	
End point type	Primary
End point timeframe: From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495 ^[2]	496 ^[3]		
Units: percentage of participants				
number (not applicable)	53.5	61.3		

Notes:

[2] - Intent-to-treat (ITT) population: all randomized participants on the basis of treatment assigned.

[3] - ITT population: all randomized participants on the basis of the treatment assigned at randomization.

Statistical analyses

Primary: Progression-free Survival (PFS) as Assessed by an IRC (Co-primary Endpoint)

End point title	Progression-free Survival (PFS) as Assessed by an IRC (Co-primary Endpoint)
End point description:	
Tumor response was assessed by an IRC according to modified RECIST. All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as TLs (on the basis of their size and their suitability for accurate repeated measurements either by imaging or clinically) and recorded at baseline. A sum of the longest diameter for all TLs was calculated as baseline SLD. All other lesions were identified as non-TLs and recorded at baseline. PD for TLs: $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or appearance of 1 or more new lesions. PD for non-TLs: appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. PFS: time from randomization to first documented PD by IRC or death from any cause (whichever occurred earlier). The median duration of PFS was estimated using Kaplan-Meier method. The 95% confidence interval (CI) was computed using the method of Brookmeyer and Crowley. ITT population.	
End point type	Primary
End point timeframe:	
From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)	

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: Months				
median (confidence interval 95%)	9.6 (8.25 to 10.64)	6.4 (5.68 to 7.06)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or greater than [$>$] 1), and visceral/ non-visceral disease. Hazard ratio (HR) (relative to Lapatinib + Capecitabine) was estimated by Cox regression.	
Comparison groups	Trastuzumab Emtansine v Lapatinib + Capecitabine
Number of subjects included in analysis	991
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.549
upper limit	0.771

Primary: Percentage of Participants Who Died: Second Interim Analysis

End point title	Percentage of Participants Who Died: Second Interim
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End point description:

The percentage of participants who died from any cause was reported. The results are reported from second interim analysis, which deemed to be the confirmatory. ITT population.

End point type	Primary
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End point timeframe:

From the date of randomization through the data cut-off date of 31 Jul 2012 (up to 3 years, 5 months)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: percentage of participants				
number (not applicable)	30.1	36.7		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival: Second Interim Analysis (Co-primary Endpoint)

End point title	Overall Survival: Second Interim Analysis (Co-primary Endpoint)
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End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. The median duration of OS was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. The results are reported from second interim analysis, which deemed to be the confirmatory. ITT population.

End point type	Primary
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End point timeframe:

From the date of randomization through the data cut-off date of 31 Jul 2012 (up to 3 years, 5 months)

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: Months				
median (confidence interval 95%)	30.9 (26.81 to 34.27)	25.1 (22.74 to 27.96)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression.	
Comparison groups	Trastuzumab Emtansine v Lapatinib + Capecitabine
Number of subjects included in analysis	991
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.682
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.548
upper limit	0.849

Primary: Percentage of Participants Who Died: Final Analysis

End point title	Percentage of Participants Who Died: Final Analysis ^[5]
End point description: The percentage of participants who died from any cause was reported. The results reported are from the final analysis. The final analysis is descriptive. ITT Population.	
End point type	Primary
End point timeframe: From the date of randomization through the data cut-off date of 31 Dec 2014 (up to 5 years, 11 months)	

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: percentage of participants				
number (not applicable)	61.2	67.1		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival: Final Analysis

End point title	Overall Survival: Final Analysis
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End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. The median duration of OS was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. The results reported are from the final analysis. The final analysis is descriptive. ITT Population.

End point type	Primary
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End point timeframe:

From the date of randomization through the data cut-off date of 31 Dec 2014 (up to 5 years, 11 months)

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: percentage of participants				
number (confidence interval 95%)	29.9 (26.32 to 34.1)	25.9 (22.74 to 28.32)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression.

Comparison groups	Trastuzumab Emtansine v Lapatinib + Capecitabine
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Number of subjects included in analysis	991
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.0003
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Method	Logrank
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Parameter estimate	Hazard ratio (HR)
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Point estimate	0.749
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Confidence interval	
level	95 %
sides	2-sided
lower limit	0.639
upper limit	0.877

Primary: Percentage of Participants Who Were Alive at Year 1

End point title	Percentage of Participants Who Were Alive at Year 1 ^[6]
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End point description:

1 year survival was defined as the percentage of participants alive 1 year after starting treatment. The results reported are from the final analysis. ITT population.

End point type	Primary
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End point timeframe:

Year 1

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: percentage of participants				
number (confidence interval 95%)	85.3 (82.15 to 88.54)	78.9 (75.19 to 82.65)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Were Alive at Year 2

End point title	Percentage of Participants Who Were Alive at Year 2 ^[7]
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End point description:

2 year survival was defined as the percentage of participants alive 2 years after starting treatment. The results reported are from the final analysis. ITT Population.

End point type	Primary
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End point timeframe:

Year 2

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: percentage of participants				
number (confidence interval 95%)	59.6 (55.1 to 64.06)	52.4 (47.81 to 57.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With PD or Death as Assessed by the Investigator

End point title	Percentage of Participants With PD or Death as Assessed by the Investigator
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End point description:

PD was assessed by the investigator using modified RECIST. All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as TLs and recorded at baseline. A sum of the longest diameter for all TLs was calculated as baseline SLD. PD for TLs was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. PD for non-TLs was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. The percentage of participants who died or experienced PD by Investigator was reported. ITT population.

End point type	Secondary
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End point timeframe:

From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: percentage of participants				
number (not applicable)	58	67.5		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by the Investigator

End point title	PFS as Assessed by the Investigator
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End point description:

Tumor response was assessed by the investigator according to modified RECIST. All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as TLs and recorded at baseline. A sum of the longest diameter for all TLs was calculated as baseline SLD. PD for TLs was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. PD for non-TLs was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. PFS was defined as the time from randomization to first documented PD by Investigator or death from any cause (whichever occurred

earlier). The median duration of PFS was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT population.

End point type	Secondary
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End point timeframe:

From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: Months				
median (confidence interval 95%)	9.4 (7.49 to 10.78)	5.8 (5.59 to 6.93)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression.

Comparison groups	Trastuzumab Emtansine v Lapatinib + Capecitabine
Number of subjects included in analysis	991
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.658
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.774

Secondary: Percentage of Participants With Objective Response (OR) as Assessed by an IRC

End point title	Percentage of Participants With Objective Response (OR) as Assessed by an IRC
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End point description:

Tumor response was assessed by an IRC according to modified RECIST. OR was defined as the percentage of participants with a complete response (CR) or partial response (PR). All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as TLs and recorded at baseline. A sum of the longest diameter for all TLs was calculated as baseline SLD. For TLs, a CR was defined as the disappearance of all TLs and a PR was defined as $\geq 30\%$ decrease in the SLD of TLs, taking as reference the baseline SLD. For non-TLs, a CR was defined as the disappearance of all non-TLs and a PR was defined as the persistence of 1 or more non-TLs. Confirmation of response at a consecutive tumor assessment at least 4 weeks apart was required. Participants without a post-baseline tumor assessment

were considered non-responders. The percentage of participants with CR or PR by IRC was reported. The 95% CI was computed using Blyth-Still Casella exact CI method. ITT population.

End point type	Secondary
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End point timeframe:

From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397 ^[8]	389 ^[9]		
Units: percentage of participants				
number (confidence interval 95%)	43.6 (38.6 to 48.6)	30.8 (26.3 to 35.7)		

Notes:

[8] - Only participants with measurable disease at baseline were included in the analysis.

[9] - Only participants with measurable disease at baseline were included in the analysis.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. The 95% CI for the difference in objective response rate (Trastuzumab emtansine minus Lapatinib + Capecitabine) was computed by using the approximate normal method.

Comparison groups	Trastuzumab Emtansine v Lapatinib + Capecitabine
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mantel-Haenszel chi-squared test
Parameter estimate	Difference in Objective Response Rates
Point estimate	12.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	19.4

Secondary: Duration of Objective Response (DOR) as Assessed by an IRC

End point title	Duration of Objective Response (DOR) as Assessed by an IRC
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End point description:

Tumor response was assessed by an IRC according to modified RECIST. DOR was defined as the time from first documented OR to first documented PD or death from any cause, whichever occurred earlier. OR was defined as a CR or PR determined on 2 consecutive tumor assessments at least 4 weeks apart. For TLs, CR was defined as the disappearance of all TLs; PR was defined as $\geq 30\%$ decrease in the SLD of TLs, taking as reference the baseline SLD; and PD was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, CR was defined as the disappearance of all non-TLs; PR was defined as the persistence of 1 or more non-TLs; and PD was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT population.

End point type	Secondary
End point timeframe:	
From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)	

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173 ^[10]	120 ^[11]		
Units: Months				
median (confidence interval 95%)	12.6 (8.38 to 20.76)	6.5 (5.45 to 7.16)		

Notes:

[10] - Only participants with an objective response were included in the analysis.

[11] - Only participants with an objective response were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Benefit as Assessed by the IRC

End point title	Percentage of Participants With Clinical Benefit as Assessed by the IRC
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End point description:

Tumor response was assessed by an IRC according to modified RECIST. Participants were considered as experienced clinical benefit if they had an OR or maintained stable disease (SD) for at least 6 months from randomization. OR: CR or PR determined on 2 consecutive tumor assessments ≥ 4 weeks apart. For TLs, CR: disappearance of all TLs; PR: $\geq 30\%$ decrease in the SLD of TLs, taking as reference the baseline SLD; PD: $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or appearance of 1 or more new lesions; and SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. For non-TLs, CR: disappearance of all non-TLs; PR/SD: persistence of 1 or more non-TLs; and PD: appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Participants without a post-baseline tumor assessment were considered non-responders. The 95% CI was computed using Blyth-Still Casella exact CI method.

End point type	Secondary
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End point timeframe:

From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397 ^[12]	389 ^[13]		
Units: percentage of participants				
number (confidence interval 95%)	58.2 (53.3 to 63.1)	44.2 (39.2 to 49.2)		

Notes:

[12] - ITT population. Only participants with measurable disease at Baseline were included in the analysis.

[13] - ITT population. Only participants with measurable disease at Baseline were included in the analysis.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: The 95% CI for the difference in clinical benefit rate (Trastuzumab emtansine minus Lapatinib + Capecitabine) was computed by using the normal approximation method.	
Comparison groups	Trastuzumab Emtansine v Lapatinib + Capecitabine
Number of subjects included in analysis	786
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Clinical Benefit Rate
Point estimate	14
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	20.9

Secondary: Percentage of Participants With Treatment Failure

End point title	Percentage of Participants With Treatment Failure
End point description: Treatment failure was defined as discontinuation of treatment for any reason, including PD (per investigator review), treatment toxicity, or death from any cause. For "Lapatinib + Capecitabine" arm, a participant was considered as treatment failure only if both drugs were discontinued. For TLs, PD was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, PD was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Percentage of participants with treatment failure was reported. ITT population.	
End point type	Secondary
End point timeframe: From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)	

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: percentage of participants				
number (not applicable)	63.2	74.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure
End point description: Time to treatment failure was defined as the time from randomization to discontinuation of treatment for any reason, including PD (per investigator review), treatment toxicity, or death from any cause. For	

"Lapatinib + Capecitabine" arm, a participant was considered as treatment failure only if both drugs were discontinued with treatment failure date as the later of the 2 discontinuation dates. For TLs, PD was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, PD was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. The median time to treatment failure was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT population.

End point type	Secondary
End point timeframe:	
From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)	

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495	496		
Units: Months				
median (confidence interval 95%)	7.9 (6.41 to 9)	5.8 (5.52 to 6.31)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression.

Comparison groups	Trastuzumab Emtansine v Lapatinib + Capecitabine
Number of subjects included in analysis	991
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.703
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.602
upper limit	0.82

Secondary: Percentage of Participants With Symptom Progression

End point title	Percentage of Participants With Symptom Progression
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End point description:

Symptom progression was defined as the documentation of a ≥ 5 -point decrease from baseline in the scoring of responses as measured by the Functional Assessment of Cancer Therapy-for participants with Breast Cancer (FACT-B) questionnaire with the Trial Outcomes Index-Physical/Functional/Breast (TOI-PFB) subscale. The FACT-B TOI-PFB subscale contained 24 items from 3 subsections of the FACT-B questionnaire: Physical well-being, functional well-being, and additional concerns for breast cancer

participants (breast cancer subscale [BCS]). All items in the questionnaire were rated by the participant on a 5-point scale ranging from 0 ("not at all") to 4 ("very much"). The total score ranged from 0 to 96 with higher score indicating better perceived quality of life. The percentage of participants with symptom progression was reported. ITT population. Only female participants with a Baseline assessment and at least 1 follow-up assessment were included in the analysis.

End point type	Secondary
End point timeframe:	
From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)	

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	450	445		
Units: percentage of participants				
number (not applicable)	54.7	57.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom Progression

End point title	Time to Symptom Progression
End point description:	
Time to symptom progression was defined as the time from randomization to the first documentation of a ≥ 5 -point decrease from baseline in the scoring of responses as measured by the FACT-B questionnaire with the TOI-PFB subscale. The FACT-B TOI-PFB subscale contained 24 items from 3 subsections of the FACT-B questionnaire: Physical well-being, functional well-being, and additional concerns for breast cancer participants (BCS). All items in the questionnaire were rated by the participant on a 5-point scale ranging from 0 ("not at all") to 4 ("very much"). The total score ranged from 0 to 96 with higher score indicating better perceived quality of life. The median time to symptom progression was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT population. Only female participants with a Baseline assessment and at least 1 follow-up assessment were included in the analysis.	
End point type	Secondary
End point timeframe:	
From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)	

End point values	Trastuzumab Emtansine	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	450	445		
Units: Months				
median (confidence interval 95%)	7.1 (5.59 to 8.44)	4.6 (4.14 to 5.78)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression.	
Comparison groups	Trastuzumab Emtansine v Lapatinib + Capecitabine
Number of subjects included in analysis	895
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0121
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.796
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.667
upper limit	0.951

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study-related SAEs were reported from randomization to first treatment; all SAEs/non-SAEs from start of treatment until 30 days after treatment; and thereafter treatment related SAEs until data cut-off date of 21-Sep-2015 (up to 6 years and 7 months)

Adverse event reporting additional description:

Safety population included participants who received at least 1 dose of study medication. Safety analyses were based on the actual treatment received. For participants who crossed over from lapatinib + capecitabine to trastuzumab emtansine, data is reported from time of cross-over until 21-Sep-2015 (up to 3 years and 2 months).

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Trastuzumab Emtansine
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Reporting group description:

Participants received trastuzumab emtansine 3.6 mg/kg IV infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination.

Reporting group title	Lapatinib + Capecitabine
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Reporting group description:

Participants received lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle + capecitabine 1000 mg/m² orally twice daily on Days 1-14 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination. Participants of this group were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.

Reporting group title	Lapatinib + Capecitabine/ Trastuzumab Emtansine
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Reporting group description:

Participants of "Lapatinib + Capecitabine" arm were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.

Serious adverse events	Trastuzumab Emtansine	Lapatinib + Capecitabine	Lapatinib + Capecitabine/ Trastuzumab Emtansine
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 490 (18.78%)	99 / 488 (20.29%)	19 / 136 (13.97%)
number of deaths (all causes)	305	277	55
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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

Infected neoplasm			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Second primary malignancy			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Uterine cancer			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Breast cancer			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lentigo maligna			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (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
Labile blood pressure			

subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Thrombosis			
subjects affected / exposed	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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			
Asthenia			
subjects affected / exposed	1 / 490 (0.20%)	2 / 488 (0.41%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	2 / 490 (0.41%)	0 / 488 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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

Mucosal inflammation			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Multi-organ failure			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Oedema peripheral			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Pain			
subjects affected / exposed	2 / 490 (0.41%)	1 / 488 (0.20%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	8 / 490 (1.63%)	3 / 488 (0.61%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	5 / 9	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Reproductive system and breast disorders			
Menometrorrhagia			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Metrorrhagia			
subjects affected / exposed	2 / 490 (0.41%)	1 / 488 (0.20%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ovarian cyst			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Uterine haemorrhage			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 490 (0.20%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Alveolitis allergic			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Asthma			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Dyspnoea			
subjects affected / exposed	2 / 490 (0.41%)	0 / 488 (0.00%)	0 / 136 (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
Epistaxis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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

Hypoxia			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (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
Pleuritic pain			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Pneumonitis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Pneumothorax			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 490 (0.00%)	9 / 488 (1.84%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Psychiatric disorders			

Agitation			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Confusional state			
subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (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
Depression			
subjects affected / exposed	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (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
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Blood bilirubin increased			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Delayed haemolytic transfusion reaction			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Extradural haematoma			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Fall			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Femoral neck fracture			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Femur fracture			
subjects affected / exposed	3 / 490 (0.61%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Hip fracture			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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 / 490 (0.20%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Wrist fracture			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Synovial rupture			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound secretion			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
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			
Angina pectoris			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Atrial fibrillation			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Cardiomyopathy			

subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Coronary artery disease			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Pericardial effusion			
subjects affected / exposed	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (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
Pericarditis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Tachycardia			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Dizziness			

subjects affected / exposed	2 / 490 (0.41%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (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
Headache			
subjects affected / exposed	1 / 490 (0.20%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Hydrocephalus			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Metabolic encephalopathy			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Parkinson's disease			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Status epilepticus			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Syncope			

subjects affected / exposed	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (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
Anaemia of malignant disease			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Thrombocytopenia			
subjects affected / exposed	4 / 490 (0.82%)	1 / 488 (0.20%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	6 / 7	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Eye disorders			
Macular hole			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 490 (0.82%)	3 / 488 (0.61%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 5	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Constipation			
subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (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
Diarrhoea			
subjects affected / exposed	3 / 490 (0.61%)	17 / 488 (3.48%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 5	19 / 19	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Fistula of small intestine			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Gastric ulcer			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Gastritis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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 haemorrhage			

subjects affected / exposed	2 / 490 (0.41%)	0 / 488 (0.00%)	0 / 136 (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
Gastrointestinal obstruction			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Intestinal obstruction			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 490 (0.41%)	3 / 488 (0.61%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Vomiting			

subjects affected / exposed	7 / 490 (1.43%)	10 / 488 (2.05%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	3 / 7	9 / 11	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Cholestasis			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Hepatitis toxic			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Hepatotoxicity			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (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
Portal hypertension			

subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Cholangitis acute			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodular regenerative hyperplasia			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Rash			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Skin haemorrhage			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Urticaria			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Renal failure			

subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Ureteric obstruction			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Urinary tract obstruction			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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			
Back pain			
subjects affected / exposed	3 / 490 (0.61%)	0 / 488 (0.00%)	0 / 136 (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
Bone pain			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Osteonecrosis of jaw			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Pain in extremity			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Pathological fracture			

subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Spinal column stenosis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Spondylitis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Bacteraemia			
subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (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
Bronchitis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Catheter site infection			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Cellulitis			
subjects affected / exposed	2 / 490 (0.41%)	3 / 488 (0.61%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			

subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (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
Device related infection			
subjects affected / exposed	2 / 490 (0.41%)	0 / 488 (0.00%)	0 / 136 (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
Enterococcal infection			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Gastroenteritis norovirus			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
H1N1 influenza			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Herpes zoster			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Infection			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Listeriosis			

subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Nasopharyngitis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Neutropenic sepsis			
subjects affected / exposed	2 / 490 (0.41%)	0 / 488 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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			
subjects affected / exposed	4 / 490 (0.82%)	1 / 488 (0.20%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Post procedural infection			

subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Salmonellosis			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Sepsis			
subjects affected / exposed	1 / 490 (0.20%)	1 / 488 (0.20%)	0 / 136 (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
Staphylococcal sepsis			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Urinary tract infection			
subjects affected / exposed	3 / 490 (0.61%)	0 / 488 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Respiratory tract infection			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unmapped (Bacteremia due to infected port)			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 490 (0.00%)	2 / 488 (0.41%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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
Hypercalcaemia			
subjects affected / exposed	0 / 490 (0.00%)	1 / 488 (0.20%)	0 / 136 (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
Hypokalaemia			
subjects affected / exposed	1 / 490 (0.20%)	0 / 488 (0.00%)	0 / 136 (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	2 / 490 (0.41%)	1 / 488 (0.20%)	0 / 136 (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

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

Non-serious adverse events	Trastuzumab Emtansine	Lapatinib + Capecitabine	Lapatinib + Capecitabine/ Trastuzumab Emtansine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	474 / 490 (96.73%)	471 / 488 (96.52%)	115 / 136 (84.56%)
Vascular disorders			
Hypertension			
subjects affected / exposed	29 / 490 (5.92%)	11 / 488 (2.25%)	7 / 136 (5.15%)
occurrences (all)	40	13	13
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	91 / 490 (18.57%)	86 / 488 (17.62%)	23 / 136 (16.91%)
occurrences (all)	230	186	47
Chest pain			
subjects affected / exposed	40 / 490 (8.16%)	27 / 488 (5.53%)	0 / 136 (0.00%)
occurrences (all)	50	30	0
Chills			
subjects affected / exposed	42 / 490 (8.57%)	16 / 488 (3.28%)	13 / 136 (9.56%)
occurrences (all)	59	20	19
Fatigue			
subjects affected / exposed	180 / 490 (36.73%)	145 / 488 (29.71%)	30 / 136 (22.06%)
occurrences (all)	360	259	65
Influenza like illness			
subjects affected / exposed	26 / 490 (5.31%)	9 / 488 (1.84%)	13 / 136 (9.56%)
occurrences (all)	36	11	41
Mucosal inflammation			
subjects affected / exposed	33 / 490 (6.73%)	93 / 488 (19.06%)	0 / 136 (0.00%)
occurrences (all)	65	172	0
Oedema peripheral			
subjects affected / exposed	38 / 490 (7.76%)	38 / 488 (7.79%)	10 / 136 (7.35%)
occurrences (all)	49	47	11
Pain			
subjects affected / exposed	35 / 490 (7.14%)	14 / 488 (2.87%)	0 / 136 (0.00%)
occurrences (all)	43	14	0
Pyrexia			

subjects affected / exposed occurrences (all)	95 / 490 (19.39%) 165	43 / 488 (8.81%) 54	18 / 136 (13.24%) 25
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	100 / 490 (20.41%)	68 / 488 (13.93%)	18 / 136 (13.24%)
occurrences (all)	148	80	27
Dyspnoea			
subjects affected / exposed	61 / 490 (12.45%)	41 / 488 (8.40%)	17 / 136 (12.50%)
occurrences (all)	72	55	25
Epistaxis			
subjects affected / exposed	121 / 490 (24.69%)	44 / 488 (9.02%)	35 / 136 (25.74%)
occurrences (all)	235	55	85
Oropharyngeal pain			
subjects affected / exposed	24 / 490 (4.90%)	26 / 488 (5.33%)	0 / 136 (0.00%)
occurrences (all)	29	32	0
Rhinorrhoea			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	11 / 136 (8.09%)
occurrences (all)	0	0	17
Psychiatric disorders			
Anxiety			
subjects affected / exposed	31 / 490 (6.33%)	15 / 488 (3.07%)	0 / 136 (0.00%)
occurrences (all)	38	17	0
Depression			
subjects affected / exposed	27 / 490 (5.51%)	30 / 488 (6.15%)	0 / 136 (0.00%)
occurrences (all)	31	33	0
Insomnia			
subjects affected / exposed	69 / 490 (14.08%)	45 / 488 (9.22%)	14 / 136 (10.29%)
occurrences (all)	86	54	19
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	92 / 490 (18.78%)	48 / 488 (9.84%)	14 / 136 (10.29%)
occurrences (all)	285	79	22
Aspartate aminotransferase increased			
subjects affected / exposed	123 / 490 (25.10%)	53 / 488 (10.86%)	25 / 136 (18.38%)
occurrences (all)	376	96	56
Blood alkaline phosphatase increased			

subjects affected / exposed occurrences (all)	26 / 490 (5.31%) 59	23 / 488 (4.71%) 25	9 / 136 (6.62%) 12
Blood bilirubin increased subjects affected / exposed occurrences (all)	21 / 490 (4.29%) 45	32 / 488 (6.56%) 83	11 / 136 (8.09%) 32
Weight decreased subjects affected / exposed occurrences (all)	38 / 490 (7.76%) 55	37 / 488 (7.58%) 45	7 / 136 (5.15%) 10
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 490 (0.00%) 0	0 / 488 (0.00%) 0	8 / 136 (5.88%) 16
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	0 / 490 (0.00%) 0	0 / 488 (0.00%) 0	8 / 136 (5.88%) 9
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	62 / 490 (12.65%) 88	50 / 488 (10.25%) 75	0 / 136 (0.00%) 0
Dysgeusia subjects affected / exposed occurrences (all)	41 / 490 (8.37%) 44	21 / 488 (4.30%) 27	0 / 136 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	146 / 490 (29.80%) 257	77 / 488 (15.78%) 95	28 / 136 (20.59%) 79
Neuropathy peripheral subjects affected / exposed occurrences (all)	59 / 490 (12.04%) 106	30 / 488 (6.15%) 38	16 / 136 (11.76%) 20
Paraesthesia subjects affected / exposed occurrences (all)	31 / 490 (6.33%) 40	20 / 488 (4.10%) 33	7 / 136 (5.15%) 11
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	36 / 490 (7.35%) 81	27 / 488 (5.53%) 34	0 / 136 (0.00%) 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	67 / 490 (13.67%)	40 / 488 (8.20%)	11 / 136 (8.09%)
occurrences (all)	169	87	24
Neutropenia			
subjects affected / exposed	37 / 490 (7.55%)	43 / 488 (8.81%)	0 / 136 (0.00%)
occurrences (all)	144	100	0
Thrombocytopenia			
subjects affected / exposed	150 / 490 (30.61%)	13 / 488 (2.66%)	23 / 136 (16.91%)
occurrences (all)	574	26	60
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	7 / 136 (5.15%)
occurrences (all)	0	0	8
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	43 / 490 (8.78%)	50 / 488 (10.25%)	0 / 136 (0.00%)
occurrences (all)	62	75	0
Abdominal pain upper			
subjects affected / exposed	60 / 490 (12.24%)	45 / 488 (9.22%)	0 / 136 (0.00%)
occurrences (all)	69	69	0
Constipation			
subjects affected / exposed	139 / 490 (28.37%)	59 / 488 (12.09%)	22 / 136 (16.18%)
occurrences (all)	204	75	30
Diarrhoea			
subjects affected / exposed	123 / 490 (25.10%)	385 / 488 (78.89%)	20 / 136 (14.71%)
occurrences (all)	192	1254	58
Dry mouth			
subjects affected / exposed	85 / 490 (17.35%)	26 / 488 (5.33%)	20 / 136 (14.71%)
occurrences (all)	115	30	29
Dyspepsia			
subjects affected / exposed	51 / 490 (10.41%)	57 / 488 (11.68%)	7 / 136 (5.15%)
occurrences (all)	67	71	7
Gingival bleeding			
subjects affected / exposed	0 / 490 (0.00%)	0 / 488 (0.00%)	8 / 136 (5.88%)
occurrences (all)	0	0	11
Nausea			

subjects affected / exposed occurrences (all)	203 / 490 (41.43%) 487	224 / 488 (45.90%) 431	35 / 136 (25.74%) 70
Stomatitis subjects affected / exposed occurrences (all)	20 / 490 (4.08%) 22	70 / 488 (14.34%) 103	0 / 136 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	98 / 490 (20.00%) 167	145 / 488 (29.71%) 250	13 / 136 (9.56%) 25
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	13 / 490 (2.65%) 31	46 / 488 (9.43%) 99	0 / 136 (0.00%) 0
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	19 / 490 (3.88%) 25	25 / 488 (5.12%) 27	0 / 136 (0.00%) 0
Dry skin subjects affected / exposed occurrences (all)	17 / 490 (3.47%) 24	54 / 488 (11.07%) 67	8 / 136 (5.88%) 11
Erythema subjects affected / exposed occurrences (all)	16 / 490 (3.27%) 19	25 / 488 (5.12%) 41	0 / 136 (0.00%) 0
Nail disorder subjects affected / exposed occurrences (all)	18 / 490 (3.67%) 22	48 / 488 (9.84%) 67	0 / 136 (0.00%) 0
Dermatitis acneiform subjects affected / exposed occurrences (all)	3 / 490 (0.61%) 3	28 / 488 (5.74%) 51	0 / 136 (0.00%) 0
Palmar–plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	7 / 490 (1.43%) 8	291 / 488 (59.63%) 927	7 / 136 (5.15%) 7
Pruritus subjects affected / exposed occurrences (all)	32 / 490 (6.53%) 44	46 / 488 (9.43%) 58	7 / 136 (5.15%) 9
Rash			

subjects affected / exposed	64 / 490 (13.06%)	133 / 488 (27.25%)	17 / 136 (12.50%)
occurrences (all)	102	223	24
Skin fissures			
subjects affected / exposed	2 / 490 (0.41%)	27 / 488 (5.53%)	0 / 136 (0.00%)
occurrences (all)	3	67	0
Skin hyperpigmentation			
subjects affected / exposed	2 / 490 (0.41%)	25 / 488 (5.12%)	0 / 136 (0.00%)
occurrences (all)	2	33	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	102 / 490 (20.82%)	46 / 488 (9.43%)	21 / 136 (15.44%)
occurrences (all)	150	56	28
Back pain			
subjects affected / exposed	78 / 490 (15.92%)	63 / 488 (12.91%)	9 / 136 (6.62%)
occurrences (all)	110	80	12
Bone pain			
subjects affected / exposed	34 / 490 (6.94%)	20 / 488 (4.10%)	0 / 136 (0.00%)
occurrences (all)	39	33	0
Muscle spasms			
subjects affected / exposed	39 / 490 (7.96%)	22 / 488 (4.51%)	8 / 136 (5.88%)
occurrences (all)	53	25	13
Musculoskeletal pain			
subjects affected / exposed	46 / 490 (9.39%)	22 / 488 (4.51%)	10 / 136 (7.35%)
occurrences (all)	58	27	11
Myalgia			
subjects affected / exposed	70 / 490 (14.29%)	20 / 488 (4.10%)	16 / 136 (11.76%)
occurrences (all)	120	31	23
Pain in extremity			
subjects affected / exposed	71 / 490 (14.49%)	61 / 488 (12.50%)	8 / 136 (5.88%)
occurrences (all)	99	84	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	50 / 490 (10.20%)	41 / 488 (8.40%)	14 / 136 (10.29%)
occurrences (all)	78	56	22
Paronychia			

subjects affected / exposed occurrences (all)	2 / 490 (0.41%) 3	59 / 488 (12.09%) 181	0 / 136 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	56 / 490 (11.43%) 92	40 / 488 (8.20%) 49	14 / 136 (10.29%) 22
Urinary tract infection subjects affected / exposed occurrences (all)	52 / 490 (10.61%) 75	21 / 488 (4.30%) 25	0 / 136 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	105 / 490 (21.43%) 149	117 / 488 (23.98%) 170	21 / 136 (15.44%) 26
Dehydration subjects affected / exposed occurrences (all)	9 / 490 (1.84%) 10	25 / 488 (5.12%) 37	0 / 136 (0.00%) 0
Hypokalaemia subjects affected / exposed occurrences (all)	47 / 490 (9.59%) 89	45 / 488 (9.22%) 82	7 / 136 (5.15%) 11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2010	Two interim analyses of the secondary efficacy endpoint OS were specified at the request of the Data Monitoring Committee. No interim analysis of the primary endpoint of PFS was included. The use of echocardiogram (ECHO) rather than multi-gated acquisition (MUGA) scans was recommended for the evaluation of cardiac function because of the anticipated shortage of technetium-99 (Tc99). Bone scans (skeletal X-rays) were included at the screening visit and as part of subsequent tumor assessments.
13 May 2010	All revisions planned for Protocol Amendment 1 were carried forward to Protocol Amendment 2, with the exception of one of the two proposed interim analyses of OS. Based on regulatory feedback, the interim analysis planned after 125 deaths, was considered to be premature and was therefore not included. The definition of PFS was updated per the United States Food and Drug Administration (US FDA) Guidance Documents regarding endpoints for oncology clinical trials to include all deaths, inclusive of deaths that occurred beyond 30 days after the last dose of study treatment.
04 October 2010	Overall survival was changed from a secondary endpoint to a co-primary endpoint to ensure more robust trial results. Further, the sample size was increased from 580 to 980 participants to ensure the study was properly powered to detect a clinically meaningful OS benefit. The number of participants in the pharmacokinetic analysis was increased from 80 to 160 participants. The frequency of the urine pregnancy test for females of childbearing potential was increased to every three cycles because of the study drugs' potential to cause harm to a fetus. The frequency of administration of the FACT-B questionnaire was increased to obtain a more accurate assessment of the changes in symptom burden due to disease progression.
30 May 2012	As per Protocol Amendment 4, eligible participants randomized to the lapatinib plus capecitabine arm could cross over to receive trastuzumab emtansine if a statistically significant OS benefit in favor of trastuzumab emtansine were demonstrated.
22 February 2013	Allowed participants in both treatment arms who developed progression in the brain but demonstrated control of their systemic and visceral disease to continue to receive treatment. Included the possibility of post-trial access to trastuzumab emtansine treatment through an extension study. Updates to safety wording were made in alignment with current recommendations.
08 August 2014	The end of study definition was updated to specify that this will occur when the last participant has completed the Study Drug Completion Visit. Updates to safety wording were made in alignment with current recommendations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported