Clinical trial results:
An Open-Label, Randomized, Multicenter, Phase II, Non Comparative, Exploratory Study on Neoadjuvant Treatment With Trastuzumab Plus Docetaxel Plus Bevacizumab According to Positon Emission Tomography (PET) Value Modification in Patients With Early Stage HER2 Positive Breast Cancer

Summary

EudraCT number	2009-013410-26
Trial protocol	FR
Global end of trial date	13 December 2017

Results information

Result version number	v1 (current)
This version publication date	21 December 2018
First version publication date	21 December 2018

Trial information

Trial identification

Sponsor protocol code	ML22229

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01142778
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2013
Global end of trial reached?	Yes
Global end of trial date	13 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was an open-label, randomized, multicenter, phase II, non comparative, exploratory study to assess the effect of adding bevacizumab to trastuzumab plus docetaxel in neoadjuvant therapy in participants with early stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The main objective was to assess the complete pathological response rates (evaluation according to Chevallier's criteria, review by an independent Committee) in patients with a relative change in [18F]-FDG tumoral uptake < 70% and randomized in the arm with trastuzumab plus docetaxel plus bevacizumab.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 152
Worldwide total number of subjects	152
EEA total number of subjects	152

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)	139

From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

152 subjects met the inclusion criteria and were enrolled into the study. All participants received 2 cycles of trastuzumab and docetaxel once every 3 weeks. 142 participants were randomized or assigned to a treatment arm. 10 subjects were not allocated or randomized to a treatment arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab, Docetaxel, and Bevacizumab

Arm description:

Participants with a response of <70% will receive trastuzumab and docetaxel along with bevacizumab in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the bevacizumab infusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

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

Dosage and administration details:

Bevacizumab at a dose of 15 mg/kg will be administered as IV infusion over 90 minutes from Cycles 3-6 (1 Cycle=21 days).

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

Dosage and administration details:

Trastuzumab will be administered as a loading dose of 8 mg/kg as IV infusion in Cycle 1, then administered as a dose of 6 mg/kg as IV infusion in Cycles 2 to 7, and during additional 11 cycles post surgery (1 Cycle=21 days).

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

Dosage and administration details:

Docetaxel at a dose of 100 mg/m^2 will be administered as IV infusion from Cycles 1-6 (1 Cycle=21 days).

Arm title	Trastuzumab and Docetaxel

Arm description:

Participants with a response of <70% will receive trastuzumab and docetaxel in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the study treatment perfusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel at a dose of 100 mg/m^2 will be administered as IV infusion from Cycles 1-6 (1 Cycle=21 days).

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

Dosage and administration details:

Trastuzumab will be administered as a loading dose of 8 mg/kg as IV infusion in Cycle 1, then administered as a dose of 6 mg/kg as IV infusion in Cycles 2 to 7, and during additional 11 cycles post surgery (1 Cycle=21 days).

Arm title	Trastuzumab and Docetaxel (Standard Regimen)

Arm description:

Participants with a response of >/=70% will receive trastuzumab and docetaxel in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the study treatment perfusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel at a dose of 100 mg/m^2 will be administered as IV infusion from Cycles 1-6 (1 Cycle=21 days).

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

Dosage and administration details:

Trastuzumab will be administered as a loading dose of 8 mg/kg as IV infusion in Cycle 1, then administered as a dose of 6 mg/kg as IV infusion in Cycles 2 to 7, and during additional 11 cycles post surgery (1 Cycle=21 days).

Arm title	Not allocated or randomized

Arm description:

Participants will receive 2 cycles of trastuzumab and docetaxel once every 3 weeks prior to assignment to a treatment arm.

Arm type	Prior to randomization

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

Dosage and administration details:

Docetaxel at a dose of 100 mg/m^2 will be administered as IV infusion in Cycles 1 and 2 (1 Cycle=21 days).

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

Dosage and administration details:

Trastuzumab will be administered as a loading dose of 8 mg/kg as IV infusion in Cycle 1, followed by subsequent dose of 6 mg/kg as IV infusion in Cycle 2 (1 Cycle=21 days).

Number of subjects in period 1	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)
Started	48	25	69
Completed	38	22	61
Not completed	10	3	8
Consent withdrawn by subject	5	-	1
Adverse event, non-fatal	-	-	-
Death	2	1	-
Lost to follow-up	1	-	1
Multiple reasons	1	2	4
Missing data	-	-	1
Protocol deviation	1	-	1

Number of subjects in period 1	Not allocated or randomized
Started	10
Completed	4
Not completed	6
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Death	-
Lost to follow-up	-
Multiple reasons	4
Missing data	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab, Docetaxel, and Bevacizumab
Reporting group description:	
Participants with a response of <70% will receive trastuzumab and docetaxel along with bevacizumab in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the bevacizumab infusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.	
Reporting group title	Trastuzumab and Docetaxel
Reporting group description:	
Participants with a response of <70% will receive trastuzumab and docetaxel in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the study treatment perfusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.	
Reporting group title	Trastuzumab and Docetaxel (Standard Regimen)
Reporting group description:	
Participants with a response of >/=70% will receive trastuzumab and docetaxel in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the study treatment perfusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.	
Reporting group title	Not allocated or randomized
Reporting group description:	
Participants will receive 2 cycles of trastuzumab and docetaxel once every 3 weeks prior to assignment to a treatment arm.	

Reporting group values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)
Number of subjects	48	25	69
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	45	24	62
From 65-84 years	3	1	7
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	50.4	47.8	49.5
standard deviation	± 11.1	± 8.9	± 10.7
Gender categorical Units: Subjects			
Female	48	25	69

Male	0	0	0

Reporting group values	Not allocated or randomized	Total	
Number of subjects	10	152	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	139	
From 65-84 years	2	13	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.9		
standard deviation	± 14.0	-	
Gender categorical Units: Subjects			
Female	10	152	
Male	0	0	

End points

End points reporting groups

Reporting group title	Trastuzumab, Docetaxel, and Bevacizumab

Reporting group description:

Participants with a response of <70% will receive trastuzumab and docetaxel along with bevacizumab in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the bevacizumab infusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

Reporting group title	Trastuzumab and Docetaxel

Reporting group description:

Participants with a response of <70% will receive trastuzumab and docetaxel in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the study treatment perfusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

Reporting group title	Trastuzumab and Docetaxel (Standard Regimen)

Reporting group description:

Participants with a response of >/=70% will receive trastuzumab and docetaxel in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the study treatment perfusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

Reporting group title	Not allocated or randomized

Reporting group description:

Participants will receive 2 cycles of trastuzumab and docetaxel once every 3 weeks prior to assignment to a treatment arm.

Primary: Percentage of Participants With Pathological Complete Response (pCR) in the Trastuzumab, Docetaxel, and Bevacizumab Treatment Arm as per Chevallier's Classification as Reviewed by an Independent Committee

End point title	Percentage of Participants With Pathological Complete Response (pCR) in the Trastuzumab, Docetaxel, and Bevacizumab Treatment Arm as per Chevallier's Classification as Reviewed by an Independent Committee[1][2]

End point description:

Pathological Complete Response (pCR) was assessed in surgical specimens of mammary tissue and lymph nodes of participants in the Trastuzumab, Docetaxel, and Bevacizumab Treatment Arm according to Chevallier's classification and reviewed by an independent committee. The Chevallier's classification for grading of therapeutic effect related to the tumor site and lymph nodes was defined by microscopic changes as follows - Grade 1: Disappearance of all tumors either in the breast or in the nodes, Grade 2: Persistence of carcinoma in situ in the breast only and no nodal invasion, Grade 3: Presence of invasive carcinoma with stromal alteration, Grade 4: Presence of invasive carcinoma without modification. Grade 1 and Grade 2 response were considered as pCR. Results are presented for the Intent to treat (ITT) population, which is described as all participants that were assigned to a treatment group according to change in Standard uptake value (SUV).

End point type	Primary

End point timeframe:

After 6 cycles (18 weeks) of neoadjuvant therapy (cycle length=21 days)

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: No statistical analyses were planned for the primary end point.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: percentage of participants				
number (confidence interval 90%)				
Missing data considered as "failure"	43.8 (31.5 to 56.6)			
Sensitivity analysis excluding missing values	51.2 (37.4 to 64.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pathological Complete Response According to Chevallier's Classification as per Local Procedures

End point title	Percentage of Participants With Pathological Complete Response According to Chevallier's Classification as per Local Procedures[3]

End point description:

PCR was assessed in surgical specimens of mammary tissue and lymph nodes according to Chevallier's classification and reviewed according to local procedures. The Chevallier's classification for grading of therapeutic effect related to the tumor site and lymph nodes was defined by microscopic changes as follows - Grade 1: Disappearance of all tumors either in the breast or in the nodes, Grade 2: Persistence of carcinoma in situ in the breast only and no nodal invasion, Grade 3: Presence of invasive carcinoma with stromal alteration, Grade 4: Presence of invasive carcinoma without modification. Grade 1 and Grade 2 response were considered as pCR. Results are presented for the ITT population, which is described as all participants that were assigned to a treatment group according to change in SUV.

End point type	Secondary

End point timeframe:

After 6 cycles (18 weeks) of neoadjuvant therapy (cycle length=21 days)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: percentage of participants				
number (confidence interval 95%)				
Missing data considered as "failure"	50.0 (35.2 to 64.8)	36.0 (18.0 to 57.5)	62.3 (49.8 to 73.7)	
Sensitivity analysis excluding missing values	57.1 (41.0 to 72.3)	37.5 (18.8 to 59.4)	65.2 (52.4 to 76.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pathological Complete Response (pCR) as per Chevallier’s Classification as Reviewed by an Independent Committee

End point title	Percentage of Participants With Pathological Complete Response (pCR) as per Chevallier’s Classification as Reviewed by an Independent Committee[4]

End point description:

Pathological Complete Response (pCR) was assessed in surgical specimens of mammary tissue and lymph nodes according to Chevallier's classification and reviewed by an independent committee. The Chevallier's classification for grading of therapeutic effect related to the tumor site and lymph nodes was defined by microscopic changes as follows - Grade 1: Disappearance of all tumors either in the breast or in the nodes, Grade 2: Persistence of carcinoma in situ in the breast only and no nodal invasion, Grade 3: Presence of invasive carcinoma with stromal alteration, Grade 4: Presence of invasive carcinoma without modification. Grade 1 and Grade 2 response were considered as pCR. Results are presented for the Intent to treat (ITT) population, which is described as all participants that were assigned to a treatment group according to change in Standard uptake value (SUV).

End point type	Secondary

End point timeframe:

After 6 cycles (18 weeks) of neoadjuvant therapy (cycle length=21 days)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: percentage of participants				
number (confidence interval 95%)				
Missing data considered as “failure”	43.8 (29.5 to 58.8)	24.0 (9.4 to 45.1)	53.6 (41.2 to 65.7)	
Sensitivity analysis excluding missing values	51.2 (35.1 to 67.1)	25.0 (9.8 to 46.7)	56.1 (43.3 to 68.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Pathological Complete Response According to Sataloff's Classification as Reviewed by an Independent Committee

End point title	Percentage of Participants With Pathological Complete Response According to Sataloff's Classification as Reviewed by

	an Independent Committee[5]

End point description:

PCR was assessed in surgical specimens of mammary tissue and lymph nodes according to Sataloff classification and reviewed by an independent committee. Pathological response was defined based on the therapeutic response at the tumor site and lymph nodes. Tumor response criteria were as follows: T-A (Total / near total therapeutic effect), T-B (Subjectively greater than [>] 50 percent [%] therapeutic effect but less than [<] T-A), T-C (<50% therapeutic effect, but effect evident), T-D (No therapeutic effect). Lymph node response: N-A (Evidence of therapeutic effect, no metastases), N-B (No therapeutic effect, no nodal metastases), N-C (Nodal metastasis but evident therapeutic effect), N-D (Nodal metastasis with no therapeutic effect). T-A and N-A or T-A and N-B responses were defined as PCR. Results are presented for the ITT population, which is described as all participants that were assigned to a treatment group according to change in SUV.

End point type	Secondary

End point timeframe:

After 6 cycles (18 weeks) of neoadjuvant therapy (cycle length=21 days)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: percentage of participants				
number (confidence interval 95%)				
Missing data considered as "failure"	50.0 (35.2 to 64.8)	28.0 (12.1 to 49.4)	65.2 (52.8 to 76.3)	
Sensitivity analysis excluding missing values	58.5 (42.1 to 73.7)	30.4 (13.2 to 52.9)	68.2 (55.6 to 79.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Ultrasound Response According to Modified Response Evaluation Criteria in Solid Tumors (RECIST)

End point title	Percentage of Participants With Ultrasound Response According to Modified Response Evaluation Criteria in Solid Tumors (RECIST)[6]

End point description:

A complete Ultrasound Response (UR) was defined as the disappearance of all measurable and assessable disease (based on RECIST criteria) with no lesion. A complete UR was considered if the largest diameter is equal to 0, during the tumoral evaluation at Cycles 3, 6 or 7, by cycle.

End point type	Secondary

End point timeframe:

Neodajuvant treatment period (21 weeks)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: percentage of participants				
number (not applicable)				
Cycle 3	21.2	21.1	34.2	
Cycle 6	72.0	50.0	81.6	
Cycle 7	29.4	15.0	37.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Conservative Surgery Post Neoadjuvant Treatment

End point title	Percentage of Participants With Conservative Surgery Post Neoadjuvant Treatment[7]

End point description:

Results were presented for the ITT population, which were described as all participants that were assigned to a treatment group according to change in SUV.

End point type	Secondary

End point timeframe:

Week 20 (between Day 28 and Day 35 after the Cycle 6, cycle length=21 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: percentage of participants				
number (confidence interval 95%)				
Missing data considered as "failure"	60.4 (45.3 to 74.2)	60.0 (38.7 to 78.9)	81.2 (69.9 to 89.6)	
Sensitivity analysis excluding missing values	67.4 (51.5 to 80.9)	62.5 (40.6 to 81.2)	84.8 (73.9 to 92.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Local Relapse-Free Interval (LRFI) According to Modified RECIST Criteria

End point title	Local Relapse-Free Interval (LRFI) According to Modified RECIST Criteria[8]

End point description:

LRFI was defined as time to local recurrence following first administration of neoadjuvant treatment, local recurrence in the ipsilateral or controlateral breast following lumpectomy. Probability to have LRFI at Month 12, Month 36 and Month 60 was estimated.

End point type	Secondary

End point timeframe:

From baseline to occurrence of relapse/disease or death of any cause (up to 5 years)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: probability of events				
number (confidence interval 95%)				
Month 12	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	
Month 36	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	
Month 60	0.024 (0.003 to 0.161)	0.091 (0.024 to 0.317)	0.052 (0.017 to 0.154)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS) According to Modified RECIST Criteria

End point title	Disease-Free Survival (DFS) According to Modified RECIST Criteria[9]

End point description:

DFS was defined as the time from first administration of neoadjuvant treatment to local recurrence, local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, occurrence of distant metastases, controlateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause. Probability to have DFS at Month 12, Month 36 and Month 60 was estimated.

End point type	Secondary

End point timeframe:

From baseline to occurrence of relapse/disease or death of any cause (up to 5 years)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: probability of events				
number (confidence interval 95%)				
Month 12	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	0.030 (0.007 to 0.113)	
Month 36	0.000 (0.000 to 0.000)	0.080 (0.021 to 0.284)	0.045 (0.015 to 0.133)	
Month 60	0.098 (0.038 to 0.241)	0.240 (0.116 to 0.458)	0.095 (0.044 to 0.200)	

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Disease-Free Interval (DDFI) According to Modified RECIST Criteria

End point title	Distant Disease-Free Interval (DDFI) According to Modified RECIST Criteria[10]

End point description:

DDFI was defined as time to distant recurrence following first administration of neoadjuvant treatment. The probability to have DDFI at Month 12, Month 36 and Month 60 following first administration of neoadjuvant treatment was estimated.

End point type	Secondary

End point timeframe:

From baseline to occurrence of relapse/disease or death of any cause (up to 5 years)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: probability of events				
number (confidence interval 95%)				
Month 12	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	0.030 (0.007 to 0.113)	
Month 36	0.000 (0.000 to 0.000)	0.040 (0.006 to 0.252)	0.045 (0.015 to 0.133)	
Month 60	0.000 (0.000 to 0.000)	0.131 (0.044 to 0.355)	0.045 (0.015 to 0.133)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[11]

End point description:

OS was defined as time from first administration of study treatment to death from any cause. The probability of dying at Month 12, Month 36 and Month 60 after first administration of study treatment was estimated.

End point type	Secondary

End point timeframe:

Baseline up to occurrence of death (up to 5 years)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary analysis only included participants in the ITT population.

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	25	69	
Units: probability of events				
number (confidence interval 95%)				
Month 12	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	
Month 36	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	0.000 (0.000 to 0.000)	
Month 60	0.049 (0.013 to 0.183)	0.042 (0.006 to 0.261)	0.000 (0.000 to 0.000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events

End point description:

Analysis of safety was performed on the Safety population (SAF), which included all participants who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline up to 5 years

End point values	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)	Not allocated or randomized
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	25	69	10
Units: percentage of participants				
number (not applicable)	100	100	98.6	70.0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to the data cut-off of 13 December 2017 (up to approximately 7.5 years)

Adverse event reporting additional description:

Serious adverse events (SAEs) causality was only evaluated for bevacizumab in the Trastuzumab, Docetaxel, and Bevacizumab arm.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Trastuzumab, Docetaxel, and Bevacizumab

Reporting group description:

Participants with a response of <70% will receive trastuzumab and docetaxel along with bevacizumab in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the bevacizumab infusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

Reporting group title	Trastuzumab and Docetaxel

Reporting group description:

Participants with a response of <70% will receive trastuzumab and docetaxel in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the study treatment perfusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

Reporting group title	Trastuzumab and Docetaxel (Standard Regimen)

Reporting group description:

Participants with a response of >/=70% will receive trastuzumab and docetaxel in Cycles 3 to 6. All participants will receive trastuzumab alone in Cycle 7, and will undergo surgery after Cycle 7 and between 4 and 6 weeks after the study treatment perfusion in Cycle 6. After surgery, all participants will receive a further 11 cycles of trastuzumab plus radiotherapy with or without hormonal therapy as per site's standard practice, and will be followed for up to 5 years from start of neoadjuvant treatment.

Reporting group title	Not allocated or randomized

Reporting group description:

Participants will receive 2 cycles of trastuzumab and docetaxel once every 3 weeks prior to assignment to a treatment arm.

Serious adverse events	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 48 (39.58%)	6 / 25 (24.00%)	18 / 69 (26.09%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Lymphocele			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Phlebitis deep			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Breast operation			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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 prosthesis removal			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	0 / 69 (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
Salpingo-oophorectomy bilateral			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	0 / 69 (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
Pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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			
Pulmonary embolism			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Bronchogenic cyst			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
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			
Arrhythmia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neuralgia			

subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Loss of consciousness			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 48 (6.25%)	2 / 25 (8.00%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	4 / 69 (5.80%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	3 / 48 (6.25%)	0 / 25 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agranulocytosis			

subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Anaemia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	0 / 69 (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
Vomiting			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibromyalgia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	3 / 48 (6.25%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Lung infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Mycoplasma infection			

subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Pelvic abscess			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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
Pharyngitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 69 (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 / 48 (0.00%)	1 / 25 (4.00%)	0 / 69 (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
Sepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Not allocated or		

	randomized		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphocele			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Phlebitis deep			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Breast operation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast prosthesis removal			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Salpingo-oophorectomy bilateral			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Impaired healing			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Bronchogenic cyst			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Agranulocytosis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholelithiasis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibromyalgia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Postoperative wound infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridial infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Localised infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mycoplasma infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis syndrome				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Trastuzumab, Docetaxel, and Bevacizumab	Trastuzumab and Docetaxel	Trastuzumab and Docetaxel (Standard Regimen)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 48 (100.00%)	25 / 25 (100.00%)	68 / 69 (98.55%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	0 / 48 (0.00%)	2 / 25 (8.00%)	0 / 69 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Hot flush			
subjects affected / exposed	13 / 48 (27.08%)	16 / 25 (64.00%)	35 / 69 (50.72%)
occurrences (all)	18	18	38
Lymphocele			
subjects affected / exposed	10 / 48 (20.83%)	9 / 25 (36.00%)	15 / 69 (21.74%)
occurrences (all)	11	9	15
Lymphoedema			
subjects affected / exposed	9 / 48 (18.75%)	5 / 25 (20.00%)	10 / 69 (14.49%)
occurrences (all)	9	5	10
Hypertension			
subjects affected / exposed	7 / 48 (14.58%)	2 / 25 (8.00%)	3 / 69 (4.35%)
occurrences (all)	7	2	3
Hypotension			
subjects affected / exposed	1 / 48 (2.08%)	2 / 25 (8.00%)	2 / 69 (2.90%)
occurrences (all)	1	2	2
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	35 / 48 (72.92%)	21 / 25 (84.00%)	51 / 69 (73.91%)
occurrences (all)	57	35	75
Mucosal inflammation			
subjects affected / exposed	23 / 48 (47.92%)	8 / 25 (32.00%)	30 / 69 (43.48%)
occurrences (all)	29	8	42
Pyrexia			
subjects affected / exposed	15 / 48 (31.25%)	7 / 25 (28.00%)	20 / 69 (28.99%)
occurrences (all)	21	14	24
Oedema peripheral			
subjects affected / exposed	13 / 48 (27.08%)	10 / 25 (40.00%)	28 / 69 (40.58%)
occurrences (all)	18	11	30
Fatigue			
subjects affected / exposed	10 / 48 (20.83%)	3 / 25 (12.00%)	10 / 69 (14.49%)
occurrences (all)	18	5	15
Pain			
subjects affected / exposed	7 / 48 (14.58%)	0 / 25 (0.00%)	7 / 69 (10.14%)
occurrences (all)	8	0	11
Oedema			
subjects affected / exposed	3 / 48 (6.25%)	3 / 25 (12.00%)	9 / 69 (13.04%)
occurrences (all)	3	3	9
Axillary pain			
subjects affected / exposed	1 / 48 (2.08%)	5 / 25 (20.00%)	2 / 69 (2.90%)
occurrences (all)	1	5	2
Chest Pain			
subjects affected / exposed	2 / 48 (4.17%)	2 / 25 (8.00%)	2 / 69 (2.90%)
occurrences (all)	2	2	2
Inflammation			
subjects affected / exposed	1 / 48 (2.08%)	2 / 25 (8.00%)	0 / 69 (0.00%)
occurrences (all)	1	4	0
Impaired healing			
subjects affected / exposed	3 / 48 (6.25%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences (all)	3	0	0
Generalised oedema			

subjects affected / exposed	0 / 48 (0.00%)	2 / 25 (8.00%)	0 / 69 (0.00%)
occurrences (all)	0	2	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	10 / 48 (20.83%)	9 / 25 (36.00%)	22 / 69 (31.88%)
occurrences (all)	10	9	22
Breast pain			
subjects affected / exposed	7 / 48 (14.58%)	1 / 25 (4.00%)	5 / 69 (7.25%)
occurrences (all)	9	1	7
Vulvovaginal dryness			
subjects affected / exposed	4 / 48 (8.33%)	5 / 25 (20.00%)	4 / 69 (5.80%)
occurrences (all)	4	6	4
Breast oedema			
subjects affected / exposed	2 / 48 (4.17%)	2 / 25 (8.00%)	6 / 69 (8.70%)
occurrences (all)	2	2	6
Metrorrhagia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 25 (8.00%)	3 / 69 (4.35%)
occurrences (all)	2	2	3
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	27 / 48 (56.25%)	3 / 25 (12.00%)	18 / 69 (26.09%)
occurrences (all)	49	5	23
Cough			
subjects affected / exposed	9 / 48 (18.75%)	3 / 25 (12.00%)	14 / 69 (20.29%)
occurrences (all)	10	4	17
Dyspnoea			
subjects affected / exposed	9 / 48 (18.75%)	7 / 25 (28.00%)	5 / 69 (7.25%)
occurrences (all)	11	7	5
Dyspnoea exertional			
subjects affected / exposed	7 / 48 (14.58%)	3 / 25 (12.00%)	12 / 69 (17.39%)
occurrences (all)	7	3	13
Rhinorrhoea			

subjects affected / exposed	7 / 48 (14.58%)	4 / 25 (16.00%)	5 / 69 (7.25%)
occurrences (all)	8	5	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 48 (16.67%)	3 / 25 (12.00%)	13 / 69 (18.84%)
occurrences (all)	8	4	13
Anxiety			
subjects affected / exposed	8 / 48 (16.67%)	2 / 25 (8.00%)	7 / 69 (10.14%)
occurrences (all)	8	2	7
Depression			
subjects affected / exposed	4 / 48 (8.33%)	1 / 25 (4.00%)	4 / 69 (5.80%)
occurrences (all)	4	1	4
Sleep disorder			
subjects affected / exposed	3 / 48 (6.25%)	2 / 25 (8.00%)	4 / 69 (5.80%)
occurrences (all)	3	2	4
Investigations			
Weight increased			
subjects affected / exposed	3 / 48 (6.25%)	2 / 25 (8.00%)	11 / 69 (15.94%)
occurrences (all)	3	2	11
Weight decreased			
subjects affected / exposed	3 / 48 (6.25%)	0 / 25 (0.00%)	3 / 69 (4.35%)
occurrences (all)	5	0	3
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	24 / 48 (50.00%)	19 / 25 (76.00%)	47 / 69 (68.12%)
occurrences (all)	25	19	51
Procedural pain			
subjects affected / exposed	1 / 48 (2.08%)	3 / 25 (12.00%)	1 / 69 (1.45%)
occurrences (all)	1	3	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 48 (2.08%)	2 / 25 (8.00%)	4 / 69 (5.80%)
occurrences (all)	1	4	4
Ventricular arrhythmia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Dysgeusia			
subjects affected / exposed	16 / 48 (33.33%)	9 / 25 (36.00%)	25 / 69 (36.23%)
occurrences (all)	18	15	28
Neuropathy peripheral			
subjects affected / exposed	13 / 48 (27.08%)	8 / 25 (32.00%)	25 / 69 (36.23%)
occurrences (all)	14	10	26
Paraesthesia			
subjects affected / exposed	6 / 48 (12.50%)	10 / 25 (40.00%)	11 / 69 (15.94%)
occurrences (all)	9	14	13
Headache			
subjects affected / exposed	12 / 48 (25.00%)	3 / 25 (12.00%)	10 / 69 (14.49%)
occurrences (all)	14	5	12
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 48 (12.50%)	4 / 25 (16.00%)	5 / 69 (7.25%)
occurrences (all)	6	4	7
Hypoaesthesia			
subjects affected / exposed	4 / 48 (8.33%)	3 / 25 (12.00%)	2 / 69 (2.90%)
occurrences (all)	4	4	2
Neuralgia			
subjects affected / exposed	2 / 48 (4.17%)	2 / 25 (8.00%)	5 / 69 (7.25%)
occurrences (all)	2	2	5
Ageusia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	5 / 69 (7.25%)
occurrences (all)	2	0	5
Dysaesthesia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	4 / 69 (5.80%)
occurrences (all)	1	0	4
Sciatica			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	2 / 69 (2.90%)
occurrences (all)	2	0	2
Presyncope			
subjects affected / exposed	0 / 48 (0.00%)	1 / 25 (4.00%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			

subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	8 / 48 (16.67%)	3 / 25 (12.00%)	11 / 69 (15.94%)
occurrences (all)	15	9	16
Anaemia			
subjects affected / exposed	7 / 48 (14.58%)	7 / 25 (28.00%)	12 / 69 (17.39%)
occurrences (all)	7	9	12
Febrile neutropenia			
subjects affected / exposed	5 / 48 (10.42%)	3 / 25 (12.00%)	12 / 69 (17.39%)
occurrences (all)	5	3	12
Leukopenia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	7 / 69 (10.14%)
occurrences (all)	0	0	11
Febrile bone marrow aplasia			
subjects affected / exposed	3 / 48 (6.25%)	1 / 25 (4.00%)	1 / 69 (1.45%)
occurrences (all)	4	1	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 48 (8.33%)	1 / 25 (4.00%)	2 / 69 (2.90%)
occurrences (all)	4	1	3
Eye disorders			
Lacrimation increased			
subjects affected / exposed	17 / 48 (35.42%)	13 / 25 (52.00%)	29 / 69 (42.03%)
occurrences (all)	18	14	32
Conjunctivitis			
subjects affected / exposed	7 / 48 (14.58%)	3 / 25 (12.00%)	10 / 69 (14.49%)
occurrences (all)	9	3	11
Dry eye			
subjects affected / exposed	3 / 48 (6.25%)	1 / 25 (4.00%)	4 / 69 (5.80%)
occurrences (all)	3	1	4
Eyelid oedema			
subjects affected / exposed	0 / 48 (0.00%)	2 / 25 (8.00%)	0 / 69 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			

Diarrhoea			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	27 / 48 (56.25%)	14 / 25 (56.00%)	32 / 69 (46.38%)
occurrences (all)	57	26	58
Nausea			
subjects affected / exposed	24 / 48 (50.00%)	11 / 25 (44.00%)	23 / 69 (33.33%)
occurrences (all)	57	17	31
Constipation			
subjects affected / exposed	22 / 48 (45.83%)	5 / 25 (20.00%)	23 / 69 (33.33%)
occurrences (all)	30	6	29
Vomiting			
subjects affected / exposed	10 / 48 (20.83%)	5 / 25 (20.00%)	6 / 69 (8.70%)
occurrences (all)	19	7	6
Abdominal pain upper			
subjects affected / exposed	9 / 48 (18.75%)	5 / 25 (20.00%)	10 / 69 (14.49%)
occurrences (all)	10	5	15
Abdominal pain			
subjects affected / exposed	7 / 48 (14.58%)	2 / 25 (8.00%)	13 / 69 (18.84%)
occurrences (all)	9	2	14
Dyspepsia			
subjects affected / exposed	5 / 48 (10.42%)	2 / 25 (8.00%)	10 / 69 (14.49%)
occurrences (all)	6	2	15
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 48 (10.42%)	3 / 25 (12.00%)	7 / 69 (10.14%)
occurrences (all)	7	6	8
Haemorrhoids			
subjects affected / exposed	10 / 48 (20.83%)	1 / 25 (4.00%)	9 / 69 (13.04%)
occurrences (all)	10	1	10
Dysphagia			
subjects affected / exposed	6 / 48 (12.50%)	2 / 25 (8.00%)	1 / 69 (1.45%)
occurrences (all)	10	3	1
Dry mouth			
subjects affected / exposed	6 / 48 (12.50%)	0 / 25 (0.00%)	6 / 69 (8.70%)
occurrences (all)	6	0	7
Aphthous stomatitis			

subjects affected / exposed	1 / 48 (2.08%)	4 / 25 (16.00%)	3 / 69 (4.35%)
occurrences (all)	1	5	4
Stomatitis			
subjects affected / exposed	3 / 48 (6.25%)	0 / 25 (0.00%)	6 / 69 (8.70%)
occurrences (all)	3	0	7
Gingivitis			
subjects affected / exposed	4 / 48 (8.33%)	1 / 25 (4.00%)	1 / 69 (1.45%)
occurrences (all)	5	2	1
Oesophagitis			
subjects affected / exposed	4 / 48 (8.33%)	0 / 25 (0.00%)	3 / 69 (4.35%)
occurrences (all)	5	0	3
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 48 (2.08%)	2 / 25 (8.00%)	0 / 69 (0.00%)
occurrences (all)	3	3	0
Anal fissure			
subjects affected / exposed	3 / 48 (6.25%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences (all)	4	0	1
Gingival bleeding			
subjects affected / exposed	5 / 48 (10.42%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences (all)	5	0	0
Abdominal rigidity			
subjects affected / exposed	1 / 48 (2.08%)	2 / 25 (8.00%)	1 / 69 (1.45%)
occurrences (all)	1	2	1
Abdominal pain lower			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	37 / 48 (77.08%)	21 / 25 (84.00%)	46 / 69 (66.67%)
occurrences (all)	37	21	47
Rash			
subjects affected / exposed	12 / 48 (25.00%)	8 / 25 (32.00%)	12 / 69 (17.39%)
occurrences (all)	19	12	17
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	12 / 48 (25.00%)	6 / 25 (24.00%)	11 / 69 (15.94%)
occurrences (all)	15	12	16
Nail toxicity			
subjects affected / exposed	12 / 48 (25.00%)	7 / 25 (28.00%)	20 / 69 (28.99%)
occurrences (all)	12	9	21
Dry skin			
subjects affected / exposed	9 / 48 (18.75%)	7 / 25 (28.00%)	13 / 69 (18.84%)
occurrences (all)	10	7	16
Erythema			
subjects affected / exposed	5 / 48 (10.42%)	4 / 25 (16.00%)	18 / 69 (26.09%)
occurrences (all)	6	5	20
Pruritus			
subjects affected / exposed	5 / 48 (10.42%)	4 / 25 (16.00%)	11 / 69 (15.94%)
occurrences (all)	6	4	14
Nail disorder			
subjects affected / exposed	6 / 48 (12.50%)	4 / 25 (16.00%)	9 / 69 (13.04%)
occurrences (all)	6	5	10
Onycholysis			
subjects affected / exposed	6 / 48 (12.50%)	1 / 25 (4.00%)	8 / 69 (11.59%)
occurrences (all)	6	1	8
Skin toxicity			
subjects affected / exposed	2 / 48 (4.17%)	3 / 25 (12.00%)	6 / 69 (8.70%)
occurrences (all)	2	4	7
Eczema			
subjects affected / exposed	5 / 48 (10.42%)	3 / 25 (12.00%)	0 / 69 (0.00%)
occurrences (all)	5	4	0
Dermatitis acneiform			
subjects affected / exposed	0 / 48 (0.00%)	2 / 25 (8.00%)	5 / 69 (7.25%)
occurrences (all)	0	2	5
Rash pruritic			
subjects affected / exposed	4 / 48 (8.33%)	1 / 25 (4.00%)	2 / 69 (2.90%)
occurrences (all)	4	1	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 48 (2.08%)	2 / 25 (8.00%)	3 / 69 (4.35%)
occurrences (all)	1	2	3

Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	24 / 48 (50.00%)	17 / 25 (68.00%)	48 / 69 (69.57%)
occurrences (all)	40	29	74
Arthralgia			
subjects affected / exposed	19 / 48 (39.58%)	12 / 25 (48.00%)	32 / 69 (46.38%)
occurrences (all)	19	22	45
Musculoskeletal pain			
subjects affected / exposed	11 / 48 (22.92%)	8 / 25 (32.00%)	12 / 69 (17.39%)
occurrences (all)	21	9	13
Pain in extremity			
subjects affected / exposed	13 / 48 (27.08%)	2 / 25 (8.00%)	6 / 69 (8.70%)
occurrences (all)	15	2	9
Bone pain			
subjects affected / exposed	6 / 48 (12.50%)	3 / 25 (12.00%)	4 / 69 (5.80%)
occurrences (all)	8	3	6
Back pain			
subjects affected / exposed	7 / 48 (14.58%)	3 / 25 (12.00%)	6 / 69 (8.70%)
occurrences (all)	7	3	7
Muscle spasms			
subjects affected / exposed	1 / 48 (2.08%)	1 / 25 (4.00%)	7 / 69 (10.14%)
occurrences (all)	1	2	9
Musculoskeletal stiffness			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	4 / 69 (5.80%)
occurrences (all)	2	0	4
Joint stiffness			
subjects affected / exposed	0 / 48 (0.00%)	3 / 25 (12.00%)	2 / 69 (2.90%)
occurrences (all)	0	3	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 48 (22.92%)	2 / 25 (8.00%)	10 / 69 (14.49%)
occurrences (all)	16	4	12
Tonsillitis			
subjects affected / exposed	4 / 48 (8.33%)	1 / 25 (4.00%)	6 / 69 (8.70%)
occurrences (all)	4	1	14
Urinary tract infection			

subjects affected / exposed	7 / 48 (14.58%)	3 / 25 (12.00%)	3 / 69 (4.35%)
occurrences (all)	7	5	3
Rhinitis			
subjects affected / exposed	3 / 48 (6.25%)	3 / 25 (12.00%)	7 / 69 (10.14%)
occurrences (all)	3	4	8
Bronchitis			
subjects affected / exposed	3 / 48 (6.25%)	3 / 25 (12.00%)	4 / 69 (5.80%)
occurrences (all)	3	4	4
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 48 (4.17%)	2 / 25 (8.00%)	6 / 69 (8.70%)
occurrences (all)	2	2	6
Cystitis			
subjects affected / exposed	4 / 48 (8.33%)	0 / 25 (0.00%)	4 / 69 (5.80%)
occurrences (all)	4	0	5
Pharyngitis			
subjects affected / exposed	3 / 48 (6.25%)	2 / 25 (8.00%)	3 / 69 (4.35%)
occurrences (all)	3	2	3
Influenza			
subjects affected / exposed	2 / 48 (4.17%)	3 / 25 (12.00%)	1 / 69 (1.45%)
occurrences (all)	2	3	1
Tracheitis			
subjects affected / exposed	1 / 48 (2.08%)	3 / 25 (12.00%)	2 / 69 (2.90%)
occurrences (all)	1	3	2
Paronychia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	4 / 69 (5.80%)
occurrences (all)	1	0	4
Sinusitis			
subjects affected / exposed	1 / 48 (2.08%)	2 / 25 (8.00%)	1 / 69 (1.45%)
occurrences (all)	1	2	1
Respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 48 (29.17%)	3 / 25 (12.00%)	12 / 69 (17.39%)
occurrences (all)	25	4	18

Fluid retention			
subjects affected / exposed	1 / 48 (2.08%)	2 / 25 (8.00%)	5 / 69 (7.25%)
occurrences (all)	1	2	5

Non-serious adverse events	Not allocated or randomized		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Lymphocele			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Lymphoedema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Pyrexia			

subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Axillary pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Chest Pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Inflammation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Impaired healing			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Generalised oedema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Amenorrhoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Breast pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Vulvovaginal dryness subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Breast oedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Metrorrhagia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Cough subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Dyspnoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Anxiety			

subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		
Investigations Weight increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		
Injury, poisoning and procedural complications Radiation skin injury subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all) Ventricular arrhythmia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 1 / 10 (10.00%) 1		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 0 / 10 (0.00%) 0		

Paraesthesia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Ageusia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dysaesthesia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Anaemia			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Febrile neutropenia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

Constipation				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Vomiting				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Abdominal pain upper				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Abdominal pain				
subjects affected / exposed	2 / 10 (20.00%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Haemorrhoids				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Dysphagia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Dry mouth				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Aphthous stomatitis				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Gingivitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			

Oesophagitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gastrointestinal motility disorder			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Anal fissure			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gingival bleeding			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Abdominal rigidity			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Abdominal pain lower			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nail toxicity			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Erythema			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nail disorder			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Onycholysis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Skin toxicity			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dermatitis acneiform			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Musculoskeletal pain			

subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Joint stiffness			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Cystitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Pharyngitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Tracheitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Paronychia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Sinusitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Fluid retention subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2010	Modified the clinical trial method from comparative phase II to non comparative phase II, Modified the trastuzumab administration during the neo=adjuvant treatment (discontinuation during the 4 weeks of the surgery period to no discontinuation of the treatment), Added a secondary endpoint - pathological complete response rate evaluated post-surgery, and Censored the survival analyses at the date of last assessment without event.
09 November 2010	Modified the samples calendar in the angiogenesis biomarkers study which led to an increase in the number of additional blood samples for participants.
26 April 2011	The duration of contraception for bevacizumab was update to 6 months after the last dose, the patient informed consent form was updated to warn of particular symptoms, a new adverse event of special interest was introduced (i.e. febrile neutropenia), and the blood glucose measurement requirement was updated to allow for the use of capillary blood glucose measurement in the absence of measurement made of plasma glucose.
02 May 2012	The informed consent form was updated with new safety information and the study exclusion criteria for bifocal tumor was expanded.
29 April 2015	Clarification was provided for the exploratory research sub-studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported