

**Clinical trial results:**

A randomized, open-label, 2-arm, multicentre, phase III study to evaluate the efficacy and safety of bevacizumab in combination with trastuzumab / docetaxel compared with trastuzumab/docetaxel alone as first line treatment for patients with HER2 positive locally recurrent or metastatic breast cancer

Summary

EudraCT number	2006-001365-42
Trial protocol	AT IT CZ ES GB
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	02 June 2016
First version publication date	06 August 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set We have performed an internal QC of the record and findings have been identified which need to be rectified in the record.

Trial information**Trial identification**

Sponsor protocol code	BO20231
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00391092
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, 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	Interim
Date of interim/final analysis	30 June 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2011
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of bevacizumab in combination with trastuzumab/docetaxel versus compared with trastuzumab/docetaxel alone as first line treatment.

Protection of trial subjects:

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the patient. For EU/EEA countries, the investigator ensured compliance with the EU Clinical Trial Directive (2001/20/EC). In other countries where "Guideline for Good Clinical Practice" existed Roche and the investigators strictly ensured adherence to the stated provisions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Russian Federation: 90
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Bosnia and Herzegovina: 10
Country: Number of subjects enrolled	Brazil: 43
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Uruguay: 3
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 79
Country: Number of subjects enrolled	Italy: 38

Worldwide total number of subjects	424
EEA total number of subjects	213

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)	347
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The participants were randomized 1:1 using a block design randomization procedure with stratification (for prior adjuvant/neo-adjuvant taxane, trastuzumab as part of adjuvant treatment versus no trastuzumab, ER/PgR hormone receptor status and measurable disease) to avoid an imbalance of important prognostic factors.

Period 1

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

Blinding implementation details:

This was an open-label study. However, the Independent Review Committee (IRC) assessment was blinded to treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab + Docetaxel

Arm description:

Trastuzumab 8 milligrams per kilogram (mg/kg) loading dose administered intravenously on Day 1 of Cycle 1, followed by docetaxel 100 milligrams per square meter (mg/m²) on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg and docetaxel at 100 mg/m² were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent, and for a minimum of 6 cycles, respectively.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 8 mg/kg trastuzumab intravenously on Cycle 1 Day 1, and thereafter 6 mg/kg trastuzumab on Day 1 of each 3-week cycle.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 100 mg/m² docetaxel intravenously on Cycle 1 Day 2, and thereafter on Day 1 of each 3-week cycle.

Arm title	Trastuzumab + Bevacizumab + Docetaxel
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Arm description:

Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by bevacizumab 15 mg/kg and docetaxel 100 mg/m² on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg, bevacizumab 15 mg/kg and docetaxel at 100 mg/m² were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent.

Arm type	Placebo
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Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 8 mg/kg trastuzumab intravenously on Cycle 1 Day 1, and thereafter 6 mg/kg trastuzumab on Day 1 of each 3-week cycle.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 100 mg/m² docetaxel intravenously on Cycle 1 Day 2, and thereafter 100 mg/m² docetaxel on Day 1 of each 3-week cycle.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 15 mg/kg bevacizumab intravenously on Cycle 1 Day 2, and thereafter 15 mg/kg bevacizumab on Day 1 of each 3-week cycle.

Number of subjects in period 1	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel
Started	208	216
Received Treatment	206	215
Completed	0	0
Not completed	208	216
Death	78	81
Lost to follow-up	13	18
Alive on treatment	29	33
Alive in follow-up	88	84

Baseline characteristics

Reporting groups

Reporting group title	Trastuzumab + Docetaxel
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Reporting group description:

Trastuzumab 8 milligrams per kilogram (mg/kg) loading dose administered intravenously on Day 1 of Cycle 1, followed by docetaxel 100 milligrams per square meter (mg/m²) on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg and docetaxel at 100 mg/m² were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent, and for a minimum of 6 cycles, respectively.

Reporting group title	Trastuzumab + Bevacizumab + Docetaxel
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Reporting group description:

Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by bevacizumab 15 mg/kg and docetaxel 100 mg/m² on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg, bevacizumab 15 mg/kg and docetaxel at 100 mg/m² were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent.

Reporting group values	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel	Total
Number of subjects	208	216	424
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	54 ± 11.71	53.5 ± 10.9	-
Gender categorical Units: Subjects			
Female	208	216	424
Male	0	0	0

End points

End points reporting groups

Reporting group title	Trastuzumab + Docetaxel
Reporting group description: Trastuzumab 8 milligrams per kilogram (mg/kg) loading dose administered intravenously on Day 1 of Cycle 1, followed by docetaxel 100 milligrams per square meter (mg/m ²) on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg and docetaxel at 100 mg/m ² were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent, and for a minimum of 6 cycles, respectively.	
Reporting group title	Trastuzumab + Bevacizumab + Docetaxel
Reporting group description: Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by bevacizumab 15 mg/kg and docetaxel 100 mg/m ² on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg, bevacizumab 15 mg/kg and docetaxel at 100 mg/m ² were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent.	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description: PFS was defined as the time from randomization to time of first documented disease progression (unequivocal progression of existing non-target lesions) or death, whichever occurred first as assessed by Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v1.0). Primary PFS variable was defined based on the investigators' assessments and the statistical conclusions on the primary efficacy end point were based on investigator assessed PFS. PFS was estimated using Kaplan-Meier methods. Intent-to-treat (ITT) population: All randomized participants, regardless of whether they actually received study treatment or not.	
End point type	Primary
End point timeframe: Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to the clinical cutoff of 30 June 2011, up to 4.75 years)	

End point values	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	216		
Units: months				
median (confidence interval 95%)	13.7 (11.4 to 16.3)	16.5 (14.1 to 19.1)		

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS)
Comparison groups	Trastuzumab + Bevacizumab + Docetaxel v Trastuzumab + Docetaxel

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0775
Method	Logrank (unstratified)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.02

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from randomization to the date of death, regardless of the cause of death. OS was estimated using Kaplan-Meier methods. ITT population. Here '99999' was used as the upper range of 95% confidence interval (CI) was not calculable due to immature OS data as greater than 50% of participants were censored at the time of clinical cutoff (30 June 2011).	
End point type	Secondary
End point timeframe:	
Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to the clinical cutoff of 30 June 2011, up to 4.75 years)	

End point values	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	216		
Units: months				
median (confidence interval 95%)	38.3 (34.3 to 99999)	38.5 (32.1 to 99999)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab + Bevacizumab + Docetaxel
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9543
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.38

Secondary: Percentage of Participants With a Best Overall Response (OR) of Confirmed Complete Response (CR) or Partial Response (PR) in Participants with Measurable Disease at Baseline

End point title	Percentage of Participants With a Best Overall Response (OR) of Confirmed Complete Response (CR) or Partial Response (PR) in Participants with Measurable Disease at Baseline
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End point description:

Best OR was assessed using RECIST v1.0 criteria. Participants were classified as responders if their best OR was either confirmed CR (disappearance of all target lesions) or confirmed PR (at least a 30% decrease in the sum of the longest diameter [LD] of target lesions, taking as reference the baseline sum LD). Participants without any post-baseline assessments were regarded as non-responders. The 95% CI for the one sample binomial using Pearson-Clopper method. ITT population.

End point type	Secondary
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End point timeframe:

Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to clinical data cutoff of 30 June 2011, up to 4.75 years)

End point values	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176 ^[1]	183 ^[2]		
Units: Percentage of participants				
number (confidence interval 95%)				
Responders	69.9 (62.5 to 76.6)	74.3 (67.4 to 80.5)		

Notes:

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

[2] - only participants with measurable disease at baseline were included in the analysis.

Statistical analyses

Statistical analysis title	% of Participants With Confirmed CR and PR
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab + Bevacizumab + Docetaxel
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3492
Method	Chi-squared
Parameter estimate	Difference in Response rates
Point estimate	4.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	14

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)
End point description:	
DR was defined as the time when response (CR or PR per RECIST v1.0) was first documented to the date of disease progression per RECIST v1.0 (unequivocal progression of existing non-target lesions) or death. ITT population.	
End point type	Secondary
End point timeframe:	
Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to clinical cutoff of 30 June 2011, up to 4.75 years)	

End point values	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123 ^[3]	136 ^[4]		
Units: months				
median (confidence interval 95%)	11.4 (9.1 to 13.2)	14.6 (12 to 17.1)		

Notes:

[3] - Only participants with a best OR of CR or PR were included in the analysis.

[4] - Only participants with a best OR of CR or PR were included in the analysis.

Statistical analyses

Statistical analysis title	Duration of Response (DR)
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab + Bevacizumab + Docetaxel
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.98

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)
End point description:	
TTF was defined as the time between randomization and date of disease progression (per RECIST v1.0; unequivocal progression of existing non-target lesions), death, or withdrawal of treatment due to adverse events, withdrawal of informed consent, insufficient therapeutic response, refusal of treatment/failure to co-operate, or failure to return, whichever occurred first. ITT population.	
End point type	Secondary
End point timeframe:	
Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to clinical cutoff of 30 June 2011, up to 4.75 years)	

End point values	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	216		
Units: months				
median (confidence interval 95%)	7.7 (6.3 to 8.6)	9.8 (7.9 to 10.9)		

Statistical analyses

Statistical analysis title	Time to Treatment Failure (TTF)
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab + Bevacizumab + Docetaxel
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5392
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.15

Secondary: Functional Assessment of Cancer Therapy-Generic (FACT-G) and Functional Assessment of Cancer Therapy-Breast (FACT-B) Subscale Scores

End point title	Functional Assessment of Cancer Therapy-Generic (FACT-G) and Functional Assessment of Cancer Therapy-Breast (FACT-B) Subscale Scores
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End point description:

FACT-G is core questionnaire of Functional Assessment of Chronic Illness Therapy (FACIT) measurement system to evaluate quality of life (QoL) in cancer population. FACT-G consisted of 27 questions grouped in 4 domains of general Health-Related QoL (HRQoL): Physical Well-being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB) and Functional Well-Being (FWB); each

ranged from 0 (not at all) to 4 (very much). FACT-G ranged between 0-108. Since questions could be reversed coded, as appropriate, before calculating FACT-G, 0 and 108 could be considered worst and best health states. FACT-B is used for assessment of HRQoL in participants with breast cancer. It consists of 36 items, summarized to 5 subscales: 7 items for each physical, functional, social/family; all 3 ranged from 0-28, emotional (6 items) ranged from 0-24, and breast cancer subscale (9 items) ranged from 0-36. All single-item measures ranges from 0-144. High score represents a better QoL. ITT population.

End point type	Secondary
End point timeframe:	
Baseline, Cycles 3, 5, 11, and post progressive disease (PD; 14 to 28 days after disease progression [up to clinical cutoff of 30 June 2011, up to 4.75 years])	

End point values	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173 ^[5]	189 ^[6]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical Well-Being: Baseline (n=173,189)	21.2 (± 5.74)	21.47 (± 5.07)		
Social Well-Being: Baseline (n=173,189)	20.59 (± 5.75)	20.88 (± 5.77)		
Emotional Well-Being: Baseline (n=173,189)	14.95 (± 4.95)	15.54 (± 4.44)		
Functional Well-Being: Baseline (n=173,189)	16.34 (± 5.83)	16.36 (± 5.57)		
Total FACT-G Score: Baseline (n=173,189)	73.3 (± 16.6)	74.49 (± 14.5)		
Breast Specific: Baseline (n=173,189)	21.67 (± 6.43)	22.84 (± 5.85)		
Total FACT-B Score: Baseline (n=173,189)	94.97 (± 20.5)	97.46 (± 17.71)		
Trial Outcome Index: Baseline (n=173,189)	59.54 (± 14.03)	60.85 (± 12.61)		
Physical Well-Being: Cycle 3 (n=145,173)	20.19 (± 4.89)	19.96 (± 5.05)		
Social Well-Being: Cycle 3 (n=145,173)	20.64 (± 5.32)	21.19 (± 5.44)		
Emotional Well-Being: Cycle 3 (n=145,173)	16.47 (± 4.19)	16.7 (± 4.36)		
Functional Well-Being: Cycle 3 (n=145,173)	15.43 (± 5.33)	16.2 (± 5.22)		
Total FACT-G Score: Cycle 3 (n=145,173)	72.94 (± 14.81)	74.05 (± 14.35)		
Breast Specific: Cycle 3 (n=145,173)	22.29 (± 5.78)	23.17 (± 5.34)		
Total FACT-B Score: Cycle 3 (n=145,173)	95.26 (± 18.52)	97.23 (± 17.81)		
Trial Outcome Index: Cycle 3 (n=145,173)	58.04 (± 12.8)	59.33 (± 12.49)		
Physical Well-Being: Cycle 5 (n=139,166)	19.51 (± 4.83)	19.67 (± 4.56)		
Social Well-Being: Cycle 5 (n=139,166)	19.36 (± 5.26)	20.68 (± 4.92)		
Emotional Well-Being: Cycle 5 (n=139,166)	16.05 (± 4.44)	17.07 (± 4.3)		
Functional Well-Being: Cycle 5 (n=139,166)	14.81 (± 5.45)	15.78 (± 4.77)		
Total FACT-G Score: Cycle 5 (n=139,166)	69.78 (± 15.04)	73.21 (± 12.49)		

Breast Specific: Cycle 5 (n=139, 166)	21.65 (± 5.83)	23.15 (± 4.9)		
Total FACT-B Score: Cycle 5 (n=139, 166)	91.43 (± 18.81)	96.36 (± 15.63)		
Trial Outcome Index: Cycle 5 (n=139, 166)	55.99 (± 13.09)	58.59 (± 11.01)		
Physical Well-Being: Cycle 11 (n=100, 133)	21.71 (± 4.54)	21.56 (± 4.53)		
Social Well-Being: Cycle 11 (n=100, 133)	19.71 (± 5.74)	20.78 (± 4.92)		
Emotional Well-Being: Cycle 11 (n=100, 133)	15.96 (± 4.5)	17.46 (± 3.7)		
Functional Well-Being: Cycle 11 (n=100, 133)	16.25 (± 5.16)	16.98 (± 4.92)		
Total FACT-G Score: Cycle 11 (n=100, 133)	73.26 (± 15.24)	76.55 (± 13.56)		
Breast Specific: Cycle 11 (n=100, 133)	21.29 (± 5.55)	23.8 (± 4.92)		
Total FACT-B Score: Cycle 11 (n=100, 133)	94.57 (± 18.58)	100.43 (± 16.97)		
Trial Outcome Index: Cycle 11 (n=100, 133)	59.19 (± 12)	62.34 (± 11.79)		
Physical Well-Being: Post PD (n=33, 39)	19.94 (± 4.99)	20.35 (± 5.37)		
Social Well-Being: Post PD (n=33, 39)	19.02 (± 5.61)	19.68 (± 4.77)		
Emotional Well-Being: Post PD (n=33, 39)	14.76 (± 4.83)	14.77 (± 4.64)		
Functional Well-Being: Post PD (n=33, 39)	14.13 (± 5.57)	15.08 (± 5.16)		
Total FACT-G Score: Post PD (n=33, 39)	67.84 (± 14.21)	70.04 (± 15.08)		
Breast Specific: Post PD (n=33, 39)	22.9 (± 4.48)	22.87 (± 5.14)		
Total FACT-B Score: Post PD (n=33, 39)	90.74 (± 16.59)	92.92 (± 18.47)		
Trial Outcome Index: Post PD (n=33, 39)	56.97 (± 11.16)	58.47 (± 12.43)		

Notes:

[5] - n (number) = number of participants assessed for the given parameter at the specified visit.

[6] - n (number) = number of participants assessed for the given parameter at the specified visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline for FACT-G and FACT-B

End point title	Change From Baseline for FACT-G and FACT-B
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End point description:

FACT-G is core questionnaire of FACIT measurement system to evaluate QoL in cancer population. FACT-G consisted of 27 questions grouped in 4 domains of general HRQoL: PWB, SWB, EWB and FWB; each ranged from 0 (not at all) to 4 (very much). FACT-G ranged between 0-108. Since questions could be reversed coded, as appropriate, before calculating FACT-G, 0 and 108 could be considered worst and best health states. FACT -B is used for assessment of HRQoL in participants with breast cancer. It consists of 36 items, summarized to 5 subscales: 7 items for each physical, functional, social/family; all 3 ranged from 0-28, emotional (6 items) ranged from 0-24, and breast cancer subscale (9 items) ranged from 0-36. All single-item measures ranges from 0-144. High score represents a better QoL. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, Cycles 3, 5, 11, and post PD (14 to 28 days after disease progression [up to clinical cutoff of 30 June 2011, up to 4.75 years])

End point values	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145 ^[7]	173 ^[8]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical Well-Being: Cycle 3 (n=145,173)	-1.01 (± 7.54)	-1.51 (± 7.16)		
Social Well-Being: Cycle 3 (n=145,173)	0.05 (± 7.83)	0.32 (± 7.93)		
Emotional Well-Being: Cycle 3 (n=145,173)	1.52 (± 6.49)	1.16 (± 6.22)		
Functional Well-Being: Cycle 3 (n=145,173)	-0.91 (± 7.9)	-0.16 (± 7.63)		
Total FACT-G Score: Cycle 3 (n=145,173)	-0.36 (± 22.25)	-0.44 (± 20.4)		
Breast Specific: Cycle 3 (n=145,173)	0.61 (± 8.65)	0.34 (± 7.92)		
Total FACT-B Score: Cycle 3 (n=145,173)	0.29 (± 27.63)	-0.24 (± 25.12)		
Trial Outcome Index: Cycle 3 (n=145,173)	-1.5 (± 18.99)	-1.52 (± 17.75)		
Physical Well-Being: Cycle 5 (n=139,166)	-1.69 (± 7.5)	-1.8 (± 6.82)		
Social Well-Being: Cycle 5 (n=139,166)	-1.23 (± 7.79)	-0.2 (± 7.58)		
Emotional Well-Being: Cycle 5 (n=139,166)	1.09 (± 6.65)	1.53 (± 6.18)		
Functional Well-Being: Cycle 5 (n=139,166)	-1.53 (± 7.98)	-0.58 (± 7.33)		
Total FACT-G Score: Cycle 5 (n=139,166)	-3.53 (± 22.4)	-1.28 (± 19.14)		
Breast Specific: Cycle 5 (n=139,166)	-0.03 (± 8.68)	0.31 (± 7.63)		
Total FACT-B Score: Cycle 5 (n=139,166)	-3.55 (± 27.82)	-1.1 (± 23.62)		
Trial Outcome Index: Cycle 5 (n=139,166)	-3.55 (± 19.19)	-2.26 (± 16.74)		
Physical Well-Being: Cycle 11 (n=100,133)	0.51 (± 7.32)	0.09 (± 6.8)		
Social Well-Being: Cycle 11 (n=100,133)	-0.89 (± 8.13)	-0.1 (± 7.58)		
Emotional Well-Being: Cycle 11 (n=100,133)	1 (± 6.69)	1.92 (± 5.78)		
Functional Well-Being: Cycle 11 (n=100,133)	-0.09 (± 7.79)	0.62 (± 7.43)		
Total FACT-G Score: Cycle 11 (n=100,133)	-0.05 (± 22.54)	2.06 (± 19.85)		
Breast Specific: Cycle 11 (n=100,133)	-0.38 (± 8.49)	0.96 (± 7.64)		
Total FACT-B Score: Cycle 11 (n=100,133)	-0.41 (± 27.67)	2.97 (± 24.53)		
Trial Outcome Index: Cycle 11 (n=100,133)	-0.35 (± 18.46)	1.49 (± 17.26)		
Physical Well-Being: Post PD (n=33,39)	-1.25 (± 7.61)	-1.12 (± 7.39)		
Social Well-Being: Post PD (n=33,39)	-1.58 (± 8.03)	-1.19 (± 7.48)		
Emotional Well-Being: Post PD (n=33,39)	-0.2 (± 6.92)	-0.78 (± 6.42)		

Functional Well-Being: Post PD (n=33, 39)	-2.22 (± 8.06)	-1.28 (± 7.59)		
Total FACT-G Score: Post PD (n=33, 39)	-5.46 (± 21.85)	-4.44 (± 20.92)		
Breast Specific: Post PD (n=33, 39)	1.22 (± 7.84)	0.03 (± 7.79)		
Total FACT-B Score: Post PD (n=33, 39)	-4.23 (± 26.37)	-4.55 (± 25.59)		
Trial Outcome Index: Post PD (n=33, 39)	-2.57 (± 17.92)	-2.38 (± 17.7)		

Notes:

[7] - n (number) = number of participants assessed for the given parameter at the specified visit.

[8] - n (number) = number of participants assessed for the given parameter at the specified visit.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of first drug intake up to 28 days after last dose study treatment (up to 4.75 years)

Adverse event reporting additional description:

Safety population included all participants who had received at least 1 dose of the trial medication, whether withdrawn prematurely or not.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Trastuzumab + Docetaxel
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Reporting group description:

Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by docetaxel 100 mg/m² on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg and docetaxel at 100 mg/m² were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent, and for a minimum of 6 cycles, respectively.

Reporting group title	Trastuzumab + Bevacizumab + Docetaxel
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Reporting group description:

Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by bevacizumab 15 mg/kg and docetaxel 100 mg/m² on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg, bevacizumab 15 mg/kg and docetaxel at 100 mg/m² were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent.

Serious adverse events	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 206 (30.58%)	72 / 215 (33.49%)	
number of deaths (all causes)	78	81	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypertension			
subjects affected / exposed	0 / 206 (0.00%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 206 (0.49%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 206 (0.97%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 206 (0.97%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Bartholinitis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast discharge			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 206 (0.97%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 206 (0.49%)	3 / 215 (1.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 206 (0.97%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
General physical condition abnormal			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Comminuted fracture			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			

subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 206 (0.00%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	14 / 206 (6.80%)	18 / 215 (8.37%)	
occurrences causally related to treatment / all	14 / 14	18 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	9 / 206 (4.37%)	6 / 215 (2.79%)	
occurrences causally related to treatment / all	9 / 9	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 206 (0.49%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 206 (1.94%)	6 / 215 (2.79%)	
occurrences causally related to treatment / all	3 / 4	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 206 (0.00%)	3 / 215 (1.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			

subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Aphthous stomatitis		
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer perforation		
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enteritis		
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric haemorrhage		
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1
Gastrointestinal haemorrhage		
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis acute		
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal obstruction		
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal haemorrhage		

subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vein thrombosis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Exfoliative rash			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	3 / 206 (1.46%)	6 / 215 (2.79%)	
occurrences causally related to treatment / all	3 / 3	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	2 / 206 (0.97%)	4 / 215 (1.86%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Abscess			
subjects affected / exposed	0 / 206 (0.00%)	4 / 215 (1.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 206 (0.49%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 206 (1.46%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 206 (0.97%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Urinary tract infection			
subjects affected / exposed	1 / 206 (0.49%)	2 / 215 (0.93%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 206 (0.49%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 206 (0.49%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess soft tissue			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina gangrenous			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			

subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	1 / 206 (0.49%)	0 / 215 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Viral infection			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 206 (0.00%)	1 / 215 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trastuzumab + Docetaxel	Trastuzumab + Bevacizumab + Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 206 (96.12%)	202 / 215 (93.95%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 206 (13.11%)	79 / 215 (36.74%)	
occurrences (all)	41	115	
Hot flush			
subjects affected / exposed	16 / 206 (7.77%)	12 / 215 (5.58%)	
occurrences (all)	19	15	
Lymphoedema			

subjects affected / exposed occurrences (all)	17 / 206 (8.25%) 17	8 / 215 (3.72%) 8	
Flushing subjects affected / exposed occurrences (all)	10 / 206 (4.85%) 19	12 / 215 (5.58%) 20	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	76 / 206 (36.89%) 154	75 / 215 (34.88%) 139	
Fatigue subjects affected / exposed occurrences (all)	48 / 206 (23.30%) 87	69 / 215 (32.09%) 183	
Oedema peripheral subjects affected / exposed occurrences (all)	72 / 206 (34.95%) 113	37 / 215 (17.21%) 43	
Pyrexia subjects affected / exposed occurrences (all)	41 / 206 (19.90%) 53	51 / 215 (23.72%) 82	
Influenza like illness subjects affected / exposed occurrences (all)	18 / 206 (8.74%) 31	17 / 215 (7.91%) 36	
Spinal pain subjects affected / exposed occurrences (all)	4 / 206 (1.94%) 4	11 / 215 (5.12%) 13	
Chills subjects affected / exposed occurrences (all)	11 / 206 (5.34%) 12	15 / 215 (6.98%) 18	
Immune system disorders			
Hypersensitivity subjects affected / exposed occurrences (all)	14 / 206 (6.80%) 19	10 / 215 (4.65%) 12	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	43 / 206 (20.87%) 65	43 / 215 (20.00%) 55	
Epistaxis			

subjects affected / exposed occurrences (all)	35 / 206 (16.99%) 59	109 / 215 (50.70%) 251	
Rhinorrhoea subjects affected / exposed occurrences (all)	18 / 206 (8.74%) 31	26 / 215 (12.09%) 36	
Dyspnoea subjects affected / exposed occurrences (all)	46 / 206 (22.33%) 61	36 / 215 (16.74%) 44	
Dysphonia subjects affected / exposed occurrences (all)	8 / 206 (3.88%) 8	21 / 215 (9.77%) 24	
Oropharyngeal pain subjects affected / exposed occurrences (all)	13 / 206 (6.31%) 19	26 / 215 (12.09%) 39	
Respiratory disorder subjects affected / exposed occurrences (all)	8 / 206 (3.88%) 9	11 / 215 (5.12%) 18	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	21 / 206 (10.19%) 24	19 / 215 (8.84%) 34	
Depression subjects affected / exposed occurrences (all)	15 / 206 (7.28%) 16	13 / 215 (6.05%) 15	
Anxiety subjects affected / exposed occurrences (all)	16 / 206 (7.77%) 17	12 / 215 (5.58%) 13	
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	6 / 206 (2.91%) 6	20 / 215 (9.30%) 22	
Weight increased subjects affected / exposed occurrences (all)	13 / 206 (6.31%) 14	8 / 215 (3.72%) 8	
Cardiac disorders			

Left ventricular dysfunction subjects affected / exposed occurrences (all)	17 / 206 (8.25%) 20	24 / 215 (11.16%) 28	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	40 / 206 (19.42%) 67	66 / 215 (30.70%) 129	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	52 / 206 (25.24%) 73	46 / 215 (21.40%) 71	
Paraesthesia subjects affected / exposed occurrences (all)	28 / 206 (13.59%) 36	37 / 215 (17.21%) 40	
Dysgeusia subjects affected / exposed occurrences (all)	32 / 206 (15.53%) 47	37 / 215 (17.21%) 60	
Neuropathy peripheral subjects affected / exposed occurrences (all)	18 / 206 (8.74%) 21	22 / 215 (10.23%) 29	
Dizziness subjects affected / exposed occurrences (all)	16 / 206 (7.77%) 22	14 / 215 (6.51%) 18	
Blood and lymphatic system disorders			
Neutropenia subjects affected / exposed occurrences (all)	51 / 206 (24.76%) 108	44 / 215 (20.47%) 76	
Anaemia subjects affected / exposed occurrences (all)	24 / 206 (11.65%) 28	16 / 215 (7.44%) 20	
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	13 / 206 (6.31%) 17	3 / 215 (1.40%) 3	
Eye disorders			
Lacrimation increased subjects affected / exposed occurrences (all)	59 / 206 (28.64%) 75	75 / 215 (34.88%) 88	

Dry eye			
subjects affected / exposed	6 / 206 (2.91%)	12 / 215 (5.58%)	
occurrences (all)	6	13	
Conjunctivitis			
subjects affected / exposed	9 / 206 (4.37%)	22 / 215 (10.23%)	
occurrences (all)	14	25	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	85 / 206 (41.26%)	107 / 215 (49.77%)	
occurrences (all)	158	265	
Stomatitis			
subjects affected / exposed	61 / 206 (29.61%)	95 / 215 (44.19%)	
occurrences (all)	95	182	
Nausea			
subjects affected / exposed	76 / 206 (36.89%)	82 / 215 (38.14%)	
occurrences (all)	163	187	
Constipation			
subjects affected / exposed	47 / 206 (22.82%)	54 / 215 (25.12%)	
occurrences (all)	65	88	
Dyspepsia			
subjects affected / exposed	18 / 206 (8.74%)	34 / 215 (15.81%)	
occurrences (all)	26	58	
Vomiting			
subjects affected / exposed	37 / 206 (17.96%)	42 / 215 (19.53%)	
occurrences (all)	72	60	
Abdominal pain			
subjects affected / exposed	15 / 206 (7.28%)	27 / 215 (12.56%)	
occurrences (all)	20	45	
Abdominal pain upper			
subjects affected / exposed	24 / 206 (11.65%)	23 / 215 (10.70%)	
occurrences (all)	33	32	
Haemorrhoids			
subjects affected / exposed	8 / 206 (3.88%)	22 / 215 (10.23%)	
occurrences (all)	13	35	
Toothache			

subjects affected / exposed	7 / 206 (3.40%)	12 / 215 (5.58%)
occurrences (all)	7	24
Gastroesophageal reflux disease		
subjects affected / exposed	11 / 206 (5.34%)	8 / 215 (3.72%)
occurrences (all)	19	17
Gingival bleeding		
subjects affected / exposed	1 / 206 (0.49%)	15 / 215 (6.98%)
occurrences (all)	2	26
Rectal haemorrhage		
subjects affected / exposed	1 / 206 (0.49%)	10 / 215 (4.65%)
occurrences (all)	1	14
Skin and subcutaneous tissue disorders		
Alopecia		
subjects affected / exposed	141 / 206 (68.45%)	135 / 215 (62.79%)
occurrences (all)	142	142
Rash		
subjects affected / exposed	41 / 206 (19.90%)	37 / 215 (17.21%)
occurrences (all)	58	52
Palmar-plantar erythrodysesthesia syndrome		
subjects affected / exposed	26 / 206 (12.62%)	27 / 215 (12.56%)
occurrences (all)	32	34
Nail disorder		
subjects affected / exposed	59 / 206 (28.64%)	68 / 215 (31.63%)
occurrences (all)	65	74
Dry skin		
subjects affected / exposed	25 / 206 (12.14%)	28 / 215 (13.02%)
occurrences (all)	29	30
Pruritus		
subjects affected / exposed	24 / 206 (11.65%)	19 / 215 (8.84%)
occurrences (all)	34	31
Nail toxicity		
subjects affected / exposed	24 / 206 (11.65%)	15 / 215 (6.98%)
occurrences (all)	27	18
Erythema		

subjects affected / exposed occurrences (all)	12 / 206 (5.83%) 14	16 / 215 (7.44%) 27	
Onycholysis subjects affected / exposed occurrences (all)	5 / 206 (2.43%) 5	16 / 215 (7.44%) 17	
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	1 / 206 (0.49%) 2	22 / 215 (10.23%) 35	
Dysuria subjects affected / exposed occurrences (all)	7 / 206 (3.40%) 8	13 / 215 (6.05%) 14	
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	60 / 206 (29.13%) 115	59 / 215 (27.44%) 137	
Musculoskeletal pain subjects affected / exposed occurrences (all)	32 / 206 (15.53%) 46	39 / 215 (18.14%) 61	
Arthralgia subjects affected / exposed occurrences (all)	41 / 206 (19.90%) 86	63 / 215 (29.30%) 109	
Pain in extremity subjects affected / exposed occurrences (all)	37 / 206 (17.96%) 54	35 / 215 (16.28%) 53	
Neck pain subjects affected / exposed occurrences (all)	10 / 206 (4.85%) 13	17 / 215 (7.91%) 17	
Back pain subjects affected / exposed occurrences (all)	26 / 206 (12.62%) 37	32 / 215 (14.88%) 39	
Bone pain subjects affected / exposed occurrences (all)	25 / 206 (12.14%) 35	23 / 215 (10.70%) 27	
Musculoskeletal chest pain			

subjects affected / exposed occurrences (all)	7 / 206 (3.40%) 8	14 / 215 (6.51%) 15	
Muscle spasms subjects affected / exposed occurrences (all)	8 / 206 (3.88%) 10	18 / 215 (8.37%) 33	
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	33 / 206 (16.02%) 58	27 / 215 (12.56%) 43	
Cystitis subjects affected / exposed occurrences (all)	17 / 206 (8.25%) 21	19 / 215 (8.84%) 27	
Rhinitis subjects affected / exposed occurrences (all)	16 / 206 (7.77%) 22	17 / 215 (7.91%) 20	
Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 206 (9.71%) 25	18 / 215 (8.37%) 26	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	11 / 206 (5.34%) 15	21 / 215 (9.77%) 47	
Bronchitis subjects affected / exposed occurrences (all)	15 / 206 (7.28%) 18	9 / 215 (4.19%) 14	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	25 / 206 (12.14%) 41	39 / 215 (18.14%) 58	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2007	<ul style="list-style-type: none">- Implemented central human epidermal growth factor receptor 2 (HER2) testing to ensure greater consistency in determination of HER2 status.- Increased sample size to accommodate an assessment of PFS by an Independent Review Committee (not all participants could be assessed by such a procedure) for an intended US filing.- Reversible posterior leukoencephalopathy syndrome (RPLS) was listed as an adverse event of special interest to ensure instances of this rare event were properly detected.- Inclusion criterion for participants who had received adjuvant trastuzumab treatment was modified to better reflect the clinical reality after the earlier than expected approval of this treatment. The washout period for prior hormone treatment was also extended.- The definition of inadequate liver function in the exclusion criteria was changed for better alignment with the labeling for docetaxel and the duration of subsequent trastuzumab administration was extended for greater compliance with the dosing recommendations at the time.- Further clarifications and correction of typographical errors.
06 March 2009	<ul style="list-style-type: none">- Monitoring of left ventricular ejection fraction (LVEF) was extended on the recommendation of the Data Safety Monitoring Board (DSMB).- Exploratory interim analyses on PFS and OS were added on the request of the DSMB to enable an assessment of the risk/benefit ratio.- Provision was made for participants randomized to the Trastuzumab+Docetaxel arm to receive bevacizumab after the end of the study if considered appropriate by DSMB on the basis of the interim analyses.- Further clarifications were made and typographical errors were corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported